Original Article

Potential therapeutic targets and biological mechanisms of Centella asiatica on hepatic fibrosis: a study of network pharmacology

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Background: Liver fibrosis is a common result of the repair process of various chronic liver diseases. This study is a network pharmacology study on the potential therapeutic targets and biological mechanisms of Centella asiatica for liver fibrosis.

Methods: The chemical components and potential targets of Centella asiatica were screened through TCMSP, PubChem database, and Swiss Target Prediction database. The DisGeNET and GeneCards databases were used to obtain targets of HF. Venn diagrams were used to find key targets, and draw protein interaction maps. Cytoscape software was used to construct an interaction network map of drug-component-target-disease-pathway. The mechanisms of action were predicted through enrichment analysis and KEGG analysis.

Results: In total, 6 main components, 297 drug targets, 337 HF targets, and 48 drug-disease targets were obtained in Centella asiatica. The key targets involved IL6, TNF, VEGFA, TP53, IL1β, MMP9, CXCL8, EGFR, JUN, SRC, MMP2, and TGF-β, among others. A total of 1293 entries were obtained by Gene Ontology (GO) enrichment analysis, which mainly involved the regulation of reactive oxygen species metabolic process, the regulation of smooth muscle cells, and the regulation of DNA-binding transcription factor activity. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment mainly screened 191 pathways, including the MAPK signaling pathway, the relaxin signaling pathway, and the Toll-like receptor signaling pathway, among others.

Conclusions: Centella asiatica may have a therapeutic effect on HF through multiple targets and pathways. Its mechanism is mainly related to the MAPK signaling pathway and the relaxin signaling pathway.

Keywords: Centella asiatica; hepatic fibrosis (HF); TGF-β; MAPK; network pharmacology

Submitted Apr 14, 2021. Accepted for publication May 26, 2021.
doi: 10.21037/atm-21-2253
View this article at: http://dx.doi.org/10.21037/atm-21-2253

Introduction

Hepatic fibrosis (HF) is a chronic liver disease in which liver cells are repeatedly destroyed and then regenerated, and extracellular matrix (ECM) is diffusely deposited and abnormally distributed in the liver, which leads to abnormal changes in liver tissue structure, thus affecting the normal physiological functions of the liver (1,2). It is a key step in the development and progression of various chronic liver diseases to cirrhosis, liver cancer, and even liver failure, and it is also an important link that affects the prognosis of chronic liver disease. Chronic liver disease is a global health problem. HF and cirrhosis are the main causes of death for patients with chronic liver disease. According to statistics, approximately 2 million people die from this disease every year worldwide (3). Because the pathogenesis of HF is relatively complicated and there are individual differences, conventional treatments can alleviate or even reverse the condition in the early stage (4), but it lacks effective treatment outcomes in the advanced HF stages.

Traditional Chinese medicine believes that the basic pathogenesis of HF is "deficiency and damage lead to accumulation" (1), and Chinese materia medica is characterized by multiple active ingredients and multiple targeted effects, which has certain advantages in the treatment of HF. Centella asiatica is a dry whole plant of Centella asiatica L. Urban in the Umbelliferae family, also known as horseshoe grass, gotu kola, and is widely distributed in the tropical and subtropical regions of the southern and northern hemispheres. It was first recorded as a medicine in Shennong's Classic of Materia Medica, and was listed as a medium-grade medicine. The dried whole herb is used as medicine, is bitter and pungent in flavor, cold in nature, with channel tropism of liver, spleen, and kidney. It has functions in clearing heat, promoting diuresis, resolving toxins, dispersing swelling, activating blood, and stopping bleeding. Previous literature recorded that the medicine has various pharmacological activities such as anti-inflammatory, anti-oxidant, anti-fibrosis, and anti-cancer effects, as well as nerve protection. Centella asiatica has been used to treat skin diseases in the past, and it has the effects of inhibiting scar hyperplasia and promoting wound healing (5). In recent years, it has been reported in the literature that Centella asiatica can improve bleomycin-induced pulmonary fibrosis (6). It can also have a certain effect on renal interstitial fibrosis (7). The above-mentioned diseases all involve the course of fibrosis, suggesting that Centella asiatica has a considerable anti-fibrosis effect.

Network pharmacology is an emerging discipline based on the integration of systems biology and computer technology. Different from the previous research methods of drug single component and single mechanism, it systematically analyzes the "disease-gene-target-drug" interaction network from a holistic perspective. It comprehensively observes the effects of drugs on the outcome of diseases through gene protein networks, thereby explaining the multi-component-multi-target mechanism of drugs. Hence, this paper adopted the method of network pharmacology to initially explore the effect of Centella asiatica on HF, and provide a theoretical basis for further clinical research.

We present the following article in accordance with the MDAR checklist (available at http://dx.doi.org/10.21037/atm-21-2253).

Methods

Materials

The following website databases and analysis software were selected: TCMSP database (https://tcmspw.com/tcmsp.php), PubChem database (https://pubchem.ncbi.nlm.nih.gov), Swiss Target Prediction database (http://www.swisstargetprediction.ch/), DrugBank database (https://go.drugbank.com/), DisGeNET database (https://www.disgenet.org/), GeneCards database (https://www.genecards.org/), STRING database (https://string-db.org/), UniProt database (https://www.uniprot.org/), KEGG Mapper database (https://www.kegg.jp/), Venny 2.1 online software drawing tool platform (https://bioinfogp.cnb.csic.es/tools/venny/), Cytoscape software 3.7.1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data collection and analysis

Collection of Centella asiatica's medicinal ingredients

The active ingredients and corresponding target proteins of Centella asiatica were searched through the TCMSP database, and the active ingredients of Centella asiatica were supplemented through literature retrieval. Through the database of traditional Chinese medicine and chemical components organized by the Shanghai Institute of Organic Chemistry (http://www.organchem.csdb.cn/scdb/default.htm), the CAS number of the relevant molecule was obtained. The chemical structure was found through

Table 1 Chinese materia medica-component-target information of Centella asiatica

Chemical composition	CAS	Number of the predicted targets
Asiatic acid	464-92-6	31
Brahmic acid	18449-41-7	46
Madasiatic acid	26532-66-1	83
Quercetin	117-39-5	145
Sitosterol	83-46-5	3
Kaempferol	520-18-3	104

the PubChem website and saved as a sdf file, then the sdf file was used to predict the oral availability and drug-like properties of the ingredients on the SwissADME website. The screening condition was "GIabsorption" as "High", and "Druglikeness" (Lipinski, Ghose, Veber, Egan, Muegge) met 3 of the 5 rules. This finally determined the active ingredient of the medicine.

Prediction of Centella asiatica's action targets

The drug sdf format file obtained through the screening was imported into the Swiss Target Prediction database, and the research species was set to "Homo sapiens" to obtain the predicted targets. The potential targets were obtained after integration and deduplication.

Acquisition of disease targets

The DisGeNET database and GeneCards database were used to search with "hepatic fibrosis" or "liver fibrosis" as keywords, and disease-related targets were obtained after integration and deduplication.

Acquisition of potential targets

The data of "Centella asiatica" action targets and "HF" disease targets were imported into Venny 2.1 mapping software to draw a Venn diagram, and the intersection of the 2 was taken as the potential targets.

Protein-protein interaction (PPI) network construction and analysis

The above-mentioned potential targets were entered into the STRING database. The species was set as "Homo sapiens" and the lowest interaction threshold was set as 0.4 to obtain protein interaction information. Then, the protein interaction network nodes were counted through the count package language of R software, and the core targets were screened and obtained.

Gene function and pathway analysis

R language was used to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis on the above-mentioned potential targets, which were displayed in a histogram, bubble chart, and pathway diagram. The biological processes and signaling pathways of Centella asiatica exerting anti-fibrosis effects were analyzed.

Network model construction and analysis

The active ingredients of the medicine, the potential action targets, the target of disease action, and the KEGG pathways were imported into Cytoscape software to construct an interaction network of "drug-component-target-disease-pathway".

Statistical analysis

The data in the article was converted, counted and processed using the Perl programming language (version 5.26.1, https://www.activestate.com/) and the ClusterProfiler and pathway software packages of the R language (version 3.6.3, https://www.r-project.org/). $P<0.05$ was considered statistically significant.

Results

Potential active ingredients and targets of Centella asiatica

After query and analysis, Centella asiatica contained more than 70 pharmacological ingredients and 6 effective chemical ingredients after being screened out through "GIabsorption" and "Druglikeness". A total of 297 potential medicine targets were obtained after integration and deduplication of the targets of all active ingredients (see *Table 1* for details).

HF targets

A total of 337 disease targets were obtained through website query, integration, deduplication, and screening (score_gda ≥0.2 in the DisGeNet database or relevance score ≥20 in the GeneCards database).

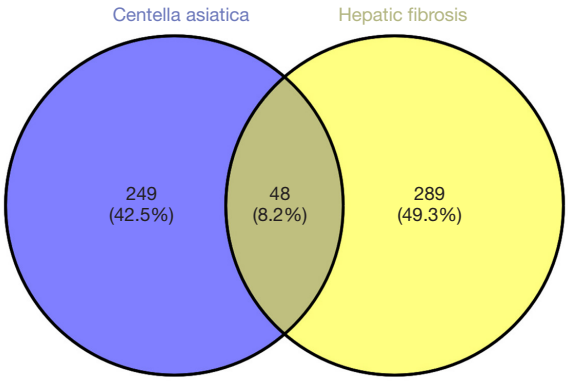

Figure 1 Venn diagram of targets in Centella asiatica and hepatic fibrosis.

Prediction of potential targets

The above medicine targets and disease targets were entered into the Venny 2.1 online mapping tool platform to draw a Venn diagram (*Figure 1*). After the 2 intersected, 48 common targets were obtained. The results showed that Centella asiatica may exert anti-HF effects through multiple potential targets.

PPI network construction

The 48 drug-disease common targets were entered into the STRING database to obtain the PPI map (*Figure 2*). The count command through the R language was used to count the protein interaction network nodes (degree) and screen to obtain the targets (*Figure 3*). Among them, the degrees of IL6, TNF, VEGFA, TP53, IL1β, MMP9, CXCL8, EGFR, JUN, SRC, MMP2, TGFβ1 exceeded the median of 21.8. It was speculated that the active ingredients of Centella asiatica may exert an anti-fibrotic effect through the above-mentioned multiple targets.

Enrichment analysis and pathway analysis

The 48 potential targets were entered into R software, and ClusterProfiler and the pathway language package were used for GO and KEGG analyses. The obtained GO analysis ($P<0.05$) included 1147 biological processes (BP), 49 cell components (CC), and 97 molecular functions (MF). The BP (*Figure 4A*) mainly involved the response and regulation of oxidative stress, leukocyte migration, regulation of smooth muscle cell proliferation, response to lipopolysaccharide, regulation of DNA binding transcription factor activity, etc. The CC (*Figure 4B*) mainly involved collagen-containing ECM, platelet α particles, RNA polymerase II transcription factor complexes, etc. The MF (*Figure 4C*) were mainly related to cytokine receptor binding, RNA polymerase II transcription factor binding, tumor necrosis factor receptor binding, and activation of transcription factor binding. KEGG analysis showed that there were mainly 191 signaling pathways, of which the first 20 pathways are shown in *Figure 4D*. It is speculated that the main mechanisms of Centella asiatica against HF are related to the MAPK signaling pathway (*Figure 5*), the relaxin signaling pathway (*Figure 6*), the Toll-like receptor signaling pathway, the IL-17 signaling pathway, the TNF signaling pathway, and the AGE-RAGE signaling pathway in diabetes complications. Therefore, the figures suggest that Centella asiatica exerts its anti-HF effects through multiple signaling pathways.

Construction of the drug component-target-disease-pathway network

The active ingredients of Centella asiatica and its targets, disease-related targets, and KEGG pathways were input into Cytoscape software to screen out isolated components that had no intersection between the ingredients and the targets, and a network diagram was drawn (*Figure 7*). As shown in the figure, the nodes represent the components, 48 co-acting targets, and the KEGG pathway. The degree value indicates the number of associations between the predicted nodes. The larger the degree value, the more important the target point. The network analyzer that comes with the software was used to analyze the network graph. The top 20 degree values were TNF, IL-1β, IL6, JUN, FOS, IFNG, TGFβ1, CXCL8, CCL2, MMP9, IL10, MMP2, STAT1, VEGFA, SRC, EGFR, MMP1, TLR9, CXCL10, COL1A1, and TP53. Together with mapping of the PPI network, it is speculated that IL6, TNF, TGF-β, VEGFA, IL1β, MMP9, CXCL8, and CCL2 may be the key targets of Centella asiatica.

Discussion

HF is a common pathological repair reaction after chronic liver injury caused by various reasons, and it is also a necessary link for the development of liver cirrhosis. The central link is focused on the activation of hepatic stellate cells (HSCs), which leads to diffuse and excessive deposition of ECM, resulting in fibrosis formation (8,9).

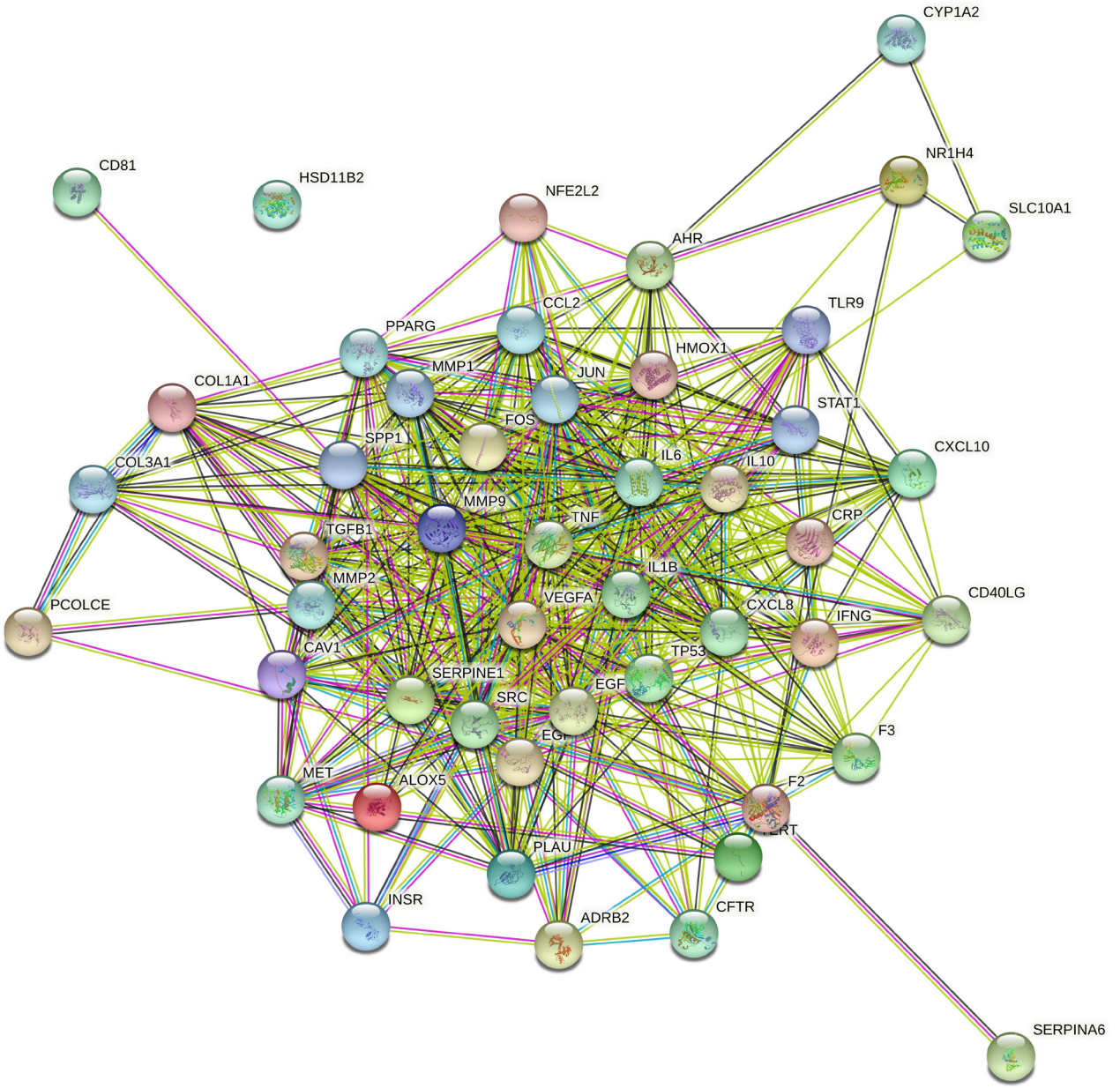

Figure 2 Protein-protein interaction network of the potential targets.

After short-term liver injury, this process can be balanced by anti-fibrotic mechanisms. In contrast, in chronic liver disease, the imbalance of pro-fibrotic and anti-fibrotic mechanisms leads to the continuous proliferation, contraction, and migration of myofibroblasts, which leads to the accumulation of ECM (10,11). The key signaling pathways involved in this process include the TGF-β/Smad signaling pathway, the MAPK signaling pathway, the platelet-derived growth factor (PDGF) pathway, the inflammasome (NLRP3)-Caspase 1 pathway, and the WNT/β-catenin signaling, among others (12-14). In recent years, it has also been found that the Notch pathway and the Hedgehog pathway are also involved (15,16). Multiple signaling pathways are intertwined and interact with each other, acting together in the whole process of HSC activation, proliferation, and HF.

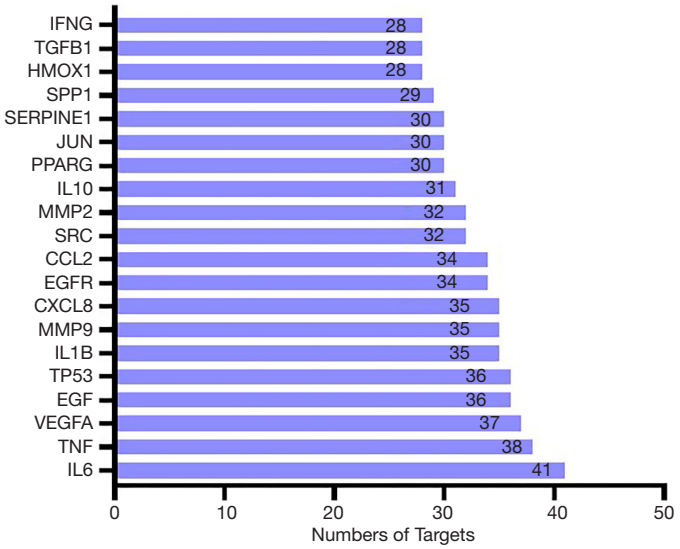

Figure 3 The core target of Centella asiatica against hepatic fibrosis.

The TGF-β/Smad signaling pathway plays an extremely important role in the course of HF. When the liver is stimulated by injury factors, TGF-β binds to TβR with high affinity on the surface of HSCs, which causes downstream R-Smad phosphorylation and I-Smad expression to decrease, transferring the signal into the nucleus, initiating HSC activation, and then inducing the synthesis of type I and type III collagen, which in turn promotes the occurrence of HF. In addition, it can also further activate other signaling pathways through Smad-independent pathways, and jointly promote the activation of HSCs (17,18). TGF-β1 promotes the production of ECM and inhibits its degradation, which is closely related to the progression of various types of chronic liver disease to fibrosis (19-21), and its concentration is also related to the severity of HF (22). Studies have shown that Centella asiatica has a protective effect on pulmonary fibrosis induced by bleomycin, and its mechanism may be related to the down-regulation of TGF-β1 expression (23). Other experiments have shown that Centella asiatica can up-regulate Smad7 protein expression in HSC-T6 cells, further blocking the activation of TGF-β/Smad signals by inhibiting the up-regulation of TGF-β1, and improving the pathological manifestations of HF (24). This study shows that Centella asiatica can fight against HF through the relaxin signaling pathway, which involves TGF-β/Smad signal transduction. Related targets include TGF-β, MMP2, MMP9, MMP1, collagen, VEGF, EFGR, AP1, and Src, among others, and correspond to "smooth muscle cell proliferation regulation" in the BP process. Therefore, we speculate that Centella asiatica can regulate the proliferation and differentiation of HSCs through TGF-β/Smad signal transduction, thereby regulating the balance between pro-fibrosis and anti-fibrosis, so as to play a related therapeutic effect.

As one of the important inflammation and intracellular transmission pathways in the human body, the MAPK pathway is involved in HSC activation, proliferation, and apoptosis, and is related to the formation and reversal of HF. Moreover, there is an interaction between the MAPK and TGF-β pathways, and they participate in the above-mentioned regulation processes (25). Studies have found that in the CCl4-induced rat HF model, the ERK, JNK, and P38 subfamilies in the MAPK signaling pathway all played important roles in the progression and reversal of HF (26-28). The ingredients of Centella asiatica have been shown in many experiments to exert anti-fibrosis and anti-inflammatory effects through the MAPK pathway. Studies have confirmed that Centella asiatica can significantly reduce LPS/D-GalN-induced liver damage in mice by blocking the phosphorylation of p38-MAPK and NF-κB pathways (29). Other researchers reported that the ECa 233 extract of Centella asiatica down-regulated NF-κB, extracellular signal-regulated kinase (ERK1/2), and p38 MAPK, providing a potential scheme for the prevention and treatment of inflammatory diseases (30). This study shows that Centella asiatica can act through the MAPK signaling pathway, and the targets involved are GF, RTK, c-fos, p53,

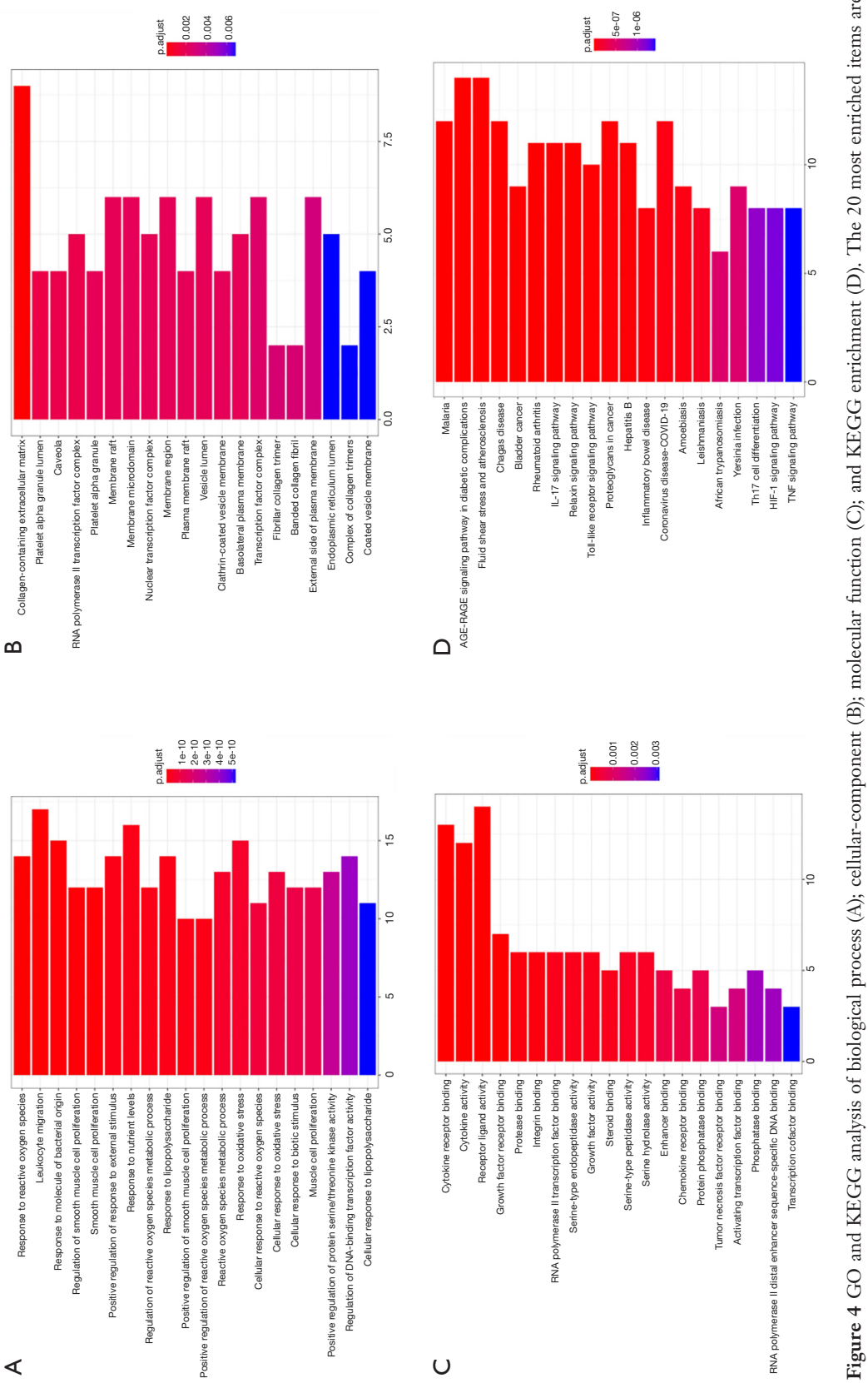

Figure 4 GO and KEGG analysis of biological process (A); cellular-component (B); molecular function (C); and KEGG enrichment (D). The 20 most enriched items are shown in each panel. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

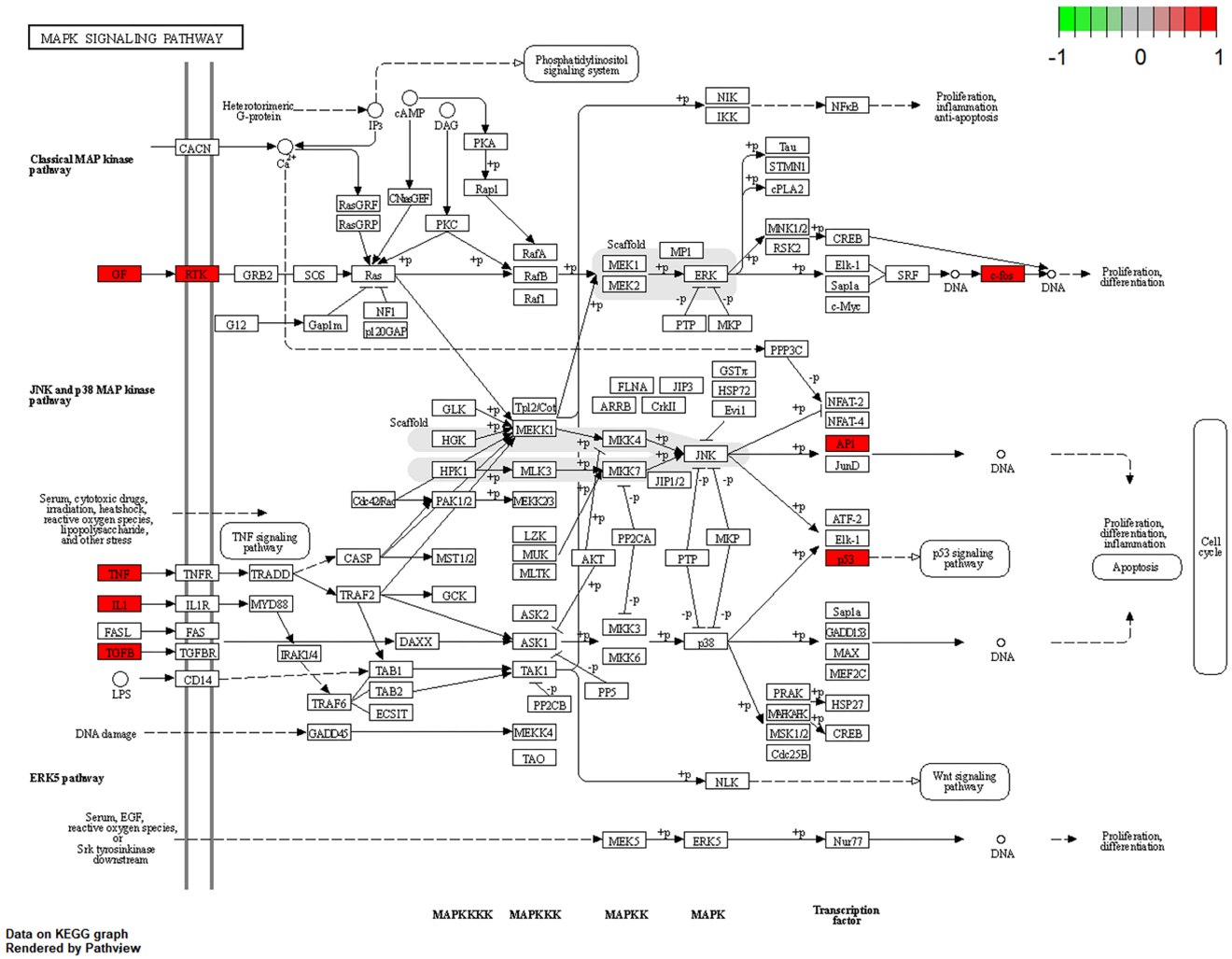

Figure 5 MAPK signaling pathway.

TNF, IL1, TGFB, and AP1. Therefore, we speculate that Centella asiatica can affect the proliferation, activation, and apoptosis of HSCs, and regulate inflammation through the 3 kinases ERK, JNK, and P38.

The chemical composition of Centella Asiatica includes triterpenoids (mainly triterpene saponins and triterpene acids), volatile oils, polyacetylenes, flavonoids, sterols, and other substances (31,32). Among them, triterpenoids, represented by asiaticoside, madecassoside, and asiatic acid, are the most abundant and most important active ingredients. The effective ingredients obtained in this study after oral availability and drug-like screening did not contain asiaticoside. The main reason is that it has a large molecular weight and poor water and fat solubility. As an oral dosage form, its gastrointestinal absorption rate is low, and as an intravenous dosage form, there are side effects such as hemolysis. Therefore, in order to maximize the pharmacological effects of Centella asiatica, it is urgent to develop new formulations to improve its ADME parameters. The asiaticoside liposomes (33) increase the stability of the medicine, significantly reduce its toxicity and side effects, effectively prolong the action time of the

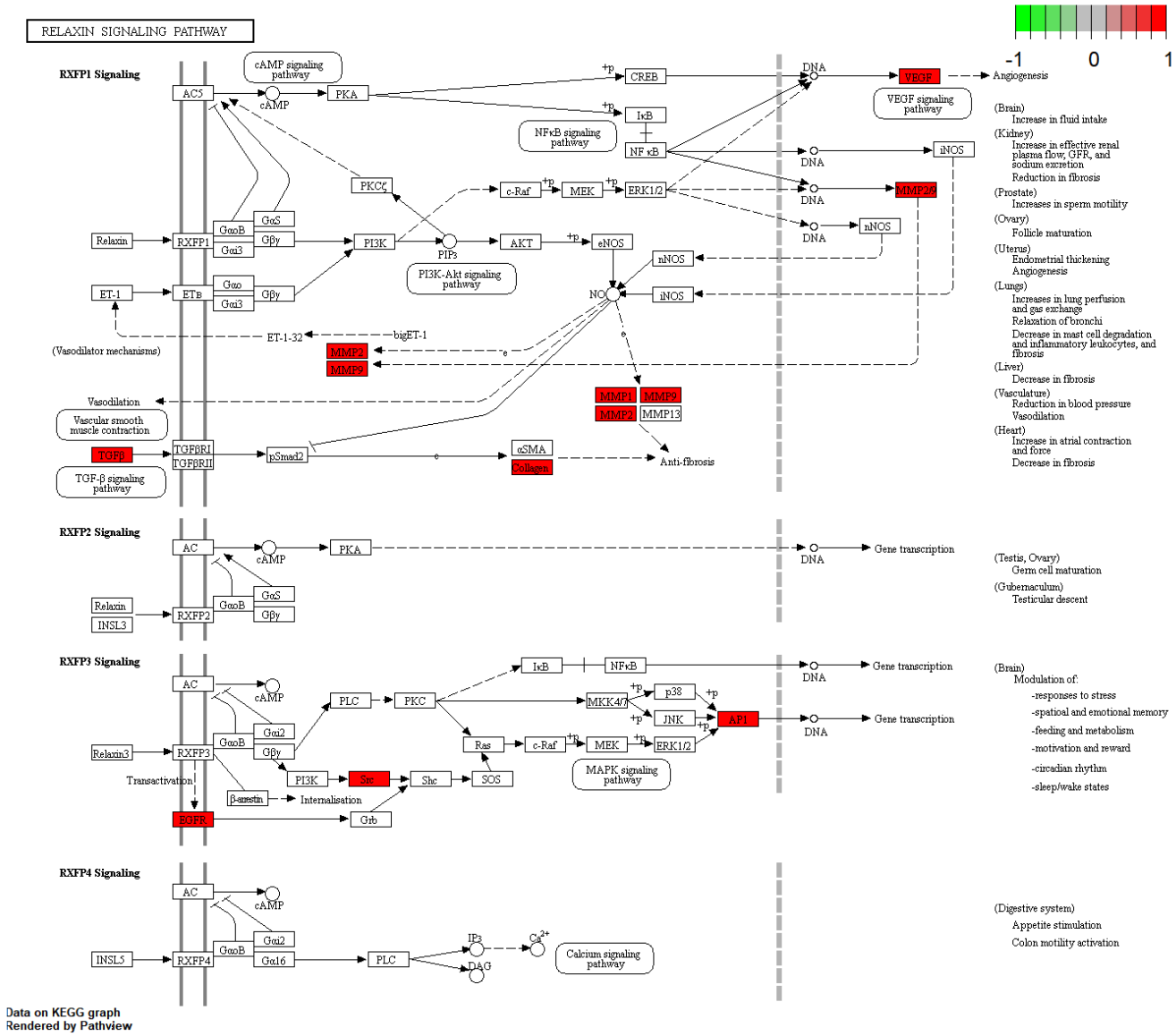

Figure 6 Relaxin signaling pathway.

medicine, and has certain organ targeting properties, which can be used as the dosage form of Centella asiatica herbal research in the future.

This study used network pharmacology methods to initially analyze the chemical components, targets, and mechanisms of Centella asiatica species, from which it can be seen that Centella asiatica resists HF through multi-component, multi-target, and multi-channel synergistic effects, providing a theoretical basis for further experimental verification. We look forward to using new and more effective formulations to conduct *in vivo* and *in vitro* experiments for further verification.

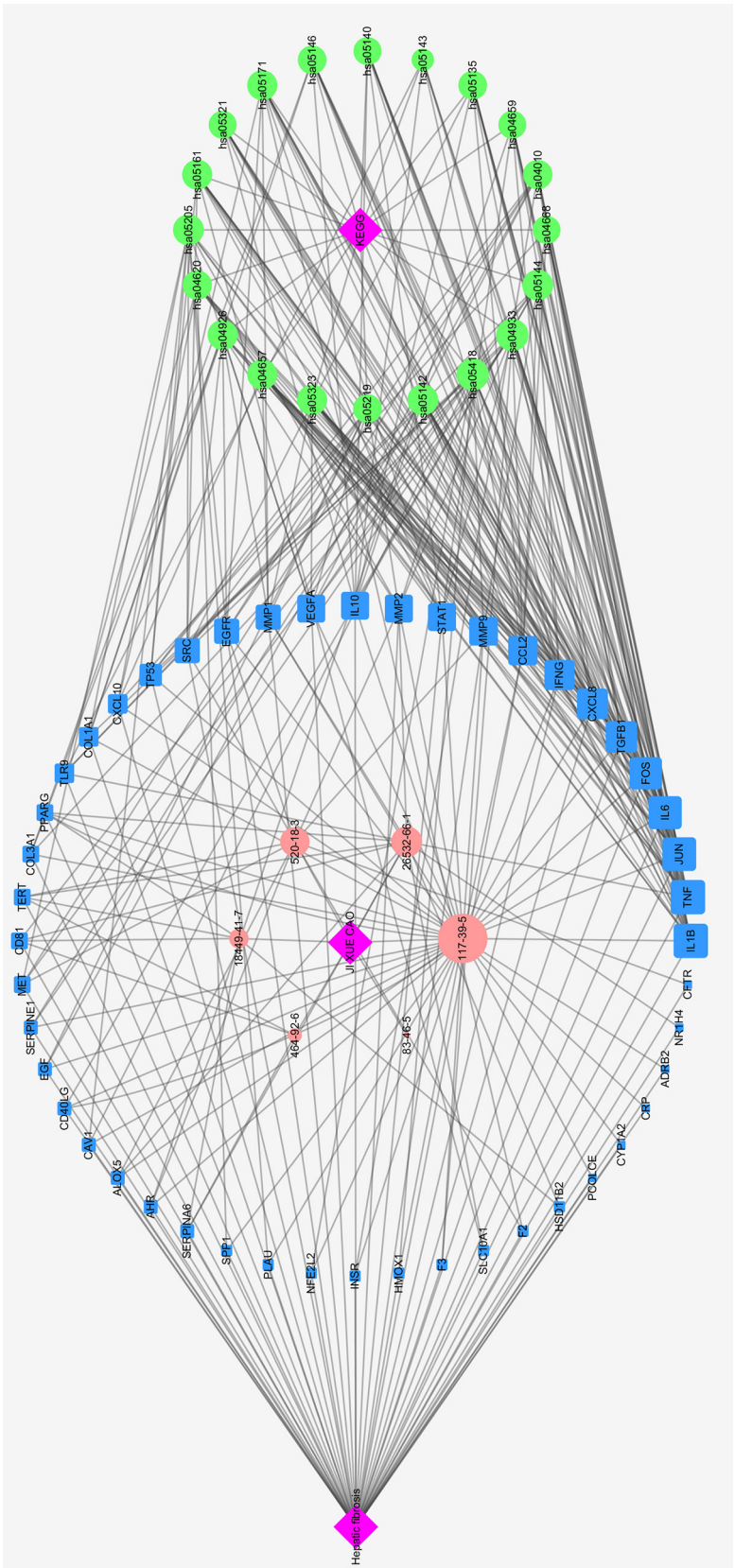

Figure 7 Drug component target disease KEGG pathway interaction network (the node size is proportional to the node degree). KEGG, Kyoto Encyclopedia of Genes and Genomes.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the MDAR checklist. Available at http://dx.doi.org/10.21037/atm-21-2253

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-2253). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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(English Language Editor: C. Betlazar-Maseh)

Cite this article as: Fan Y, Yin X. Potential therapeutic targets and biological mechanisms of Centella asiatica on hepatic fibrosis: a study of network pharmacology. Ann Transl Med 2021;9(11):932. doi: 10.21037/atm-21-2253