Exploring the Mechanism and Material Basis of Sophorae Tonkinensis Radix et Rhizoma in Treating Liver Cirrhosis Based on Bioinformatics

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Abstract

Objective: To investigate the mechanism of action and material basis of Sophorae Tonkinensis Radix et Rhizoma in treating liver cirrhosis through bioinformatics approaches. Methods: The chemical constituents of the traditional Chinese medicine were obtained via LC-MS. The SuperPred and TTD databases were employed to screen the targets of the traditional Chinese medicine and the disease, respectively. Intersection analysis was performed using the Venny database. Network diagrams were constructed through Cytoscape software. GO and KEGG enrichment analyses were conducted using the Metascape database. Molecular docking was completed using CB-DOCK2 software. Results: The screening identified 85 therapeutic components and 46 intersecting targets. Core targets included HIF1A, TNF-α, PTGS2, MAPK1, among others. Sophorae Tonkinensis Radix et Rhizoma in treating liver cirrhosis primarily involves cancer pathways, apoptosis, as well as lipid and atherosclerosis signaling pathways. Conclusion: Bioinformatics methodology was utilized to predict the mechanism of action and material basis of Sophorae Tonkinensis Radix et Rhizoma for liver cirrhosis, offering novel insights and directions for further investigation.

Full Text

Exploring the Mechanism and Material Basis of Sophora tonkinensis in the Treatment of Liver Cirrhosis Based on Bioinformatics

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Abstract

[**Objective**] To explore the mechanism and material basis of Sophora tonkinensis in treating liver cirrhosis based on bioinformatics. [**Methods**] LC-MS was used to obtain the components of the traditional Chinese medicine. SuperPred and TTD databases were employed to screen the targets of the medicine and disease, respectively. Venny database was used for intersection analysis, Cytoscape software for network diagram construction, Metoscape database for GO and KEGG enrichment analysis, and CB-DOCK2 software for molecular docking. [**Results**] The experiment identified 85 components with therapeutic effects and 46 intersection targets. Core targets include HIF1A, TNF-α, PTGS2, MAPK1, etc. Sophora tonkinensis treats liver cirrhosis mainly through pathways related to cancer, apoptosis, and lipid and atherosclerosis signaling. [**Conclusion**] Bioinformatics methods were used to predict the mechanism of action and material basis of Sophora tonkinensis in treating liver cirrhosis, providing new ideas and clues for further research.

Keywords: Sophora tonkinensis; Liver cirrhosis; Bioinformatics; Mechanism of action; Material basis

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Liver cirrhosis is a chronic disease resulting from long-term, repeated progression of one or more chronic liver diseases, characterized pathologically by hepatic inflammation, persistent fibrosis, pseudolobules, regenerative nodules, and vascular proliferation that continues to deteriorate [1]. Hepatic fibrosis is the necessary pathway for chronic liver disease to progress to cirrhosis, with activation of hepatic stellate cells (HSC) and excessive deposition of extracellular matrix (ECM) in the liver being the primary mechanisms [2]. Cirrhosis represents a major cause of morbidity and mortality among patients with chronic liver disease worldwide [3]. Global assessments of liver disease-related mortality indicate that cirrhosis causes 1.16 million deaths annually, ranking as the 11th leading cause of death globally [4]. Currently, China has approximately 7 million patients with cirrhosis, imposing a severe disease burden and economic burden on families and society.

In traditional Chinese medicine (TCM), cirrhosis is classified as "hypochondriac pain," "accumulation," or "tympanites." Early-stage cirrhosis generally falls under the categories of hypochondriac pain and accumulation, while advanced-stage disease belongs to the tympanites category [5]. The *Lan Shi Mi Cang* (Secret Treasury of the Lan Family) also proposed that tympanites disease arises from weakness of spleen and stomach qi that cannot transport essence, leading to accumulation without dispersion.

Sophora tonkinensis Gagnep is the dried root and rhizome of *Sophora tonkinensis*, a leguminous plant primarily distributed in southeastern and central-southern China and Vietnam [5]. It enters the lung and stomach meridians and possesses heat-clearing and detoxifying effects [6, 7]. The *Kaibao Ben-*

cao recorded that Sophora tonkinensis could treat damp-heat jaundice. Our research group previously identified 147 chemical components in Sophora tonkinensis, including naringin, narirutin, and quercetin, with anti-inflammatory, anti-hepatitis B virus, and hepatoprotective pharmacological activities [8, 9].

Bioinformatics enables exploration of the effects and mechanisms of active components in Sophora tonkinensis against cirrhosis. Traditional Chinese medicine features multi-component, multi-target, and multi-pathway characteristics, making it difficult to reveal its scientific connotation through research on single targets or signaling pathways. Bioinformatics approaches problems from an interrelated perspective, studying drug effects and mechanisms at the holistic level and providing new ideas for understanding the complex action patterns of TCM [10]. Based on bioinformatics methods to investigate the pharmacodynamic components and potential targets of Sophora tonkinensis [11], exploring the correlation between TCM and disease from a holistic perspective aligns with the holistic view and syndrome differentiation and treatment principles of TCM [12], offering new ideas and methods for further research on the mechanism of Sophora tonkinensis in treating cirrhosis.

1. Materials and Methods

1.1 Acquisition of Active Components and Targets of Sophora tonkinensis

A total of 147 components of Sophora tonkinensis were obtained through liquid chromatography-mass spectrometry (LC-MS) (see Table 1). The PubChem database (https://pubchem.ncbi.nlm.nih.gov) was used to obtain the SMILES numbers of the active components. These SMILES numbers were then input into the SuperPred database (https://www.rcsb.org/) for target prediction of Sophora tonkinensis, selecting targets with credibility $ $98% and known targets. The targets were merged and deduplicated, and the UniProt database (https://www.uniprot.org) [13] was used to collect gene names corresponding to the active component targets, with species limited to *Homo sapiens*.

1.2 Acquisition of Cirrhosis-Related Targets

Using “cirrhosis” as the keyword, searches for cirrhosis-related targets were conducted in the GeneCards database (https://www.genecards.org/) [14], OMIM database (https://omim.org/) [15], DrugBank database (https://www.drugbank.ca/) [16], and TTD database (http://db.idrblab.net/ttd/). After merging and removing duplicate genes, the relevant targets were collected, and the UniProt database was used to convert the protein names of the obtained cirrhosis disease targets into gene names.

1.3 Construction of Core Target Protein-Protein Interaction (PPI) Network

Disease-related targets and TCM-related targets were imported into the Venny 2.1.0 database [17] to obtain intersection targets. These intersections were then imported into STRING (https://string-db.org/), a system for searching known and predicted protein-protein interactions [18], with species set to human, minimum interaction score set to 0.900, and isolated proteins hidden. The TSV file was downloaded to construct the protein-protein interaction network (PPI).

1.4 Construction of "Herb-Active Ingredient-Disease Target-Disease" Regulatory Network

The intersection targets were imported into the STRING database to construct the protein-protein interaction network. The PPI network was imported into Cytoscape software, and the CytoNCA plugin was used to obtain Degree values [19] to screen core targets while constructing the "herb-active ingredient-disease target-disease" interaction network diagram.

1.5 Gene Ontology (GO) Enrichment Analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Analysis

To investigate the main biological processes and metabolic pathways of Sophora tonkinensis in treating cirrhosis, the intersection targets of Sophora tonkinensis and cirrhosis were imported into the Metoscape database (https://metascape.org/) for GO enrichment analysis and KEGG pathway analysis. Biological process (BP), molecular function (MF), and cellular component (CC) categories were selected for GO biological process enrichment analysis of Sophora tonkinensis targets against cirrhosis. GO processes and KEGG pathways were functionally sorted by q-value, with the top 10 items in each category selected for visualization analysis using the Bioinformatics website (http://www.bioinformatics.com.cn) to comprehensively predict the molecular mechanism of Sophora tonkinensis in treating cirrhosis.

The intersection targets were imported into the Metoscape database to screen the main active components of the TCM for disease treatment.

1.6 Molecular Docking

The SDF structure files of compounds were obtained through the PubChem database (https://pubchem.ncbi.nlm.nih.gov), and the PDB structure files of receptors were obtained from the UniProt database (https://www.uniprot.org). Molecular docking was performed using CB-DOCK2 software.

2. Results

2.1 Screening of Effective Components and Target Prediction of Sophora tonkinensis

A total of 147 components of Sophora tonkinensis were obtained through LC-MS. Based on the SuperPred database, targets of Sophora tonkinensis components were identified, selecting known targets and those with probability $ $98%. After merging and deduplication, 47 targets and 85 effective active components with potential therapeutic effects on cirrhosis were obtained.

2.2 Prediction of Cirrhosis-Related Targets

Cirrhosis-related target genes were obtained from the GeneCards, OMIM, CTD, and DrugBank databases. After merging and deduplication, a total of 37,585 cirrhosis-related target genes were obtained. A Venn diagram was drawn to obtain the intersection targets between Sophora tonkinensis and cirrhosis, representing the anti-cirrhosis targets of Sophora tonkinensis (see Figure 1 [Figure 1: see original paper]).

2.4 "Herb-Active Ingredient-Disease Target-Disease" Interaction Network and PPI Analysis

The core components of Sophora tonkinensis against cirrhosis were screened through the Metoscape database as naringin, narirutin, quercitrin, kaempferol-7-O-neohesperidoside, and spiculisporic acid. Using the CytoNCA plugin to screen by degree value, eight core targets of Sophora tonkinensis against cirrhosis were identified: interleukin 2 (IL2), HIF1A, tumor necrosis factor (TNF), cyclooxygenase 2 (PTGS2), MAPK1, MMP9, MTOR, and TP53. The "herb-active ingredient-disease target-disease" network contained 131 nodes, including 85 from compounds and 46 from genes (see Figure 2 [Figure 2: see original paper]).

2.5 GO and KEGG Enrichment Analysis

GO analysis through the Metoscape database yielded 224 GO terms. The top 10 items in each category (BP, CC, MF) were selected for visualization (see Figure 3 [Figure 3: see original paper]). The results showed that Sophora tonkinensis targets against cirrhosis were mainly concentrated in biological processes such as positive regulation of gene expression, aging, and positive regulation of apoptotic process; cellular components including cytoplasm, plasma membrane, and nucleoplasm; and molecular functions such as identical protein binding, zinc ion binding, and DNA binding. KEGG analysis identified 98 signaling pathways, with the top 10 selected as important pathways for Sophora tonkinensis against cirrhosis (see Figure 4 [Figure 4: see original paper]). The pathways with more enriched targets were IL-17 signaling pathway, apoptosis, and lipid and atherosclerosis pathways, suggesting that Sophora tonkinensis may exert anti-cirrhosis effects mainly through these signaling pathways.

2.6 Molecular Docking Validation

The molecular docking results between active components and core targets are shown in Table 2 . Among 40 molecular docking relationships, 25 pairs (62.5%) had binding energy <-7.0 kcal · mol^{-1}, and 15 pairs (37.5%) were between -7 and -4 kcal · mol^{-1}, indicating that the predicted core targets and potential components have good binding characteristics.

3. Discussion

Based on bioinformatics analysis, this study investigated Sophora tonkinensis against cirrhosis and screened five active components: naringin, narirutin, quercitrin, kaempferol-7-O-neohesperidoside, and spiculisporic acid. Naringin is a flavonoid with antioxidant, anti-fibrotic, anti-inflammatory, and anti-cancer properties that can prevent liver damage induced by various drugs. Naringin reduces inflammatory cell infiltration in the liver [20], prevents transdifferentiation of hepatic stellate cells (HSC), leading to decreased collagen synthesis and greatly reduced ECM synthesis and deposition, thereby preventing hepatic fibrosis [21]. Quercitrin can be converted to quercetin through hydrolysis and can thus be considered a quercetin derivative. Studies show that quercetin can regulate MMP-9 levels and inhibit ECM formation, thereby exerting anti-inflammatory and anti-fibrotic effects [22]. Additionally, quercetin inhibits macrophage infiltration, regulates macrophage polarization, and strongly suppresses inflammatory cytokines, effectively alleviating liver inflammation and fibrosis [23]. Research indicates that quercetin has therapeutic effects on cirrhosis, though the therapeutic effect of quercitrin, as its derivative, on cirrhosis remains to be verified.

The study also found that Sophora tonkinensis may exert therapeutic effects on cirrhosis by acting on eight core targets: interleukin 2 (IL2), HIF1A, tumor necrosis factor (TNF-α), cyclooxygenase 2 (PTGS2), MAPK1, MMP9, MTOR, and TP53. PTGS2 (cyclooxygenase 2) participates in major pathogenic mechanisms of hepatic fibrosis, such as inflammation, apoptosis, and cellular senescence. Also known as COX2, PTGS2 is a potent enzyme and one of the targets of non-steroidal drugs. PTGS2 is involved in major pathogenic mechanisms of hepatic fibrosis, including inflammation, apoptosis, and cellular senescence. Moreover, PTGS2 shows abnormal expression in patients with cirrhosis and animal models. These findings suggest that PTGS2 overexpression triggers inflammatory responses, leading to the occurrence and development of hepatic fibrosis, playing an extensive and critical role in its development [24], and that inhibiting PTGS2 can reduce hepatic inflammatory damage [25].

TP53 (tumor protein p53) is an important tumor suppressor gene in humans, located on chromosome region 17p13. The p53 protein it encodes can inhibit the cell cycle, promote DNA repair, and control cell apoptosis. Under normal conditions, p53 protein activity is extremely low, but when DNA damage occurs due to stimulation, activated p53 induces apoptosis by regulating downstream

target gene expression [26]. During hepatic fibrosis development, p53 protein expression is significantly upregulated, thereby initiating apoptosis-related proteins, causing cell apoptosis and slowing the progression of hepatic fibrosis [27].

Hypoxia-inducible factor 1α (HIF1A) is a transcription factor. During cirrhosis or hepatic fibrosis, liver tissue is in a state of ischemia and hypoxia, accompanied by increased expression of HIF-1α [28, 29]. Hypoxia and its inducible factors can accelerate liver inflammation, fibrosis, and even tumor occurrence and development. TNF-α is a pro-inflammatory factor [30] closely related to the degree of liver necrosis and fibrosis, participating in the liver injury-repair cycle during cirrhosis development, ultimately causing massive ECM synthesis and deposition, leading to hepatic fibrosis or cirrhosis. The more obvious the degree of hepatic fibrosis, the more TNF-α-positive cells in liver tissue, while normal liver tissue has none or only a few [31]. TNF-α levels can reflect the degree of liver inflammation [32].

IL-2 is an important anti-inflammatory and immunomodulatory factor that can activate cellular immunity and participate in immune response reactions. Its expression level increases with the deepening of hepatic fibrosis degree, exerting anti-hepatic fibrosis effects by inhibiting intrahepatic inflammation development and regulating immune function [31]. Napoli et al. [33] showed that IL-2 expression levels still rise in late-stage cirrhosis and even in pre-liver transplantation stages when treated with glucocorticoids.

MAPK1/ERK2/ERK, as a member of the mitogen-activated protein kinase (MAPK) family, mainly functions to regulate cell proliferation, differentiation, and death. Upregulated MAPK1 gene expression promotes the occurrence of hepatic fibrosis [34, 35]. mTOR is a serine/threonine protein kinase that plays a key role in sensing nutritional signals and regulating cell growth and proliferation [36]. Hepatic stellate cells (HSC) are the main source of myofibroblasts, and mTOR overactivation leads to increased accumulation of myofibroblasts in the liver, inhibiting apoptosis of activated HSC and thereby promoting fibrosis progression [37].

In summary, this study indicates that Sophora tonkinensis treatment of cirrhosis involves active components such as naringin, narirutin, and quercitrin, as well as targets including interleukin 2 (IL2), HIF1A, tumor necrosis factor (TNF), cyclooxygenase 2 (PTGS2), and MAPK1. Based on network pharmacology, this study explored the mechanism of Sophora tonkinensis in treating cirrhosis, elucidating the complex network interactions among multiple components and targets, providing a theoretical basis for further animal model experiments.

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Note: Figure translations are in progress. See original paper for figures.