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Clarifying of the potential mechanism of Sinisan formula for treatment of chronic hepatitis by systems pharmacology method

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ABSTRACT

Chronic hepatitis is a general designation class of diseases, which results in different degrees of liver necrosis and inflammatory reaction, followed by liver fibrosis, may eventually develop into cirrhosis. However, the molecular pathogenesis of chronic hepatitis is too complex to elucidate. Herbal medicines, featured with multiple targets and compounds, have long displayed therapeutic effect in treating chronic hepatitis, though their molecular mechanisms of contribution remain indistinct. This research utilized the network pharmacology to confirm the molecular pathogenesis of chronic hepatitis through providing a comprehensive analysis of active chemicals, drug targets and pathways' interaction of Sinisan formula for treating chronic hepatitis. The outcomes showed that 80 active ingredients of Sinisan formula interacting with 91 therapeutic proteins were authenticated. Sinisan formula potentially participates in immune modulation, anti-inflammatory and antiviral activities, even has regulating effects on lipid metabolism. These mechanisms directly or indirectly are involved in curing chronic hepatitis by an interaction way. The network pharmacology based analysis demonstrated that Sinisan has multi-scale curative activity in regulating chronic hepatitis related biological processes, which provides a new potential way for modern medicine in the treatment of chronic diseases.

1. Introduction

Chronic hepatitis is a general class of diseases, which can be caused by some various factors such as hepatitis virus infection, alcoholism, hepatotoxic drugs and so on. The disease usually begins with different degrees of liver necrosis and inflammatory reaction, followed by liver fibrosis may be eventually developed into cirrhosis. Infectious viral hepatitis is the most common hepatitis disease has an important challenge for health in the world. Between 1990 and 2013, global viral hepatitis deaths increased from 0.89 million to 1.45 million. In 2013, viral hepatitis was the seventh leading cause of death worldwide, compared with the tenth (tenth to twelfth) in 1990 [1]. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are endemic in many low-income countries [2]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) also cause acute illness but more commonly lead to progressive liver fibrosis, cirrhosis, and increased the risk of liver cancer [3,4]. In the past ten years, great progress has been achieved in the treatment of chronic hepatitis particularly with the clinical application of nucleic acid analogs and polyethylene glycol which promote the antiviral therapy for chronic hepatitis to be a conventional therapy. However, the vast majority of patients cannot be completely cured as antiviral therapy should be taken for long periods leading to some adverse reactions and increased the economic burden of the patients.

Traditional Chinese Medicine (TCM) has defended Chinese people's health for thousands of years ago. Among the experience of thousands of years' clinical treatment, a great number of Chinese herbal formulas has been effectively used to cure chronic hepatitis; most of them come from Sinisan formula, which is the basic formula of liver stagnation and spleen deficiency syndrome. This formula was first described in "Treatise on Cold-induced Febrile Diseases (Shanghan Lun)," written by the famous Chinese physician Zhang Zhongjing (150 to 219 CE in the Chinese Eastern Han Dynasty). The formula is composed of *Radix*

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Bupleuri, Radix Paeoniae Alba, Fructus Aurantii Immaturus and Radix Glycyrrhizae of the same amounts, and has the efficacy of dispelling melancholy diathermy, clearing liver and invigorating spleen. Since the born of Sinisan formula, doctors of traditional Chinese medicine have used it and its modified formula to treat chronic hepatitis and other liver diseases for 2000 years. Modern pharmacological research showed that Sinisan formula can treat hepatitis by improving the anti-inflammatory reaction [5], promoting the apoptosis of liver cells infected by virus [6], displaying liver protection function [7], and even more, it can regulate lipid metabolism [8], to prevent the accumulation of fat in the liver which leads to disease [9]. There has been reported that the Sinisan formula can be anti- depression [10] medicine, and have effects on "depression with liver-qi stagnation and spleen deficiency syndrome" [11]. Although the therapeutic result of Sinisan formula in treating hepatitis is agreeable; the molecular mechanism of action has not been entirely clarified. The traditional medicine methods are covering the Sinisan formula with biochemistry appraisal and chemical composition analysis but its pharmacological mechanism in treating chronic hepatitis is not completely clear.

Fortunately, the establishment of the bridge between development of systems biology and pharmacokinetics pharmacodynamics(PK/PD) promoted the development of systems pharmacology, which applied a new method to study TCM by multiple scales of complicacy scope from molecular to specific individual[12]. Systems pharmacology is an emerging field that combines pharmacokinetic data (ADME characteristics of a drug that mean absorption, distribution, metabolism, and excretion), screening, drug targets prediction with network analysis to understand the active compounds and therapeutic targets of TCM [13–15]. So many systemic pharmacological achievements have elucidated the mechanisms of TCM awareness, such as traditional Chinese medicine treatment of cardiovascular diseases [16], vitiligo [17] and lung diseases [18].

In order to reveal the pathogenesis of chronic hepatitis and the therapeutic mechanism of Sinisan formula, we utilized the systems pharmacology network. First of all, the active ingredients were screened out according to pharmacokinetic parameters (oral bioavailability, drug-likeness and Caco-2 permeability) evaluation and network parameters as well. Afterwards, we exploited the compounds to match the potential targets, not just a compound to the sole target, one compound may map two or more targets. With the targets, we built a compound-target interaction in bioinformatics and pharmacological aspect. Subsequently, the targets were exploited to search the corresponding pathways from the KEGG database (Kyoto Encyclopedia of Genes and Genomes, http://www.genome.jp/kegg/). Meanwhile, we used the data to build a disease-pathway network. By this time, all the preparation work had been finished. Ultimately, we established a monolithic "chronic hepatitis pathway" to clarify the molecular pathogenesis at a systematic level. The outcomes can enormously increase our understanding of hepatitis, and disclose the therapeutic mechanism of Sinisan formula. Obviously, it will help more people to recognize the TCM, so as to benefit all mankind.

2. Materials and methods

The study of system and pharmacology used the following 4 steps (Fig. 1):

(1) Database construction. The compounds of the four herbs in Sinisan formula,*Radix Bupleuri*, *Radix Paeoniae Alba*, *Fructus Aurantii Immaturus* and *Radix Glycyrrhizae*, were collected from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP, http://lsp.nwu.edu.cn/) [19].
(2) Pharmacokinetic selection. In Sinisan formula, oral bioavailability screening, drug-likeness evaluation, and Caco-2 permeability were filtered as the parameters to get high activity compounds.
(3) Compound-target and disease-target network construction. All the targets of every compound were searched used Cytoscape to depict the network interaction of the ingredients of Sinisan formula and their targets. Similar to this, the diseases which we selected with the correlation of chronic hepatitis were used to build a network of disease-target.
(4) Pathway establishment. Pathogenesis analysis depended on the pathway of chronic hepatitis and other liver diseases to investigate the comprehensive mechanisms of Sinisan formula.

2.1. Compounds selection

In order to screen out the possible active compounds of Sinisan formula, a systematic model in TCMSP were used, which has PreOB (predicted oral bioavailability), PreDL (predicted drug-likeness) and PreCaco-2(predicted Caco-2 permeability); the three parameters to be calculated.

(1) PreOB The TCM is mainly oral; the parameter of oral bioavailability is one of the most significant pharmacological performances. Low OB values are often one of the major causes of drug candidate compounds that are difficult to continue to develop as a drug. So, we used an effective computer simulation model for predicting OB values. To screen out more effective medical molecules, we set 33% as the inferior limit of OB value.
(2) PreDL The DL value was calculated by using a mathematical formula with Tanimoto index.

$$\mathbf{F}(\alpha, \beta) = \frac{\alpha * \beta}{\alpha * \alpha + \beta * \beta - \alpha * \beta}$$

Where α is the molecular descriptors of herbal ingredients, and β represents the average molecular properties of all molecules in Drug-Bank database (http://www.drugbank.ca/). We set DL ≥ 0.18 as the threshold of candidate compounds evaluation.
(3) PreCaco-2 The absorbed drug also needs to be effectively distributed. A good correlation often exists between human oral drug absorption, intestinal epithelial cells (Caco-2) and drug permeability coefficients. Caco-2 cell is an in vitro model which is widely used to study the intestinal absorption. So, we cited a Caco-2 prediction model which predicted the absorption of drugs effectively. To make sure the compounds have great transmissivity, we increased the selection criteria to Caco-2 ≥ 0.4. Until then, the screen of compounds was done; we used the threshold of OB ≥ 33%, DL ≥ 0.18, Caco-2 ≥ 0.4 to as the data of next step.

2.2. Target searching and network establishment

Chinese formula often has multiple compounds and multiple targets. It is usually easy to make a formula for treatment of a specific disease, but it is difficult to figure out how it works. So, we screen out the targets from the TCMSP Database and normalize them in UniPort (http://www.uniprot.org/). Then, the target name was inputted to the CTD (http://ctdbase.org/) to find the disease associated with the gene and selected out the diseases about chronic hepatitis. Put the data into excel, plotting the network graph of the compound-target network (C–T network) and disease-target network (D-T network) with Cytoscape. So, that we used nodes to represent the compounds, targets, and diseases, and the lines between two nodes represented the interaction. We also used the degree to determine the size of each node, ensured that the graph would be obvious.

2.3. Chronic hepatitis pathway analysis

After studying the pathology of existed research, we established a systematic pathway analysis. The literature on liver disease were investigated, then short names of genes were inputted into DAVID (The Database for Annotation, Visualization, and Integrated Discovery,

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