Study of the Mechanism of *Oxalis corniculata* (L.) in the Treatment of Hepatitis based on Network Pharmacology

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Abstract. Objective: The molecular mechanism of Oxalis corniculata (L.) in the treatment of hepatitis was studied by network pharmacology. Methods: The active ingredients of that were screened using network pharmacology. The "drug-active ingredient-target-disease" network was constructed. The signal pathway and biological process of the target was analysed by DAVID database. Results: Screen out 8 active compounds and 30 potential targets, the target proteins are TP53, AKT1, ALB, and IL6, respectively. 42 biological processes and 39 signaling pathways were screened. It exerts anti-hepatic effects by regulating signaling pathways (such as cancer pathways, hepatitis B and PI3K-Akt signaling pathways). Conclusion: Network pharmacology provides new ideas and methods for revealing the anti-hepatic mechanism of Oxalis corniculata (L), and provides scientific basis for further research and development of Oxalis corniculata (L).

Key words: Oxalis corniculata (L.), Hepatitis, Active ingredient, Network pharmacology, Mechanism.

1. Introduction

At present, hepatitis is one of the public health problems that are widely concerned around the world, and is an infectious inflammation caused by the hepatotropic virus inroad the human body. The hepatitis B is a highly epidemic disease in China, and patients need a huge amount of money in the treatment of hepatitis[1]. In addition, The pathogenic factors of hepatitis are harm to liver cells and liver function, causing a series of uncomfortable symptoms of the body. Finally, it lead to liver damage even cirrhosis and liver cancer[2-3]. The pathogenesis of hepatitis in Chinese medicine is caused by the interaction of wet and heat, which is lead to the damage of liver, gallbladder, spleen, stomach and effluence of the bile. So it should be based on Clearing heat and draining dampness to treat the hepatitis, and often use methods of clearing heat and draining dampness with relieving exterior syndrome, removing Jaundice and clearing heat to treat hepatitis [4].

Suaib mib mib is a fresh or dried whole grass of Oxalis corniculata (L.)(Cu jiăng-cao). Originally published in the Compendium of Materia Medica, it is included in the 2003 edition of Quality Standards for Traditional Chinese Medicine and National Medicinal Materials of Guizhou Province [5]. It has the functions of calming the liver and distressing, dampening and swelling, anti-
inflammatory and analgesic, cooling blood and dissipating blood stasis, etc. It is mostly used to treat diseases such as jaundice, acute hepatitis, mumps [6]. It is documented that the compatibility of Oxalis corniculata (L.) and pork has the effect of treating infectious hepatitis[7]. There are various chemical components such as protocatechuic aldehyde, isovitexin, quercetin, β-tocopherol, and carotene in Oxalis corniculata (L.)[8-11]. Pharmacological studies showed that it has antibacterial, antioxidant, anti-inflammatory and analgesic effects [12-14]. Studies have been carried out to extract sorrel with distilled water, hydrochloric acid ethanol, and ethanol to obtain polysaccharides, anthocyanins, and flavonoids, respectively. The results show that it has anti-oxidation and protective effects on liver injury induced by a-naphthalene isothiocyanate (ANIT) in rats. It has been reported that 70% of the extracts of Oxalis corniculata (L.) are mainly acylquinic acid and flavonoids, and humulin, isohumulin and isovitexin are clearly identified. At present, its research mainly focuses on the material basis of pharmacodynamic effects, but the research on its mechanism of action is not clear. This article uses network pharmacology to study the active compounds and target targets of Oxalis corniculata (L.) for treating hepatitis, and provides a reference for the further development and clinical application of Oxalis corniculata (L.).

Traditional Chinese medicine has the characteristics of multiple components, multiple targets, and multiple pathways. It regulates the therapeutic targets in human tissues and restores the physiological regulation network of human imbalance, thereby achieving the purpose of treating diseases. However, it hinders the development of new traditional Chinese medicines, due to the complexity of traditional Chinese medicines' multiple components, multiple targets, and multiple pathways and the limitations of traditional experimental research methods. In recent years, the holistic and systematic characteristics of network pharmacology coincide with the "multi-component, multi-target, and multi-path" characteristics of traditional Chinese medicine. The research on the intervention and impact of drugs on diseases is based on a multi-level and multi-angle interaction network. It provides new ideas and methods for the substance basis and mechanism of action of traditional Chinese medicine [17-18]. From the perspective of network pharmacology, this study explores its mechanism of treatment for hepatitis.

2. Methods

2.1. Screening active ingredients and targets
Search all the chemical components of Oxalis corniculata (L.) by consulting literature in CNKI, PubMed and TCMSP database. The TCMSP database was used to screen active chemical components of Oxalis corniculata (L.) with Absorption Distribution Metabolism Excretion (ADME) parameters (Oral Bioavailability, OB ≥ 30% and Drug-Likeness, DL ≥ 0.18)[19], and get the structural formula and targets of Oxalis corniculata (L.). Finally, the screened targets were transformed into UniProtID format through UniProt database (https://www.uniprot.org/).

2.2. Screening disease targets
GeneCard (https://www.genecards.org/) database was used to screen protein targets of Oxalis corniculata (L.) for hepatitis, and to establish a hepatitis target data set.

2.3. Network construction and analysis
The Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/index.html) website was used to establish the intersection target of diseases and drugs. The Protein Interaction Network (PINetwork) Analysis was Based on STRING Database. Then, import the results into Cytoscape 3.7.1 software to optimize the protein interaction map, and obtained the Degree, Betweenness centrality, and Closeness centrality values of the nodes, and visualized Degree values by size. Selecting the target that the above 3 topological parameter values that meet the median values of all the points as the significance target of Oxalis corniculata (L.) to treat hepatitis. The active ingredients, diseases and targets of Oxalis
corniculata (L.) were import into the Cytoscape 3.7.1 software to establish a network analysis diagram of "drug-active ingredients-targets-disease".

2.4. Biological process and signaling pathways analysis
The selected target targets were analyzed by the DAVID (https://david.ncifcrf.gov/) database for the Kyoto Gene and Genomic Encyclopedia (KEGG) pathway enrichment analysis and Gene Ontology (GO) biological process analysis, to find biological processes and signaling pathways related to Oxalis corniculata (L.) for hepatitis.

3. Results

3.1. Screening active ingredients
On the TCMSP database and the literature of CNKI, PubMed, and TCMSP database, 8 active compounds and related targets were screened by ADME parameters (OB≥30% and DL≥0.18). The number of targets was shown in Table 1.

| MolID       | Chemical            | Number of targets | OB(%) | DL  |
|-------------|---------------------|-------------------|-------|-----|
| MOL001452   | Protocatechu aldehyde | 10                | 38.35 | 0.03 |
| MOL002268   | Rhein               | 7                 | 47.07 | 0.28 |
| MOL002773   | Beta-carotene       | 21                | 37.18 | 0.58 |
| MOL001525   | Daucoosterol        | 2                 | 36.91 | 0.75 |
| MOL002322   | Isovitexin          | 6                 | 31.29 | 0.72 |
| MOL001689   | Acacetin            | 24                | 34.97 | 0.24 |
| MOL000006   | Luteolin            | 3                 | 36.16 | 0.25 |
| MOL000098   | Quercetin           | 152               | 46.43 | 0.28 |

3.2. Screening the target of drug and disease
A total of 225 targets corresponding to the active chemical components of Oxalis corniculata (L.) were screened by the TCMSP database. The results were shown in Table 1. 10720 hepatitis-related targets were found in GeneCard database. Established 159 targets that Oxalis corniculata (L.) components intersect with hepatitis on the Venny website. The intersection targets were import into the Cytoscape 3.7.1 software to obtain the Degree value, and visualized it as different color according to the value shown in Figure 1.
3.3. Topological parameters of the target

The intersection targets were imported into the STRING database to obtain protein interaction data, and the data was imported into the Cytoscape 3.7.1 software to build an optimized protein interaction relationship graph, then, got the nodes' Degree, Betweenness centrality, and Closeness centrality values, and visualized it as a picture according to the Degree values shown in picture 1. Selecting the target that satisfies 3 topological parameter values greater than the median of all points as the important target of Oxalis corniculata (L.), the median value were 0.0018, 0.5304, 58. The results were shown in Table 2. The active ingredients, diseases and targets of Oxalis corniculata (L.) were import into Cytoscape 3.7.1 software to establish a network analysis diagram of "drug-active ingredient-target-disease" (Figure 2).

Figure 1 The intersection targets of Oxalis corniculate (L.) and hepatitis

Figure 2 The "drug-active ingredient-target-disease" network
Table 2. Topological parameter results of *Oxalis corniculata* (L.) targets

| Uniprot ID | Gene name | Degree | Betweenness centrality | Closeness centrality |
|------------|-----------|--------|------------------------|----------------------|
| P31749     | AKT1      | 109    | 0.0549                 | 0.7548               |
| P04637     | TP53      | 104    | 0.0516                 | 0.7371               |
| P02768     | ALB       | 101    | 0.0617                 | 0.7269               |
| P05231     | IL6       | 100    | 0.0393                 | 0.7169               |
| P15692     | VEGFA     | 96     | 0.0323                 | 0.7072               |
| P42574     | CASP3     | 93     | 0.0322                 | 0.7009               |
| P01375     | TNF       | 92     | 0.0297                 | 0.6916               |
| P05412     | JUN       | 92     | 0.0312                 | 0.7009               |
| P28482     | MAPK1     | 89     | 0.0258                 | 0.6856               |
| P01106     | MYC       | 87     | 0.0206                 | 0.6797               |
| P01133     | EGF       | 85     | 0.0500                 | 0.6826               |
| P35354     | PTGS2     | 82     | 0.0178                 | 0.6709               |
| P14780     | MMP9      | 79     | 0.0116                 | 0.6515               |
| P24385     | CCND1     | 76     | 0.0149                 | 0.6461               |
| P10145     | CXCL8     | 75     | 0.0133                 | 0.6461               |
| P01100     | FOS       | 70     | 0.0134                 | 0.6305               |
| P60484     | PTEN      | 70     | 0.0112                 | 0.6331               |
| P04626     | ERBB2     | 68     | 0.0306                 | 0.6331               |
| P13500     | CCL2      | 68     | 0.0067                 | 0.6181               |
| P07900     | HSP90AA1  | 67     | 0.0141                 | 0.6255               |
| Q04206     | RELA      | 67     | 0.0133                 | 0.6230               |
| P22301     | IL10      | 66     | 0.0057                 | 0.6157               |
| P08253     | MMP2      | 66     | 0.0102                 | 0.6206               |
| P10275     | AR        | 62     | 0.0128                 | 0.6157               |
| P37231     | PPARG     | 61     | 0.0078                 | 0.6038               |
| P35222     | CTNNB1    | 61     | 0.0075                 | 0.6085               |
| P05362     | ICAM1     | 61     | 0.0040                 | 0.6038               |
| O15519     | CASP8     | 59     | 0.0048                 | 0.6038               |
| Q07817     | BCL2L1    | 59     | 0.0048                 | 0.6015               |
| P09601     | HMOX1     | 59     | 0.0080                 | 0.6015               |

3.4. Bioprocess enrichment analysis of *Oxalis corniculata* (L.) for hepatitis target

The 30 target targets were imported into the DAVID database to get the biological process of *Oxalis corniculata* (L.) treatment of hepatitis, 265 biological processes were obtained, 26 were obtained with P-value (P <0.0001), the result was shown in table 3. The target for treating hepatitis by *Oxalis corniculata* (L.) was marked in response to drug, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, etc.
| Term                                                                 | Count | Count (%) | P-Value     |
|---------------------------------------------------------------------|-------|-----------|-------------|
| Response to drug                                                   | 14    | 0.3       | 8.9E-16     |
| Positive regulation of transcription, DNA-templated               | 13    | 0.3       | 2E-11       |
| Positive regulation of transcription from RNA polymerase II        | 13    | 0.3       | 3E-08       |
| promoter                                                           |       |           |             |
| Negative regulation of apoptotic process                          | 12    | 0.2       | 1.1E-10     |
| Angiogenesis                                                       | 9     | 0.2       | 2.9E-09     |
| Inflammatory response                                              | 9     | 0.2       | 1.8E-07     |
| Negative regulation of cell proliferation                         | 9     | 0.2       | 2.5E-07     |
| Positive regulation of cell proliferation                         | 9     | 0.2       | 8.5E-07     |
| Aging                                                              | 8     | 0.2       | 1E-08       |
| Positive regulation of apoptotic process                          | 8     | 0.2       | 6E-07       |
| Positive regulation of smooth muscle cell proliferation            | 7     | 0.1       | 7.2E-10     |
| Response to estradiol                                              | 7     | 0.1       | 9.2E-09     |
| Cellular response to hypoxia                                       | 7     | 0.1       | 1.3E-08     |
| Positive regulation of sequence-specific DNA binding               | 7     | 0.1       | 2.2E-08     |
| Transcription factor activity                                      |       |           |             |
| Cellular response to lipopolysaccharide                            | 7     | 0.1       | 3.4E-08     |
| Positive regulation of ERK1 and ERK2 cascade                      | 7     | 0.1       | 4.6E-07     |
| Positive regulation of gene expression                            | 7     | 0.1       | 4.8E-06     |
| Cell proliferation                                                 | 7     | 0.1       | 0.000032    |
| Response to antibiotic                                             | 6     | 0.1       | 2.1E-09     |
| Positive regulation of nitric oxide biosynthetic process           | 6     | 0.1       | 9.8E-09     |
| Cellular response to interleukin-1                                 | 6     | 0.1       | 1.3E-07     |
| Response to ethanol                                                | 6     | 0.1       | 9.2E-07     |
| Positive regulation of protein phosphorylation                     | 6     | 0.1       | 2.3E-06     |
| MAPK cascade                                                       | 6     | 0.1       | 0.000078    |
| Response to amino acid                                             | 5     | 0.1       | 2.2E-07     |
| Response to cold                                                   | 5     | 0.1       | 4.1E-07     |
| Cellular response to organic cyclic compound                       | 5     | 0.1       | 3.1E-06     |
| Response to glucocorticoid                                         | 5     | 0.1       | 4.5E-06     |
| Response to estrogen                                               | 5     | 0.1       | 4.5E-06     |
| Canonical Wnt signaling pathway                                    | 5     | 0.1       | 0.000012    |
| Cellular response to tumor necrosis factor                         | 5     | 0.1       | 0.000036    |
| Positive regulation of NF-kappaB transcription factor Activity      | 5     | 0.1       | 0.000077    |
| Mammary gland alveolus development                                 | 4     | 0.1       | 3.1E-06     |
| Regulation of sequence-specific DNA binding transcription Factor activity | 4     | 0.1       | 0.00001    |
| Liver regeneration                                                 | 4     | 0.1       | 0.000016    |
| Regulation of angiogenesis                                         | 4     | 0.1       | 0.00002     |
| Lipopolysaccharide-mediated signaling pathway                      | 4     | 0.1       | 0.000022    |
| Protein kinase B signaling                                         | 4     | 0.1       | 0.000024    |
| ERBB2 signaling pathway                                            | 4     | 0.1       | 0.000038    |
| Ovarian follicle development                                       | 4     | 0.1       | 0.000051    |
| Positive regulation of neuron apoptotic process                    | 4     | 0.1       | 0.000055    |
| Response to heat                                                   | 4     | 0.1       | 0.000076    |
3.5. Enrichment analysis of KEGG signaling pathway for Oxalis corniculata (L.) treatment of hepatitis

The predicted 30 target targets were annotated in the KEGG database of the DAVID platform. According to the KEGG channel distribution, 91 channels were observed, and 39 channels were selected with the P-value (P < 0.00001). Including PI3K-Akt signaling pathway, TNF signaling pathway, Hepatitis B, Pathways in cancer, etc. The result was shown in table 4.

Table 4. Enrichment analysis of KEGG signaling pathway for Oxalis corniculata (L.) treatment of hepatitis

| Term                                           | Count | Count (%) | P-Value  |
|------------------------------------------------|-------|-----------|----------|
| Pathways in cancer                             | 24    | 0.5       | 1E-24    |
| Hepatitis B                                    | 15    | 0.3       | 5.5E-17  |
| TNF signaling pathway                          | 13    | 0.3       | 2.6E-15  |
| Proteoglycans in cancer                        | 12    | 0.2       | 1.3E-10  |
| HTLV-I infection                               | 12    | 0.2       | 1.7E-09  |
| PI3K-Akt signaling pathway                     | 12    | 0.2       | 4.3E-08  |
| Prostate cancer                                | 11    | 0.2       | 7.6E-13  |
| Chagas disease (American trypanosomiasis)      | 11    | 0.2       | 4.2E-12  |
| Bladder cancer                                 | 10    | 0.2       | 2.4E-14  |
| MAPK signaling pathway                         | 10    | 0.2       | 4E-07    |
| MicroRNAs in cancer                            | 10    | 0.2       | 1.1E-06  |
| Endometrial cancer                             | 9     | 0.2       | 1.7E-11  |
| Colorectal cancer                              | 9     | 0.2       | 7.4E-11  |
| Pancreatic cancer                              | 9     | 0.2       | 1.1E-10  |
| Pertussis                                      | 9     | 0.2       | 3.6E-10  |
| Toll-like receptor signaling pathway           | 9     | 0.2       | 5.9E-09  |
| Influenza A                                    | 9     | 0.2       | 2.9E-07  |
| Herpes simplex infection                       | 9     | 0.2       | 4.2E-07  |
| Focal adhesion                                 | 9     | 0.2       | 0.000001 |
| NOD-like receptor signaling pathway            | 8     | 0.2       | 1.7E-09  |
| Small cell lung cancer                         | 8     | 0.2       | 3.3E-08  |
| Rheumatoid arthritis                           | 8     | 0.2       | 4.2E-08  |
| HIF-1 signaling pathway                        | 8     | 0.2       | 7.7E-08  |
| Toxoplasmosis                                  | 8     | 0.2       | 2E-07    |
| Non-alcoholic fatty liver disease (NAFLD)       | 8     | 0.2       | 1.7E-06  |
| Transcriptional misregulation in cancer        | 8     | 0.2       | 3.4E-06  |
| Tuberculosis                                   | 8     | 0.2       | 0.000005 |
| Apoptosis                                      | 7     | 0.1       | 1.4E-07  |
| Leishmaniasis                                  | 7     | 0.1       | 3.1E-07  |
| Chronic myeloid leukemia                       | 7     | 0.1       | 3.3E-07  |
| Estrogen signaling pathway                     | 7     | 0.1       | 2.2E-06  |
| T cell receptor signaling pathway              | 7     | 0.1       | 2.4E-06  |
| Thyroid cancer                                 | 6     | 0.1       | 8.5E-08  |
| Malaria                                        | 6     | 0.1       | 1.3E-06  |
| Legionellosis                                  | 6     | 0.1       | 2.1E-06  |
| Non-small cell lung cancer                     | 6     | 0.1       | 2.5E-06  |
| Central carbon metabolism in cancer            | 6     | 0.1       | 0.000005 |
| Glioma                                         | 6     | 0.1       | 5.4E-06  |
| Melanoma                                       | 6     | 0.1       | 8.3E-06  |
4. Discussion

The effect of Oxalis corniculata (L.) on treating hepatitis is that the components of it, including Protocatechual, Quercetin, Beta-carotene and Isostatin, etc. These components play a multi-target and multi-pathway role in treating hepatitis. Studies have shown that Protocatechual can inhibit the inflammatory response of vascular endothelium, and its mechanism of inhibiting inflammatory response is closely related to mitogen-activated protein kinase (MAPK) signal transduction pathway [20]. Quercetin can up-regulate the expression of ADPN and Adipo R2 in rats with alcoholic liver injury, to improve liver function, blood lipids, and liver tissue fatty lesions. Finally, to reduce liver inflammation [21]. Beta-carotene can reduce the degree of rat liver fibrosis induced by carbon tetrachloride, and its effect may be to inhibit the expression of FGFβ1 in liver tissues[22]. Isovitexin has the effects on anti-inflammatory, antioxidant and anti-alzheimer [23]. The above studies suggest that Oxalis corniculata (L.) is effective in inhibiting inflammation and treating liver diseases, and has great research value.

In this paper, 37 chemical components of Oxalis corniculata (L.) were obtained, and 8 active chemical components and 225 corresponding targets were screened. A total of 159 targets of Oxalis corniculata (L.)’s components related to disease were identified, and filter 30 target targets, The Cytoscape 3.7.1 software built a "drug-active ingredient-target-disease" interaction network and obtained related topological parameters. The target proteins with the highest degree value include 30 target proteins such as AKT1, TP53, IL6, and ALB, the higher Degree value means that the protein target has an important role in the treatment of hepatitis by Oxalis corniculata (L.). AKT1 is one of the three closely related serine / threonine protein kinases (AKT1, AKT2 and AKT3) of AKT kinase, which is participate in regulating cell metabolism and proliferation. AKT1 as an important downstream target of the PI3K signaling pathway, the activated AKT regulates cell functions by phosphorylating avariety of enzymes, kinases, transcription factors and other downstream factors, to make the PI3K / AKT signaling pathway participate in regulate the release of inflammatory factors and promote the generation of osteoclasts [24]. TP53 plays an inhibitory role in many types of tumors, studies have shown that TP53 can induce TP53-induced hepatocellular carcinoma glycolysis and apoptosis regulator (TIGAR), and TIGAR can control the metabolism of hepatocellular carcinoma and prevent apoptosis [25]. IL6 is a cytokine with a variety of biological functions, it act on B cells, T cells, liver cells, hematopoietic stem cells and cells of the central nervous system, and play a major role in B cell differentiation and T cell proliferation [26]. IL6 can up-regulate the expression of NHE1, NCX1 and Calmodulin in hepatocyte cancer cells, to promote the proliferation, migration and invasion of hepatocyte cancer cells [27]. A study [28] have found that liver epithelial cells undergo apoptosis or fibrosis in patients with liver cirrhosis, and affect physiological processes such as autoimmunity, nutrient circulation, and body cell metabolism.

After pathway enrichment analysis, 42 biological processes and 39 signaling pathways were obtained. The significant signaling pathways are PI3K-Akt signaling pathway, TNF signaling pathway, Hepatitis B, Pathways in cancer, etc. At the same time, the biological processes involved are positive regulation of transcription, DNA-templated, response to drug, and positive regulation of transcription from RNA polymerase II promoter and so on.

The enrichment of signal pathways and biological processes indicated that the core targets of Oxalis corniculata (L.)’s active components were mapped to different signal pathways and biological processes, so that Oxalis corniculata (L.) has an anti-hepatitis effect by regulates the expression of related genes such as cell proliferation, differentiation and apoptosis in coordination of different signal pathways and biological processes.

The preliminary analysis indicated that the main potential active ingredients, action targets and related pathways of Oxalis corniculata (L.) provide a reference for further exploration of the mechanism of it. However, in-depth basic research and clinical experiments are needed to support the predicted results.
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