

The Targets Prediction of ZYJSW on LDH by Network Pharmacology

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Abstract: This is a network pharmacology about Zhuangyaojianshenwan (ZYJSW) treats Lumbar disc herniation (LDH), we will talk about the mechanisms. We used oral bioavailability and drug-likeness filtration to find the active ingredients of ZYJSW. At the same time, we sought out the targets. Gene Cards and OMIM were used to find the targets of LDH. So Venn diagram was easy to be drawn out. We used the genetic intersection between the drug and the disease to structure a PPI network, at the same time, bar plot was shown. At last, KEGG pathway analysis and Gene Ontology enrichment analysis were conducted. We could see the top three pathways from the analysis, they were AGE-RAGE signaling pathway in diabetic complications, Lipid and atherosclerosis and Kaposi sarcoma-associated herpesvirus infection. This study uses network pharmacology and provides a strategy that can help us to explore the mechanisms by which ZYJSW treats LDH.

Keywords: Active ingredients; Lumbar disc herniation; Network pharmacology; Zhuangyaojianshenwan

1. Introduction

LDH is a common disease which is closely related to age. The main clinical manifestations of LDH are back pain, radiating pain in the lower extremities and paresthesia. Conservative treatment is effective for patients^[1]. Patients with severe LDH may even develop lower limb paralysis and incontinence, this will seriously affect people's health and quality of life^[2]. When it is activated, patients will spend most of their time in the hospital^[3]. In the treatment of LDH, it is very important to reduce pain and disability rate^[4].

ZYJSW is a classic formula which is made of *Kadsurae Coccineae Radix Et Caulis*, *Rhizoma Cibotii*, *Herba Taxilli*, *Flemingia Prostrata* *Roxb*, *Fructus Ligustri Lucidi*, *Cuscutae Semen*, *Rosae Laevigatae Fructus*, *Spatholobus Suberectus* *Dunn* and *Milletiiae Speciosae Radix*^[5]. It has an effect of promoting blood circulation and removing blood stasis, which works by improving the supply of blood and oxygen to relieve pain^[6]. In addition, it can strengthen waist and kidney. Dehumidifying is also its effect^[7]. It is found that ZYJSW can enhance osteoblast activity and increase bone mineral density^[8], this lays a good foundation for the treatment of lumbar disc herniation.

Network pharmacology is a new discipline, which helps us to analyze the signaling pathway of drug therapy^[9]. It combines medicine with informatics, and has developed into the multi-drug, multi-target and multi-disease network^[10]. As a means of data mining, it is of great significance to Chinese medicine, especially the prescription of Chinese medicine.

In this study, we used network pharmacology to analyze how ZYJSW treats LDH. We began from targets of drugs and diseases, and then carried out a series of programming operations. At last, we got a series of charts and pictures, especially the enrichment analysis of GO and KEGG pathways. We hope to find its signaling pathway to explore its possible mechanisms.

2. Method

2.1 Acquisition of drug targets

At first, we opened TCMSP (<http://www.tcmspw.com/tcmsp.php>)^[11]. We typed all the herb names of ZYJSW and collected the chemical ingredients, the ingredients satisfied the following conditions: (i) oral bioavailability (OB) $\geq 30\%$ and (ii) drug-likeness (DL) ≥ 0.18 . This was documented^[12,13]. In addition, the targets came from the same web page^[14]. However, we couldn't use ingredients or targets directly. We need to change their forms. Here we took a programmatic approach to get the conversion.

2.2 Acquisition of disease targets

Here we used two classical web pages, they were Gene Cards (<https://www.genecards.org/>, version 5.5.0) and Online Mendelian Inheritance in Man (OMIM) database (<http://www.omim.org/>)^[11]. So we could get the targets of disease, and then we took all the targets together and took the union. We took the intersection of drug and disease targets, so we got a Venn diagram.

2.3 PPI networks construction and bar plot

As we had got the intersection of drug and disease targets, so these targets were inputted into the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, <https://string-db.org/>)^[15]. And then we could get a picture, that was the protein-protein interaction

(PPI). However, because of the complex interactions, we had to make a sort diagram, which is a bar graph, and R programming helped us do that.

2.4 Gene ontology enrichment analysis and KEGG enrichment analysis

We used R programming to change the form of the intersection of drug and disease targets. Besides, R programming was also used to get Gene ontology (GO) enrichment analysis and KEGG enrichment analysis. The GO and KEGG enrichment analysis results were selected by P value less than .05^[1].

3. Results

3.1 Venn diagram

We could see the ingredients from the TCMSP. When we used the value of OB that is greater than 30 and the value of DL that is greater than 0.18, we got our ingredients. Besides, targets were also seen in the TCMSP. We took a programmatic approach to attain the forms we wanted, which is the targets of drug. We used two types of web pages to get the targets of disease, and then Venn diagram was present (Figure 1). We could see that there were 48 intersection targets in the Venn diagram.

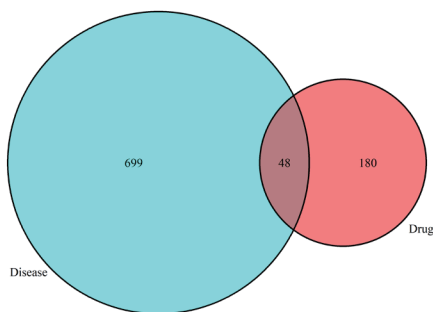


Figure 1 Venn diagram

3.2 PPI network and bar plot

We used STRING database to get our PPI network and we made a ranking based on the complex connections between the various networks, this is the bar plot (Figure 2). We could see the top 30 targets from the bar plot, and the top three were IL6, IL1-β and JUN.

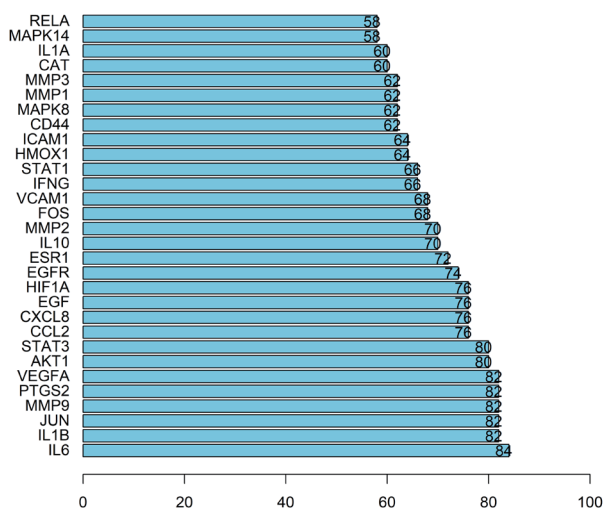


Figure 2 Bar plot of PPI network

3.3 Gene ontology enrichment analysis and KEGG

enrichment analysis

We used R programming to get Gene ontology enrichment analysis (Figure 3) and KEGG enrichment analysis (Figure 4). Gene ontology enrichment analysis and KEGG enrichment analysis both included bar plot and dot plot, we choose bar plot here. We could see the top three descriptions of Gene ontology enrichment analysis were cytokine receptor binding, receptor ligand activity and cytokine activity. The same was that we could see the top three pathways from the KEGG enrichment analysis, they were AGE-RAGE signaling pathway in diabetic complications, Lipid and atherosclerosis and Kaposi sarcoma-associated herpesvirus infection. Here we put the top one pathway AGE-RAGE signaling pathway (Figure 5).

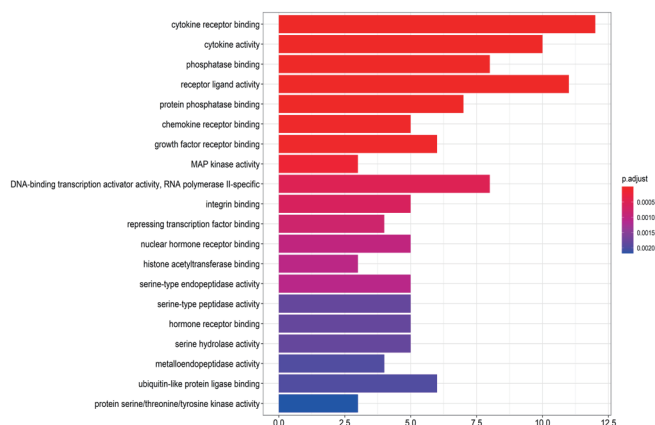


Figure 3 Bar plot of Gene ontology enrichment analysis

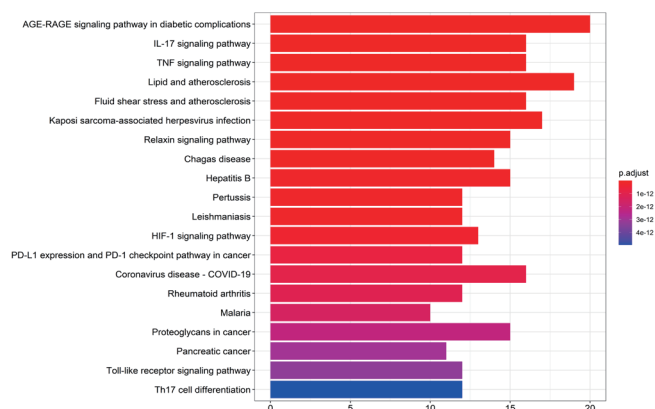


Figure 4 Bar plot of KEGG enrichment analysis

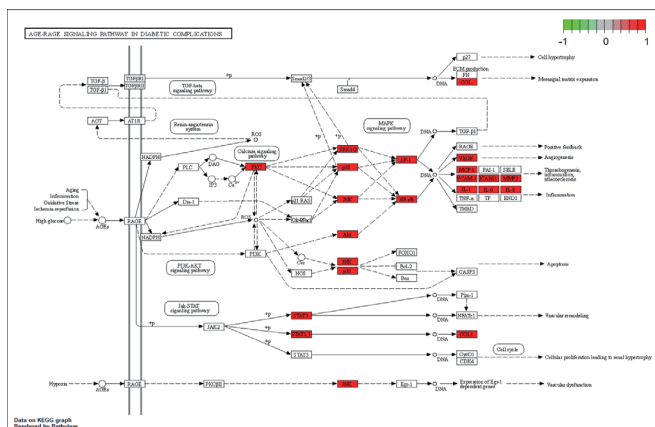


Figure 5 AGE-RAGE signaling pathway

4. Discussion

LDH is the most common spinal disease, which is closely related to aging and is a degenerative change. As work habits change and life pressures increase, more and more young people are either standing or sitting too long, leading to a younger trend of the disease. ZYJSW is a proprietary Chinese medicine for kidney loss and low back pain, but it is often overlooked in the treatment of LDH. In fact, the therapeutic effect of ZYJSW is related to the content of various traditional Chinese medicines, especially *Millettiae Speciosae Radix* and *Kadsurae Coccineae Radix Et Caulis*. These two medicines are grown in remote mountains and valleys, they are very difficult to be obtained. If they are not enough, ZYJSW will not be as effective. Network pharmacology is a new developing subject, It brings together pharmacology, biology and informatics. We can use the programming method to mine the database of Traditional Chinese medicine, which is an efficient, simple and fast way. Data mining is a hot and difficult approach to learn, we should make full use of the existing network technology for data mining. From the mined data, we can find out the direction of the next research or the content that has not been studied before.

5. Conclusion

In this study, 48 intersection targets of medicine and disease were mined. And then we did a ranking of those targets and found that first place went to IL6. We guessed that ZYJSW treats LDH through an anti-inflammatory pathway. From the Gene ontology enrichment analysis we could see the top one description was the cytokine receptor binding. And the top one pathway of the KEGG enrichment analysis was AGE-RAGE signaling pathway. We guessed that these were the mechanisms how ZYJSW treats LDH. However, we need to study it further. In conclusion, this study provides another strategy to understand the mechanisms by which ZYJSW treats LDH.

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