**Predicting the Anti-Inflammatory Mechanism of Polygonum perfoliatum L based on Network Pharmacology**

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**Abstract.** Objective: To study the mechanism of anti-inflammation of Polygonum perfoliatum L by network pharmacology. Method: The active ingredients of Polygonum perfoliatum L were screened using TCMSP database, the active ingredients-target network and protein interaction network were established. The biological functions and pathways involved in the target were analyzed. Results: 11 active ingredients were obtained by screening. The network analysis indicated that the active components of Polygonum perfoliatum L involved 183 protein targets including Serpine1, Akt1, Nos3, Tnf, Casp8, Bcl2l1 and multiple protein targets related to the MAPK signaling pathway, etc. The medicine had anti-inflammatory effects by regulating many signaling pathways such as PI3K-Akt signaling pathway, MAPK signaling pathway, Toll-like receptor signaling pathway, and HIF-1 signaling pathway. Conclusion: This study reflects the medicine multi-component-multi-target-multi-path therapy. It provides new ideas and new directions for further research on the mechanism of anti-inflammatory effects of Polygonum perfoliatum L.

1. Introduction

Inflammation is what people usually call “agnail”. It refers to a kind of defense reaction of organism after external injury such as burn, chemical stimulation or toxin. The development of inflammation involves many cells and active ingredients. Moderate inflammatory response is beneficial to the human body, while excessive or sustained inflammatory response can cause tissue damage or induce other diseases [1]. Chinese Medicine believes that the symptoms of diseases caused by the evil of heat, such as “there is more than heat, hot meat is meat rot, and meat rot is pus” and other diseases are the same as the inflammation considered by Western medicine [2].

Polygonum perfoliatum L (Gangbangui) [3] is commonly used Chinese medicine, distributed throughout the country. It was beginning in Curative Measures for All Diseases, now contained in 2015 Chinese Pharmacopoeia. Commonly used for the treatment of sore throat, damp and hot diarrhea, eczema and other diseases. It is also a common medicinal material of miao people, which is widely used in the treatment of heat poisoning by miao medicine [4]. Preparations Compound of anti-fuyan capsules, Polygonum perfoliatum L capsules (GBG), and Fuping capsules contain the medicinal materials, which have a good effect in anti-inflammation [5-7]. In recent years, it has become a hot research topic, mainly focusing on the cultivation of medicinal materials, chemical composition and pharmacological activity.
Among them, the anti-inflammatory effects of the medicine have been reported in the literature. This studied the anti-inflammatory and bacteriostatic activity sites of *Polygonum perfoliatum* L and the result showed that the N-butanol site had anti-inflammatory activity and ethyl acetate site had obvious bacteriostatic activity [8]. Research has shown that the extract had a significant inhibitory effect of inflammation in the early stage [9]. Another study found that the decoction of the medicine could effectively relieve pulmonary inflammation in infected mice [10]. At present, the anti-inflammatory research on crude *Polygonum perfoliatum* L extract is rich, but its material basis and related molecular mechanisms for anti-inflammatory are not clear, which is not conducive to clinical application. Therefore, it is necessary to study the anti-inflammatory mechanism of *Polygonum perfoliatum* L from a holistic perspective by method of network pharmacology.

Traditional Chinese medicine treats diseases according to the concept of holism, and its application of Chinese material medica has the characteristics of multiple components, multiple targets, and multiple approaches to treat human diseases. However, due to its complexity, the development of traditional Chinese medicine is limited [11]. The emergence of bioinformatics has changed this situation. The use of network pharmacology can establish the interaction between the molecular network of complex components of traditional Chinese medicine and multiple targets, and achieve a comprehensive analysis of drug effects from the perspective of multiple targets. It is widely used to predict the potential active ingredients and the targets of Chinese medicine [12-13]. Therefore, the network pharmacology method was adopted in this paper to analyze the targets and signal pathways of the active ingredient of *Polygonum perfoliatum* L for anti-inflammation.

2. Method

2.1. Screening of active ingredients and targets
Through referring to relevant literatures (CNKI, guizhou digital library, PubMed) and TCMSP (Traditional Chinese Medicine Systems Pharmacology), the chemical components contained of *Polygonum perfoliatum* L were retrieved. The active chemical components of the medicine were screened according to the value of Oral Bioavailability (OB) and Drug – Likeness (DL): OB≥30%, DL ≥0.18. Finally, all the targets obtained by the screening are transformed into UniProt ID format by querying the UniProt database (https://www.uniprot.org/).

2.2. Screening of disease targets
GeneCard (https://www.genecards.org/) was used to screen genes for inflammation, and a dataset of inflammation targets was established.

2.3. Network Construction and Analysis
First of all, using venny2.1.1 (https://www.genecards.org/) to screen for intersections targets of the median and diseases. Secondly, Cytoscape 3.6.1 was used to analyze the targets and obtain the protein interaction diagram. Then, to screen potential targets of the medicine treatment inflammation according to the median of degree, betweenness centrality, and closeness centrality. Finally build a “drug-active ingredient-target-disease” network.

2.4. Biological process analysis
KEGG pathway and GO (Gene Ontology) biological process of the targets were analyzed using DAVID (https://david.ncifcrf.gov/) database.

3. Result

3.1. Screening of active ingredients
Through TCMSP database and TCMID database, 11 active compounds were screened by ADME parameters (OB≥ 30% and DL≥0.18), the result shown in table 1. It is that beta-Sit sterol and quercetin
have good anti-inflammatory effects [14-15]. The results suggested that the compounds of effects are consistent with the literature reports.

Table 1. Active compounds and target Numbers of Polygonum perfoliatum L

| Mol ID    | Chemical composition   | The number of target | OB (%) | DL  |
|-----------|------------------------|----------------------|--------|-----|
| MOL000354 | Isorhamnetin           | 25                   | 49.6   | 0.31|
| MOL000098 | Quercetin              | 151                  | 46.64  | 0.23|
| MOL000471 | Aloe emodin            | 18                   | 88.38  | 0.24|
| MOL000422 | Kaempferol             | 28                   | 41.88  | 0.24|
| MOL000358 | beta-Sitosterol        | 37                   | 36.90  | 0.23|
| MOL001002 | Ellagic acid           | 17                   | 43.06  | 0.43|
| MOL001525 | Daucosterol            | 2                    | 36.91  | 0.75|
| MOL000492 | Catechin               | 7                    | 54.83  | 0.24|
| MOL008206 | Moslossoflavone        | 20                   | 44.09  | 0.25|
| MOL002844 | Pinocembrin            | 10                   | 64.72  | 0.18|
| MOL004576 | Taxifolin              | 9                    | 57.84  | 0.27|

3.2. Screening target of drug and disease
Through the comprehensive analysis of TCMSP database, BATMAN-TCM database and Chinese medicine target database, 324 targets corresponding to active chemical components of the medicine were screened. The results are shown in table 1. Through Genecard database, 9006 targets related to inflammation were found. Veny website was used to screen out 183 targets where the active ingredients of the medicine intersected with inflammation.

3.3. The direct targets and topological parameters of the active ingredients of the medicine for the treatment of inflammation.
The protein interaction diagram constructed by ytoscape3.7.1 software (see figure 1). The 36 selected anti-inflammatory targets and their topological parameters are shown in table 2. The network analysis diagram of "drug-active ingredient-targe-disease" was constructed. (See figure 2).
Figure 1. *Polygonum perfoliatum* L - interaction of inflammatory proteins

Figure 2. *Polygonum perfoliatum* L “drug - active ingredients - target - disease”
### Table 2. Results of topological parameters of target of *Polygonum perfoliatum* L

| uniport | name          | BetweennessCentrality | ClosenessCentrality | Degree |
|---------|---------------|------------------------|---------------------|--------|
| P05121  | SERPINE1      | 0.005814               | 0.569182            | 54     |
| BOLPE5  | AKT1          | 0.070411               | 0.735772            | 118    |
| P29474  | NOS3          | 0.019753               | 0.601329            | 64     |
| P01375  | TNF           | 0.028058               | 0.67037             | 95     |
| Q14790  | CASP8         | 0.003223               | 0.574603            | 58     |
| Q07817  | BCL2L1        | 0.003606               | 0.580128            | 59     |
| P04637  | TP53          | 0.031664               | 0.69084             | 106    |
| P37231  | AR            | 0.014947               | 0.599338            | 64     |
| P05412  | JUN           | 0.025175               | 0.665441            | 95     |
| P01100  | FOS           | 0.031422               | 0.635088            | 79     |
| P42574  | CASP3         | 0.024707               | 0.67037             | 96     |
| P37231  | PPARG         | 0.015473               | 0.591503            | 64     |
| Q04206  | RELA          | 0.01705                | 0.599338            | 67     |
| P03372  | ESR1          | 0.02383                | 0.630662            | 82     |
| P22301  | IL10          | 0.004279               | 0.589577            | 65     |
| P05231  | IL6           | 0.035018               | 0.685606            | 103    |
| P60484  | PTEN          | 0.01239                | 0.611486            | 72     |
| P01584  | IL1B          | 0.011386               | 0.617747            | 74     |
| P04040  | CAT           | 0.034329               | 0.626298            | 78     |
| P04626  | ERBB2         | 0.017442               | 0.605351            | 67     |
| P01133  | EGF           | 0.046489               | 0.663004            | 91     |
| Q16539  | MAPK1         | 0.02024                | 0.658182            | 92     |
| P09601  | HMOX1         | 0.007816               | 0.585761            | 63     |
| P10145  | CXCL8         | 0.009194               | 0.617747            | 75     |
| P01106  | MYC           | 0.019284               | 0.65343             | 91     |
| P13500  | CCL2          | 0.005649               | 0.603333            | 70     |
| Q16539  | MAPK14        | 0.007304               | 0.59736             | 66     |
| P19320  | VCAM1         | 0.002221               | 0.570978            | 55     |
| P15692  | VEGFA         | 0.039761               | 0.688213            | 101    |
| P14780  | MMP9          | 0.013954               | 0.626298            | 80     |
| P42224  | STAT1         | 0.009421               | 0.580128            | 60     |
| P01579  | IFNG          | 0.002487               | 0.567398            | 55     |
| P05362  | ICAM1         | 0.003354               | 0.587662            | 62     |
| P08253  | MMP2          | 0.005398               | 0.595395            | 65     |
| P60568  | IL2           | 0.005126               | 0.569182            | 58     |
| P35354  | PTGS2         | 0.01631                | 0.637324            | 83     |

#### 3.4. GO biological function analysis

Thirty-six potential targets were imported into the DAVID database for GO functional enrichment analysis. 307 biological processes were obtained, including 28 biological processes with a P value less than 0.000001. Among the biological processes, positive regulation of transcription from RNA polymerase II promoter, MAPK cascade, inflammatory response and negative regulation of apoptotic process have the strongest correlation. The results are shown in table 3. Among the molecular functions, cytosol, extracellular space and nucleolene have the strongest correlation the results are shown in table 4. Among the cell components protein binding and identity protein binding have the strongest correlation the results are shown in table 5. Through analysis, it is found that these biological processes are closely related to the occurrence and development of inflammation. It reflects that the action mechanism of the
medicine involves multiple biological processes in vivo, and also indicates that the active components of the medicine may play an anti-inflammatory role by regulating these biological processes.

### Table 3. Partial GO function analysis results of biological processes

| Term                                                      | Count | Count% | P-Value       |
|-----------------------------------------------------------|-------|--------|---------------|
| response to drug                                          | 14    | 0.2    | 1.8E-14       |
| positive regulation of transcription from RNA polymerase II promoter | 19    | 0.3    | 9.5E-14       |
| angiogenesis                                              | 12    | 0.2    | 5.6E-13       |
| positive regulation of transcription, DNA-templated       | 15    | 0.3    | 7E-13         |
| cellular response to lipopolysaccharide                    | 10    | 0.2    | 1.2E-12       |
| positive regulation of nitric oxide biosynthetic process   | 8     | 0.1    | 2.8E-12       |
| positive regulation of smooth muscle cell proliferation    | 8     | 0.1    | 3.2E-11       |
| Aging                                                     | 10    | 0.2    | 3.9E-11       |
| lipopolysaccharide-mediated signaling pathway              | 7     | 0.1    | 4.5E-11       |
| negative regulation of apoptotic process                  | 13    | 0.2    | 6.4E-11       |
| positive regulation of sequence-specific DNA binding transcription factor activity | 8     | 0.1    | 1.8E-09       |
| response to ethanol                                        | 8     | 0.1    | 1.8E-09       |
| cellular response to organic cyclic compound               | 7     | 0.1    | 2.2E-09       |
| positive regulation of gene expression                    | 10    | 0.2    | 2.4E-09       |
| positive regulation of cell proliferation                  | 11    | 0.2    | 2.4E-08       |
| response to estradiol                                      | 7     | 0.1    | 3.1E-08       |
| cellular response to hypoxia                              | 7     | 0.1    | 4.2E-08       |
| inflammatory response                                     | 10    | 0.2    | 5.8E-08       |
| negative regulation of cell proliferation                 | 10    | 0.2    | 8.5E-08       |
| regulation of sequence-specific DNA binding transcription factor activity | 5     | 0.1    | 1.9E-07       |
| positive regulation of NF-kappaB transcription factor activity | 7     | 0.1    | 3E-07         |
| cellular response to interleukin-1                        | 6     | 0.1    | 3.4E-07       |
| response to amino acid                                    | 5     | 0.1    | 4.8E-07       |
| response to antibiotic                                    | 5     | 0.1    | 5.5E-07       |
| negative regulation of extrinsic apoptotic signaling pathway via death domain receptors | 5     | 0.1    | 6.2E-07       |
| protein kinase B signaling                                | 5     | 0.1    | 6.2E-07       |
| MAPK cascade                                              | 8     | 0.1    | 9.6E-07       |
| positive regulation of chemokine biosynthetic process      | 4     | 0.1    | 9.9E-07       |

### Table 4. Partial GO function analysis results of molecular functions

| Term                                                      | Count | Count% | P-Value       |
|-----------------------------------------------------------|-------|--------|---------------|
| extracellular space                                       | 17    | 0.3    | 7.7E-10       |
| extracellular region                                      | 14    | 0.2    | 4.4E-06       |
| Cytosol                                                   | 19    | 0.3    | 8.6E-06       |
| Caveola                                                   | 4     | 0.1    | 0.00026       |
| nucleoplasm                                               | 15    | 0.3    | 0.00035       |
| nuclear chromatin                                         | 5     | 0.1    | 0.00049       |
| mitochondrion                                            | 10    | 0.2    | 0.00071       |
| external side of plasma membrane                          | 5     | 0.1    | 0.00072       |
| neuron projection                                         | 5     | 0.1    | 0.0011        |
| protein complex                                           | 6     | 0.1    | 0.0011        |
| Cytoplasm                                                | 19    | 0.3    | 0.0037        |
| platelet alpha granule lumen                              | 3     | 0.1    | 0.005         |
| Nucleus                                                   | 19    | 0.3    | 0.0057        |
| membrane raft                                            | 4     | 0.1    | 0.0071        |
Table 5. Partial GO function analysis results of cell components

| Term                                                                 | Count | Count % | P-Value     |
|----------------------------------------------------------------------|-------|---------|-------------|
| enzyme binding                                                      | 12    | 0.2     | 4.1E-11     |
| identical protein binding                                           | 15    | 0.3     | 9.9E-11     |
| transcription factor binding                                         | 9     | 0.2     | 9.2E-08     |
| cytokine activity                                                   | 7     | 0.1     | 1.5E-06     |
| transcription regulatory region DNA binding                         | 7     | 0.1     | 4.5E-06     |
| RNA polymerase II core promoter proximal region sequence-specific DNA binding | 7     | 0.1     | 0.000       |
| transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding | 6     | 0.1     | 0.000       |
| chromatin binding                                                  | 7     | 0.1     | 0.000       |
| protein binding                                                    | 30    | 0.5     | 0.000       |
| protein phosphatase binding                                         | 4     | 0.1     | 0.000       |
| growth factor activity                                              | 5     | 0.1     | 0.000       |
| protein heterodimerization activity                                 | 7     | 0.1     | 0.000       |
| sequence-specific DNA binding                                       | 7     | 0.1     | 0.000       |
| transcription factor activity, sequence-specific DNA binding        | 9     | 0.2     | 0.000       |
| protein homodimerization activity                                   | 8     | 0.1     | 0.000       |
| protease binding                                                    | 4     | 0.1     | 0.001       |
| protein phosphatase 2A binding                                      | 3     | 0.1     | 0.001       |
| tumor necrosis factor receptor binding                              | 3     | 0.1     | 0.001       |
| RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding | 3     | 0.1     | 0.002       |
| heme binding                                                        | 4     | 0.1     | 0.002       |
| core promoter sequence-specific DNA binding                         | 3     | 0.1     | 0.003       |
| DNA binding                                                         | 10    | 0.2     | 0.005       |
| steroid hormone receptor activity                                   | 3     | 0.1     | 0.006       |
| protein complex binding                                             | 4     | 0.1     | 0.008       |
3.5. Analysis of KEGG signaling pathway enrichment

The 36 predicted core targets were mapped to the DAVID database for KEGG pathway enrichment analysis, 95 signal pathways were obtained, 43 signal pathways were obtained by filtering with p-value (P < 0.00001). The anti-inflammatory effect of the medicine is closely related to the regulation about TNF signaling pathway, PI3K-Akt signaling pathway, MAPK signaling pathway, Toll-like receptor signaling pathway and other inflammatory signaling pathways. The main regulated signal pathways of A are shown in table 6.

Table 6. Enrichment analysis of KEGG signaling pathway

| Term                                           | Count | count% | P-Value |
|------------------------------------------------|-------|--------|---------|
| Pathways in cancer                             | 22    | 0.4    | 5E-18   |
| Chagas disease (American trypanosomiasis)      | 16    | 0.3    | 4.3E-19 |
| TNF signaling pathway                          | 16    | 0.3    | 6.8E-19 |
| Hepatitis B                                    | 15    | 0.3    | 2.9E-15 |
| Influenza A                                    | 13    | 0.2    | 2.4E-11 |
| Toll-like receptor signaling pathway           | 12    | 0.2    | 2.1E-12 |
| Tuberculosis                                   | 12    | 0.2    | 5.9E-10 |
| Herpes simplex infection                       | 12    | 0.2    | 8.4E-10 |
| Proteoglycans in cancer                        | 12    | 0.2    | 2.2E-09 |
| MAPK signaling pathway                         | 12    | 0.2    | 2.6E-08 |
| HTLV-1 infection                               | 12    | 0.2    | 2.7E-08 |
| PI3K-Akt signaling pathway                     | 12    | 0.2    | 6.1E-07 |
| Leishmaniasis                                  | 11    | 0.2    | 1.1E-12 |
| Pertussis                                      | 11    | 0.2    | 1.9E-12 |
| HIF-1 signaling pathway                        | 11    | 0.2    | 2.4E-11 |
| Toxoplamosis                                   | 11    | 0.2    | 9.5E-11 |
| Osteoclast differentiation                     | 11    | 0.2    | 5.4E-10 |
| Rheumatoid arthritis                           | 10    | 0.2    | 3.3E-10 |
| T cell receptor signaling pathway              | 10    | 0.2    | 1E-09   |
| Bladder cancer                                 | 9     | 0.2    | 1.6E-11 |
| Malaria                                        | 9     | 0.2    | 7.4E-11 |
| NOD-like receptor signaling pathway            | 9     | 0.2    | 2.3E-10 |
| Inflammatory bowel disease (IBD)               | 9     | 0.2    | 6.9E-10 |
| Pancreatic cancer                              | 9     | 0.2    | 7.9E-10 |
| Salmonella infection                           | 9     | 0.2    | 5.8E-09 |
| Hepatitis C                                    | 9     | 0.2    | 2.4E-07 |
| Non-alcoholic fatty liver disease (NAFLD)      | 9     | 0.2    | 6.4E-07 |
| NF-kappa B signaling pathway                   | 8     | 0.1    | 2E-07   |
| Prostate cancer                                | 8     | 0.1    | 2.2E-07 |
| Estrogen signaling pathway                     | 8     | 0.1    | 5E-07   |
| Amoebiasis                                     | 8     | 0.1    | 8E-07   |
| Sphingolipid signaling pathway                 | 8     | 0.1    | 1.9E-06 |
| Measles                                        | 8     | 0.1    | 3.7E-06 |
| FoxO signaling pathway                         | 8     | 0.1    | 3.9E-06 |
| Jak-STAT signaling pathway                     | 8     | 0.1    | 6.6E-06 |
| African trypanosomiasis                        | 7     | 0.1    | 1.1E-08 |
| Endometrial cancer                             | 7     | 0.1    | 1.9E-07 |
| Legionellosis                                  | 7     | 0.1    | 2.4E-07 |
| Colorectal cancer                              | 7     | 0.1    | 5.5E-07 |
| Apoptosis                                      | 7     | 0.1    | 5.5E-07 |
| Prolactin signaling pathway                    | 7     | 0.1    | 1.3E-06 |
| Small cell lung cancer                         | 7     | 0.1    | 3.6E-06 |
| Amyotrophic lateral sclerosis (ALS)            | 6     | 0.1    | 4.6E-06 |
4. Discuss

Chinese medicine treats diseases in accordance with the holistic view, moreover, the composition of Chinese material medicine is complex, with characteristics such as multi-component, and multi-target, multi-path. Network pharmacology is a new method to study Chinese materia medica. Its integrity and system city coincide with the theory of traditional Chinese medicine [16]. So, using network pharmacology to study the efficacy of Chinese material medicine has significant advantages. Modern research shows Polygonum perfoliatum L has anti-inflammatory effects. This article screened out 11 active ingredients of Polygonum perfoliatum L and constructed “drug-active ingredient-target-disease” interactive network diagram. 36 potential anti-inflammatory activity targets was screened in active compounds and diseases common target. DAVID database was used for enrichment analysis of biological processes and signaling pathways. It was found that 28 biological processes were closely related to the anti-inflammatory effect of the medicine. The main biological processes include positive regulation of transcription from RNA polymerase II promoter, MAPK cascade, inflammatory response and negative regulation of apoptotic process etc. Through pathway enrichment, it was found that there were 43 pathways closely related to the treatment of inflammation by the medicine. This study predicted that the anti-inflammatory mechanism of the medicine was closely related to TNF signaling pathway, PI3K-Akt signaling pathway, MAPK signaling pathway, Toll-like receptor signaling pathway, etc. The results also indicated the action characteristics of multi-components, multi-targets and multi-paths of the medicine. It provides new ideas and new directions for further revealing the anti-inflammatory mechanism of the medicine, which is conducive to the further development and application of the medicinal materials in anti-inflammatory.

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