



## Original Article

# Exploring the Modern Pharmacological Mechanism of Special Ingredients of Panax Ginseng for Ulcerative Colitis based on Network Pharmacology



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## Abstract

**Background and Objective:** To explore the main action targets and key pathways, along with their mechanisms of action, of Panax ginseng's special ingredients in the treatment of ulcerative colitis using network pharmacology methods. To provide a theoretical basis for subsequent laboratory experiments and clinical trials.

**Methods:** The main active ingredients of Panax notoginseng were obtained through the TCMSP database and the specific ingredients were screened. The targets of Panax notoginseng-specific components were obtained from the Swiss Target Prediction database. The GeneCards, OMIM, and DisGent databases were used to obtain the targets related to ulcerative colitis. The protein interaction network (PPI) of intersecting targets was constructed using the STRING database. GO function and KEGG pathway enrichment analysis were performed in R language software. Construction of the herb-component-target-disease-KEGG pathway network was achieved using Cytoscape software.

**Results:** Seven major active ingredients of Panax notoginseng were obtained, and ginsenoside f2 was found to be a special ingredient, corresponding to 16 potential targets. A search of the disease database yielded 5,536 targets for ulcerative colitis. Eight core targets were obtained by protein interaction analysis of the intersecting targets: STAT3, VEGFA, HSP90AA1, FGF2, IL2, MET, BCL2L1, and RORC, respectively. 417 entries were obtained by GO functional enrichment analysis, and 22 statistically significant pathways were obtained by KEGG enrichment analysis.

**Conclusion:** The mechanism of action of ginsenoside f2 in the treatment of ulcerative colitis features multi-target and multi-pathway interactions. The receptors may be related to STAT3, VEGFA, HSP90AA1, FGF2, IL2, MET, and other targets, and the main signaling pathways may be related to the PI3K-Akt signaling pathway, Th17 cell differentiation, and inflammatory bowel disease among others and this provides a theoretical basis for the next in-depth experimental study.

## Introduction

Ulcerative colitis (UC) is a chronic digestive system disorder characterized by abnormal inflammation in the rectum and colon, resulting in the formation of ulcers. It usually emerges between the ages

of 15 and 30 but can occur at any age,<sup>1</sup> and is associated with recurring flare-ups throughout one's life, accompanied by various symptoms. Common symptoms include abdominal pain, cramps, frequent diarrhea (often with blood, pus, or mucus in the stools),<sup>2</sup> nausea, loss of appetite, fatigue, and fever. Chronic bleeding from the inflamed bowel may lead to anemia,<sup>3</sup> while difficulties in nutrient absorption often cause weight loss. In children affected by UC, growth may be slower than average.<sup>4</sup> Although less common, UC can also affect other parts of the body such as the skin, joints, eyes, kidneys, or liver due to abnormal inflammation. Toxic megacolon, a rare and life-threatening complication, involves an

**Keywords:** Bioinformatics; Panax ginseng; Ulcerative colitis; Signaling pathway.

**Abbreviations:** BC, betweenness centrality; BP, Biological Process; CC, cellular component; CD, Crohn's disease; DL, drug class; IBD, inflammatory bowel disease; MF, molecular function; NOD, nucleotide-binding oligomerization domain; OB, oral benefit; PPI, protein interaction network; TCM, traditional Chinese medicine; UC, ulcerative colitis.

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enlarged colon and severe bacterial infections (sepsis). Moreover, individuals with UC have an increased risk of developing bowel cancer, particularly if the entire colon is inflamed or if the condition persists for more than eight years.<sup>5,6</sup> Ulcerative colitis falls under the broader category of inflammatory bowel diseases (IBD), alongside Crohn's disease. While UC primarily affects the colon's lining, Crohn's disease can cause inflammation in any part of the digestive system, involving deeper layers of the bowel tissue.<sup>7</sup>

Currently, there are no targeted drugs for ulcerative colitis. The treatment of UC in China comprises mainly Western medicine, supplemented by traditional Chinese medicine (TCM). There are, however, problems with Western medicine in the treatment of ulcerative colitis such as a high recurrence rate, many adverse reactions, and unsatisfactory efficacy in some refractory patients. For mild to moderate ulcerative colitis, traditional Chinese medicine can significantly improve the clinical symptoms, and even play a role in the maintenance of the remission phase of Western medicine. Ulcerative colitis belongs to the category of "dysentery" in traditional Chinese medicine. It is based on the weakness of the spleen and stomach and is related to the causes of an unclean diet, emotional disorders, and the feeling of external evil.<sup>8</sup> Based on previous studies, we believe that stasis is involved in the process of onset and in each syndrome type. As such, syndrome differentiation treatment combined with the treatment of traditional Chinese medicine for removing blood stasis has a good clinical effect. *Panax notoginseng*,<sup>9</sup> which can be used to stop bleeding from dysentery and relieve intestinal stasis, is the main blood-activating drug in the prescription. Pharmacological studies have shown that *Panax notoginseng* can activate blood circulation and has hemostatic, anti-inflammatory, and immune regulation qualities.<sup>10</sup> Therefore, in this study, network pharmacology was used to analyze the effective components of *Panax notoginseng* in treating ulcerative colitis at the molecular level and to predict its target and signal pathway, providing ideas and a basis for clinical and experimental research.

## Research methods

### Screening of active ingredients and targets of *Panax notoginseng*

*Panax notoginseng* was input into the TCMSP platform (<https://tcmsp-e.com/>)<sup>11</sup> with the keyword "*Panax notoginseng*", and the effective ingredients were screened with drug class (DL)  $\geq 0.18$  and oral benefit (OB)  $\geq 30\%$  as the conditions. In addition, the relevant Chinese medicines made from the effective ingredients of *Panax notoginseng* were searched on the TCMSP platform, and the ingredients with the least associated Chinese medicines were selected as the special components. The special composition and structural information of *notoginseng* was retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>).<sup>12</sup> The structural information was retrieved from the Swiss Target Prediction database (<http://www.swisstargetprediction.ch/>)<sup>13</sup> to ascertain the related targets. The target was screened with "Probability > 0" as the screening condition.

### Acquisition of disease targets

The search terms "Ulcerative Colitis" and "human" were used as the retrieval objects to obtain disease targets through the GeneCards database (<https://www.genecards.org/>),<sup>14</sup> OMIM database (<https://www.omim.org/>),<sup>15</sup> and DisGeNET database (<https://www.disgenet.org/>).<sup>16</sup>

### Acquisition of intersection targets

Application Venny (<https://bioinfo.gp.cnb.csic.es/tools/venny/>)<sup>17</sup> software was used to ascertain *notoginseng* special ingredients targets and disease intersection targets, as *notoginseng* special components in the treatment of Ulcerative Colitis of potential targets.

### Protein interaction network (PPI) construction and network topology analysis

Using the String (<https://string-db.org/>) platform,<sup>18</sup> the intersection target was imported, the object was set as "homo sapiens", the highest confidence was 0.900, and the free gene nodes were hidden to obtain the protein interaction relationship. The results were imported into Cytoscape (3.9.1) software and a network analyzer was selected to obtain network topology parameters. The degrees, betweenness centrality, and closeness centrality of the PPI network nodes were analyzed and calculated.

### GO and KEGG enrichment analysis

Bioinformatics open-source software was used to install and run clusterProfiler,<sup>19</sup> DOSE,<sup>20</sup> and Pathview<sup>21</sup> packages in R language software (3.5.1) for the GO and KEGG enrichment analysis. Visual display was achieved through the microscopic letter platform (<https://www.bioinformatics.com.cn/>). The GO enrichment analysis annotated *Panax notoginseng* therapy ulcerative from three aspects: biological process (BP), cellular component (CC), and molecular function (MF) of the target of colitis. The first ten GO items of BP, CC, and MF were screened out according to the *P*-value size, and the bubble map was drawn. Cnetplot belongs to the Gene-Concept Network, which describes the links between genes and biological pathways as a network. It is possible to intuitively observe the genes involved in these items and the interactive genes between the items. Cnetplot was used to display the interacting genes of the first 10 KEGG pathways. Emapplot shows the overlapping relationship between the enriched pathways.

### Drawing the network diagram of the herb-component-target-disease-KEGG pathway

The contents of *Panax notoginseng*, special components, target sites, and KEGG pathway were collected and imported into Cytoscape software to draw the network diagram of the herb-component-target-disease-KEGG pathway.

## Results

### Natural drug active ingredients, diseases, and intersection targets

With "*Panax notoginseng*" as the keyword, 119 *Panax notoginseng* components were screened on the TCMSP platform, among which 8 components met the screening conditions (OB  $\geq 30\%$ , DL  $\geq 0.18$ ). Among the eight ingredients, ginsenoside f2 was the least associated with traditional Chinese medicine (Table 1), only *Panax notoginseng* and *Gynostaphyllum pentaphyllum*. Finally, ginsenoside f2 was determined to be the special component of *Panax notoginseng*. The screening process is shown in Figure 1. Through the Swiss Target Prediction database retrieval, 16 ginsenoside f2 targets were obtained with "Probability > 0" as the screening condition. By searching GeneCards, OMIM, and DisGeNET databases, 5,536 disease targets were obtained after removing duplicates. Venny software was used to take the intersection of TCM targets

**Table 1. Quantity of Chinese medicine associated with Panax notoginseng components**

| Mol ID    | Component name  | Related herbs number |
|-----------|-----------------|----------------------|
| MOL001494 | mandenol        | 35                   |
| MOL001792 | DFV             | 10                   |
| MOL002879 | Diop            | 14                   |
| MOL000358 | beta-sitosterol | 245                  |
| MOL000449 | stigmasterol    | 133                  |
| MOL005344 | ginsenoside rh2 | 5                    |
| MOL007475 | ginsenoside f2  | 2                    |
| MOL000098 | quercetin       | 188                  |

DFV, dried fruit vinegar; Diop, diopside; Mol ID, molecule ID.

and disease targets and 12 intersection targets were obtained, which were potential targets of ginsenoside f2 in the treatment of Ulcerative Colitis (Fig. 2). The four targets of PTAFR, GSAP, FGF1 and LGALS8 in ginsenoside f2 were not associated with ulcerative colitis.

**PPI network construction and network topology analysis**

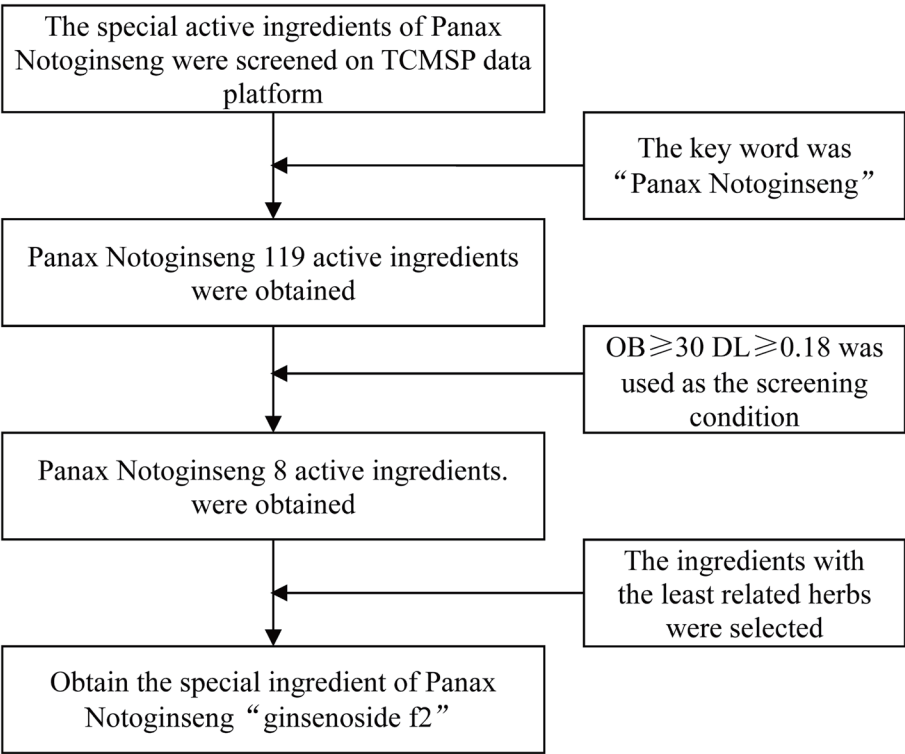
The topology of the PPI network was analyzed using Cytoscape software, which contains 8 nodes and 11 edges (Fig. 2). The targets were STAT3, VEGFA, HSP90AA1, FGF2, IL2, MET, BCL2L1, and RORC, which were sorted by Degree size and listed in the key target information table (Table 2). Among them, the STAT3 target had the highest Degree value of 7.

**GO and KEGG enrichment analysis**

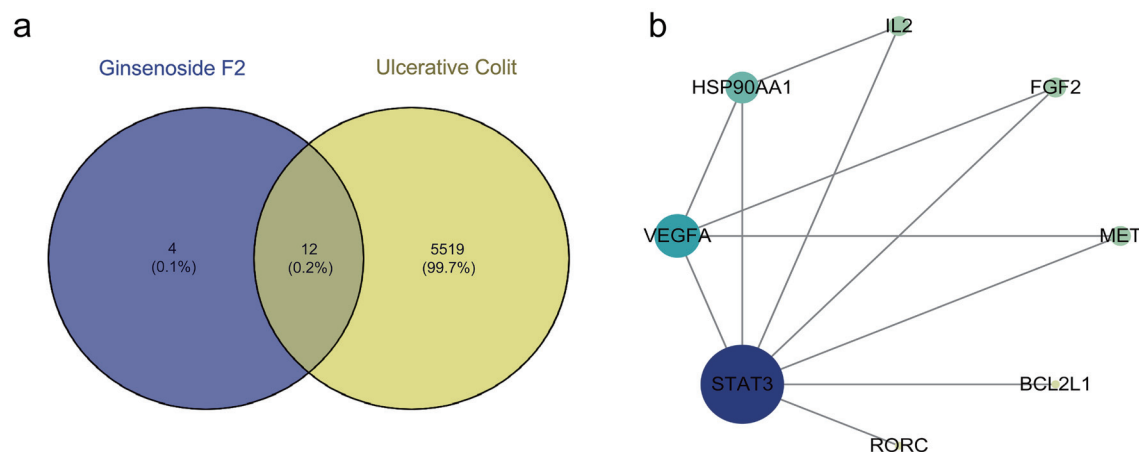
The results of the GO enrichment analysis involved a total of 417 statistically significant pathways ( $p < 0.05$ ) (Fig. 3), among which 365 statistically significant BP entries were involved in positive chemotaxis, positive regulation of endothelial cell chemotaxis, regulation of endothelial cell chemotaxis, T cell activation involved in immune response, *etc.* And 8 statistically significant CC entries, mainly related to secretory granule lumen, cytoplasmic vesicle lumen, vesicle lumen, lysosomal lumen, *etc.* And 44 statistically significant MF entries, mainly related to chemoattractant activity, growth factor receptor binding, and protein phosphatase binding, *etc.* The KEGG enrichment analysis yielded 22 statistically significant pathways, and the top ten KEGG enrichment analyses are shown in Figure 3. The analysis mainly involved EGFR tyrosine kinase inhibitor resistance, PI3K-Akt signaling pathway, proteoglycans in cancer, Th17 cell differentiation, inflammatory bowel disease, *etc.* The information on the top ten pathways analyzed by KEGG enrichment is shown in Table 3. It shows that ginsenoside f2 can treat ulcerative colitis by acting on different signaling pathways. Cnetplot analysis can visualize the interacting genes between each KEGG pathway (Fig. 4), STAT3, VEGFA, HSP90AA1, FGF2, IL2, MET, BCL2L1, and the Emapplot plot is shown in Figure 5.

**Construction of the network diagram of the herb-component-target-disease-KEGG pathway**

The contents of the first 10 KEGG pathways of Panax notoginseng, ginsenoside f2, target, ulcerative colitis, and enrichment fraction were summarized. The above information was mapped into the herb-component-target-disease-KEGG pathway network diagram using Cytoscape software (Fig. 6). The network diagram has 25 nodes and 63 edges.



**Fig. 1. Flow chart of screening special components of Panax notoginseng.**



**Fig. 2. (a) Drug target and disease target intersection map; (b) PPI network topology analysis diagram.** The darker the color and the larger the dot, the larger the degree value.

## Discussion

Ulcerative colitis was first seen in “intestinal pi” in Neijing, with further records of “diarrhea, dysentery, and intestinal wind” in later generations. Its pathogenesis is based on spleen deficiency and loss of transport, marked by dampness-heat connotation and blood stasis, which runs through the whole process of the disease occurrence. Panax notoginseng can promote blood circulation to remove blood stasis and stop bleeding. It can treat “bright red blood under dysentery for a long time, intestinal rot, and ulcers”. Based on existing studies, we found that Panax notoginseng has a positive effect on ulcerative colitis, but its mechanism of action is still unclear. Network pharmacology studies the intervention and influence of drugs on diseases based on the interaction network of the herb-component-target-disease-KEGG pathway, which is a new method of studying the molecular mechanism of drugs and can comprehensively and systematically analyzing the relationship between drugs and diseases.

In this study, eight active components of Panax notoginseng were obtained by network pharmacological analysis, and the special component of Panax notoginseng “ginsenoside f2” was found. Through PPI analysis of intersection targets, it is speculated that STAT3, VEGFA, HSP90AA1, FGF2, IL2, MET, BCL2L1, and RORC are the key targets of ginsenoside f2 in the treatment of ulcerative colitis.

The STAT3 gene encodes a protein and is linked to diseases

such as autosomal dominant hyper-IgE recurrent infection syndrome 1 and infantile-onset multisystem autoimmune disease.<sup>22</sup> This gene is involved in several pathways, including IL-9 signaling and prolactin signaling.<sup>23</sup> Gene Ontology annotations suggest that the protein coded by this gene possesses DNA-binding transcription factor activity and sequence-specific DNA binding capabilities.<sup>24</sup> The VEGFA gene encodes a protein and is associated with diseases such as microvascular complications of diabetes 1 and POEMS syndrome.<sup>25</sup> This gene is also involved in pathways related to the response to elevated platelet cytosolic calcium and the VEGF pathway, according to its related pathways.<sup>26</sup> Gene Ontology annotations suggest that the protein encoded by this gene possesses the ability to both homodimerize and heterodimerize.<sup>25</sup> The HSP90AA1 gene encodes a protein and is associated with diseases such as hepatocellular carcinoma and candidiasis. This gene is involved in pathways related to the resistance of ERBB2 KD mutants to osimertinib and the loss of Nlp from mitotic centrosomes.<sup>27</sup> Gene Ontology annotations suggest that the protein encoded by this gene has RNA binding and identical protein binding capabilities.<sup>28</sup> The FGF2 gene encodes a protein and is associated with diseases such as corneal neovascularization and chronic skin ulcers. This gene is involved in pathways related to downstream signaling of activated FGF2 and apoptotic pathways in synovial fibroblasts.<sup>29</sup> Gene Ontology annotations suggest that the protein encoded by this gene has cytokine activity and heparin-binding capabilities.<sup>30</sup> The IL2 gene encodes a protein and is associated with diseases such as breast cancer and smallpox. This gene is involved in pathways related to apoptotic pathways in synovial fibroblasts and MIF-mediated glucocorticoid regulation.<sup>31</sup> Gene Ontology annotations suggest that the protein encoded by this gene has carbohydrate binding and growth factor activity capabilities.<sup>32</sup> The MET gene encodes a protein and is associated with diseases such as renal cell carcinoma, papillary, deafness, and autosomal recessive. This gene is involved in pathways related to apoptotic pathways in synovial fibroblasts and the GPCR pathway.<sup>33</sup> Gene Ontology annotations suggest that the protein encoded by this gene has transferase activity, transferring phosphorus-containing groups, and protein tyrosine kinase activity capabilities.<sup>34</sup> The BCL2L1 gene encodes a protein and is associated with diseases such as absolute glaucoma and B-cell lymphoma. This gene is involved in pathways related to the RAF/MAP kinase cascade and death receptor signaling pathway. Gene Ontology annotations suggest that the

**Table 2. Key target information table**

| Name     | Degree | Betweenness Centrality | Closeness Centrality |
|----------|--------|------------------------|----------------------|
| STAT3    | 7      | 0.714285714            | 1                    |
| VEGFA    | 4      | 0.071428571            | 0.7                  |
| HSP90AA1 | 3      | 0.023809524            | 0.636363636          |
| FGF2     | 2      | 0                      | 0.583333333          |
| IL2      | 2      | 0                      | 0.583333333          |
| MET      | 2      | 0                      | 0.583333333          |
| BCL2L1   | 1      | 0                      | 0.538461538          |
| RORC     | 1      | 0                      | 0.538461538          |



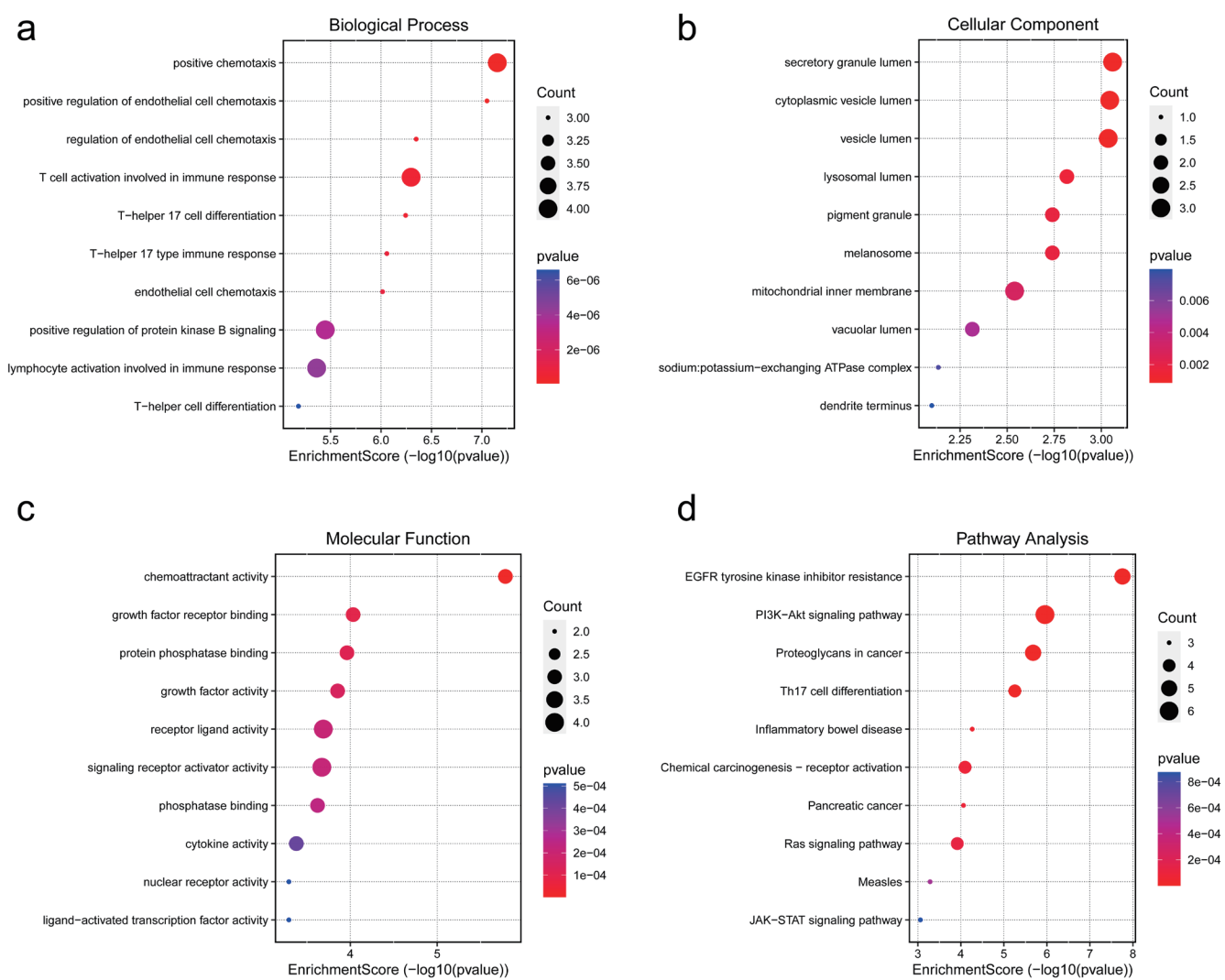


Fig. 3. (a) Bubble diagram of GO-BP enrichment analysis; (b) Bubble diagram of GO-CC enrichment-analysis bubble map; (c) Bubble diagram of GO-MF enrichment analysis; (d) Bubble map of the top ten channels with KEGG enrichment fraction.

Table 3. Data of the top ten pathways of KEGG enrichment

| ID       | Description                                   | GeneRatio | BgRatio  | P-value     | Count |
|----------|---|-----------|----------|-------------|-------|
| hsa01521 | EGFR tyrosine kinase inhibitor resistance     | 5/10      | 79/8223  | 1.74788E-08 | 5     |
| hsa04151 | PI3K-Akt signaling pathway                    | 6/10      | 354/8223 | 1.10709E-06 | 6     |
| hsa05205 | Proteoglycans in cancer                       | 5/10      | 205/8223 | 2.08813E-06 | 5     |
| hsa04659 | Th17 cell differentiation                     | 4/10      | 108/8223 | 5.56195E-06 | 4     |
| hsa05321 | Inflammatory bowel disease                    | 3/10      | 65/8223  | 5.43815E-05 | 3     |
| hsa05207 | Chemical carcinogenesis - receptor activation | 4/10      | 212/8223 | 7.98371E-05 | 4     |
| hsa05212 | Pancreatic cancer                             | 3/10      | 76/8223  | 8.69082E-05 | 3     |
| hsa04014 | Ras signaling pathway                         | 4/10      | 236/8223 | 0.000121222 | 4     |
| hsa05162 | Measles                                       | 3/10      | 139/8223 | 0.000519983 | 3     |
| hsa04630 | JAK-STAT signaling pathway                    | 3/10      | 166/8223 | 0.000873491 | 3     |

BgRatio, Background Ratio.

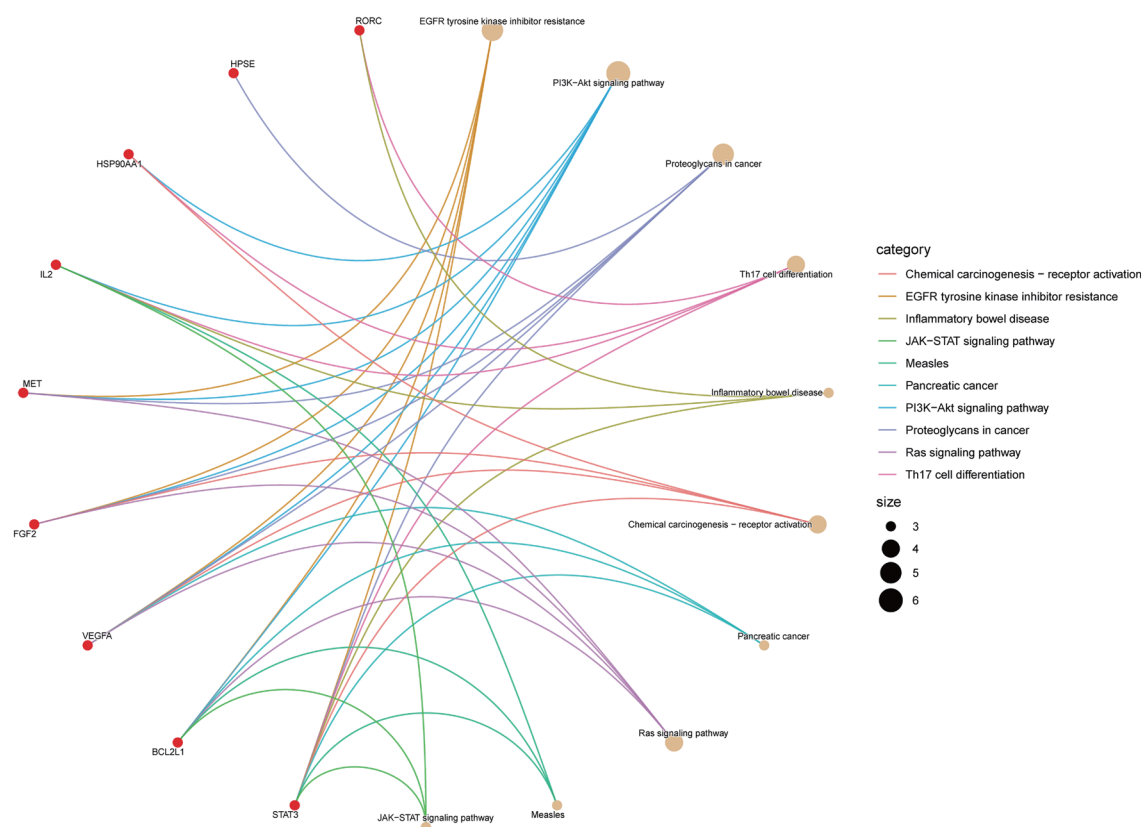


Fig. 4. Cnetplot diagram.

protein encoded by this gene has protein homodimerization activity and protein heterodimerization activity capabilities.<sup>35,36</sup> The RORC gene encodes a protein and is associated with diseases such as immunodeficiency and inflammatory bowel disease. This gene is involved in pathways related to gene expression (transcription) and cytokine production by Th17 cells in CF (Mouse model).<sup>37</sup> Gene Ontology annotations suggest that the protein encoded by this gene has DNA-binding transcription factor activity and nuclear steroid receptor activity capabilities.<sup>38</sup>

KEGG enrichment analysis mainly involved EGFR tyrosine kinase inhibitor resistance, PI3K-Akt signaling pathway, proteoglycans in cancer, Th17 cell differentiation, inflammatory bowel disease, *etc.* The KEGG pathway, which is mainly associated with ulcerative colitis, was analyzed.

The PI3K-Akt signaling pathway is a signal transduction pathway that regulates a variety of biological processes, including cell growth, proliferation, survival, metabolism, and immune response.<sup>39</sup> In immune responses, the PI3K-Akt signaling pathway is involved in immune response and immune tolerance by regulating the proliferation, survival, activation, and function of immune cells such as T cells, B cells, dendritic cells, and macrophages.<sup>40</sup> The PI3K-Akt signaling pathway also plays an important role in ulcerative colitis. Several studies have shown that the PI3K-Akt signaling pathway is involved in the regulation of intestinal epithelial cell proliferation, survival, differentiation, and inflammatory response in the pathogenesis of ulcerative colitis.<sup>41</sup> Specifically, the activation of the PI3K-Akt signaling pathway in intestinal epithelial cells can promote their proliferation and survival, as well as promote the infiltration of inflammatory cells and the production

of inflammatory factors, thus exacerbating the degree of intestinal inflammation.<sup>39</sup> In addition, the PI3K-Akt signaling pathway also plays an important role in the activation and function of intestinal immune cells.<sup>42</sup> The PI3K-Akt signaling pathway can promote the proliferation, survival, and activation of immune cells such as T cells, B cells, and macrophages, thereby enhancing intestinal immune response and inflammatory response.<sup>42</sup>

IBD, which comprises Crohn's disease (CD) and UC, is characterized by chronic inflammation of the gastrointestinal tract with various causes such as environmental and genetic factors, infectious microbes, and an imbalanced immune system.<sup>43</sup> While numerous environmental factors such as geographic locations and smoking can contribute to the development of IBD, the luminal environment of the epithelial cells is believed to be the most crucial factor.<sup>44</sup> Certain pathogens are more prevalent in individuals with IBD, and their microbial components, such as flagellin, peptidoglycan, and lipopolysaccharide, are recognized by receptors, including toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD) proteins, as well as antigen-presenting cells (APCs), in genetically susceptible hosts. TLR recognition activates NF-kappaB, which triggers an inflammatory response.<sup>43,45</sup> The APC-expressed gene NOD2 has been linked to Crohn's disease, and mutations in NOD2 result in reduced negative regulation of IL-12 production, leading to CD. Moreover, APCs are responsible for differentiating naive T cells into effector T cells (Th1, Th17, Th2) and natural killer T (NKT) cells. Th1 and Th17 cells produce high levels of IFN-gamma and IL-17, -22, respectively, both of which contribute to CD. On the other hand, Th2 cells produce IL-4, -5, and -10, which, together with IL-13 from NKT, induce UC.<sup>46,47</sup>

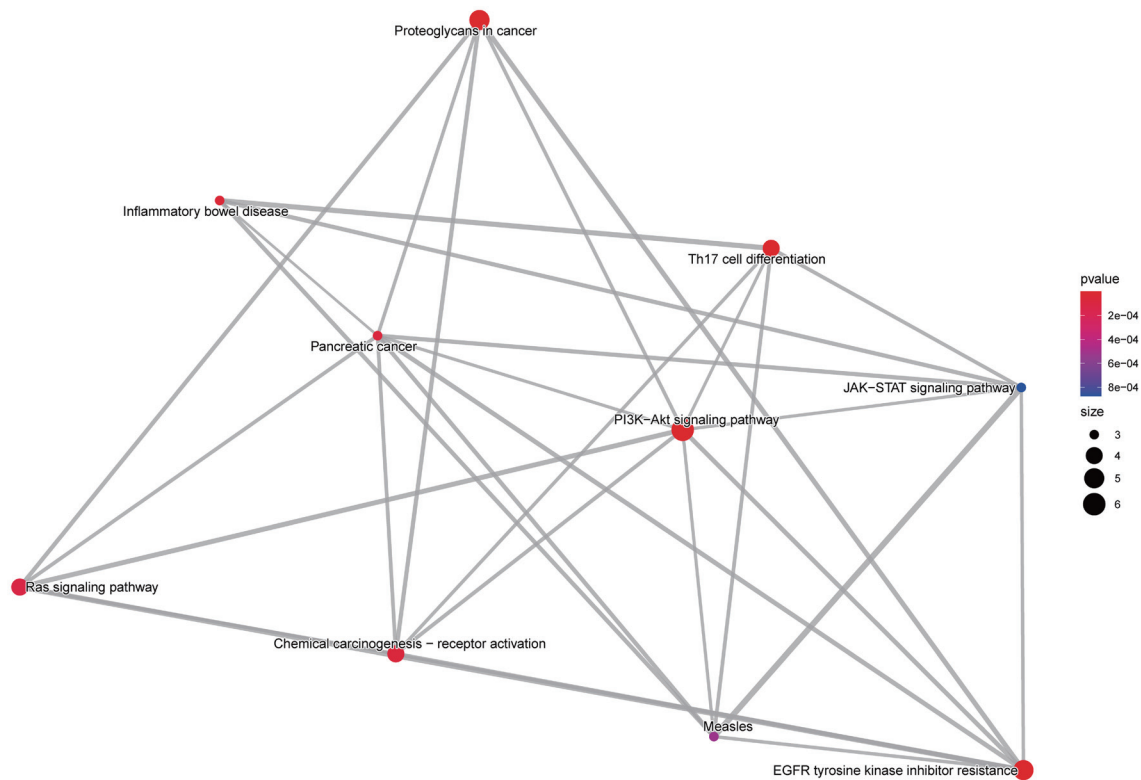


Fig. 5. Emapplot diagram.

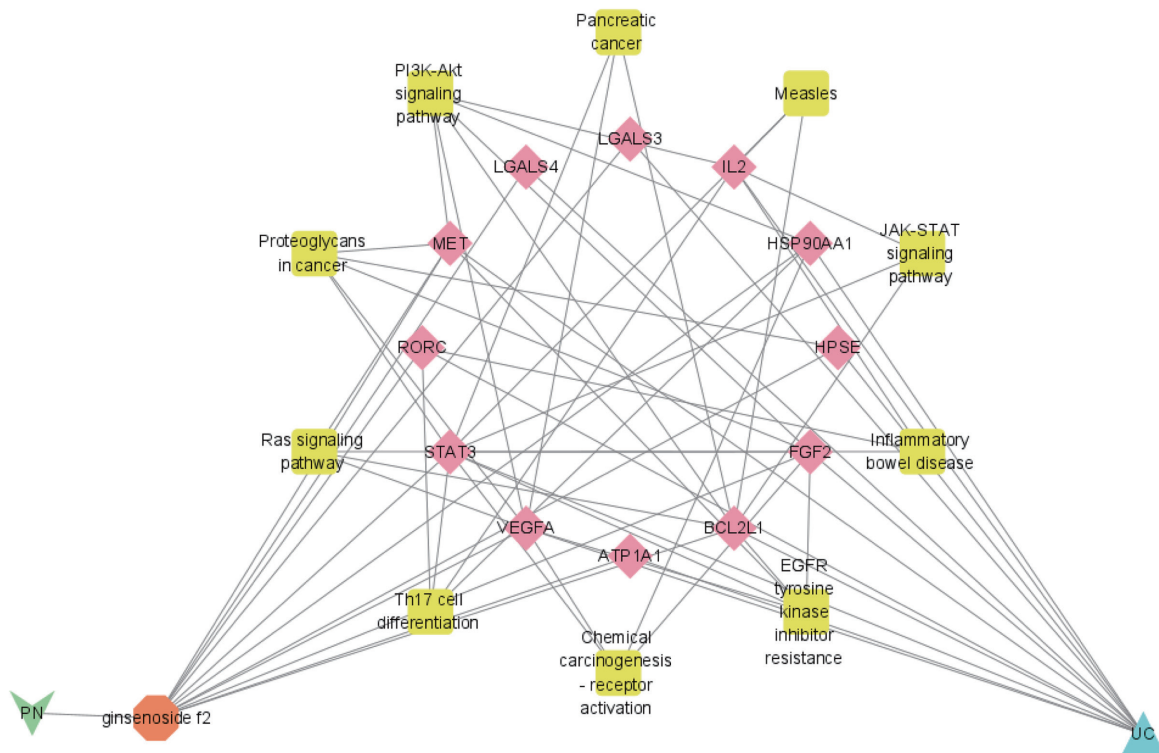


Fig. 6. Network diagram of herb-component-target-disease-KEGG pathway. Green represents traditional Chinese medicine; orange represents a particular active ingredient; pink represents the target; yellow represents the pathway; blue represents disease.

## Conclusion

This study used network pharmacological methods to predict the special active ingredients, key targets, and action pathways of *Panax notoginseng* in the treatment of ulcerative colitis. It was found that the therapeutic mechanism of ginsenoside f2 for ulcerative colitis had multi-target and multi-pathway interactions. Studies have shown that the active component of ginsenoside f2 acts on key targets such as STAT3, VEGFA, HSP90AA1, FGF2, IL2, and MET. The GO enrichment analysis results involved 417 statistically significant pathways, among which 365 BP entries were statistically significant. It mainly involves positive chemotaxis, positive regulation of endothelial cell chemotaxis, regulation of endothelial cell chemotaxis, and T cell activation involved in immune response; there were 8 CC items with statistical significance, which mainly involved secretory granule lumen, cytoplasmic vesicle lumen, vesicle lumen, and lysosomal lumen. There were 44 MF entries with statistical significance mainly involving chemoattractant activity, growth factor receptor binding, protein phosphatase binding, growth factor activity, *etc.* KEGG enrichment analysis mainly involved EGFR tyrosine kinase inhibitor resistance, PI3K-Akt signaling pathway, proteoglycans in cancer, Th17 cell differentiation, inflammatory bowel disease, *etc.* The study provides a theoretical basis for further experimental research.

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## Conflict of interest

The author has no conflict of interest related to this publication.

## Data sharing statement

The data used in support of the findings of this study are available from the corresponding author at weichens14@outlook.com or weichens14@163.com upon request.

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