# Mechanism of Peony and Licorice and Aconite Decoction in the Treatment of Osteoarthritis Based on Network Pharmacology and Molecular Docking

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**Research Article**

**Keywords:** osteoarthritis, Network pharmacology, Targets, Molecular docking, Radix paeoniae alba.Licorice, Lateral root, Signaling pathways

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**Mechanism of Peony and Licorice and Aconite Decoction in the treatment of osteoarthritis based on network pharmacology and molecular docking**

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**Abstract: Objective:** To predict the key molecular mechanism of Shaoyao Liquorice Aconite Decoction in the treatment of osteoarthritis by using network pharmacology and molecular docking technology, and to provide a new target for the treatment of osteoarthritis. Methods: by means of traditional Chinese medicine database TCMSP screening peony licorice monkshood soup main active component of radix paeoniae alba, radix glycyrrhizae, and the corresponding targets, lateral root of aconite and retrieve OMIM, GeneCards, TDD, PharmGKB and Drugbank database related target for treatment of osteoarthritis, and then forecast drug targets and disease targets for intersection get peony licorice monkshood soup targets for the treatment of osteoarthritis**.**Then, STRING database and Cytoscape software were used to construct the "drug active component - action target" network and protein interaction network of Shaoyaogaofuzi Decoction in the treatment of osteoarthritis, and David database was used for GO function enrichment analysis and KEGG pathway enrichment analysis of shaoyaogaofuzi Decoction in the treatment of osteoarthritis.Finally, PyMOL, Chem3D, AutoDock, OpenBabel and other software were used to verify the molecular docking of the key active ingredients and key targets of Shaoyao Liquorice Aconite Decoction. Results: 162 active components were screened out.A total of 954 disease targets were collected, and a total of 72 disease targets were obtained after weight removal.Protein interaction analysis suggested that TNF, AKT1, IL6, IL1B

and TP53 were the core targets of protein interaction network.Through GO enrichment analysis, 393 biological processes were obtained, and it was found that biological processes were mainly enriched in cell differentiation, migration, apoptosis, and cell stress response to organisms.A total of 116 Pathways were obtained through KEGG pathway enrichment analysis, mainly involving Pathways in cancer, TNF Signaling Pathway, Tuberculosis, Chagas disease, Hepatitis B, etc. Finally, the molecular docking of key active molecules and key targets was realized for verification.Conclusions: this study of compound Chinese medicine pharmacology, through the network of peony licorice monkshood soup ingredients with osteoarthritis, targets, pathway analysis, you can see that drugs in the treatment of osteoarthritis is not a simple single targeted therapy, but by many components, multi-channel, mutual communications between the multiple targets, on the treatment of osteoarthritis in the future to provide more advice.

**Key words:** osteoarthritis;Network pharmacology;Targets;Molecular docking;Radix paeoniae alba.Licorice;Lateral root.Signaling pathways

**Introduction:**

Osteoarthritis is defined as a group of overlapping different joint diseases that have been centered on changes in articular cartilage.This concept has evolved to the point where osteoarthritis is thought of as a disease of the whole joint, including changes in articular cartilage, subchondral bone, ligaments, capsules and synovium that eventually lead to joint failure[1].In addition to affecting people's physical health, it may also have a negative impact on people's mental health, and the quality of life of

patients is greatly reduced.[2]In recent years, many treatments for osteoarthritis have emerged, but they have many limitations. For example, stem cell therapy and platelet rich plasma (PRP) injection are suitable for short-term treatment of pain.Joint replacement will not survive forever, it will fail after a while;Long-term use of Nonsteroidal Antiinflammatory Drugs(NSAIDs) is associated with gastrointestinal and cardiovascular side effects[3].Therefore, drugs that can reverse, delay, or stabilize the underlying pathological changes in osteoarthritis have yet to be developed.

Traditional Chinese Medicine(TCM) has potential benefits for patients with osteoarthritis.These benefits include pain relief, improved function, and the presence of fewer adverse events.The limitations of method quality mainly include the lack of prior protocol or protocol registration and incomplete literature search[4]。 Peony liquorice aconite soup is a classic Chinese medicine pair for the treatment of osteoarthritis. "Treatise on Febrile Diseases": "Sweating, disease puzzled, anti-cold, deficiency also.Peony liquorice aconite soup of the Lord."The formula has the effects of tonifying liver and kidney, warming the meridian and clearing the pulse, helping Yang and benefiting Yin. The clinical effect is definite, but the mechanism of action is still unclear.

Network pharmacology is a new subject which analyzes the network of biological system and selects specific signal nodes to design multi-target drug molecules based on the theory of systems biology [5].Based on the ideas and methods of network pharmacology, this study aims to obtain the main active ingredients of Shaoyao Liquorice Aconite Decoction, screen out the core targets and main biological

pathways, and explore the molecular targets and potential mechanism of action in the treatment of osteoarthritis.

## Materials and Methods

### Database and Software

TCM Pharmacology database and analysis platform TCMSP (https://tcmsp-e.com/); OMIM Database (https://omim.org/);GeneCard database (https://www.genecards.org/); Providing database (http://db.idrblab.net/ttd/);PharmGKB database (https://www.pharmgkb.org/); DrugBank Database (https://go.drugbank.com/);Jvenn website (http://jvenn.toulouse.inra.fr/app/example.html);Venn online mapping web site (https://bioinfogp.cnb.csic.es/tools/venny/) micro letter online mapping web site (http://www.bioinformatics.com.cn/);String database (https://www.string-db.org/); DAVID database (https://david.ncifcrf.gov/);UniProt database (https://sparql.uniprot.org/);PDB database (https://www.rcsb.org/);Pubchem database (https://pubchem.ncbi.nlm.nih.gov/);Cytoscape 3.8.2 software;Pymol 2.4.0 software;AutoDockTools - 1.5.6 software;OpenBabelGUI 2.4.1;Chem3D15. 1 software;

### Screening of active ingredients and prediction of targets

Pharmacological database and analysis platform in this paper, through the use of Traditional Chinese Medicine System (TCMSP) (https://tcmsp-e.com/) query peony licorice monkshood soup of the three traditional Chinese medicine chemical composition: radix paeoniae alba, radix glycyrrhizae and monkshood, setting of oral bioavailability (OB 30% or higher) of similarity (DL 0.18 or higher) and drug

screening standard [6] the key active ingredients of TCM, peony licorice monkshood soup a collection of active ingredients.[6]Using TCMSP database for each active ingredient in the corresponding target protein, and through the UniProt database (https://sparql.uniprot.org/) to select the species of "Homo Sapiens", limited search results for "Reviewed", get all authenticated gene targets for human being and the related information, import the Excel table.VLOOKUP, Trim and other functions in Excel were used to obtain the target gene names corresponding to the target proteins of each active ingredient of drugs, establish the collection of target gene names obtained, delete the duplicate genes, and the result is the target of peony Liquorice Aconite decoction.

**Prediction of therapeutic targets for osteoarthritis**

"Osteoarthritis" as keywords in OMIM database (https://omim.org/), GeneCard database (https://www.genecards.org/),Providing database (http://db.idrblab.net/ttd/) PharmGKB database (https://www.pharmgkb.org/) and DrugBank database (https://go.drugbank.com/) to retrieve related targets,And use the Jvenn website (http://jvenn.toulouse.inra.fr/app/example.html) integrated five database disease targets set for osteoarthritis with the related targets.

**Prediction of potential action targets**

The peony licorice targets and osteoarthritis of the active ingredients in the soup of lateral related target posted Venn online mapping web site (https://bioinfogp.cnb.csic.es/tools/venny/) mapping intersection, obtain peony

licorice monkshood soup potential targets for treatment of osteoarthritis, painted peony licorice monkshood soup and osteoarthritis intersection targets Wayne figure.

**Construction of drug-active component-disease target interaction network and protein-protein interaction network of potential target**

The drug, the obtained drug active ingredient and the potential target for the treatment of osteoarthritis were imported into Cytoscape 3.8.2 software, and the color and shape of the node were set according to the node properties to construct the network of drug - active ingredient - potential target for the treatment of osteoarthritis.The obtained potential targets were imported into String database (https://www.string-db.org/), and the species were limited to human. Protein interactions were analyzed and the string-Interactions. TSV file was obtained, which was imported into Cytoscape 3.8.2 software.

**GO, KEGG enrichment analysis and KEGG relationship network construction**

By DAVID database (https://david.ncifcrf.gov/) about potential targets to GO enrichment and KEGG pathway enrichment analysis function, respectively, the peony licorice aconite decoction treatment of osteoarthritis of biological functions and the main signaling pathways, limited species for "Homo Sapiens", screening, $P < 0.05$ items, including $P < 0.05$ representative enrichment results significantly,And through microscopic letter online mapping web site (http://www.bioinformatics.com.cn/) to make the GO enrichment analysis diagram and KEGG enrichment analysis bubble chart, and establish the pathway, gene interactions and node properties, gene interaction relations, and import the Cytoscape 3.8.2 software, according to the

number of genes KEGG enrichment before selecting 20 KEGG signaling pathways, remove the tumor, relationship between osteoarthritis, influenza, the parasites in smaller access, access is a potential target network diagram.

**Molecular docking**

To verify the interaction between the predicted key active ingredients and key targets, molecular docking was performed.From the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) to download the core protein gene receptor 2 d structure, according to the core protein gene Uniprot ids from PDB database (https://www.rcsb.org/) for 2 d structure of the core protein ligand.Chem3d15.1 software was used to transform 2D ligand and receptor structures into 3D structures, and Pymol2.4.0 software was used to remove water and residues from proteins.OpenBabelGUI 2.4.1 software was used for file format conversion of compounds and core proteins, AutoDockTools-1.5.6 software was used for docking, and Pymol 2.4.0 software was used for visual operation of docking results.

**Results**

**Active ingredients and corresponding target proteins of Shaoyao Liquorice Aconite Decoction**

A total of 199 chemical components of Paeonia lactiflora, glycyrrhiza and Aconite were collected by TCMSP database, including 14, 164 and 21 components of paeonia lactiflora, glycyrrhiza and aconite, respectively.According to the set of OB acuity 30% DL acuity 0.18 with the standard of screening, screening active rest after delete duplicate values 102 active chemical composition, chemical composition of radix

paeoniae alba, radix glycyrrhizae and aconitic active ingredients of 8, 88 and six respectively, the root of herbaceous peony and licorice has two intersection compound, radix paeoniae alba, radix glycyrrhizae and have an intersection of lateral root compound.Due to too many screening results, only the active ingredients that act together and the top 5 oral bioavailability (OB) values of each drug are listed. The basic information of active ingredients is shown in Table 1.The corresponding protein targets of 102 screened active components were searched through TCMSP database, and 162 corresponding targets of the active components of Shaoyao Liquorice Aconite Decoction were obtained after the repeated items were deleted.

**Prediction of disease targets and determination of drug-disease common targets**

Osteoarthritis targets were collected by searching OMIM database, GeneCard database, TTD database, PharmGKB database and DrugBank database, and 954 targets were collected as disease targets, as shown in Figure 1A.Uniprot database and Excel tables were used to convert protein targets into gene targets.The intersection of drug and disease was taken as the common target of 72, namely the potential target of Shaoyao Liquorice Aconite Decoction in the treatment of osteoarthritis, as shown in Figure 1B.

**Construction of single drug-component target-disease target network**

According to the prediction results of potential targets obtained from the above analysis, Cytoscape software was used to construct a network of "Single drug - active

ingredient target - disease target of Shaoyao Liquorice Aconite Decoction", as shown in Figure 2.

**Protein interaction network construction**

Potential targets will be gained by the import String database, select Multiple protein, a qualified species, and keep the default Settings, the related parameters are preliminary protein interaction diagram, export string_interactions_short. TSV file, the file import cytoscape 3.8.2 software, and according to the degree value and target attribute set the node size and color, construction of protein interaction network diagram, as shown in figure 3.

**GO and KEGG enrichment analysis results and pathway-target network construction**

The potential target genes of Shaoyao Glycyrrhiza Fuzi Decoction in the treatment of osteoarthritis were imported into DAVID data platform (restricted species for human) for KEGG pathway enrichment analysis and GO biofunctional enrichment analysis.A total of 240 GO items ($P < 0.05$) were obtained, including 150 biological processes (BP), 38 cell components (CC) and 52 molecular functions (MF). Visualization was performed based on the top 20 items with the lowest P value, as shown in Figure 4.116 were enriched by KEGG, and 87 were screened according to $P<0.05$. Bubble charts were drawn according to the top 20 with the lowest P value, as shown in Figure

4.The first 15 signaling pathways were selected and Cytoscape 3.8.2 software was used to draw a network diagram of signaling pathways and potential targets, as shown in Figure 5.

**Molecular Docking**

Some core targets (TNF, AKT1, IL1B, IL6 and TP53) were screened from 3.5 for molecular docking with some core components (Quercetin, Kaempferol and Paeoniflorin).It is generally believed that the docking affinity is strong when the binding energy is less than -5.0 kcal/mol, and the docking activity is very strong when the binding energy is less than -7.0 kcal/mol[7].It is generally believed that the more stable the ligand binds to the receptor, the lower the binding energy and the greater the possibility of action. With the binding energy ≤ -5.0 kJ/mol as the standard, the molecular docking verification of the predicted key active ingredients and key targets was carried out.The molecular docking results showed that the docking affinity between the key active ingredients and the key target of multiple Peony and licorice Aconite Decoction was far less than -5.0 kJ/mol, which indicated that the predicted key target of Peony and Licorice Aconite Decoction was reliable.Quercetin and IL1B with the lowest affinity were selected for molecular docking display, as shown in Figure 6.

**Discussion**

Network pharmacology is a reasonable method to analyze the potential biological mechanism of TCM in treating and preventing various diseases, especially chronic and chronic diseases, such as osteoarthritis[8].As shown in Figure 2 and Figure

5, Shaoyao Liquorice Aconite Decoction treats osteoarthritis through multiple components, multiple targets and multiple approaches, which also indicates that TCM plays a synergistic role in disease treatment.The results showed that there were 162 active components in Paeoniflorin and Quercetin, Kaempferol and Paeoniflorin in paeonioniflorin, which might be the key components in the treatment of osteoarthritis.Quercetin inhibits IL-1β -induced inflammation and cartilage degradation by inhibiting the IRAK1/NLRP3 signaling pathway[9].Kaempferol inhibits inflammation and extracellular matrix degradation by regulating the XIST/ Mir-130A /STAT3 axis in chondrocytes[10].However, there is no basic study on paeoniflorin and osteoarthritis, which is worthy of further exploration.

In the PPI network analysis of shaoyaogaofuzi Decoction in the treatment of osteoarthritis, there were 72 target proteins, among which MAPK,TNF,AKT1, IL1B, IL6 and TP53 were the main targets of Shaoyaogaofuzi Decoction in the treatment of osteoarthritis.MAPK is a member of the serine-threonine protein kinases family and a transduction center for cell multidirectional changes involved in the development of OA[11]。TNF, IL1B and IL6 are important inflammatory cytokines.Interleukin (IL) and tumor necrosis factor (TNF)-α in particular control the degeneration of articular cartilage, making it a prime target for therapeutic strategies for osteoarthritis (OA)[12].Il-6, IL1B and their family members constitute a very broad field of research, opening up many possibilities for the treatment of various acute and chronic human inflammation[13].AKT signaling pathway regulates cell proliferation and growth, and participates in cellular processes including apoptosis and glucose metabolism. Studies

have confirmed that AKT1 and AKT/mTOR signaling pathway can enhance chondrocyte apoptosis and senescence and promote OA development[14].TP53 is a tumor suppressor that regulates cell death.Studies have shown that TP53 inactivation by removal of ADAMTS-5 can prevent cartilage destruction at the onset of OA[15].

According to the GO enrichment analysis, the treatment of osteoarthritis by Shaoyao Liquorice Fuzi Decoction mainly involves biological processes such as cell proliferation, cell apoptosis and inflammatory reaction.KEGG pathway enrichment analysis showed that potential targets of Shaoyaogaofuzi Decoction for OA mainly involved TNF signaling pathway, osteoclast differentiation, sphingolipid signaling pathway, Toll-like receptor signaling pathway and Neurotrophin signaling pathway.TNF signaling pathway, especially TNF- α, is known to play an important role in the pathological progression of OA.TNF- α binds to two membrane receptors: TNF-R1 and TNF-R2.Tnf-r1 can be activated in its soluble and membrane form, while TNF-R2 is mainly bound in its membrane form[16].TNF signaling pathway is an inflammatory mediator with a variety of biological effects.TNF- α induces il-6 production and activates proteases that break down cartilage and synovium[17].Osteoclasts are mature multinucleated osteoclasts differentiated and formed under the stimulation of various cytokines. They are the main participants in bone resorption and are closely related to physiological processes such as hematopoietic function regulation, bone formation, intraosseous angiogenesis and osteocalcin regulation[18].Abnormal activation of osteoclasts will affect bone absorption and cause degenerative changes in bone and joints, such as osteoporosis,

cancer bone metastasis, arthritis, etc[19].Osteoclast is one of the main causes of RA occurrence and development.Toll-like receptor (TLR) is a transmembrane signal transduction receptor.TLR was expressed in articular cartilage and upregulated in OA cartilage.TLR expression and signal transduction are related to the pathogenesis of OA[20].Activation of toll-like receptor signaling pathway can release inflammatory factors such as IL and TNF, activate NF- κB in its downstream signaling pathway, and induce articular chondrocyte apoptosis[21].Sphingolipids represent one of the main classes of eukaryotic lipids. The main bioactive sphingolipids are ceramide, sphingolipids and S1P[22].The sphingolipid signaling pathway is a process in which ceramide (Cer) and sphingolipin-1-phosphosphingolipin (S1P), hydrolyzed products of sphingolipin, act in a variety of signaling pathways.Sphingolipids play important structural roles, especially in cell membranes, and they also have signaling properties that regulate a variety of cellular functions, such as apoptosis, cell proliferation, differentiation, and inflammation[23].Neurotrophic factors are a family of nutritional factors involved in the differentiation and survival of nerve cells[24].Neurotrophin acts through two neuron membrane receptors: Trk tyrosine kinase receptor and P75 neurotrophin receptor (p75NTR)[25]**.**Trk signaling is regulated by a cascade of intracellular signals, and ultimately transmits signals that have positive effects on promoting nerve survival and growth.P75NTR transmits signals with both positive and negative effects, and the active Trk/p75NTR ratio is important in neural development, survival, and apoptosis[26].

The molecular docking results showed that the active ingredients of Shaoyao Liquorice Aconite Decoction matched well with the hub gene.This indicates that the molecular docking results are consistent with the screening results of network pharmacology, and the reliability of network pharmacology is verified by molecular docking.

In conclusion, the main active ingredients and efficacy of Shaoyao Liquorice Aconite Decoction were similar to the results of network pharmacology analysis.It provides a new direction for the treatment of osteoarthritis.This study only searched through the database.It was not validated in cell and animal experiments.Therefore, further experimental verification and clinical studies are needed in the next step.

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**Table 1: Compound information of Shaoyao Liquorice Aconite Decoction**

| source | MOL ID | Molecule name | OB (30% or higher) | DL (0.18 or higher) |
|---|---|---|---|---|
| peony | MOL001918 | paeoniflorgenone | 87.59 | 0.37 |
| | MOL001925 | paeoniflorin_qt | 68.18 | 0.40 |
| | MOL001928 | albiflorin_qt | 66.64 | 0.33 |
| | MOL001910 | 11alpha,12alpha-epoxy-3beta-23-dihydroxy 20-30 - norolean - 28, 12 - en - beta - olide | 64.77 | 0.38 |
| | MOL000211 | Mairin | 55.38 | 0.78 |
| Lateral root | MOL002421 | ignavine | 84.08 | 0.25 |

| | | | | |
|---|---|---|---|---|
| | MOL002419 | (R)-Norcoclaurine | 82.54 | 0.21 |
| | MOL002398 | Karanjin | 69.56 | 0.34 |
| | MOL002388 | Delphin_qt | 57.76 | 0.28 |
| | MOL002395 | Deoxyandrographolide | 56.30 | 0.31 |
| licori | | | | |
| | MOL002311 | Glycyrol | 90.78 | 0.67 |
| ce | | | | |
| | MOL004990 | 7, 2 ', 4 '- trihydroxy - 5 - methoxy - 3 - arylcoumarin | 83.71 | 0.27 |
| | MOL004904 | licopyranocoumarin | 80.36 | 0.65 |
| | MOL004891 | shinpterocarpin | 80.30 | 0.73 |
| | MOL005017 | Phaseol | 78.77 | 0.58 |

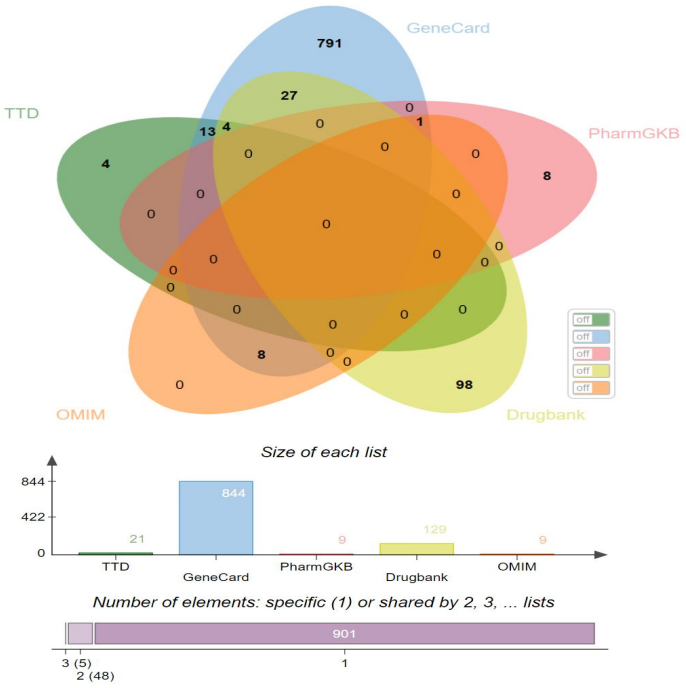


Figure 1A: Venn diagram of disease targets

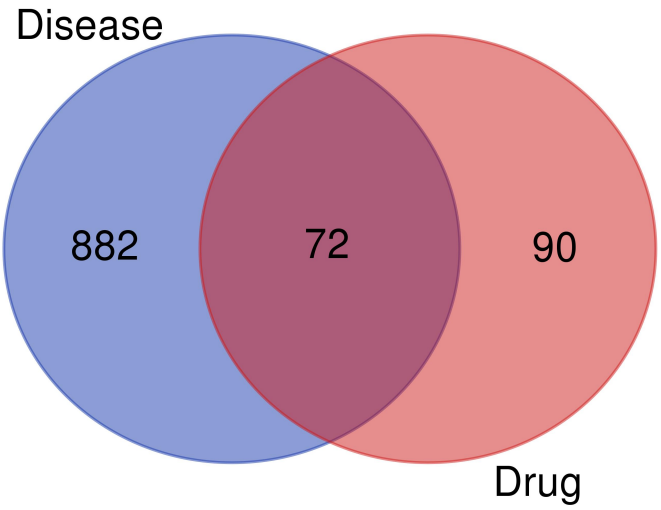


Figure 1B: Venn diagram of common targets of drug disease

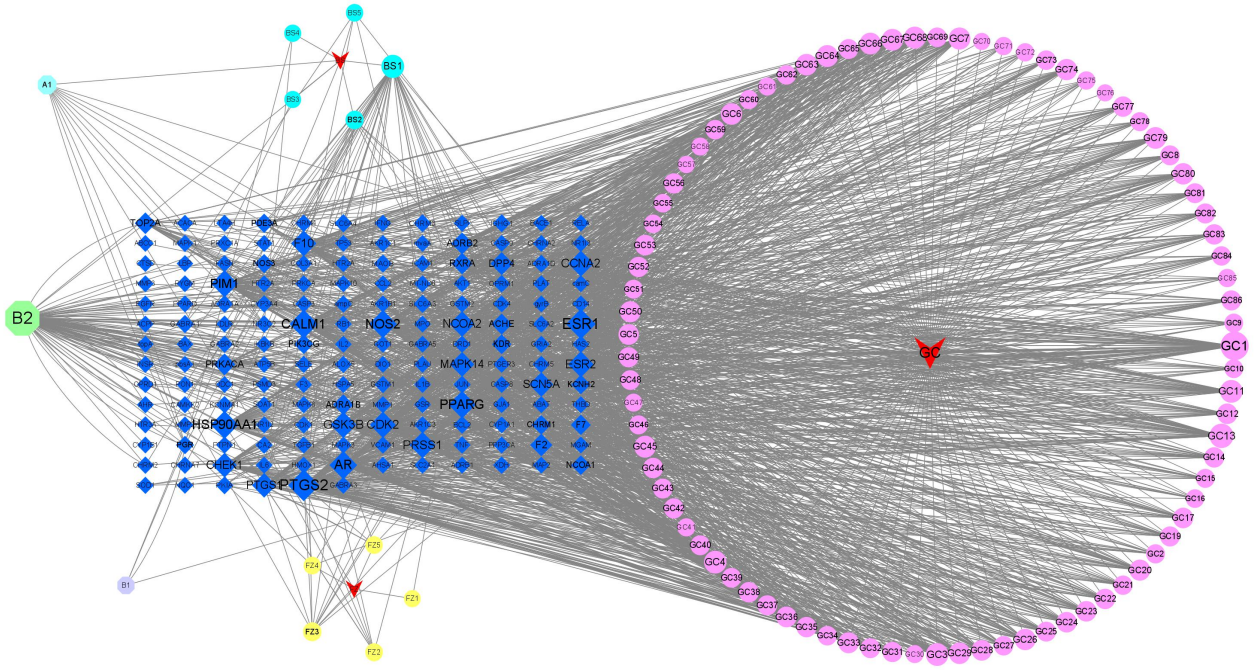


FIG. 2 Single drug - active component target - disease target network diagram of Shaoyao Glycyrrhiza Fuzi Decoction

Note: Red is the medicine, GC (licorice), FZ (Aconite) and BS (paeonia lactiflora);Pink, yellow and light blue were the active components of glycyrrhiza alba, Aconite fructus and Radix paeoniae alba, respectively. A1 was the common component of the three, B2 and B1 were the common components of radix paeoniae alba and radix paeoniae alba.Disease targets are shown in blue.

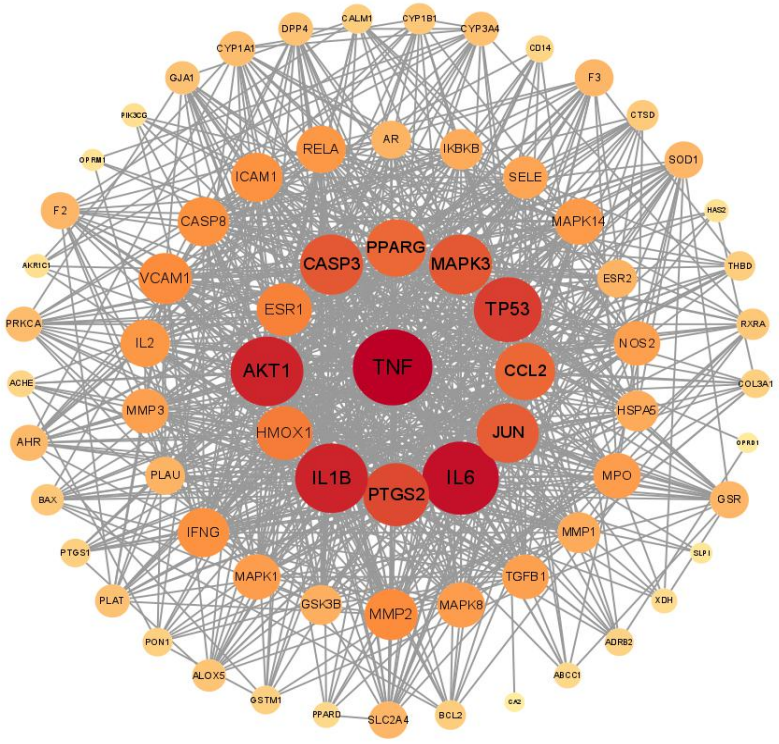


**Fig.3 The network diagram of OA target protein interaction in group Shaoyao-GanCao-Fuzi was shown**

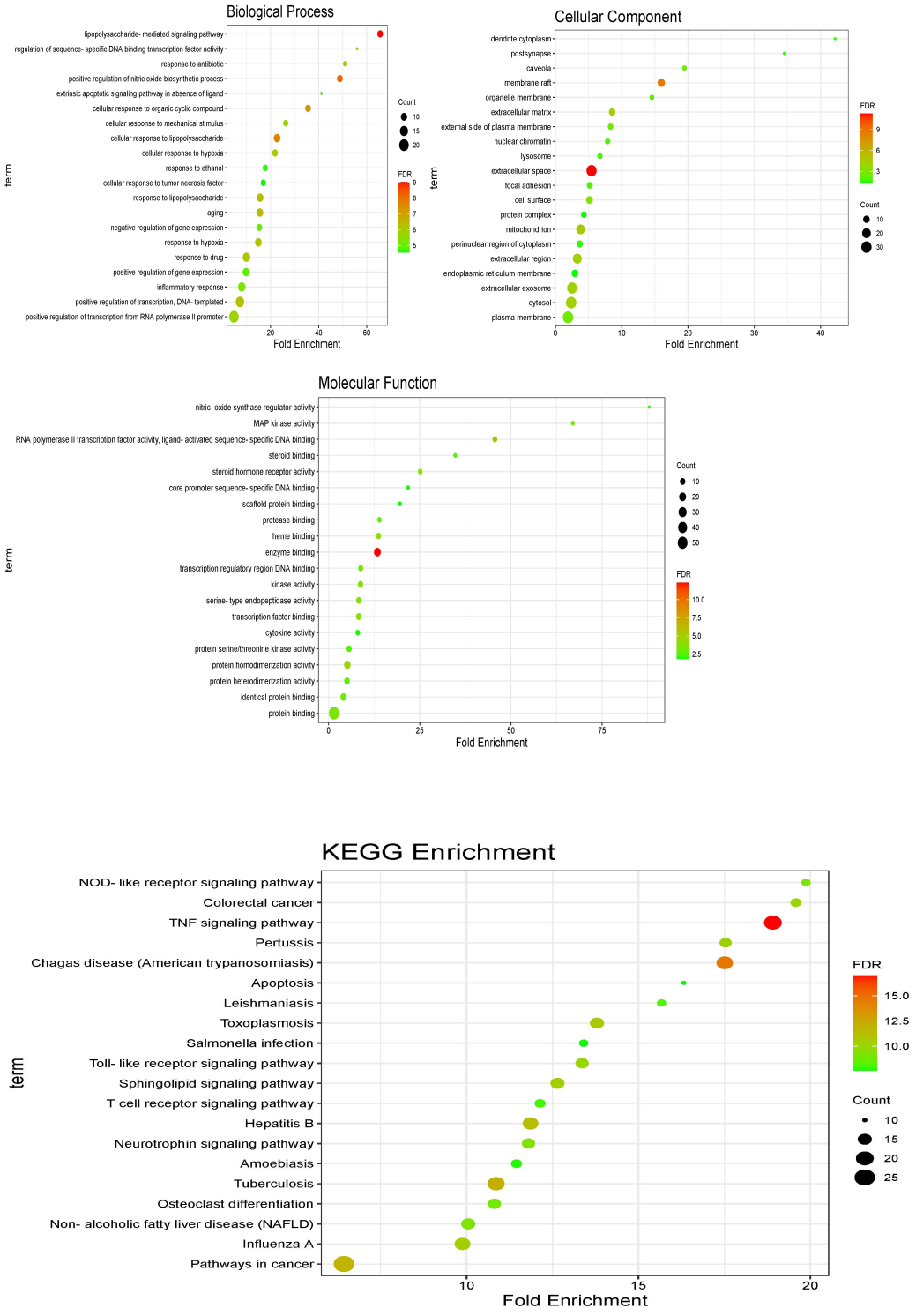


**Figure 4 Enrichment analysis of GO and KEGG**

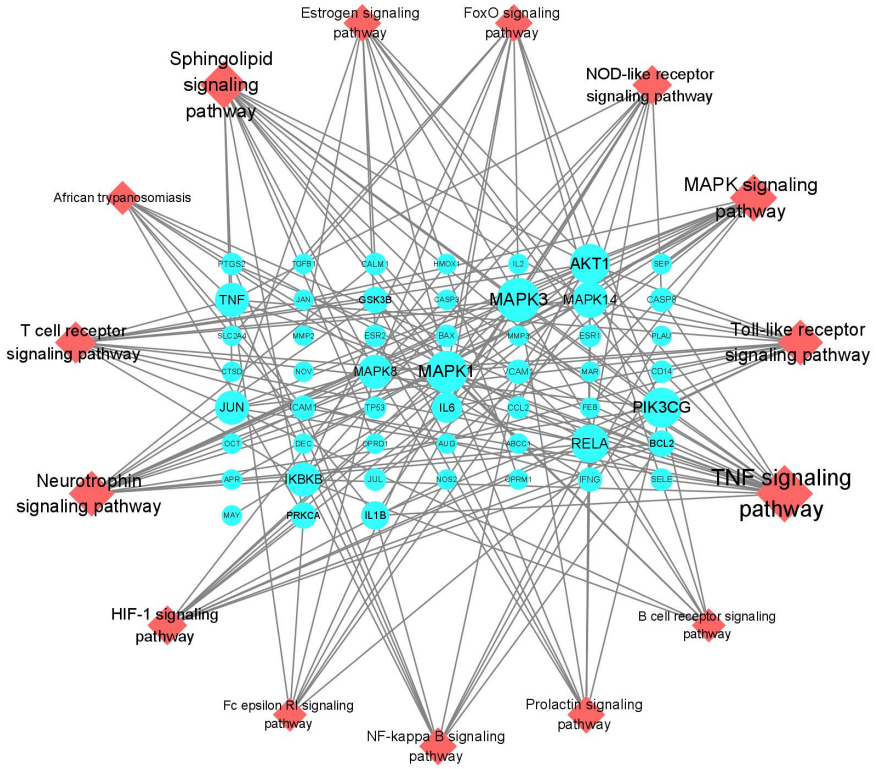


**FIG. 5 Signal pathways-potential target network diagram**

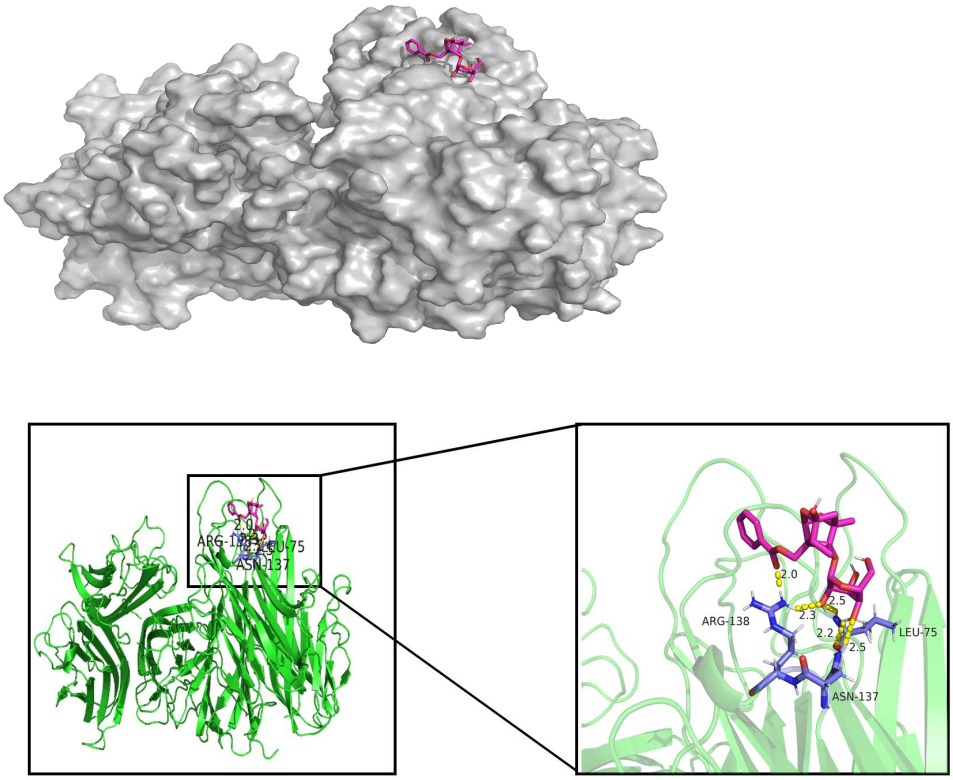


**FIG. 6 Quercetin and IL1B molecule docking**