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Probe into Mechanism of Treatment of Ulcerative Colitis by Using Network Pharmacology and Molecular Docking Techniques

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Abstract: The main compounds and targets of herbal medicine of Chun genpi and Di jincao in the treatment of ulcerative colitis were studied by network pharmacology and molecular docking techniques, and the mechanism of its therapeutic effect was analyzed. Drug active components and drug targets were screened by TCMSP database, UC disease genes were searched by Genecards and OMIM databases, and the relationship network of "compound-drug target-disease gene" was constructed. The DAVID database could analyze the GO of the candidate targets and the R language package could analyze the biological pathway enrichment of the candidate targets. Molecular docking was carried out by Autodock software, and the binding sites and binding energy were obtained. There are 16 active compounds corresponding to 314 targets in the drug pair. 102 genes of UC disease are affected. 570 GO items were screened by GO functional analysis of intersection targets, including 444 items in biological process, 43 items in cell composition and 83 items in molecular function. 163 pathways were screened by KEGG. The results of molecular docking show that the key targets have good binding activity with the corresponding compounds. The drug pair has the characteristics of multi-component, multi-target and multi-pathway in the treatment of UC. It provides a theoretical basis for the further study of the drug pair in the treatment of UC.

Ulcerative colitis(UC)is a normol disease[1-2].The clinical manifestations were abdominal pain,mucus, purulent and bloody stool[3-4].

Dijincao was first published in Jiayuan Materia Medica: "it tastes pungent and is non-toxic."[5]Dijincao,special heat-clearing and detoxification, cooling blood to stop bleeding, dampness and yellowing, often used in the treatment of bacillary dysentery, hematochezia and other diseases[6]. The root bark of Toona sinensis was originally contained in "newly repaired Materia Medica"[7]. Modern studies have shown that[8],It can be seen that Toona sinensis root bark is important in the treatment of UC.

Network pharmacology explains the disease mechanism and drug action mechanism from the overall point of view of biological network[9]. In this way, the methods can explore the material basis and mechanism of Toona sinensis root bark-Dijin herbs to treatment UC.

1. Data and Methods

1.1. Screening of Active Components of Toona Sinensis Root Bark-Dijin Herbs

The active components of Toona sinensis root bark and Herba Euphorbiae pairs were obtained by searching the TCMSP database, and screened according to the conditions of oral bioavailability (OB) ≥ 30% and drug-likeness(DL) ≥ 0.18.

1.2. Component Target Acquisition

The action targets are mined by TCMSP database, and the standard names by Uniprot database.

1.3. Acquisition of Targets for Ulcerative Colitis

Search and filter the relevant targets of UC in OMIM database and GeneCards database.

1.4. Construction of Protein-Protein Interaction (PPI) Network

The key target was obtained by intersecting the active component and Herba Euphorbiae pair with the UC target. The proteins interaction was predicted by STRING database.

1.5. Construction of Drug-Component-Target-Disease Network Map

The drug-ingredient-target-disease network used Cytoscape 3.7.2 software.

1.6. Analysis of GO and KEGG Enrichment

DAVID database and R language package are used to analyze biological processes and pathways by using GO and KEGG pathway database of intersection targets.

1.7. Molecular Docking Verification

The core components screened by the network diagram in 2.1.5 were docked with the target. The 3D structure of core protein in PDB format was obtained from RSCB PDB database. Get the mol2 file for the core components from the TCMSP database. The target proteins and small molecular ligands were pretreated by AutoDockTools 1.5.6 software. The docking and binding energy were calculated by AutoDock software, and then the binding activity was analyzed. Pymol 2.4.0 software was used for visualization.

2. Results

2.1. Screening of Chemical Constituents

Ten active components of Toona sinensis root bark and 6 active components of Herba Euphorbiae were screened from TCMSP database, and there were 2 common active components between them (Table 1).

Table 1. Active ingredients of Toona sinensis root bark-Dijin herbal medicine

herbal Name	MOL ID	Chemical compound	OB (%)	DL
Di Jincao	MOL006331	4-dihydroxyflavonoids	48.55	0.19
Di Jincao	MOL006326	Enshakulin	45.76	0.86
Di Jincao	MOL001002	Ellagic acid	43.06	0.43
Di Jincao	MOL000359	Sitosterol	36.91	0.75
Chun Genpi	MOL006279	Neo-Junolactone B	98.4	0.47
Chun Genpi	MOL006303	4,5-Dihydrogen-6-Anthracenone	48.58	0.28
Chun Genpi	MOL000449	Stigma sterol	43.83	0.76
Chun Genpi	MOL006277	New ginger lactone	43.56	0.74
Chun Genpi	MOL006311	Atrin	41.23	0.22
Chun Genpi	MOL000358	β-sitosterol	36.91	0.75
Chun Genpi	MOL001755	2,4-Ethyl cholest-4-Alkene-3- Ketone	36.08	0.76
Chun Genpi	MOL006304	4-hydroxy-6-gliadin ketone	35.11	0.25
Di Jincao, Chun Genpi	MOL000098	Quercetin	46.43	0.28
Di Jincao, Chun Genpi	MOL000422	Kaempferol	41.88	0.24

2.2. Active Components Acting on Targets

After screening,163 targets of Toona sinensis root bark and 151 targets of Radix Rehmanniae were obtained.

2.3. UC Related Targets

The UC-related targets have 2409.

2.4. PPI Network Construction

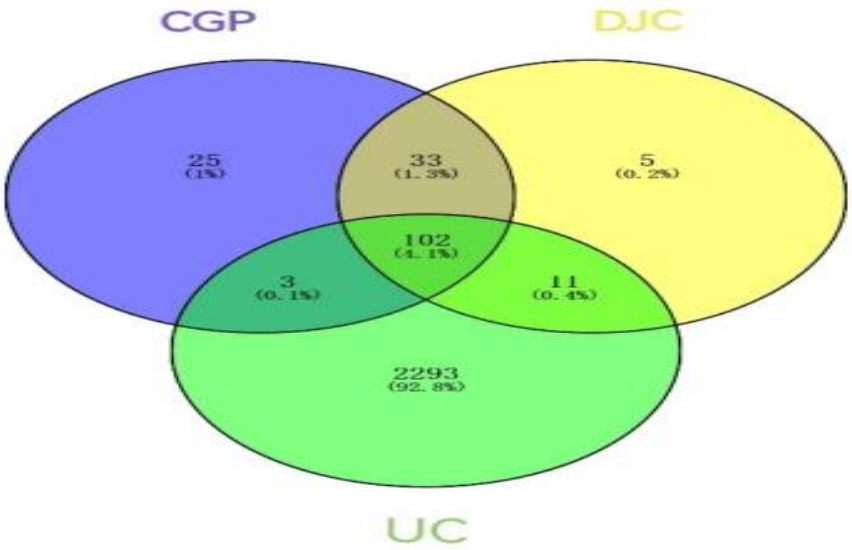

Figure 1. Intersection Venny diagram of Toona sinensis root bark-Dijin herbal pair and ulcerative colitis targets

Rely on the effective component and the disease targets, 102 targets were obtained, and the Venny diagram was drawn by Venny2.1. The STRING network of key targets (figure 1-2) and the relationship between targets are obtained through PPI database.According to the complexity of the network, the minimum interaction score and the highest confidence level of 0.7 is set, so that the network contains 102 key nodes, 653 edges.

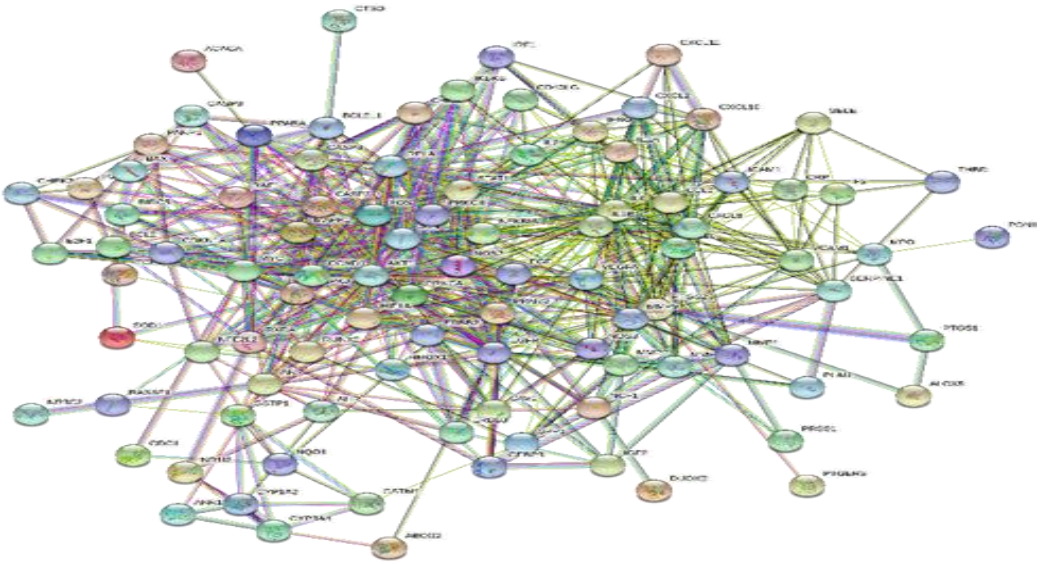

Figure 2. PPI network diagram between key targets

2.5. To build Drug-Ingredient-Target-Disease Network

Use Cytoscape3.7.2 to construct a network of drug-component-target-disease (figure 3). The network consists of 120 nodes, including 1 disease target, 2 traditional Chinese medicine nodes, 15 component nodes and 102 target nodes. According to its value size, the core components and targets are selected and drawn into a bar chart (figure 4). The results show that quercetin, kaempferol, serine / threonine protein kinase B signal (AKT1) and sarcoma virus 17 oncogene homologue (JUN) are the core nodes of the network (Table 2).

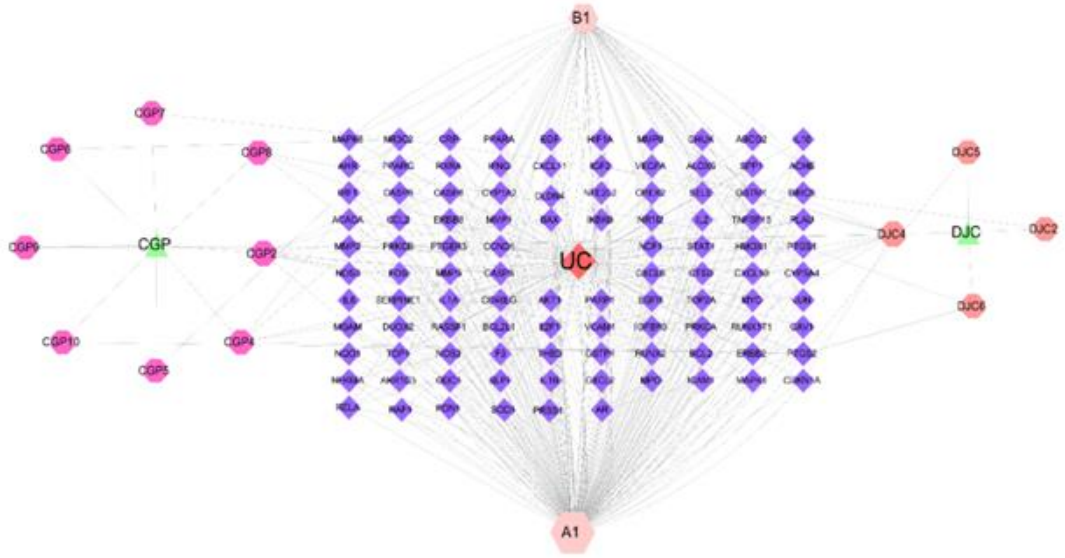

Figure 3. Drug-ingredient-target-disease network

(note: the red diamond represents the disease node, the triangle represents the traditional Chinese medicine node, the six sides represent the component node, and the blue diamond represents the target node.)

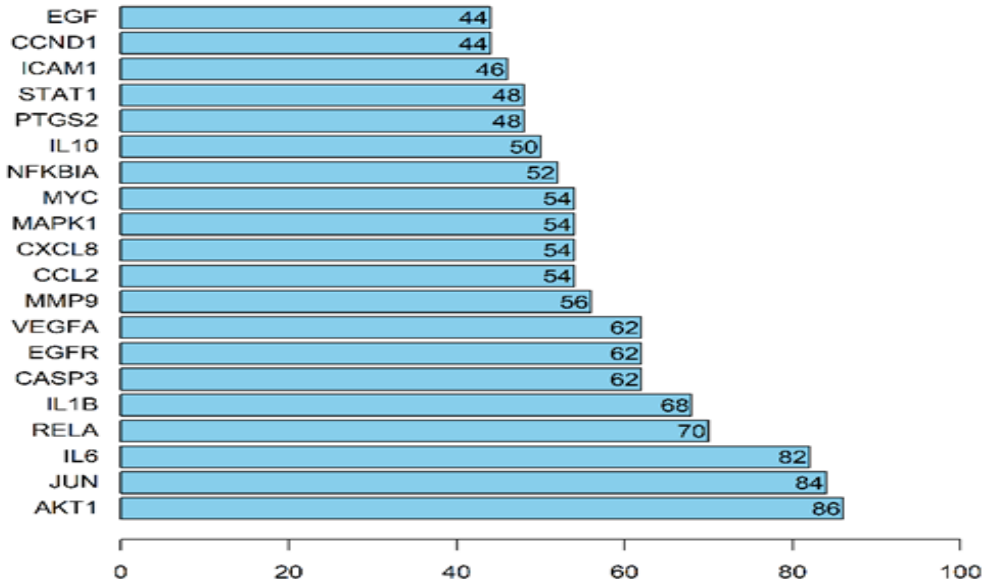

Figure 4. Histogram of gene values of common targets

Table 2. Important ingredients or targets of Toona sinensis root bark-Dijin herbs in the treatment of UC

Node	Protein / gene	Types	Value
MOL000098	Quercetin	Effective ingredients	35
MOL000422	Kaempferol	Effective ingredients	20
AKT1	Serine/threonine protein kinase	Target point	86
JUN	Transcription factor AP-1	Target point	84

2.6. Drug-Component-Target-Disease Pathway Analysis

The DAVID was used to carry out the GO function and KEGG enrichment analysis by R language package. Through the analysis,570 GO items were screened, including 444 items related to biological process,43 entries related to cell composition and 83 items related to molecular function (figure 5). The first five biological processes with significant enrichment of key targets (Table 3) are responses to varietys of biological processes.

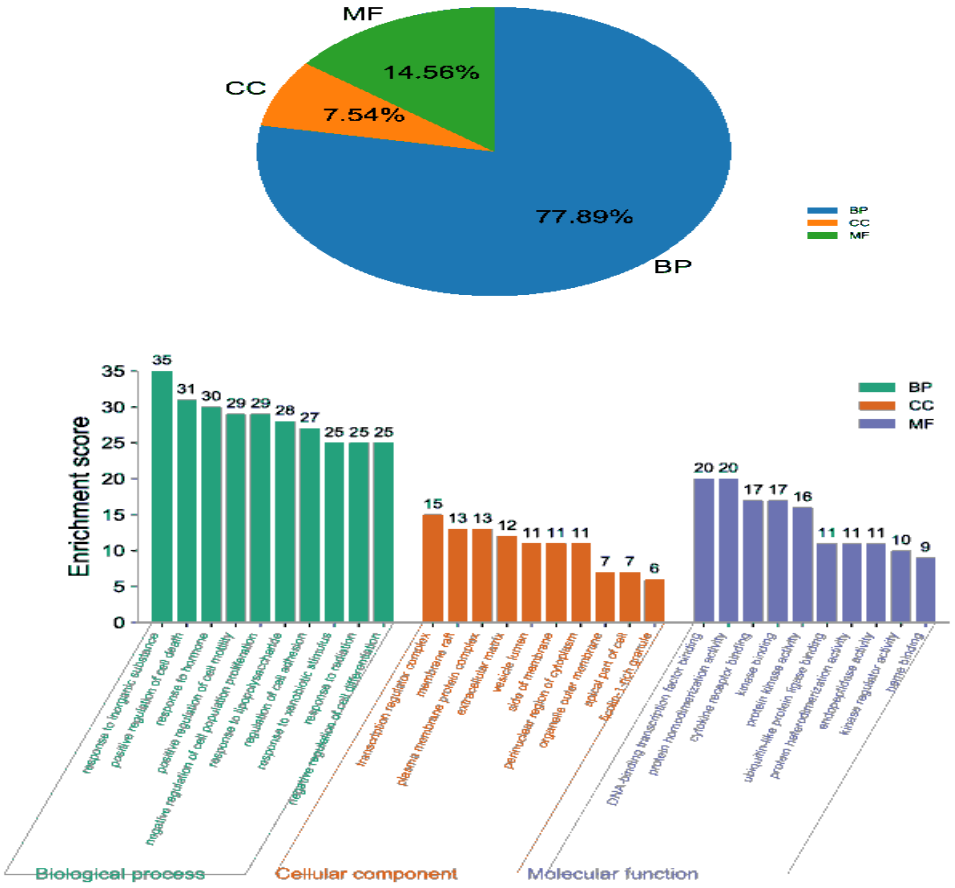

Figure 5. Functional enrichment analysis of gene ontology (GO)

(note: BP is a biological process, CC is a cellular composition, MF molecular function; the three biological processes show the first 10 GO items according to the enrichment score.)

Table 3. Biological process enrichment control table

Enrichment processID	Enrichment entry	pvalue	p.adjust	Count
GO:0140297	DNA-binding transcription factor binding	5.49E-12	6.46E-10	18
GO:0005126	cytokine receptor binding	1.41E-13	4.97E-11	17
GO:0048018	receptor ligand activity	1.44E-09	1.02E-07	17
GO:0030546	signaling receptor activator activity	1.84E-09	1.08E-07	17
GO:0005125	cytokine activity	3.35E-12	5.91E-10	15

163 pathways were screened by KEGG enrichment analysis.The pathways of significant enrichment of key targets have five(figure 6).

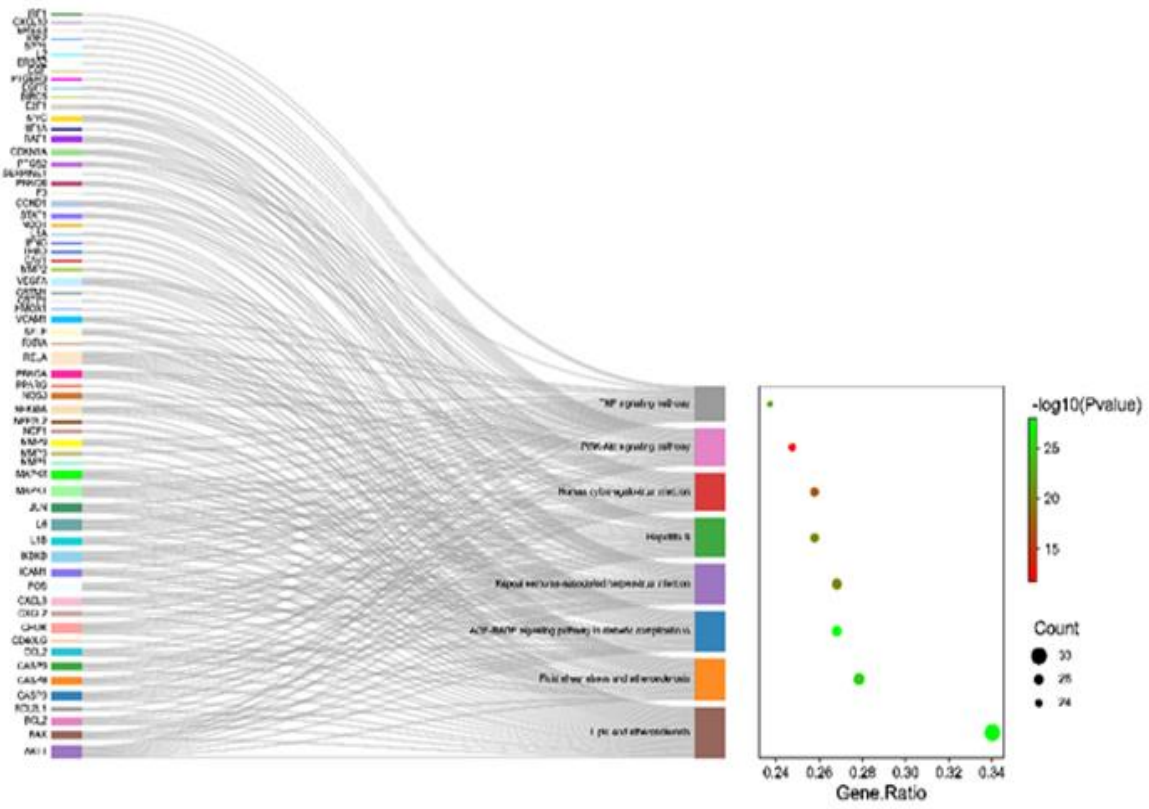

Figure 6. Bubble diagram of signal pathway enrichment analysis

2.7. Molecular Docking Prediction

The two core components (quercetin (MOL000098) and kaempferol (MOL000422)) and the core targets AKT1 and JUN were docked. It is

the PDBID and binding energy of the docking target gene (Table 4), the docking binding site (figure 7-10) The results showed that the components quercetin and kaempferol had strong interaction and binding affinity with core proteins AKT1 and JUN, which had potential research value.

Table 4. Docking results of core components and targets of Toona sinensis root bark and Herba Euphorbiae pairs

Target protein	PDB ID	Ligand molecule	Binding energy (kal ·mol ⁻¹)
AKT1	4EJN	Kaempferol(MOL000422)	-4.43
AKT1	4EJN	Quercetin(MOL000098)	-5.92
JUN	2G01	Kaempferol(MOL000422)	-4.27
JUN	2G01	Quercetin(MOL000098)	-4,38

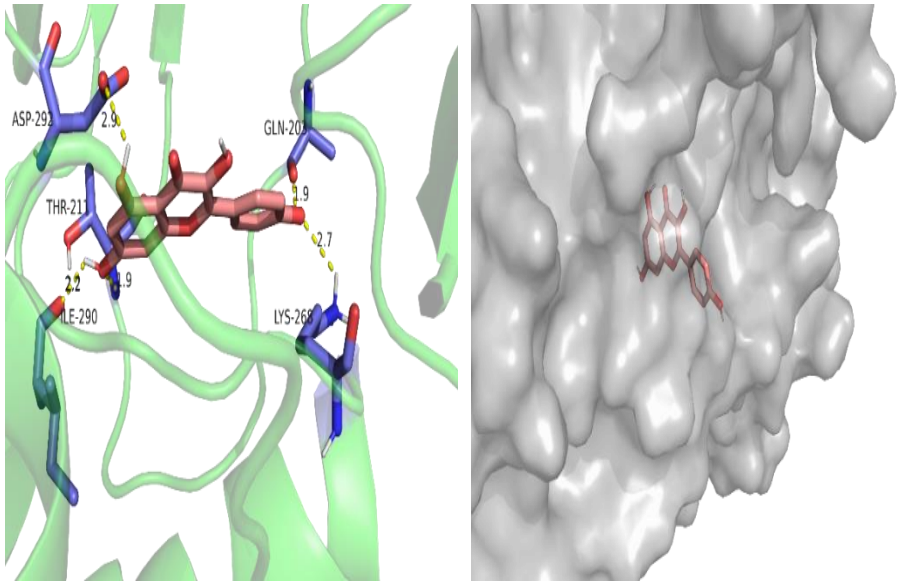

Figure 7. Map of docking binding sites of AKT1-kaempferol molecules

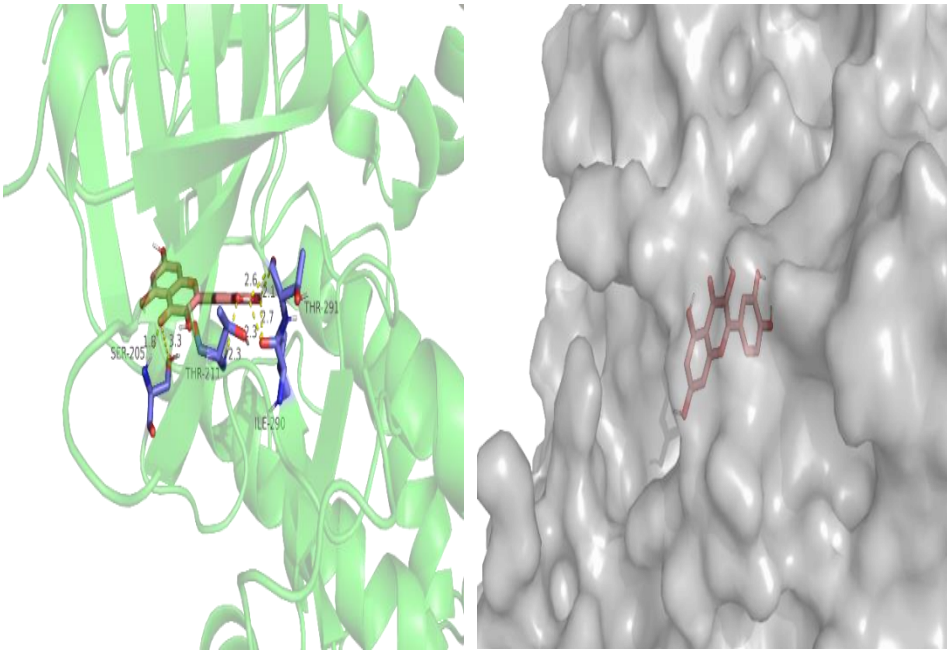

Figure 8. Map of docking binding sites of AKT1-quercetin molecules

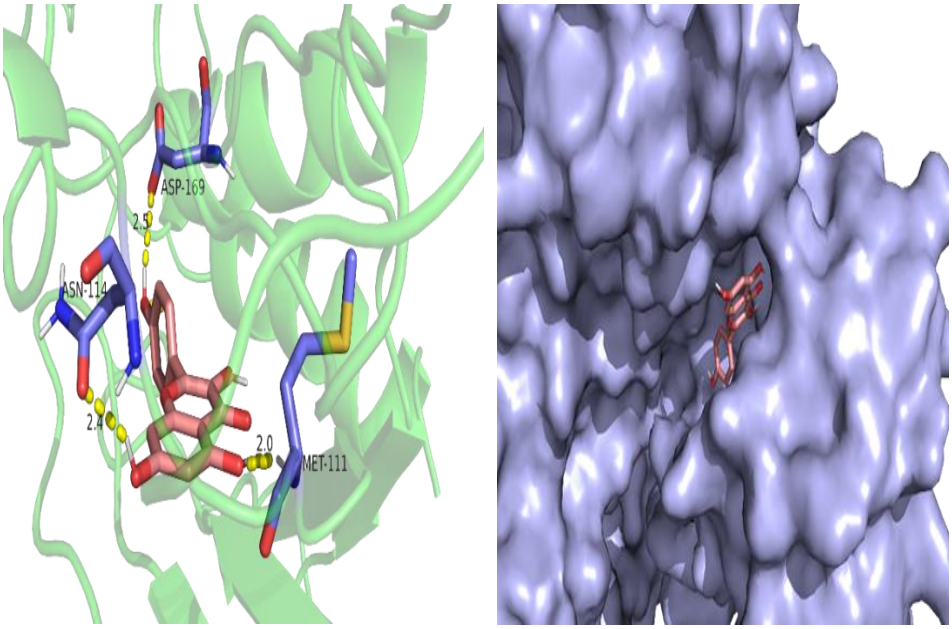

Figure 9. Map of docking binding sites of Jun-kaempferol molecules

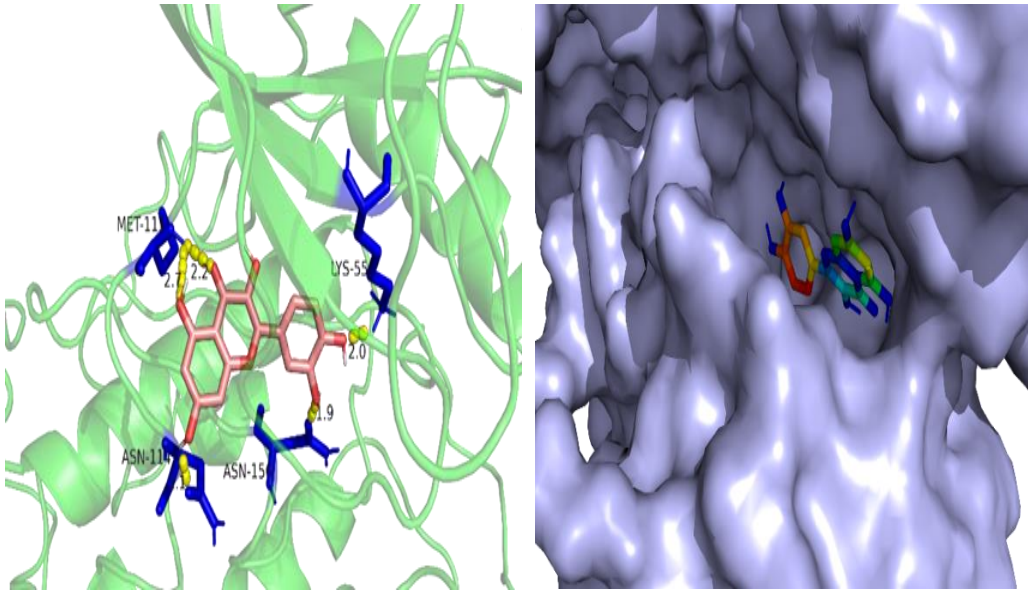

Figure 10. Map of docking binding sites of Jun-quercetin molecules

3. Discussion

Through the information mining of traditional Chinese medicine and disease-related database, it is found that the common active components of Toona sinensis root bark-Dijin herb used to ulcerative colitis are quercetin and kaempferol.They can inhibit the secretion of IL6, IL1 β and TNF-α[10],quercetin has anti-inflammatory activity[11]. 2409 target genes related to UC were collected by GeneCards platform and OMIM database. For example: MAPK1,participates in the process of cell differentiation, migration, senescence and apoptosis, and is closely related to immune system, digestive system, cardiovascular system, tumor and other diseases[12]. The expression of MAPK1 in intestinal mucosa of UC model rats is higher[13],indicating that it may be an important target for intestinal mucosa to initiate self-repair function.IL-6 in active UC patients

was significantly higher than that in remission UC patients[14-15].VEGF is the strongest known angiogenesis promoting factor.Studies have confirmed that VEGF is important in the repair and healing of many skin injuries and ulcers[16]. CXCL8 is an inflammatory chemokine and induces tumor proliferation and angiogenesis[17]. MMP9 plays a regulatory role in the survival of tumor cells[18]. AKT1 can inhibit apoptosis and promote cell growth[19]. CCL2[20]is involved in the process of inflammation, angiogenesis and injury repair, and is involved in tumorigenesis, progression and tumor angiogenesis.

In KEGG enrichment analysis,Toll-like receptor signal pathway is related to chronic inflammation and tumorigenesis[21]. MAPK signaling pathway can regulate cell growth, differentiation, migration and other cellular processes[22-23]. Animal experiments showed that[24] inhibition of the activation of MAPK signal pathway could down-regulate the content of TNF-αin serum of UC model rats and reduce the degree of intestinal mucosal injury[25-26].TNF-αcan induce thrombin formation, affect mucosal microcirculation, destroy intestinal mucosal barrier[27],and lead to inflammatory bowel disease.

The Autodock software was used to remove water, hydrogenation and ligand removal of the macromolecular protein extracted from the PDB database, and the macromolecular protein was semi-flexibly docked with small molecular ligands to check the binding energy. The results of molecular docking showed that the active compounds of quercetin and kaempferol in Toona sinensis root bark-kaempferol pair had good binding activity with AKT1 and JUN.

4. Summary

At present, the etiology of UC is not clear, western medicine treatment has limitations, and can not control its recurrence. On the other hand, TCM syndrome differentiation and treatment of UC has unique advantages. Through network pharmacology and molecular docking technology, the possible complex mechanism of multi-component, multi-target and multi-pathway in the treatment of UC was preliminarily explored, and the effectiveness of Toona sinensis-Dijin herbal medicine in the treatment of UC was confirmed. However, data mining is limited by the total amount of data collected in the existing database, and the prediction results may be different. at the same time, different active components of traditional Chinese medicine can be assembled to form different supramolecular structures induced by weak bonds[28].As a result, there may be a deviation between the action mechanism of Toona sinensis root bark-Dijin herb pair in vivo and the predicted results. Therefore, more experimental models and clinical cohort studies are needed to further study the mechanism of Toona sinensis-Dijin herbs in the treatment of UC.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

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