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Network Pharmacology and Molecular Docking Study of Gardenia-Phellodendrin in the Treatment of Ulcerative Colitis

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Abstract: *To explore the mechanism of the treatment of ulcerative colitis by using network pharmacology and molecular docking techniques. How: The main active ingredients, action targets and ulcerative colitis of Gardenia and Cypress were screened using TCMSP, Uniprot, Gene-Cards, OMIM and other databases. The active ingredients and targets were analyzed by using Cytoscape 3.9.1 software. Construct the network diagram of "drug - active chemical - disease - action target"; The protein network interaction map was obtained by the STRING database, and the GO analysis and KEGG pathway enrichment analysis were performed by the DAVID database. Molecular docking was performed by AutoDock Vina1.1.2, and the docking results were analyzed by PyMOL2.3.0 and Ligplot V2.2.8. Results: 20 active ingredients, 200 gene targets and 784 ulcerative colitis disease targets were screened out. 55 common targets were obtained by the Venn diagram. The involved signaling pathways include the TNF signaling pathway, NF-kB signaling pathway, inflammatory bowel disease, etc. The results of molecular docking showed that AKT1, IL6, IL1B, TNF, and VEGFA could spontaneously bind to the two active components of the gardenia-yellow juniper pair, and the proteins showed low binding energy with small molecular ligands. Gardenia-yellow cedar drug has anobvious effect on the treatment of ulcerative colitis, and provides a new idea for the clinical treatment and mechanism research of ulcerative colitis.*

Keywords: *Gardenia Phellodendron chinense, Ulcerative colitis (UC), Network pharmacology, Molecular docking*

1. Research background and significance

The Decoction of Cape Jasmine and Phellodendron, which iscomposed of gardenia, phellodendron, and licoriceis, is derived fromthe *Treatise on Cold-Attack*. Sovereign drug gardenia has the effect of purging fire, clearing heat, removing dampness, cooling blood, and detoxification[1]; ministerial drug Phellodendron chinense is good at purging the fire of lower Jiao and has the function of clearing heat, drying dampness, and detoxifying;Conductant druglicorice regulatesthe stomach, alleviate the bitter and cold nature of Gardenia and Phellodendron chinense. The three drugs play the effect of clearing heat and removing dampness together, so that the evil can be removed from the urine, and the dampness can be removed from the heat. With the inheritance and development of traditional Chinese medicine by doctors in the past dynasties, later generations of doctors also have new elaboration and application of the Decoction of Cape Jasmine and Phellodendron.Zhang Bi(Yuan Dynasty)'s *Yun Qi Zi Bao Ming Ji* uses gardenia, Phellodendron chinense Schneid, and coptis to treat dry heat and yellowing; Xu Yongcheng(Ming Dynasty)'s *Yujiweiyi* uses gardenia, Phellodendron chinense Schneid, and coptis to treat those with general fever, smooth excrement, and yellow body skin; Wu Tang(Qing Dynasty)'s *Wenbing Tiaobian* proposed that "Gardenia clears the muscle surface, relieves five yellows, and treats internal restlessness; Phellodendron chinensemakes bladder excrete andtreats skin heat; licorice benefits both internal and external".Modern clinical studies have shown that this prescription can be used for the treatment of malignant tumors[2], such as rash after targeted therapy for lung adenocarcinoma, elevated bilirubin after chemotherapy for rectal adenocarcinoma, radiation enteritis after chemotherapy for cervical squamous cell carcinoma, etc. Meanwhile, it is also used in inflammatory diseases such as tibial

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fatigue periostitis and atopic dermatitis[3].Traditional Chinese medicine classifies ulcerative colitis into the categories of “diarrhea”, “intestinal Pi”, “red urine”, and so on. The pathogenesis is mostly an exogenous pathogenic toxin, accompanied by internal injury, which hurts the spleen, stomach, and intestines. This disease occurs if the intestinal vein isdamagedand blood and flesh are rotten. Therefore, the Decoction of Cape jasmine and Phellodendron is consistent with the pathogenesis of spleen deficiency and damp-heat toxin accumulation.

In this study, the compatibility of target drug pairs was analyzed and predicted by using network pharmacology and molecular docking technology, and the active components, key targets, and related pathways of UC were studied deeply, which provided a reference for the follow-up study on the mechanism of gardenia-Phellodendron chinense regulating UC. Therefore, it has long-term innovative application significance and provides a theoretical basis for clinical guidance.

2. Materials and Methods

2.1. Screening and summary of component information of Gardenia -Phellodendron chinense drug pair

The Traditional Chinese Medicine Systems Pharmacology And Analysis Plat-form (TCMSP) was used to collect the main chemical components of Gardenia and Phellodendron chinense and the oral bioavailability (OB≥30%) and drug-likeness (DL≥0.18) were set to screen the eligible active ingredients and related target information.

2.2. Acquisition and collection of targets of active ingredients

The target information of the active ingredients of “Gardenia-Phellodendron chinense”was input into the Uniprot database to sort out the relevant gene data that conforms to the source species as “human”, and the target of the active ingredients was obtained. Then, Cytoscape 3.9.1 software was used for visual analysis.

2.3. Collection of key targets of ulcerative colitis

Gene-Cards database and OMIM database were adopted to obtain the targets of UC-related diseases, and then the target data obtained from the two databases were de-reintegrated.

2.4. “Compound-Target-Disease”network construction

Venny 2.1.0 software was used to obtain the overlapping part of drug targets and disease targets, and the overlapping part was the key target data for drug treatment of UC.

2.5. Construction of PPI network of key targets

The STRING online database platform was used to search for the drug pair of“Gardenia - Phellodendron chinense”, and the key target protein interaction (PPI) relationship for the treatment of UC was obtained. Then the obtained data were imported into Cytoscape for visual analysis, and the corresponding PPI network diagram was drawn.

2.6. Biological process and pathway analysis of key targets

GO functional enrichment analysis and KEGG pathway enrichment analysis were performed on the key targets on the DAVID database platform to obtain the biological information of the key targets, and their mechanism of action was analyzed.

2.7. Molecular docking verification of key targets and components of Gardenia -Phellodendron chinense drug pair

AutoDockVina1.1.2 was used for docking, and PyMOL2.3.0 and Ligplot V2.2.8 were used to analyze the interaction mode of docking results.

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3. Results

3.1. Active ingredient information of Gardenia -Phellodendron chinense drug pair

By searching the TCMSP database, 98 chemical constituents of Gardeniaand 140 chemical constituents of Phellodendron amurense were obtained. Among them, there were 15 and 37 potential active ingredients of Gardenia and Phellodendron chinensewith OB ≥ 30 % and DL ≥ 0.18, respectively, and 20 were obtained after deduplication, as shown in Figure 1. Through the TCMSP database, the number of active ingredient targets of Gardenia and Phellodendron chinensewas 330 and 309, respectively. The targets of the active ingredient were introduced into Uniprot, and after deduplication, a total of 200 target corresponding genes were obtained.

Molecular coding	Chemical name	Oral bioavailability（%）	Drug-likeness	Source
MOL001454	berberine	36.86	0.78	Phellodendrin
MOL001458	coptisine	30.67	0.86	Phellodendrin
MOL001458	Kihadalactone A	34.21	0.82	Phellodendrin
MOL013352	Obacunone	43.29	0.77	Phellodendrin
MOL002641	Phellavin qt	35.86	0.44	Phellodendrin
MOL002643	delta 7-stigmastenol	37.42	0.75	Phellodendrin
MOL002644	Phellopterin	40.19	0.28	Phellodendrin
MOL002651	Dehydrotanshinone II A	43.76	0.4	Phellodendrin
MOL002652	delta7-Dehydrosophoramine	54.45	0.25	Phellodendrin
MOL002656	dihydroniloticin	36.43	0.81	Phellodendrin
MOL002659	kihadanin A	31.6	0.7	Phellodendrin
MOL002660	niloticin	41.41	0.82	Phellodendrin
MOL002662	rutaecarpine	40.3	0.6	Phellodendrin
MOL002663	Skimmianin	40.14	0.2	Phellodendrin
MOL002666	Chelerythrine	34.18	0.78	Phellodendrin
MOL002668	Worenine	45.83	0.87	Phellodendrin
MOL002670	Cavidine	35.64	0.81	Phellodendrin
MOL002671	Candletoxin A	31.81	0.69	Phellodendrin
MOL002672	Hericenone H	39	0.63	Phellodendrin
MOL002673	Hispidone	36.18	0.83	Phellodendrin
MOL000622	Magnograndiolide	63.71	0.19	Phellodendrin
MOL000762	Palmidin A	35.36	0.65	Phellodendrin
MOL000785	palmatine	64.6	0.65	Phellodendrin
MOL000787	Fumarine	59.26	0.83	Phellodendrin
MOL000790	Isocorypalmine	35.77	0.59	Phellodendrin
MOL000098	quercetin	46.43	0.28	Phellodendrin
MOL001131	phellamurin_qt	56.6	0.39	Phellodendrin
MOL001455	(S)-Canadine	53.83	0.77	Phellodendrin
MOL001771	poriferast-5-en-3beta-ol	36.91	0.75	Phellodendrin
MOL002894	berberrubine	35.74	0.73	Phellodendrin
MOL005438	campesterol	37.58	0.71	Phellodendrin
MOL006392	dihydroniloticin	36.43	0.82	Phellodendrin
MOL006401	melianone	40.53	0.73	Phellodendrin
MOL006413	phellochin	35.41	0.26	Phellodendrin
MOL006422	thalifendine	44.41	0.76	Phellodendrin
MOL001406	crocetin	35.3	0.22	Gardenia
MOL001663	(4aS,6aR,6aS,6bR,8aR,10R,12aR,14bS)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid	32.03	0.59	Gardenia
MOL001941	Ammidin	34.55	0.22	Gardenia
MOL004561	Sudan III	84.07	0.59	Gardenia
MOL000098	quercetin	46.43	0.28	Gardenia
MOL000358	beta-sitosterol	36.91	0.75	Gardenia
MOL000422	kaempferol	41.88	0.24	Gardenia
MOL000449	Stigmasterol	43.83	0.76	Gardenia
MOL001494	Mandenol	42	0.19	Gardenia
MOL001506	Supraene	33.55	0.42	Gardenia
MOL001942	isoimperatorin	45.46	0.23	Gardenia
MOL002883	Ethyl oleate (NF)	32.4	0.19	Gardenia
MOL003095	5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl)chromone	51.96	0.41	Gardenia
MOL007245	3-Methylkempferol	60.16	0.26	Gardenia
MOL009038	GBGB	45.58	0.83	Gardenia

Figure 1: Map of active ingredient of Gardenia -Phellodendron chinense drug pair

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3.2. "Active ingredient-target"network construction analysis

The effective active components of Gardenia and Phellodendron chinensewere numbered, and two common effective active components were found, namely A1 and A2, as shown in Fig.2, representing beta-sitosterol and Stigmasterol, respectively. The 20 effective active components of the drug and the corresponding genes of 200 component targets were imported into Cytoscape 3.9.1 software to construct a network and visual analysis, as shown in Figure 2.

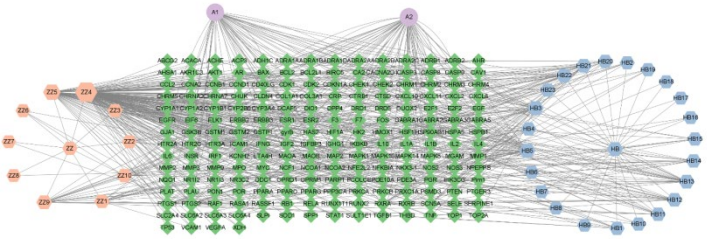

Figure 2: Network map of active components and target gene of Gardenia -Phellodendron chinense drug pair

3.3. Screening of key targets for ulcerative colitis

A total of 5139 disease-related targets were collected through the Gene-Card platform, and 323 targets were screened according to the condition relevance score ≥ 7.38. The OMIM database was used to collect 531 UC-related target genes, and then the results of the two databases were deduplicated, and finally, 784 were obtained.

3.4. "Drug target-disease target" network construction and visualization analysis

Venny2.1.0 software was used to intersect the corresponding 200 drug targets with 784 disease targets to obtain 55 common target genes, as shown in Figure 3. The key targets are:PTGS2,VCAM1, PIK3CG, PTGS1, PPARG, MMP3, RELA, EGFR, AKT1, VEGFA, CCND1, BCL2, CDKN1A, BAX, MMP2, MMP9, IL10, EGF, TNF, IL6, TP53, XDH, CASP8, SOD1, MMP1, STAT1, ERBB2, HMOX1, CYP3A4, F3, ICAM1, IL1B, CCL2, SELE, CXCL8, DUOX2, TGFB1, IL2, SERPINE1, IFNG, PTEN,IL1A, MPO, NCF1, GSTP1, CHEK2, CLDN4, CRP, CXCL10, SPP1, IGF2, CD40LG, NOS2, IKBKB, IL4.

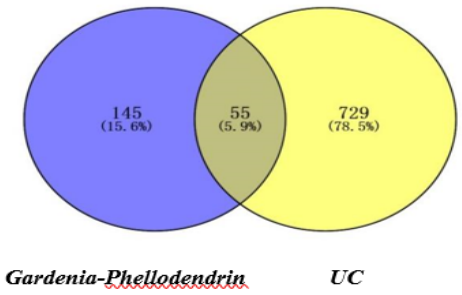

Figure 3: Venn diagram of drug pairs active ingredients targets and disease targets

3.5. PPI network analysis of Gardenia - Phellodendron chinense in the treatment of UC

The above 55 drug-disease target protein interaction maps were obtained using the STRING database platform, as shown in Figure 4. The confidence level was set to be greater than 0.4, and then the obtained 55 key target proteins were imported into Cytoscape 3.9.1 software for visual analysis, and the network diagram was drawn, as shown in Figure 5. The top 10 key targets were: AKT1, VEGFA, IL6, TNF, IL1B, PTGS2, TP53, MMP9, CCL2, CXCL8.

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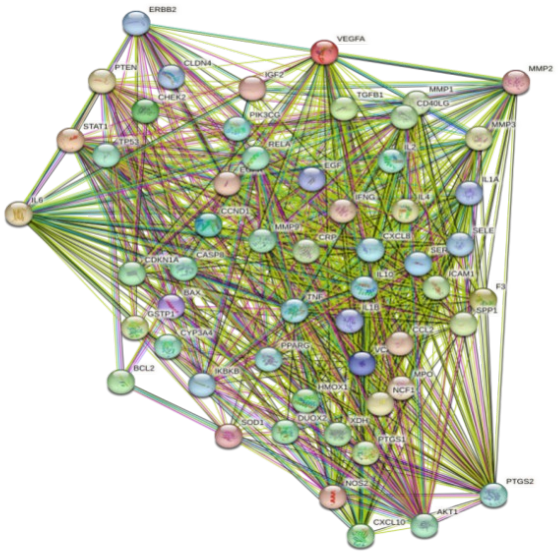

Figure 4: PPI network map of drug pairs against ulcerative colitis related targets

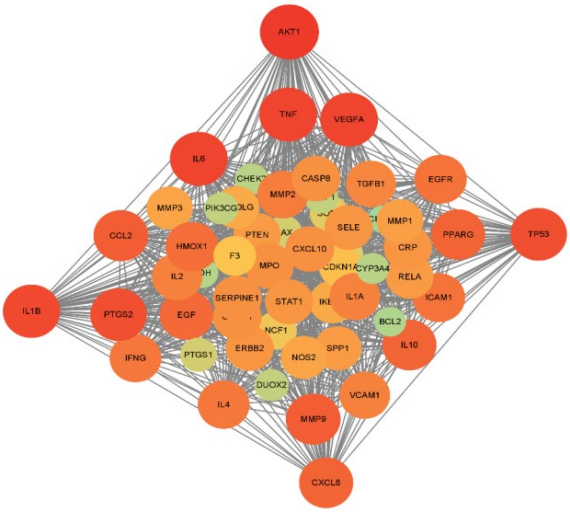

Figure 5: PPI network map of drug pairs against ulcerative colitis related targets

3.6. GO enrichment analysis of key targets

A total of 559 key target genes were obtained by GO enrichment analysis onthe DAVID website. Among them, there were 463 biological processes, 38 cellular components, and 58 molecular functions, and the top 10 were selected, respectively. The results are shown in Figure 6. They mainly involve inflammatory response, negative regulation of the apoptosis process, positive regulation of gene expression, positive regulation of protein phosphorylation, positive regulation of cell proliferation, positive regulation of theapoptosis process, positive regulation of transcription, and DNA template.

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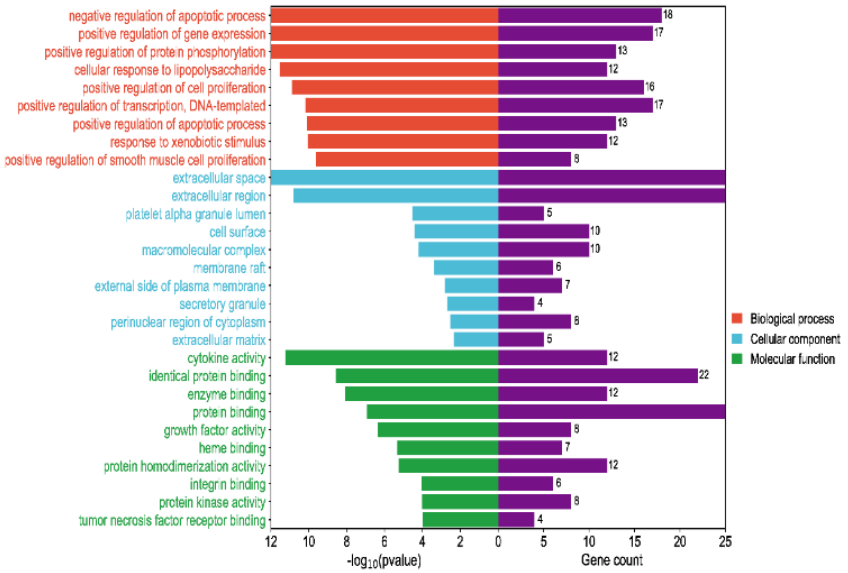

Figure 6: Enrichment analysis diagram of key targets

3.7. KEGG Pathway Analysis

KEGG pathway analysis of key target genes was performed using the DAVID website. There were 129 pathways associated with $P < 0.05$ targets, and the main pathways were: cancer pathway, TNF signaling pathway, malaria, prostate cancer, pancreatic cancer, bladder cancer, colorectal cancer, P53 signaling pathway, NF-kB signaling pathway, rheumatoid arthritis, hepatitis B, inflammatory bowel disease, human cytomegalovirus infection, Toll-like receptor signaling pathway, etc.

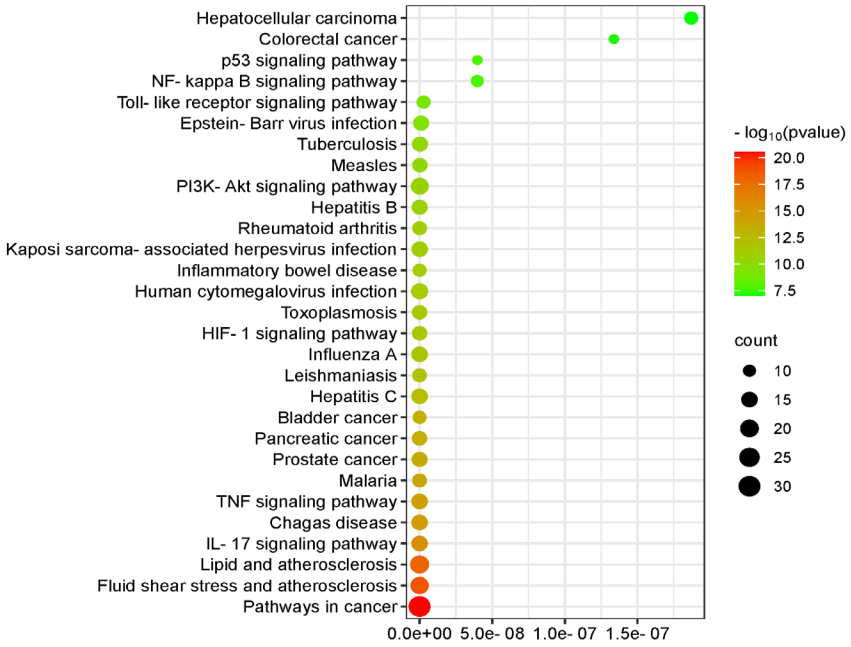

Figure 7: Enrichment analysis diagram of signaling pathways for the treatment of ulcerative colitis

3.8. Molecular docking results

Stigmasterol and beta-sitosterol with the highest degree value in the PPI network were selected for

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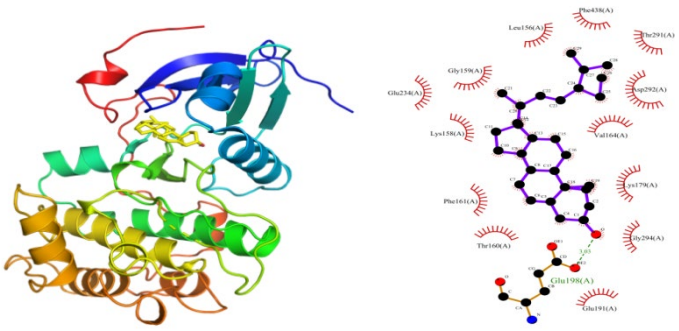
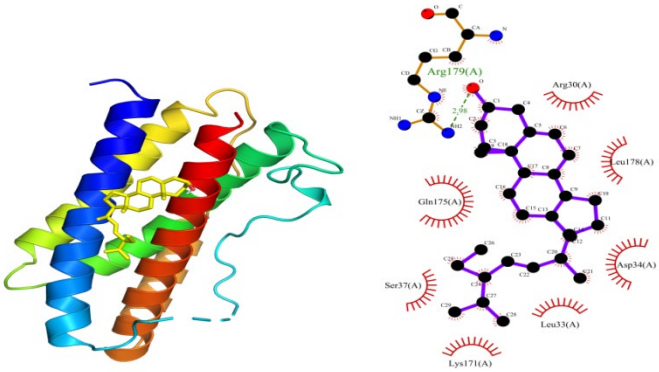
docking, as shown in Table 1. The smaller the binding energy, the more stable the binding conformation. According to the binding energy, the docking simulation diagram was drawn. Figure 8 shows the molecular docking simulation diagram of stigmasterol and AKT1 and IL6, and β-sitosterol and IL1 B, TNF and VEGFA. Among them, TNF and β-sitosterol, AKT1 and stigmasterol showed lower binding energy.

Table 1: Binding energy of molecular docking between the components of Gardenia - Phellodendron chinense drug pairs and target proteins

Target	PDB ID	Compound	Binding energy(kcal/mol)	Target	PDB ID	Compound	Binding energy(kcal/mol)
IL6	1ALU	MOL000098	-6.9	TNF	2E7A	MOL000098	-9
		MOL000358	-6.7			MOL000358	-9.1
		MOL000422	-6.8			MOL000422	-9
		MOL000449	-7			MOL000449	-8.9
		MOL000790	-6.4			MOL000790	-8
AKT1	6NPZ	MOL000098	-7.8	IL1B	6I8Y	MOL000098	-6.8
		MOL000358	-7.4			MOL000358	-7.1
		MOL000422	-7.8			MOL000422	-6.2
		MOL000449	-7.9			MOL000449	-6.7
		MOL000790	-7.6			MOL000790	-6.6
VEGFA	4KZN	MOL000098	-5.5				
		MOL000358	-6.5				
		MOL000422	-5.4				
		MOL000449	-6.4				
		MOL000790	-5.8				



a. Stigasterol-AKT1



b. Stigmasterol-IL6

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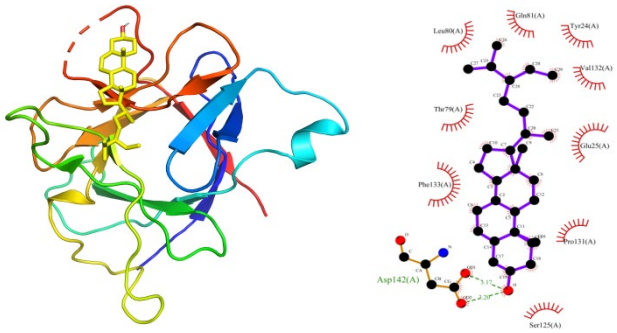
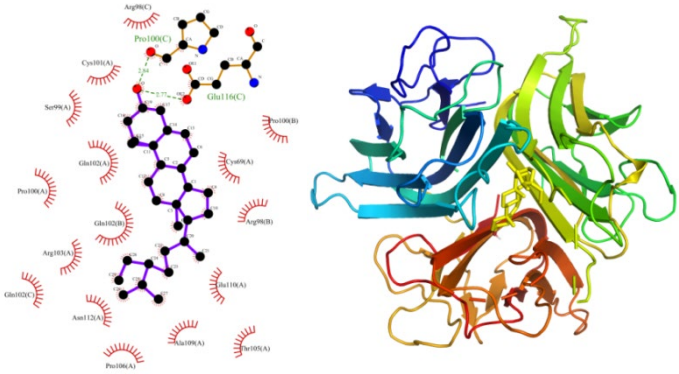
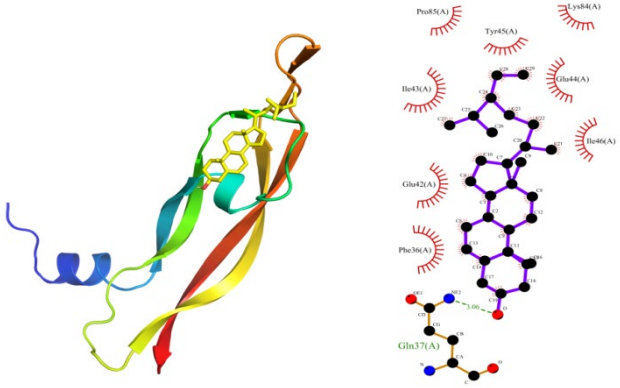


c. β-Quebrachol-IL1B



d. β-Quebrachol-TNF



e. β-Quebrachol-VEGFA

Figure 8: Molecular docking simulation diagram of the components and key targets of Gardenia - Phellodendron chinense drug pairs

4. Discussion

At present, western medicine has a high short-term remission rate in the treatment of ulcerative colitis, but it is easy to relapse after drug withdrawal. Meanwhile, Long-term use is prone to adverse reactions such as adverse reactions and drug dependence. Therefore, seeking possible alternative treatment options from classical prescriptions of traditional Chinese medicine is a feasible direction for promoting the treatment of ulcerative colitis and the development of traditional Chinese medicine. Through network pharmacology, the main drug components of Gardenia - Phellodendron chinense drug pairs in the treatment of UC were stigmasterol, β-sitosterol, quercetin, berberine, rutaecarpine, and so on. They mainly interact with AKT1, VEGFA, IL6, TNF, IL1 B, PTGS2, TP53, etc., and act on PI3K-AKT, NF-κB, Toll-like, IL-17, TNF, HIF-1, p53, and other pathways to exert UC therapeutic effects. Stigmasterol can prevent the occurrence of colon cancer, ovarian cancer, and other cancers. Studies have found that foods rich in phytosterols can inhibit cholesterol absorption and reduce serum cholesterol levels by competing for intestinal absorption.As one of the sterols containing the most abundant phytosterol, β-sitosterol has strong anti-inflammatory, anti-atherosclerosis, anti-diabetes and anti-cancer effects [4]. β-sitosterol can also inhibit TNBS-induced ulcerative colitis and inhibit the secretion of inflammatory factors such as IL1 B and TNF [5]. Quercetin can reduce the early inflammatory response by reducing the

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expression of IL-1β, IL-6, TNF-α, and NF-κB, or play a role by changing the ability of intestinal flora[6].Studies have shown that [7-8], berberine plays a therapeutic role in UC by reducing the expression of inflammatory factor TNF-α in serum and Toll-like receptor protein in colon tissue, up-regulating the expression level of tight junction protein in colon tissue, inhibiting the apoptosis of intestinal epithelial cells, and improving the local inflammatory state of the intestinal tract.Rutaecarpine has a therapeutic effect on UC mice [9]. It can significantly up-regulate the mRNA expression of Nrf2 downstream antioxidant stress genes in the ileum and colon tissues and down-regulate the mRNA expression of related inflammatory factors, thereby significantly improving DSS-induced ulcerative colitis symptoms.

AKT1 has been confirmed to be significantly expressed in the intestinal mucosa of UC patients and is closely related to the regulation of tumor cell proliferation and apoptosis, so it is of great significance in the diagnosis and prognosis of colon cancer. VEGFA plays a role in promoting angiogenesis and endothelial cell proliferation and is usually highly expressed in the mucosa of UC patients. IL1 B has been used as a clinical index to judge the degree of UC ulcer and the curative effect. TP53, as a tumor suppressor gene, can be used as a biomarker for early colon cancer. Therefore, effectively regulating its expression level is an important idea in the treatment of UC.

Studies have found that the PI3K/AKT signal transduction pathway plays an important regulatory role in the immune process of UC inflammatory response. Inhibiting the expression of PI3K / AKT signaling pathway, reducing the release of pro-inflammatory cytokines TNF-α, IL-12 and IL-6, and increasing the release of anti-inflammatory cytokines IL-4 and IL-10 play an important role in promoting apoptosis, reducing colon tissue inflammation, repairing mucosal tissue, and inhibiting the transformation of ulcerative colitis into colon cancer [10].NF-κB is a transcription factor that regulates various inflammatory cytokines, chemokines, and adhesion factors. It plays a key role in immune regulation and can induce the expression of inflammatory mediators, but excessive activation can lead to the release of a large number of pro-inflammatory factors. The released cytokines further activate NF-κB and aggravate the level of inflammation [11]. Probiotics can protectthe intestinal barrier and improve immune regulation. Toll-like receptor signaling pathway is involved in the process of probiotics in the treatment of enteritis.Probiotics can not only affect the signal exchange between immune cells and regulate the degree of immune response by changing the antigen to increase the expression level of the Toll-like receptor signaling pathway in cells, but also inhibit the Toll-like receptor signaling pathway to treat UC to a certain extent [12]. IL1 B has been used as a clinical indicator to judge the degree of ulceration and curative effect of UC.Inhibiting the activation of the IL-17 signaling pathway can reduce the inflammatory response and play its role in the treatment of UC[13].As a tumor suppressor gene, p53 plays its role in regulating inflammation by promoting blood cell apoptosis, tissue cell cycle, and induced phosphatase. These pathways are important molecular pathways for the treatment of UC by Gardenia - Phellodendron chinense drug pairs.

To sum up, the possible active components, targets, and related pathways of Gardenia - Phellodendron chinense drugs in the treatment of ulcerative colitis were preliminarily expounded using network pharmacology and molecular docking, and then its potential therapeutic mechanism was speculated from the molecular level, which has certain reference significance for exploring the mechanism of the Decoction of Cape jasmine and Phellodendron in the treatment of inflammatory bowel diseases. However, the conclusions still need to be verified by further in vivo and in vitro studies, expecting to find a treatment plan for difficult diseases from classical Chinese medicine prescriptions.

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