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# Network Pharmacology Integrated Molecular Docking Revealed the Mechanism of Jianpi Yiqi Taohua Decoction Against Ulcerative Colitis

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Statistical Analysis C  
Data Interpretation D  
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**Background:** Jianpi Yiqi Taohua decoction (JYTD) has shown therapeutic effects in ulcerative colitis (UC). However, the pharmacological mechanism of JYTD against UC remains unclear.





**Material/Methods:** Compounds and targets of JYTD and UC-related genes were screened from public databases. Integrated analysis was performed to identify therapeutic targets of UC, followed by functional enrichment analysis. Protein-protein interaction (PPI) and pharmacological networks were then established. Molecular docking was used to validate the affinity of compounds and their targets. Further, the efficacy of JYTD was evaluated by meta-analysis. Relevant studies were searched from 5 databases. Outcomes were complete response rate (CRR) and overall response rate (ORR), and pooled results were estimated by risk ratio (RR) with corresponding 95% confidence intervals (CIs).

**Results:** The pharmacological network identified 13 herbal medicines, 28 compounds, 54 targets, and 20 pathways. Stigmasterol, liquiritigenin, and naringenin were potential active compounds, and *PRKCA*, *NFKB1*, *ESR1*, *NTRK1*, *AKT1*, *PPARG*, *RXRA*, and *VDR* were hub targets. Pathway analysis revealed that genes were mainly involved in the cellular response to lipids. Molecular docking indicated that *AKT1*, *NFKB1*, *ESR1*, *NTRK1*, *PRKCA*, and *PPARG* exhibited good affinity to 6 key compounds of JYTD. Then, meta-analysis revealed that Tao Hua decoction treatment significantly improved CRR (RR, 1.21; 95% CI, 1.06-1.37;  $P=0.004$ ) and ORR (RR, 1.16; 95% CI, 1.08-1.24;  $P<0.001$ ).

**Conclusions:** JYTD was found to have preventive and therapeutic effects on UC through multiple compounds, targets, and pathways. These findings enhanced our understanding of the potential pharmacological mechanisms of JYTD against UC.

**Keywords:** **Molecular Docking Simulation • Pediatric Ulcerative Colitis • Pharmacology**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/933537>

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## Background

Ulcerative colitis (UC) is a chronic idiopathic bowel disease characterized by intestinal (colon and rectum) inflammation [1], with clinical symptoms that include bloody diarrhea, acute pain, hemafecia, and weight loss [2]. UC is a common gastrointestinal disease in China. To date, UC has been predominantly treated with 5-aminosalicylate, cyclosporine, and ustekinumab. However, these drugs may produce a series of adverse events that can increase the risk of infection and neoplasia [3,4]. Moreover, the main objective of these drug therapies for patients with UC is to induce and maintain the relief of symptoms and mucosal inflammation [5]. Therefore, it is necessary to explore safe and effective treatments.

Jianpi Yiqi Taohua decoction (JYTD) is a common traditional Chinese medicine (TCM) that derives from the basis of the classic prescription “Tao Hua decoction” and has been used to treat UC with various causes [6]. According to TCM theory, UC can be divided into different TCM syndromes, mainly including Pi-Xu-Shi-Yun syndrome (syndrome of spleen deficiency and dampness) and Da-Chang-Shi-Re syndrome (syndrome of dampness-heat in the large intestine) [7]. JYTD has been most effective in patients with UC who have Pi-Xu-Shi-Yun syndrome. The usage of this prescription is as follows: “when UC is characterized by Shaoyin disease with purulent bloody stool syndrome, the Tao Hua decoction is prescribed”. This formula is composed of *Codonopsis pilosula* (Dangshen, DS), *Atractylodes Macrocephalae* Rhizoma (Baizhu, BZ), *Astragalus membranaceus* (Huangqi, HQ), *Zingiberis Rhizoma* (Ganjiang, GJ), *Halloysitum Rubrum* (Chishizhi, CSZ), *Coptis chinensis* Franch. (Huanglian, HL), *Dolichos lablab* L. (Baibiandou, BBD), *Terminalia chebula* Retz. (Hezi, HZ), *Dioscorea opposita* Thunb. (Shanyao, SY), *Rhizoma Curculiginis* (Xianmao, XM), *Amomi fructus* (Sharen, SR), *Corydalis yanhusuo* (Yuanhu, YH), *Semen Coicis* (Yiyiren, YZR), *Aucklandia lappa* Dence. (Muxiang, MX), *Citrus reticulata* Blanco (Chenpi, CP), *Oryza sativa* L. (Jingmi, JM), *Paeonia lactiflora* Pall. (Baishao, BS), and *Glycyrrhiza uralensis* Fisch. (Zhigancao, ZGC). TCM studies have indicated that UC is related to the spleen and kidneys [8], and spleen deficiency is the main cause of UC [9]. Evidence indicates that the TCM in JYTD can alleviate UC injury by relieving diarrhea, dispelling cold, nourishing the stomach, and strengthening the spleen [10]. However, the potential molecular mechanisms of JYTD have not been fully elucidated.

TCM is used to treat diseases through multiple compounds and targets, rather than through a single compound or target. Similarly, network pharmacology studies emphasize network targets and multi-compound therapeutics, which is consistent with the principle of TCM [11]. In addition, other bioinformatics resources, including molecular docking, have been developed to provide good opportunities for comprehensive drug

mechanism studies. Molecular docking is an important tool for computer-aided drug design [12] and can evaluate the binding potential of protein ligands based on network pharmacological prediction and analysis [13]. In this study, network pharmacology and molecular docking methods were employed to investigate potential core compounds and their targets for JYTD in the treatment of UC. Further, meta-analysis was performed to evaluate the effectiveness of JYTD. The flow chart of this analysis is shown in **Supplementary Figure 1**. The goal of this study is to provide evidence-based scientific support for the use of JYTD against UC in clinical practice.

## Material and Methods

### Identification of Compounds in JYTD

All chemical compounds of each herb in the JYTD were extracted from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) (<http://sp.nwu.edu.cn/browse.php?qc=herbs>) [14] and the Traditional Chinese Medicine Integrated Database (TCMID) (<http://119.3.41.228:8000/tc-mid/search/>) [15]. In brief, we searched these online databases using the names of the herbal medicines to obtain the corresponding compound information.

### Screening of Active Compounds

The absorption, distribution, metabolism, and excretion (ADME) parameters obtained from the TCMSP database were used to identify potential active compounds [16]. Oral bioavailability and drug-likeness are the most significant pharmacokinetic parameters in ADME. Oral bioavailability is defined as “the extent to which the active compounds are used by the human body, including the dose and rate of entry into the blood” [17]. The degree of oral bioavailability largely determines the effect of the compound on disease, and high oral bioavailability is a key indicator to confirm the similarity of bioactive molecules as therapeutic drugs [18]. Drug-likeness is a qualitative concept for drug design, and the accurate early evaluation of drug-likeness properties of a compound can assist in determining whether the compound is chemically suitable for use as a drug [19]. Thus, molecular drug-likeness evaluation is related to parameters that affect its pharmacodynamics, which ultimately influence its ADME properties [20]. In this study, the active compounds in JYTD were selected according to the criteria of oral bioavailability  $\geq 40\%$  and drug-likeness  $\geq 0.2$ .

### Prediction of Targets of Compound

The BATMAN database [21] (<http://bionet.ncpsb.org/batman-tcm/>) was used to predict target proteins corresponding to compounds. BATMAN can predict the potential targets of TCM

compounds based on the similarity approach. First, the targets existing in the Therapeutic Target Database, Drugbank, and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases were obtained; then, the predicted targets were ranked in decreasing order based on the interactions between potential targets and similarities of known targets. In the present study, target proteins with scores >20 were selected for further analysis [22].

### Cross-Validation of Target Proteins

The Comparative Toxicogenomics Database (CTD) [23] (<http://ctdbase.org/>) was published by the Mount Desert Island Biological Laboratory. The purpose of the CTD is to promote a comprehensive understanding of how environmental risks affect human health, and the CTD provides information on chemical-gene/protein interactions and chemical-disease and gene-disease relationships to help formulate disease mechanisms for environmental impacts. In the CTD, “ulcerative colitis” was used as a keyword to search for genes related to UC, and then genes were sorted by inference score [24,25]. Target proteins with scores >20 and target proteins predicted in the previous step were intersected to narrow the target protein range. The inference score was calculated from the log-transformed product of 2 public neighborhood statistics and then used to assess the functional correlation between proteins in the PPI network.

### Functional Enrichment Analysis

To explore the biological function of these targets, the Gene Ontology biological processes (GO-BP), KEGG pathways, and Reactome Gene Sets enrichment analyses were performed by using the online tool “Metascape” [26] (<http://metascape.org>) with the default parameters. The terms that conformed to the above parameters were then obtained. According to the kappa coefficient, further clustering was conducted based on the similarity of the genes enriched in each term. The top 20 clusters were presented as bar graphs. To further understand the relationship between the terms, the interactions were screened. In brief, terms with the best *P* value from each cluster were selected, and terms with similarity >0.3 were connected by edges. The network was visualized using Cytoscape software [27] (version 3.4.0, <http://chianti.ucsd.edu/cytoscape-3.4.0/>).

### PPI Network and Module Analysis

PPI pairs were explored using Metascape, and PPI enrichment analysis was conducted using the following databases: BioGrid [28], InWeb\_IM [29], and OmniPath [30]. Cytoscape software was used to construct the PPI network. Next, modules were excavated from the PPI network via the molecular complex detection (MCODE) [31] algorithm in Metascape. In addition, the

GO-BP, KEGG pathway, and Reactome enrichment analyses of genes in each module were performed.

### Construction of Pharmacological Network

Based on the herbs-compound-targets-pathways interactions, the pharmacological network was visualized using Cytoscape software.

### Molecular Docking Technology

The hub nodes with the highest connectivity in the PPI network were selected for molecular docking analysis. The 3D structure of these targets were downloaded from the Protein Data Bank (PDB) database (<http://www.rcsb.org/>) [32], and the conformations were screened according to the following conditions: (1) the protein structure was obtained using the X-ray diffraction method, (2) the resolution of protein structure was <3, (3) type was set to protein, and (4) protein ranked first in descending order of score for further study. Then, PyMol software (version 2.0 Schrödinger, LLC) was applied to remove other ligands and water molecules, and the isolated proteins were used for subsequent molecular docking. In this analysis, the compounds that targeted these key proteins and had higher degrees in the pharmacological network were regarded as the key compounds. The molecular structures of key compounds were downloaded from the PubChem Compound database (<https://pubchem.ncbi.nlm.nih.gov/>) [33] and converted to PDB format files using PyMol for further analysis. Finally, the Lamarckian GA algorithm in AutoDock (version 4.2.6) software [34] was used to dock the active compounds with the receptor protein.

### Validation of the Clinical Effect Therapeutic Effects of JYTD on UC by Using Meta-Analysis

#### Literature Search

The meta-analysis was performed in accordance with the Preferred Reporting Item for Systematic Review and Meta-Analyses (PRISMA) [35]. JYTD is derived from the classic prescription “Tao Hua decoction”, and it is widely used in UC caused by various etiologies. Thus, we used the compounds of Tao Hua decoction to verify the efficacy of the drug. Randomized controlled trials (RCTs) were searched from PubMed, Wanfang data, the China National Knowledge Infrastructure, the China Science and Technology Journal database, and the China Biology Medicine disc through September 3, 2021, with the keywords “Taohua Tang, Taohua decoction, ulcerative colitis, and UC”. The reference lists of relevant reviews and eligible RCTs were also searched to obtain additional studies that could be used for meta-analysis.

### Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients with UC diagnosed by pathology, imaging, or histology; (2) experimental group for Tao Hua decoction alone or Tao Hua decoction combined with other Chinese medicines or a control group of Western medicine treatment; (3) studies were designed as RCTs; and (4) outcome indicators were complete response rate (CRR) or overall response rate (ORR). The exclusion criteria were as follows: (1) nonrandomized trials; and (2) incomplete data on the clinical curative effect. For the same data used in multiple publications, only the study with the most complete information was included.

### Data Extraction and Quality Assessment

Two reviewers independently extracted the following information from each included study: the first author, year of publication, country of study, basic characteristics of research (sample size, sex, and age), treatment protocols, and clinical outcomes. The Cochrane Collaboration's tool [36] was used to assess the quality of included studies.

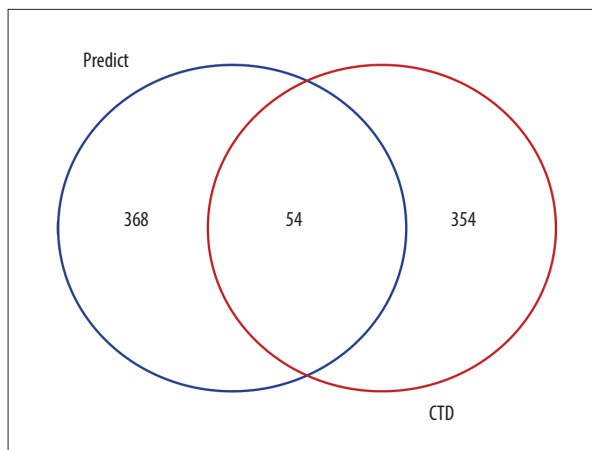
### Statistical Analysis

The odds ratio (OR) with 95% confidence interval (CI) was applied to evaluate the difference in CRR and ORR between the experimental group and control group. The Cochran's Q test and  $I^2$  test were used to measure heterogeneity among studies [37]. A value of  $P < 0.05$  and/or  $I^2 > 50\%$  were considered as significant heterogeneity, and the random effects model was selected for meta-analysis; otherwise, the fixed effects model was used to pool results ( $P \geq 0.05$  and  $I^2 \leq 50\%$ ). The Egger test was employed to assess publication bias. All statistical analyses were conducted by using RevMan 5.3 (Cochrane Collaboration, Oxford, UK) and Stata12.0 (StataCorp LP, College Station, TX, USA) software.

## Results:

### Screening of Compounds

The chemical compounds of YJTD were initially obtained from the TCMSP and TCMID databases, and 1158 compounds were identified. After filtering with 2 ADME parameters (oral bioavailability  $\geq 40\%$  and drug-likeness  $\geq 0.2$ ), 106 active compounds were obtained from 16 different herbs, including 12 from DS, 4 from BZ, 15 from HQ, 2 from GJ, 1 from CSZ, 8 from HL, 6 from HZ, 9 from SY, 2 from XM, 4 from SR, 7 from YH, 2 from YYR, 3 from MX, 4 from CP, 10 from BS, and 17 from ZGC.



**Figure 1.** Integration analysis of potential targets and ulcerative colitis-related genes using Venn online tool (<https://bioinfogp.cnb.csic.es/tools/venny/>).

### Prediction of Target Genes of YJTD

The active compounds screened in the TCMSP and TCMID databases were retrieved from the BATMAN database, and 13 core herbs and 36 active compounds with 422 potential targets were collected.

### Identification of JYTD Targets for UC Treatment

UC-related genes were searched from the CTD database using the keyword "ulcerative colitis", and 408 targets were obtained. Then, these targets were integrated with JYTD-related targets, and 54 overlapping targets were identified as effective targets for JYTD intervention in UC (Figure 1).

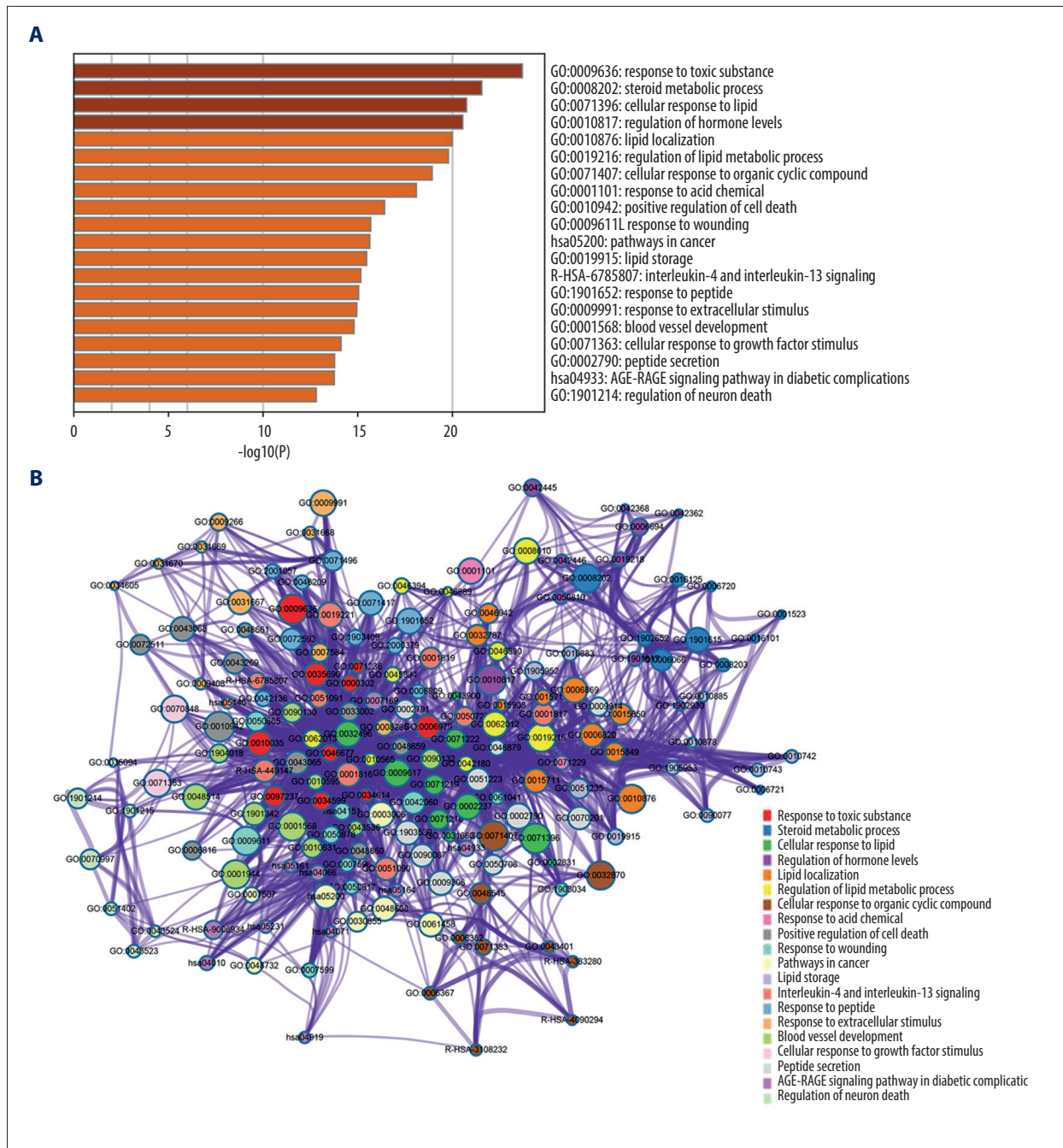
### GO and KEGG Enrichment Analysis of Effective Targets

For these overlapping genes, GO-BP and pathway enrichment analyses were carried out with the following sources: GO-BP, KEGG pathway, and Reactome Gene Sets analyses. The results showed that 1146 GO-BP terms, 111 KEGG pathways, and 81 Reactome Gene Sets were significantly enriched. After the similarity clustering analysis, 77 clusters were obtained; the top 20 clusters are displayed in Figure 2A. To further investigate the relationships between the terms in each cluster, we constructed an interactive network (Figure 2B). In brief, genes were mainly enriched in several GO-BP terms, such as response to toxic substances, steroid metabolic processes, and cellular responses to lipids; and genes were primarily involved in pathways such as pathways in cancer and the AGE-RAGE signaling pathway in diabetic complications.

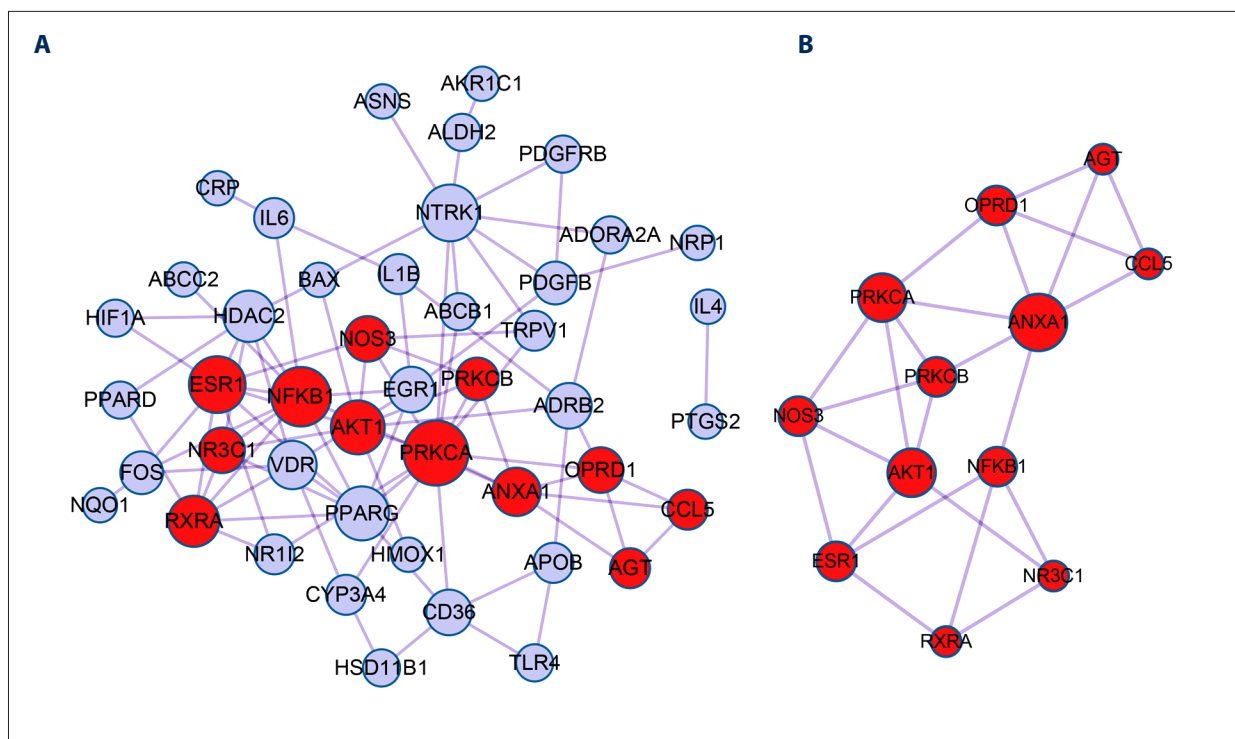
### Construction of PPI Network and Module Network

To further investigate the relationship between targets, PPI analysis was performed. The PPI network was composed of 45





**Figure 2. Functional enrichment analysis of target proteins by Metascape (<http://metascape.org>). (A) Top 20 clusters of functional enrichment; (B) interactive network of terms. Different node color indicates different clusters, the connection indicates the gene similarity between terms, and the node size indicates the number of enriched genes.**



**Figure 3.** Construction of protein-protein interaction (PPI) network using Cytoscape (version 3.4.0, <http://chianti.ucsd.edu/cytoscape-3.4.0/>). (A) Identification of PPI pair via online tool Metascape. Edge represents the protein-protein interaction and red node represents gene in module. (B) Screening of module from PPI network by using MCODE algorithm. The size of the node represents the degree value of node.

nodes and 87 connected edges (Figure 3A). The top 10 nodes with higher degrees were considered as hub genes, including *PRKCA*, *NFKB1*, *ESR1*, *NTRK1*, *AKT1*, *PPARG*, *HDAC2*, *RXRA*, *ANXA1*, and *VDR*. Next, the MCODE plugin was used to extract modules from the PPI network, and a significant module composed of 12 genes and 23 edges was identified (Figure 3B).

Functional enrichment analysis of the genes in the module was also conducted. GO enrichment analysis indicated that genes were significantly associated with cellular responses to lipids and hormone stimuli. Pathway analysis revealed that these genes were observably involved in the sphingolipid signaling pathway, AGE-RAGE signaling pathway in diabetic complications, and HIF-1 signaling pathway.

### Construction of Pharmacological Network

To more intuitively represent the relationship among herbs, compounds, targets, and pathways, a pharmacological network was constructed. This network included 13 herbal medicines, 28 compounds, 54 targets, and 724 relation pairs (Figure 4). Among these, the top 5 compounds were stigmasterol, tetrahydropalmatine, mairin, 18alpha-glycyrrhetic acid, and 18beta-glycyrrhetic acid; the top 5 targets with the greatest number of edges included *AKT1*, *ESR1*, *PTGS2*, *ANXA1*, and *IL1B*;

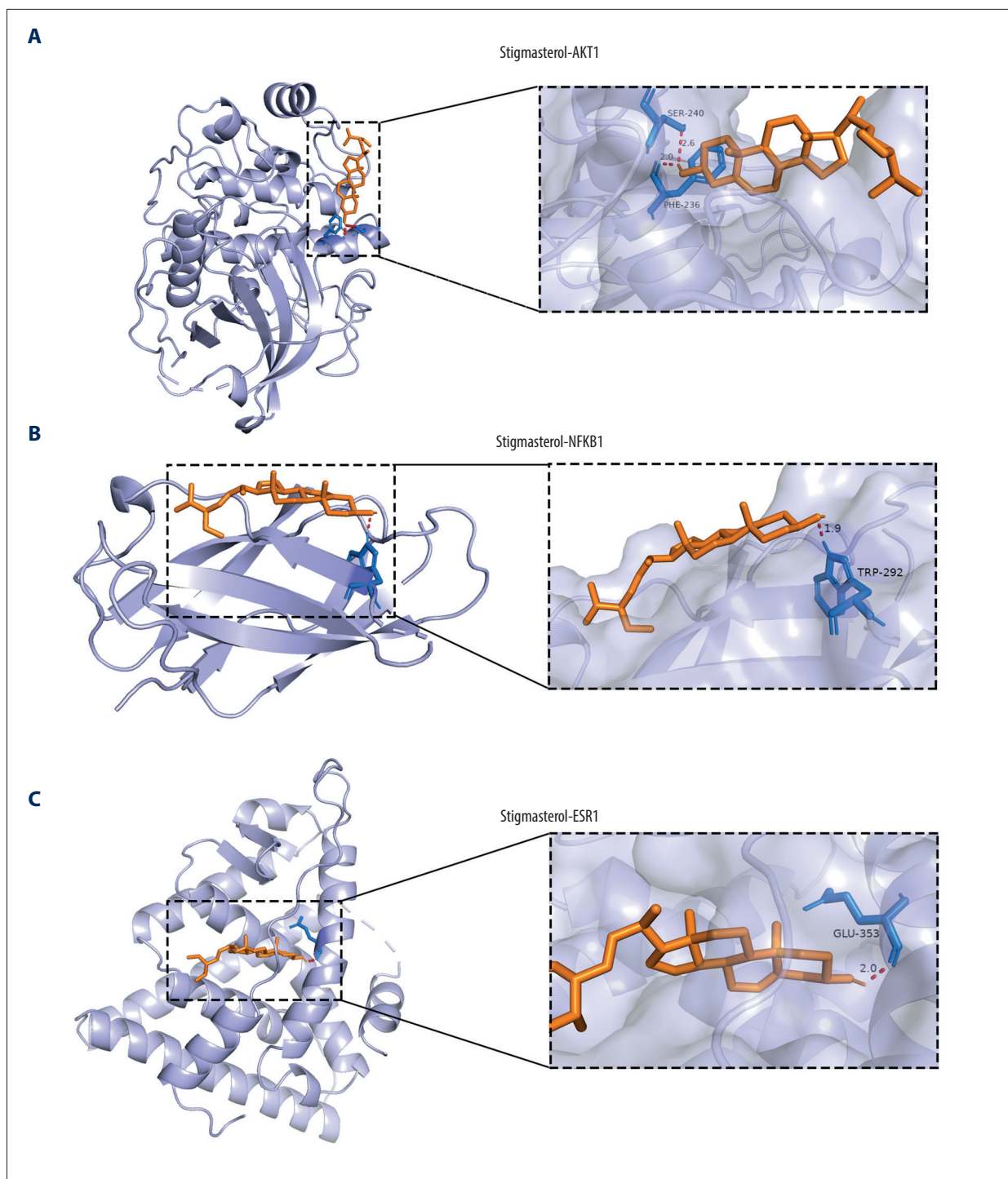
and pathways enriched by more genes primarily included interleukin-4 and interleukin-13 signaling, AGE-RAGE signaling pathway in diabetic complications, and response to peptide.

### Molecular Docking Verification

Molecular docking is an important tool in drug research and can be used to study the interactions between small ligand molecules and receptor biomacromolecules. Moreover, molecular docking can predict ligand conformation and assess binding affinity [12]. In this study, to further validate potential targets in UC treatment, molecular docking was performed on the top 6 hub genes in the PPI network (*PRKCA*, *NFKB1*, *ESR1*, *NTRK1*, *AKT1*, and *PPARG*). Specifically, drug molecules corresponding to these genes in the pharmacological network were identified. For multiple small molecules targeting the same target, we selected small molecules with higher degrees for molecular docking analysis. Finally, 6 compounds were obtained, namely, stigmasterol, protopine, (+)-catechin, 18alpha-glycyrrhetic acid, 18beta-glycyrrhetic acid, and glycyrrhetic acid. Next, the molecular docking model was generated. In brief, stigmasterol bound to the active pockets of *AKT1* and interacted with SER240 and PHE236 to form hydrogen bonds (Figure 5A); stigmasterol bound to *NFKB1* via a hydrogen bond interaction with TRP292 (Figure 5B); and stigmasterol bound to *ESR1* by

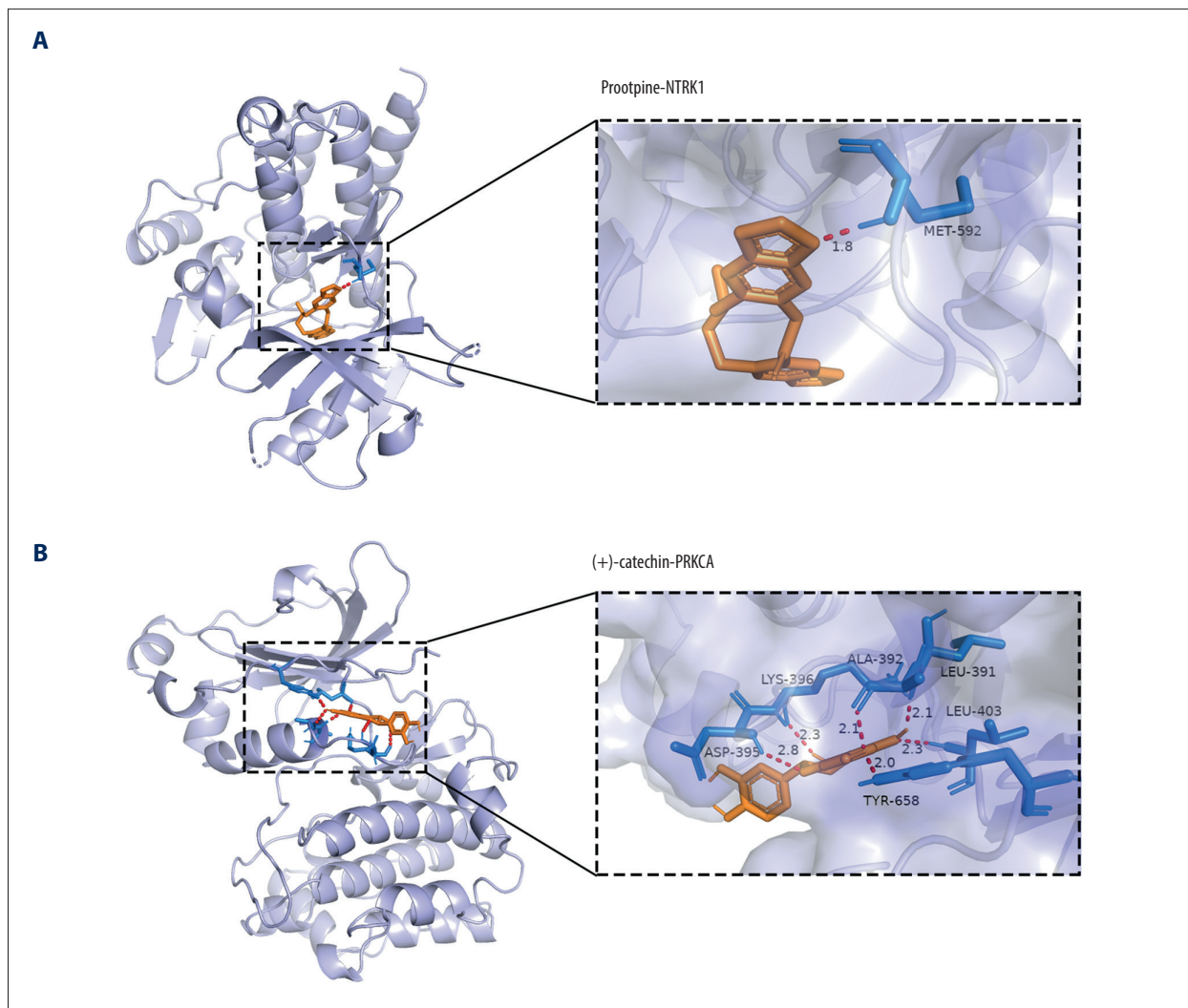






**Figure 5. Molecular docking analysis of stigmasterol with *AKT1* (A), *NFKB1* (B), and *ESR1* (C) using AutoDock 4.2 software (Sousa, Fernandes & Ramos). Purple, orange, red, and blue represent protein receptor, small drug ligand, hydrogen bond, and amino acid residue, respectively. The length of bond is added to the bond.**





**Figure 6.** The docking model of core active compounds with *NTRK1* and *PRKCA* by AutoDock 4.2 software. Protopine binds to *NTRK1* (A), and (+)-catechin binds to *PRKCA* (B). Purple, orange, red, and blue represent protein receptor, small drug ligand, hydrogen bond, and amino acid residue, respectively. The length of bond is added to the bond.

listed in **Table 1**. Moreover, high risk of bias was not observed in all studies; however, more unclear risk was found. The risk of the included literature is shown in **Figure 9**.

### Results of Meta-Analysis

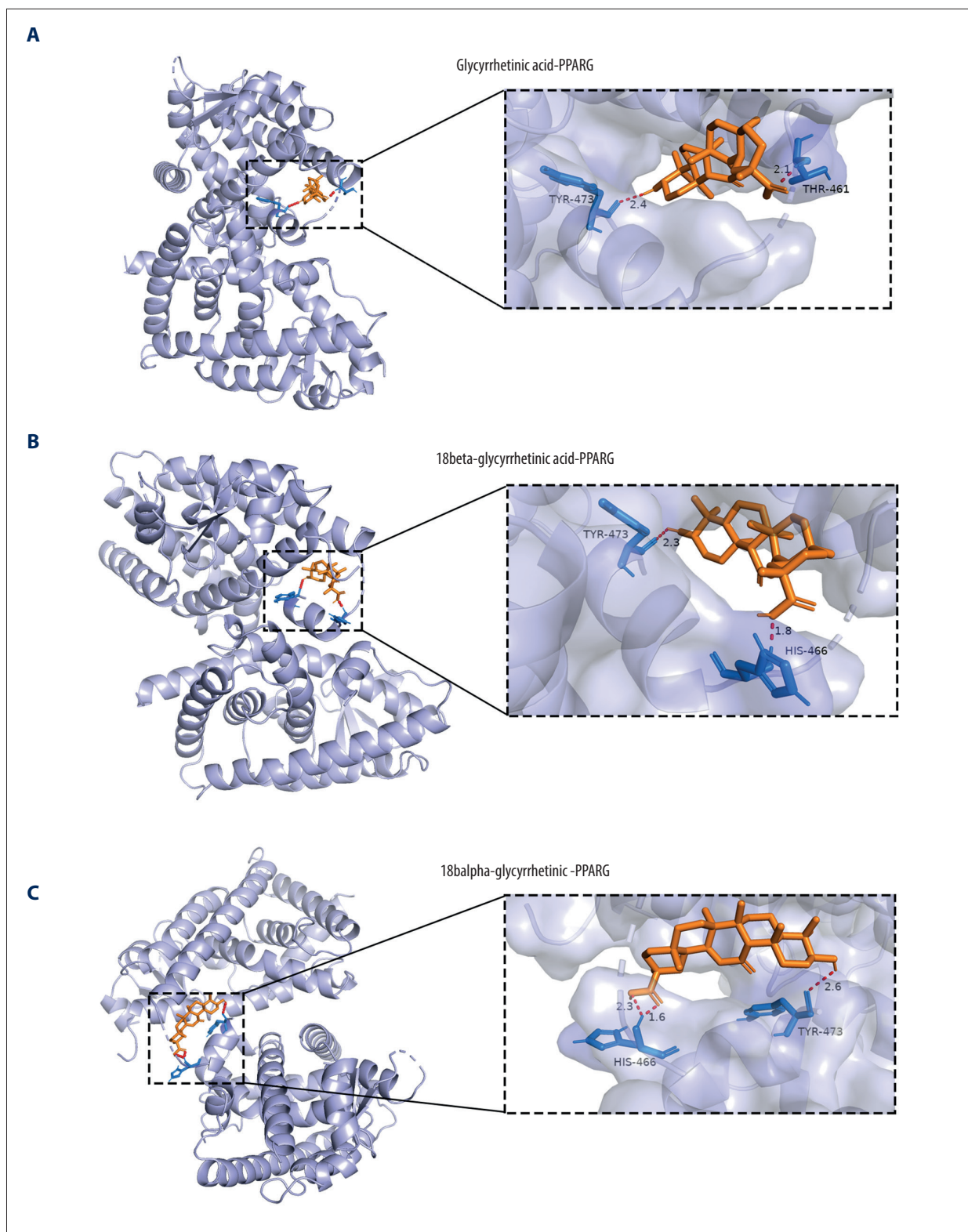
All studies reported information in CRR between the experimental groups and control groups. Due to no significant heterogeneity ( $I^2=0\%$ ;  $P=0.93$ ), a fixed effects model was selected to merge the results of CRR. The CRR was improved in the experimental group compared with the control group (RR, 1.21; 95% CI, 1.06-1.37;  $P=0.004$ ; **Figure 10A**). In addition, 6 studies reported the ORR of patients with UC after treatment. Meta-analysis showed that patients in the experimental group had higher ORR than those in the control group (RR, 1.16; 95% CI, 1.08-1.24;  $P<0.001$ ;  $I^2=0\%$ ;  $P=0.83$ ; **Figure 10B**). Further, the

Egger test indicated that there was no significant publication bias among the included studies (CRR:  $P=0.672$ ; ORR:  $P=0.659$ ).

### Discussion

UC is a nonspecific chronic colitis characterized by inflammation and ulceration of the mucosa and submucosa. As UC etiology remains unknown and no effective treatment is available, this disease generally progresses to a chronic refractory relapse. Conventional treatment can lead to poor effects on multiple pro-inflammatory and safety variables of patients with UC; thus, many TCMs have been used for UC treatment [43].

In the present study, we used the network pharmacology method to identify the potential compounds and targets of JYTD. The



**Figure 7.** Molecular docking models of glycyrrhetic acid (A), 18beta-glycyrrhetic acid (B), and 18alpha-glycyrrhetic acid (C) binding to PPARG by AutoDock 4.2 software. Purple, orange, red, and blue represent protein receptor, small drug ligand, hydrogen bond, and amino acid residue, respectively. The length of bond is added to the bond.

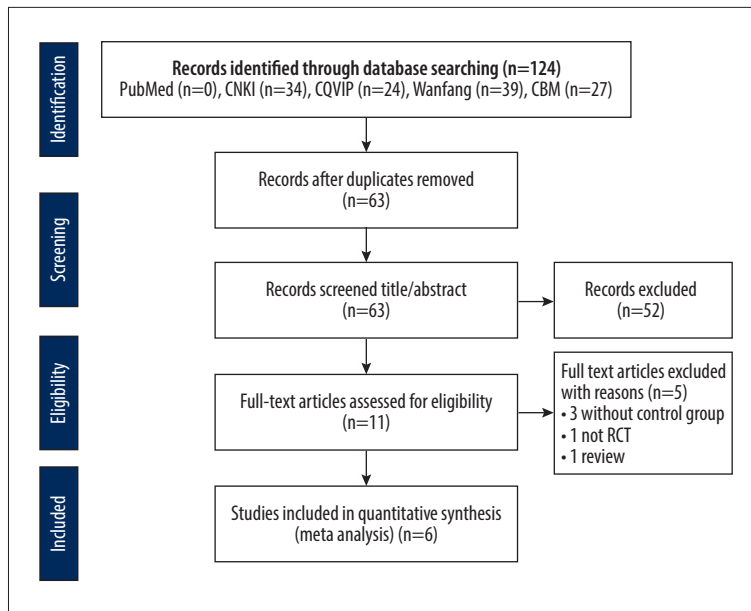
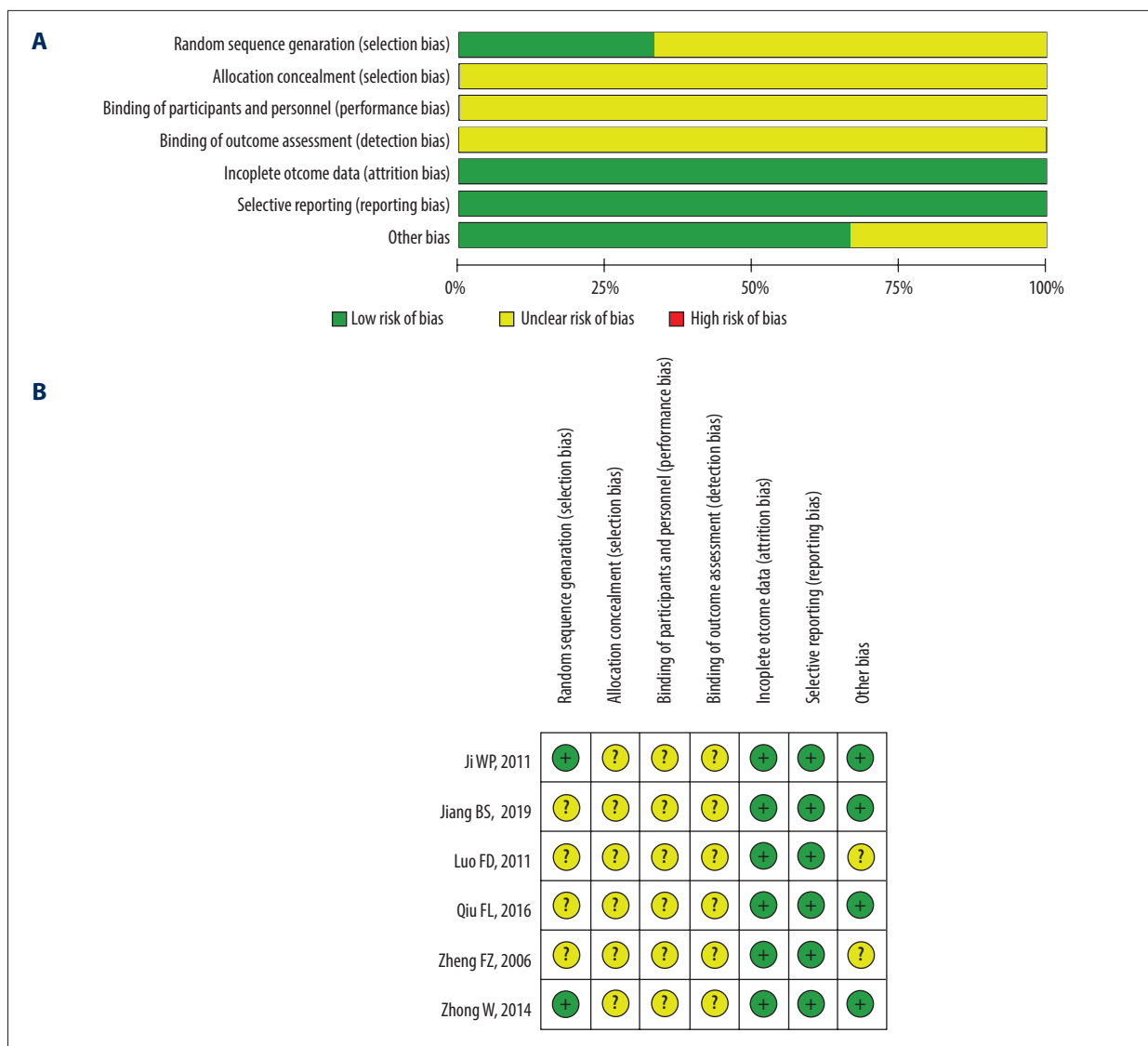


Figure 8. Flow chart of the research retrieval process.

Table 1. The characteristics of all included studies.

Study	Group	Therapeutic regimen	n, M/F	Age, years
Ji WP, 2011	Experimental	Taohua Decoction (2 times/day, 1 month/course, 2 courses)	52, 30/22	45.8±11.2
	Control	Sulfasalazine tablet 1 g (4 times/day, 1 month/course, 2 courses)	34, 20/14	44.6±11.6
Jiang BS, 2019	Experimental	Shenling Baizhu Powder + Taohua Decoction (2 times/day, 3 months/course, 1 course)	57, 32/25	36.54±6.62
	Control	Salazine tablet 1g (4 times/day, 3 months/course, 1 course)	57, 30/27	36.51±6.68
Luo FD, 2011	Experimental	Shenling Baizhu Powder + Taohua Decoction (2 times/day, 10 days/course, 3 courses)	35, NR	NR
	Control	Sulfasalazine tablet 1-2 g (4 times/day, 10 days/course, 3 courses)	33, NR	NR
Qiu FL, 2016	Experimental	Shenling Baizhu Powder + Taohua Decoction (2 times/day, 3 months/course, 1 course)	60, 34/26	38.42±8.74
	Control	Salazine tablet 1 g (3 times/day, 3 months/course, 1 course)	60, 36/24	39.25±8.84
Zheng FZ, 2006	Experimental	Taohua Decoction (2 times/day, 1 month/course, 1 course)	62, 38/24	37.2
	Control	Sulfasalazine tablet 1 g + prednisone 10 mg (4 times/day, 1 month/course, 1 course)	40, 22/18	36.4
Zhong W, 2014	Experimental	Taohua Decoction (2 times/day, 8 weeks/course, 1 course)	45, 28/17	42.5±10.6
	Control	Oxalazine sodium capsule 1 g (4 times/day, 8 weeks/course, 1 course)	45, 30/15	41.9±11.1

F – female; M – male; NR – not report.



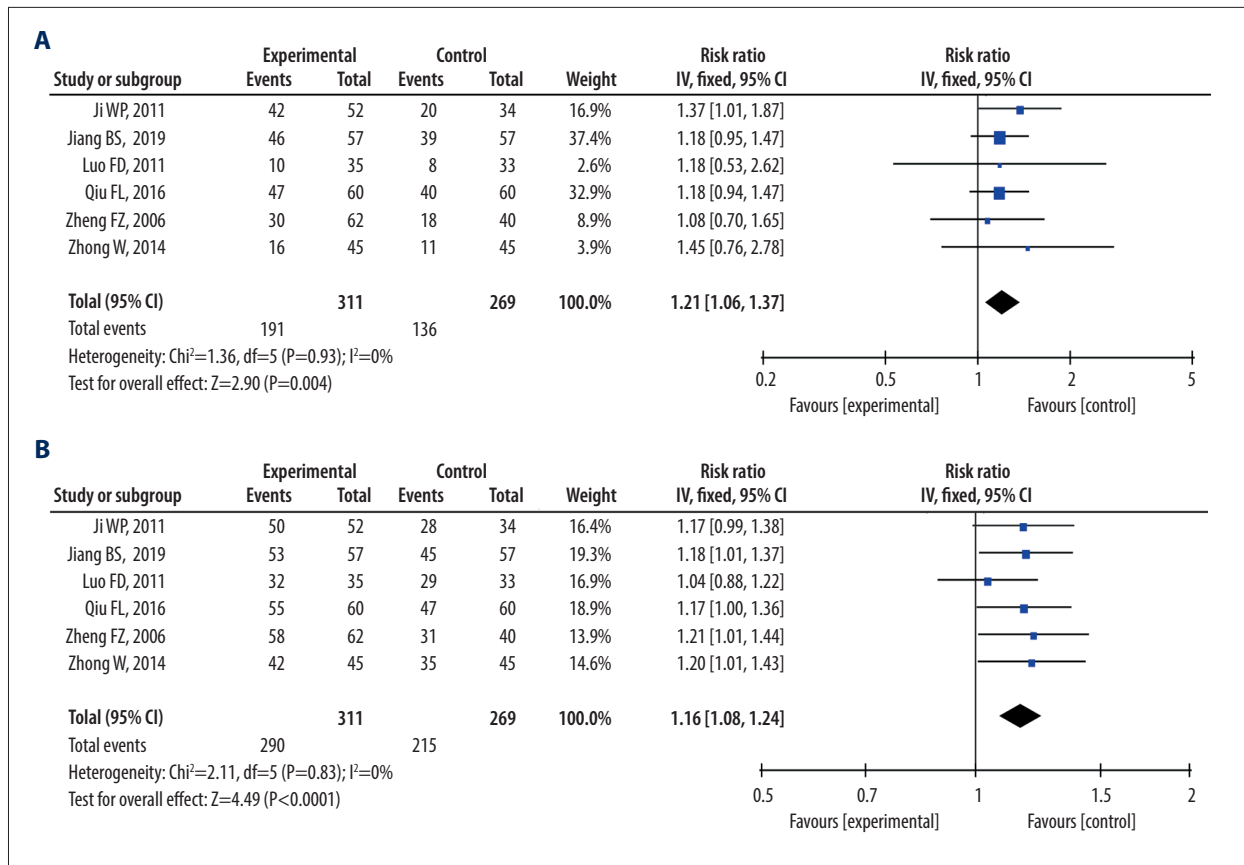
**Figure 9. Quality assessment of all included studies by using Cochrane Collaboration's tool. (A) Risk of bias graph. (B) Risk of bias summary. Green box/node represents low risk of bias, yellow box/node represents unclear risk of bias, and red box/node represents high risk of bias.**

pharmacological network revealed 28 compounds, 54 targets, and 20 pathways. Among these, the top 10 targets (*PRKCA*, *NFKB1*, *ESR1*, *NTRK1*, *AKT1*, *PPARG*, *HDAC2*, *RXRA*, *ANXA1*, and *VDR*) in the PPI network were considered as hub genes. Meanwhile, pathway analysis revealed these genes were significantly involved in the cellular response to lipids and the regulation of the lipid metabolic process. Furthermore, molecular docking indicated *PRKCA*, *NFKB1*, *ESR1*, *NTRK1*, *AKT1*, and *PPARG* had good affinity with 6 core compounds, namely stigmasterol, protopine, (+)-catechin, 18alpha-glycyrrhetic acid, 18beta-glycyrrhetic acid, and glycyrrhetic acid. Moreover, meta-analysis indicated that Tao Hua decoction showed significant efficacy for treating patients with UC, and TCMs based on Tao Hua decoction treatment observably improved ORR and

CRR compared with those of the control group (treatment with Western medicine).

Among the identified compounds, stigmasterol, liquiritigenin, and naringenin were regarded as key active compounds in the treatment of UC. Stigmasterol is an unsaturated phytosterol found in various medicinal plants and has pharmacological effects, such as anti-osteoarthritis, anti-tumor, and anti-inflammatory effects [44]. Feng et al [45] demonstrated that stigmasterol significantly inhibited colon cancer and decreased severe colitis also in the distal colon, suggesting that stigmasterol might improve colitis. In addition, Junior et al [46] observed that the extract of *Physalis angulata* L. (including stigmasterol) could regulate inflammatory mediator expression and





**Figure 10. Forest plot of Tao Hua decoction treatment versus control for CRR (A) and ORR (B) using RevMan 5.3 (Cochrane Collaboration, Oxford, UK). CRR – complete response rate; ORR – overall response rate.**

had potential use in the treatment of inflammatory bowel disease. Liquiritigenin is the main compound of Huangqin-Tang, which is widely used to treat UC in China [47]. Also, liquiritigenin had a protective effect against colitis damage, and, in a colitis mouse model treated with liquiritigenin, inflammatory factor expression was significantly suppressed [48]. Another key compound, naringenin, is a dihydroflavonoid with multiple beneficial effects, such as antibacterial, anti-inflammatory, antioxidant, and anti-tumor effects [49]. Al-Rejaie et al [50] observed that naringenin protected UC by inhibiting inflammation and oxidation biomarkers. These studies supported our findings that these key compounds might play important role in UC treatment.

The key genes identified in the PPI network were *PRKCA*, *NFKB1*, *ESR1*, *NTRK1*, *AKT1*, *PPARG*, *HDAC2*, *RXRA*, *ANXA1*, and *VDR*. *NFKB1* is an inflammatory pathway gene and its polymorphism is associated with an increased risk of inflammatory bowel disease [51,52]. *ESR1*, *PPARG*, and *AKT1* were predicted targets of the Gegen-Qinlian decoction, which was used in UC treatment [53], and these targets might be considered as potential therapeutic targets for UC. Histone deacetylase (HDAC) isoforms, such as *HDAC2*, appeared to be specifically

involved in chronic intestinal inflammation [54]. *HDAC* inhibitors significantly suppressed the development of inflammation and tumors and might be useful in UC treatment [55]. *RXRA* played an important role in regulating inflammation in acute colitis [56]. Intestinal *VDR* gene disruption affected phenotypic changes that might exacerbate inflammatory bowel disease [57]. Furthermore, *ANXA1* expression was upregulated in inflamed intestinal mucosal tissues and used as a potential biomarker for treating inflammatory bowel disease [58]. Taken together, these genes were mainly correlated with inflammation and may be potential targets of JYTD against UC.

Moreover, our study revealed that these genes were primarily involved in the cellular response to lipids and the regulation of lipid metabolic processes. Lipids play a vital role in the pathogenesis and treatment of UC. Schneider et al [59] indicated that lipids were applied to UC therapy, and phospholipids had the potential to treat inflammatory bowel disease. Moreover, Belouqui et al [60] showed that berberine could improve colitis by inhibiting lipid peroxidation. Thus, we speculate that these targets may serve a role in UC treatment via affecting lipid metabolism-related pathways.

Molecular docking revealed the interaction between compounds and targets in the pharmacological network. Results indicated that stigmasterol bound to the active pockets of *AKT1*, *NFKB1*, and *ESR1* to form hydrogen bonds; protopine bound to the active pockets of *NTRK1*; (+)-catechin was linked to *PRKCA*; glycyrrhetic acid bound to the active pocket of *PPARG*; and 18beta-glycyrrhetic acid and 18alpha-glycyrrhetic acid bound to the active pocket of *PPARG*. Andújar et al [61] found that catechin, as a major phenolic, had anti-inflammatory properties against UC in mice. As a parent constituent of Gegen-Qinlian decoction, glycyrrhetic acid was effective against inflammatory intestinal diseases such as UC [62]. These results suggested that active JYTD compounds could effectively treat UC by binding core genes.

Further, meta-analysis systematically collected the available data and measured the current clinical evidence supporting the efficacy of JYTD in providing benefits in UC treatment. Unfortunately, only a few studies reported the direct relationship between JYTD and UC. Nevertheless, JYTD was derived from the basis of “Tao Hua decoction”; therefore, we used “Tao Hua decoction and UC” as keywords to screen relevant studies. Finally, 6 RCTs were included, and from these, the TCMs in the experimental group included “Tao Hua decoction” and “Shenling Baizhu powder combined with Tao Hua decoction”. Although the meta-analysis did not include a JYTD-related study, the key herbs in these 2 TCMs were all contained in JYTD, such as DS, BZ, HQ, CSZ, GJ, and JM. Meta-analysis results revealed that these TCMs based on the Tao Hua decoction could significantly improve the therapeutic effect of UC. Importantly, there was no significant heterogeneity among included studies; thus, the studies had good consistency and the results were reliable. These results provide a clue for further research related to JYTD-based therapy in UC treatment.

Notably, there are limitations in the current study. First, not all compounds from JYTD, such as JM, are identified in the TCMSP database, and therefore several key compounds and their targets may be missing. Second, all targets are obtained via predicting, and molecular docking analysis can only reveal the

binding between compounds and targets, while it cannot reflect whether gene expression is inhibited or promoted. Third, the dose effect is very important in the clinic, and the network pharmacology approach cannot offer dose-effect outcomes. Fourth, gut microbiota can transform drugs and herbal compounds and impact their efficacy and toxicity [63]; however, network pharmacology cannot accurately predict the effects of drugs on the gut microbiota. Moreover, the function of gut microbiota varies from person to person, and thus personalized research is required to reveal a drug response in depth. Finally, although a meta-analysis was used to verify the pharmacological results, the number of included studies as well as their sample sizes were small, and few studies directly reported the role of JYTD in UC. In addition, the biological function of identified targets and compounds has not been explored. Therefore, in vivo experiments and clinical trials should be performed to validate our findings.

## Conclusions

In conclusion, network pharmacological analysis and meta-analysis revealed that JYTD had therapeutic effects on patients with UC partly by regulating multiple compounds, targets, and lipid metabolism-related pathways. Meanwhile, molecular docking results further revealed that several JYTD compounds exhibited a good affinity for their core targets. Our study provides a new perspective for further elucidating the mechanisms of JYTD in UC treatment.

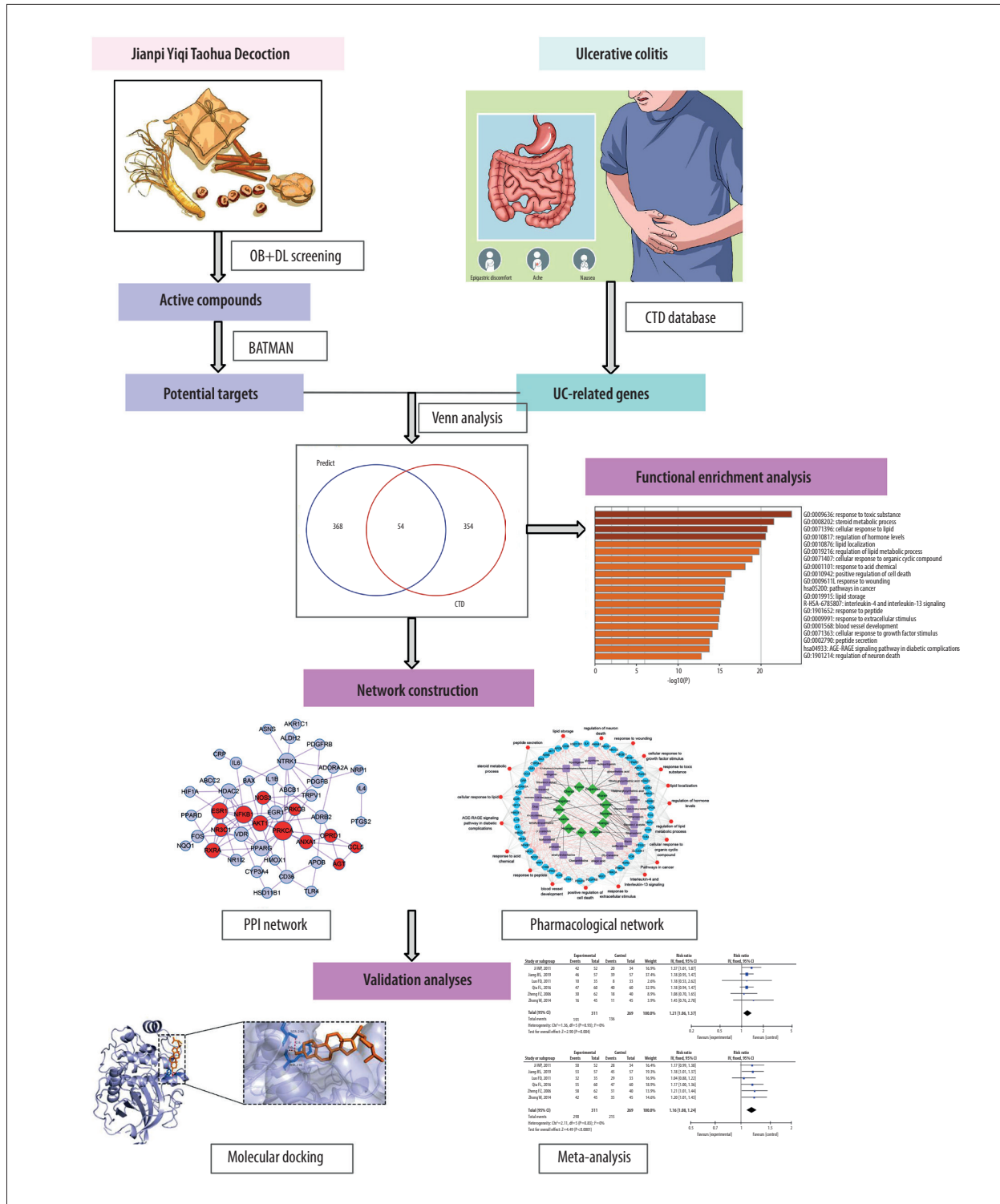
## Department and Institution Where Work Was Done

The work was done in the Department of Traditional Chinese Medicine, Taian City Central Hospital, Taian, Shandong, China.

## Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Supplementary Material



Supplementary Figure 1. The flow chart of this analysis.

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