ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 September 16; 9(26): 7614-7962

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 9 Number 26 September 16, 2021

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 26 September 16, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 26 September 16, 2021

Contents

LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 26 September 16, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Alessandro Leite Cavalcanti, DDS, MSc, PhD, Associate Professor, Department of Dentistry, State University of Paraiba, Campina Grande 58429500, Paraiba, Brazil. alessandrouepb@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
September 16, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2021 September 16; 9(26): 7653-7670

DOI: 10.12998/wjcc.v9.i26.7653

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Basic Study

Mechanism of Jianpi Qingchang Huashi Recipe in treating ulcerative colitis: A study based on network pharmacology and molecular docking

Lie Zheng, Xin-Li Wen, Yan-Cheng Dai

ORCID number: Lie Zheng 0000-0002-8243-3736; Xin-Li Wen 0000-0001-5003-862X; Yan-Cheng Dai 0000-0002-4754-1897.

Author contributions: Zheng L and Dai YC performed the writing and revising of the manuscript; Zheng L and Wen XL contributed to the design of the work and performed overall supervision; Zheng L wrote and revised the paper.

Supported by Shaanxi Province Natural Science Basic Research Program-General Project, No. 2019JM-580 and No. 2021SF-314; Project of Shaanxi Administration of Traditional Chinese Medicine, No. 2019-ZZ-JC010; and Key Clinical Specialty Construction Project supported by Hongkou District Health Committee, No. HKZK2020A01.

Institutional review board statement: Since this article is a molecular mechanism study of network pharmacology and does not involve animal experiments and clinical experiments, it does not require the approval of the ethics committee.

Conflict-of-interest statement: The authors declare that there are no

Lie Zheng, Xin-Li Wen, Department of Gastroenterology, Shaanxi Hospital of Traditional Chinese Medicine, Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an 730000, Shaanxi Province, China

Yan-Cheng Dai, Department of Gastroenterology, Shanghai Traditional Chinese Medicine Integrated Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200082, China

Corresponding author: Yan-Cheng Dai, MD, Director, Professor, Department of Gastroenterology, Shanghai Traditional Chinese Medicine Integrated Hospital, Shanghai University of Traditional Chinese Medicine, No. 230 Baoding Road, Shanghai 200082, China. daiyancheng2005@sohu.com

Abstract

BACKGROUND

Ulcerative colitis (UC) is a refractory intestinal disease with alternating onset and remission and a long disease course, which seriously affects the health and quality of life of patients. The goal of treatment is to control clinical symptoms, induce and maintain remission, promote mucosal healing, and reduce recurrence. Clinical trials have shown unsatisfactory clinical response rates. As a supplementary alternative medicine, traditional Chinese medicine has a rich history and has shown good results in the treatment of UC. Because of the quality of herbal medicine and other factors, the curative effect of traditional Chinese medicine is not stable enough. The mechanism underlying the effect of Jianpi Qingchang Huashi Recipe (JPQCHSR) on inducing UC mucosal healing is not clear.

AIM

To investigate the potential mechanism of JPQCHSR for the treatment of UC based on network pharmacology and molecular docking.

METHODS

Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform was used to extract the active components and action targets of JPQCHSR, and the target names were standardized and corrected through UniProt database. The related targets of UC were obtained through GeneCards database, and the intersection targets of drugs and diseases were screened by

conflicts of interest.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 24, 2020
Peer-review started: December 24, 2020
First decision: May 8, 2021
Revised: May 28, 2021
Accepted: July 7, 2021
Article in press: July 7, 2021
Published online: September 16, 2021

P-Reviewer: Nakaji K
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Li JH

jvenn online analysis tool. The visual regulatory network of "Traditional Chinese medicine-active components-target-disease" was constructed using Cytoscape software, the protein interaction network was constructed using STRING database, and enrichment analysis of gene ontology and Kyoto Encyclopedia of Genes and Genomes pathways was conducted through R software. At last, the active components were docked with the core target through SYBYL-X 2.1.1 software.

RESULTS

Through database analysis, a total of 181 active components, 302 targets and 205 therapeutic targets were obtained for JPQCHSR. The key compounds include quercetin, luteolin, kaempferol, *etc.* The core targets involved STAT3, AKT1, TP53, MAPK1, MAPK3, JUN, TNF, *etc.* A total of 2861 items were obtained by GO enrichment analysis, and 171 items were obtained by KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis. The results of molecular docking showed that the key active components in JPQCHSR had certain affinity with the core target.

CONCLUSION

The treatment of UC with JPQCHSR is a complex process of multi-component, multi-target and multi-pathway regulation. The mechanism of this Recipe in the treatment of UC can be predicted through network pharmacology and molecular docking, so as to provide theoretical reference for it to better play its therapeutic role.

Key Words: Jianpi Qingchang Huashi Recipe; Ulcerative colitis; Network pharmacology; Molecular docking; Inflammatory disease

Core Tip: Ulcerative colitis (UC) is a chronic non-specific inflammatory disease that can cause varying degrees of mucosal inflammation from the rectum to the proximal colon. The mechanism of this Recipe in the treatment of UC can be predicted through network pharmacology and molecular docking, so as to provide theoretical reference for it to better play its therapeutic role.

Citation: Zheng L, Wen XL, Dai YC. Mechanism of Jianpi Qingchang Huashi Recipe in treating ulcerative colitis: A study based on network pharmacology and molecular docking. *World J Clin Cases* 2021; 9(26): 7653-7670
URL: https://www.wjgnet.com/2307-8960/full/v9/i26/7653.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i26.7653

INTRODUCTION

Ulcerative colitis (UC) is a chronic non-specific inflammatory disease that can cause varying degrees of mucosal inflammation from the rectum to the proximal colon[1]. Its typical clinical manifestations include diarrhea, mucus and blood in stools, and abdominal pain[2]. The disease can affect the intestinal mucosa and muscularis mucosa and is featured by a recurrent and prolonged course. Its pathogenesis involves genetic susceptibility, epithelial barrier defects, dysregulated immune response, and environmental factors[3]. As one of the common refractory diseases in the digestive system, UC has unclear and complex pathogenic mechanisms. Western medicine-based treatments for UC rely mostly on drug therapies. Although these drugs can achieve quick remission in most patients, there is no radical cure. Furthermore, patients receiving Western medicine-based therapies often suffer from problems including hormone dependence, drug resistance, and treatment-related toxicities[4]. Therefore, many patients with UC as well as physicians and researchers are increasingly considering complementary and alternative medicine (CAM) option[5]. In North American and European studies, the rate of current or past use of CAM for the

treatment of UC is 21%-60%[6,7], of which herbal medicine, especially CAM intervention, is the first choice[8]. As a supplementary alternative medicine, traditional Chinese medicine (TCM) has a long history and has shown good results in the treatment of UC. Through multi-component, multi-target holistic therapies, TCM can effectively improve intestinal inflammation.

Jianpi Qingchang Recipe (JPQCR, or spleen-invigorating and intestine-clearing recipe) is modified from Shenling Baizhu Powder, which was recorded in *Taiping Huimin Heji Ju Fang* (Prescriptions of the Bureau of Taiping People's Welfare Pharmacy), and Diyu Powder, which was described in *Sheng Ji Zonglu* (General Records of Holy Universal Relief). Previous studies from our group showed that oral Chinese medicine compounds were effective for the treatment of UC, inducing and maintaining remission, although the time until the effect was evident was relatively slow. Many studies have shown that JPQCR can markedly improve dextran sulphate sodium (DSS)-induced UC in mouse models[9], which may be explained that JPQCR can inhibit the activation of nuclear factor-kappa B (NF-κB), down-regulate inflammatory mediators [*e.g.*, MPO, interleukin (IL)-1β, IL-8, and tumor necrosis factor alpha (TNF-α)], and improve the barrier function of the intestinal epithelium. In addition, JPQCR can regulate DSS-induced abnormal intestinal motility in UC mice by inhibiting the cascade of intestinal inflammation and reducing autophagy in interstitial cells of Cajal[10,11]. Based on JPQCR, the Jianpi Qingchang Huashi Recipe (JPQCHSR) has newly added TCM drugs including *Poria, Tangerine Peel, Coix Seed, Alisma, and Radix Scutellariae*. The prescription is composed of *Codonopsis, Astragalus, Rhizoma Coptis, Poria cocos, Tangerine Peel, Coix Seed, Alisma, Purslane, Radix Sanguisorbae, Radix Aucklandiae, Scutellaria, and Radix Glycyrrhizae* and is effective for clinical treatment of UC.

TCM drugs are characterized by multi-component, multi-target, and multi-pathway. The TCM formulas are prepared in accordance with the principles of "Sovereign, Minister, Assistant, and Courier". Under the guidance of a patient-centered holistic view, TCM formulas start from the integration between “whole” and “parts” and systematically regulate human body through the *in vivo* metabolism of the active components in the drugs. However, it is often difficult to identify the mechanisms of action of a specific formula. Compared with western medicine[12], traditional Chinese medicine formula may not quickly induce UC remission and control clinical symptoms. In addition, because of the quality of herbal medicine and other factors, the curative effect of TCM is not stable enough. The patients reported a poor taste of traditional Chinese medicine formula and had poor follow-up compliance. TCM drugs exert their effects in both independent and synergistic manners. The “independence” is reflected in the direct or indirect influence or action of a certain drug component on a target, whereas the “synergy” refers that there are synergistic or antagonistic effects among multiple components of a TCM drug and they treat diseases as a whole. In recent years, network pharmacology has been proposed for overall, multi-level, and multi-grade research on TCM formulas. Based on systems biology and computer networks, network pharmacology is the study of the interactions among related nodes, so as to explain the mechanisms of action of drugs in treating diseases. The core concept of "multi-component, multi-target, and multi-pathway" of network pharmacology is consistent with the "holistic view" of TCM theory, and thus network pharmacology may enable the accurate prediction and analysis of the mechanisms of action of TCM compound prescriptions[13]. Molecular docking is a receptor-based virtual screening technology that mainly studies the interaction among molecules and predicts the binding mode and affinity between ligands and receptors[14,15]. In recent years, molecular docking has become an important technology in computer-aided drug design[16,17]. This study aims to explore the mechanisms of action of JPQCHSR in the treatment of UC through network pharmacology and molecular docking, in an attempt to further promote the development and use of JPQCHSR and provide new insights into the treatment of UC.

MATERIALS AND METHODS

Databases and software

Data were searched from databases including Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (https://tcmspw.com/tcmsp.php)[18], UniProt (https://www.uniprot.org/), GeneCards (https://www.genecards.org/), Jvenn (http://jvenn.toulouse.inra.fr/app/index.html)[19], STRING 11.0 (https://string-db.org/), and Chemical Book (https://www.chemicalbook.

com/ProductIndex.aspx)[20]. The software used included Cytoscape version 3.7.2, R version 3.6.3, cluster Profiler, and SYBYL-X version 2.1.1.

Active components and targets of action of JPQCHSR

Using the keywords "*Radix Codonopsis*", "*Astragalus*", "*Coptis*", "*Poria*", "*Tangerine Peel*", "*Coix Seed*", "*Alismaceae*", "*Herba Portulacae*", "*Radix Sanguisorbae*", "*Radix Aucklandiae*", "*Radix Scutellariae*" *and* "*Radix Glycyrrhizae*", we retrieved the active components of 12 TCM drugs in JPQCHSR in the TCMSP database. According to the pharmacokinetic principles, the active components were screened using the criteria including oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. The relevant targets of the active components were extracted from the TCMSP database, and the targets of action were standardized and corrected using the human genes that have been validated in the UniProt database. Components without action targets and targets without standard names were deleted and active components and validated targets were collected, thus yielding the active components of JPQCHSR and the related targets of action in human beings.

Predicting the UC-related targets

Using the keyword "ulcerative colitis", we searched the GeneCards database for UC-related targets.

Establishing the "TCM drugs-Active Components-Targets-Diseases" network

Using the jvenn online analysis tool, we mapped the active component targets obtained in Section 1.2 with the disease targets in Section 1.3, and the intersection was the potential targets of JPQCHSR in the treatment of UC. Files containing TCM drugs, active components, targets, disease information and their attribute files were imported into the Cytoscape version 3.7.2 to construct a visual network of "TCM Drugs-Active Components-Targets-Diseases". With the help of the "Network analyzer" plug-in in the software, the topological properties of network nodes were analyzed, and the key active components of JPQCHSR for treating UC were obtained according to the "degree" values.

Establishing a protein-protein interaction network

The "Active components-Diseases" intersection target genes obtained in Section 1.4 were imported into the STRING 11.0 database (http://string-db.org), and the species were limited to "homo sapiens". Data with a confidence level higher than 0.900 were selected, and isolated nodes were removed. Then, a protein-protein interaction (PPI) network was constructed. According to the "degree" values, the core targets of JPQCHSR in the treatment of UC were screened.

GO and KEGG enrichment analysis

Based on the cluster Profiler package in the R 3.6.3 software, we performed GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analyses on the potential targets of active components. The results were filtered based on P values ($P < 0.05$). R 3.6.3 software was used to visualize the results, during which bubble charts and bar charts were drawn.

Molecular docking

The Chemical Book database was searched to obtain the active components (mol. files), and the results were imported into the SYBYL-X 2.1.1 software for energy optimization. The PDB files of the crystal structure of the core target proteins were downloaded from the RSCB PDB database. After a series of optimization steps (including ligand extraction, hydrogenation, and water extraction) in the SYBYL-X 2.1.1 software, molecular docking was performed using the Surflex-Dock module in the software, and the binding activity was evaluated through function scoring.

RESULTS

Active components and targets of action of JPQCHSR

After the TCM drugs in JPQCHSR were searched in the TCMSP database, 251 active components were obtained. Using the OB ≥ 30% and a DL index ≥ 0.18 as potential active compounds and excluding both non-target compounds and duplicate compounds, 181 active components corresponding to 302 targets were derived. The

Table 1 Jianpi Qingchang Huashi Recipe main active ingredients

No.	MOL ID	Compound	Source	No.	MOL ID	Compound	Source
1	MOL001006	*poriferasta-7,22E-dien-3beta-ol*	*Codonopsis*	92	MOL004806	*euchrenone*	*Radix Glycyrrhizae*
2	MOL002140	*Perlolyrine*	*Codonopsis*	93	MOL004808	*glyasperin B*	*Radix Glycyrrhizae*
3	MOL003036	*ZINC03978781*	*Codonopsis*	94	MOL004810	*glyasperin F*	*Radix Glycyrrhizae*
4	MOL004355	*Spinasterol*	*Codonopsis*	95	MOL004811	*Glyasperin C*	*Radix Glycyrrhizae*
5	MOL005321	*Frutinone A*	*Codonopsis*	96	MOL004814	*Isotrifoliol*	*Radix Glycyrrhizae*
6	MOL006774	*stigmast-7-enol*	*Codonopsis*	97	MOL004815	*(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one*	*Radix Glycyrrhizae*
7	MOL007059	*3-beta-Hydroxymethyllenetanshiquinone*	*Codonopsis*	98	MOL004820	*kanzonols W*	*Radix Glycyrrhizae*
8	MOL007514	*methyl icosa-11,14-dienoate*	*Codonopsis*	99	MOL004824	*(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one*	*Radix Glycyrrhizae*
9	MOL008393	*7-(beta-Xylosyl)cephalomannine_qt*	*Codonopsis*	100	MOL004827	*Semilicoisoflavone B*	*Radix Glycyrrhizae*
10	MOL008397	*Daturilin*	*Codonopsis*	101	MOL004828	*Glepidotin A*	*Radix Glycyrrhizae*
11	MOL008400	*glycitein*	*Codonopsis*	102	MOL004829	*Glepidotin B*	*Radix Glycyrrhizae*
12	MOL008407	*(8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-1,2,4,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one*	*Codonopsis*	103	MOL004833	*Phaseolinisoflavan*	*Radix Glycyrrhizae*
13	MOL008411	*11-Hydroxyrankinidine*	*Codonopsis*	104	MOL004835	*Glypallichalcone*	*Radix Glycyrrhizae*
14	MOL000033	*(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol*	*Astragalus*	105	MOL004838	*8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol*	*Radix Glycyrrhizae*
15	MOL000371	*3,9-di-O-methylnissolin*	*Astragalus*	106	MOL004841	*Licochalcone B*	*Radix Glycyrrhizae*
16	MOL000378	*7-O-methylisomucronulatol*	*Astragalus*	107	MOL004848	*licochalcone G*	*Radix Glycyrrhizae*
17	MOL000379	*9,10-dimethoxypterocarpan-3-O-β-D-glucoside*	*Astragalus*	108	MOL004849	*3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin*	*Radix Glycyrrhizae*
18	MOL000380	*(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol*	*Astragalus*	109	MOL004855	*Licoricone*	*Radix Glycyrrhizae*
19	MOL000387	*Bifendate*	*Astragalus*	110	MOL004856	*Gancaonin A*	*Radix Glycyrrhizae*
20	MOL000433	*FA*	*Astragalus*	111	MOL004857	*Gancaonin B*	*Radix Glycyrrhizae*
21	MOL000439	*isomucronulatol-7,2'-di-O-glucosiole*	*Astragalus*	112	MOL004863	*3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone*	*Radix Glycyrrhizae*
22	MOL000442	*1,7-Dihydroxy-3,9-dimethoxy pterocarpene*	*Astragalus*	113	MOL004864	*5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone*	*Radix Glycyrrhizae*
23	MOL001454	*berberine*	*Rhizoma Coptis*	114	MOL004866	*2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone*	*Radix Glycyrrhizae*
24	MOL002894	*berberrubine*	*Rhizoma Coptis*	115	MOL004879	*Glycyrin*	*Radix Glycyrrhizae*
25	MOL002903	*(R)-Canadine*	*Rhizoma Coptis*	116	MOL004882	*Licocoumarone*	*Radix Glycyrrhizae*
26	MOL002904	*Berlambine*	*Rhizoma Coptis*	117	MOL004883	*Licoisoflavone*	*Radix Glycyrrhizae*
27	MOL002907	*Corchoroside A_qt*	*Rhizoma Coptis*	118	MOL004884	*Licoisoflavone B*	*Radix Glycyrrhizae*
28	MOL000622	*Magnograndiolide*	*Rhizoma Coptis*	119	MOL004885	*licoisoflavanone*	*Radix Glycyrrhizae*

29	MOL000785	*palmatine*	*Rhizoma Coptis*	120	MOL004891	*shinpterocarpin*	*Radix Glycyrrhizae*
30	MOL002668	*Worenine*	*Rhizoma Coptis*	121	MOL004898	*(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one*	*Radix Glycyrrhizae*
31	MOL000273	*(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid*	*Poria cocos*	122	MOL004903	*liquiritin*	*Radix Glycyrrhizae*
32	MOL000275	*trametenolic acid*	*Poria cocos*	123	MOL004904	*licopyranocoumarin*	*Radix Glycyrrhizae*
33	MOL000279	*Cerevisterol*	*Poria cocos*	124	MOL004907	*Glyzaglabrin*	*Radix Glycyrrhizae*
34	MOL000282	*ergosta-7,22E-dien-3beta-ol*	*Poria cocos*	125	MOL004908	*Glabridin*	*Radix Glycyrrhizae*
35	MOL000283	*Ergosterol peroxide*	*Poria cocos*	126	MOL004910	*Glabranin*	*Radix Glycyrrhizae*
36	MOL005815	*Citromitin*	*Tangerine Peel*	127	MOL004911	*Glabrene*	*Radix Glycyrrhizae*
37	MOL005828	*nobiletin*	*Tangerine Peel*	128	MOL004912	*Glabrone*	*Radix Glycyrrhizae*
38	MOL001323	*Sitosterol alpha1*	*Coix Seed*	129	MOL004913	*1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone*	*Radix Glycyrrhizae*
39	MOL001494	*Mandenol*	*Coix Seed*	130	MOL004914	*1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone*	*Radix Glycyrrhizae*
40	MOL008121	*2-Monoolein*	*Coix Seed*	131	MOL004915	*Eurycarpin A*	*Radix Glycyrrhizae*
41	MOL000953	*CLR*	*Coix Seed*	132	MOL004924	*(-)-Medicocarpin*	*Radix Glycyrrhizae*
42	MOL000831	*Alisol B monoacetate*	*Alisma*	133	MOL004935	*Sigmoidin-B*	*Radix Glycyrrhizae*
43	MOL000849	*16β-methoxyalisol B monoacetate*	*Alisma*	134	MOL004941	*(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one*	*Radix Glycyrrhizae*
44	MOL000853	*alisol B*	*Alisma*	135	MOL004945	*(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one*	*Radix Glycyrrhizae*
45	MOL000856	*alisol C monoacetate*	*Alisma*	136	MOL004948	*Isoglycyrol*	*Radix Glycyrrhizae*
46	MOL002464	*1-Monolinolein*	*Alisma*	137	MOL004949	*Isolicoflavonol*	*Radix Glycyrrhizae*
47	MOL000862	*[(1S,3R)-1-[(2R)-3,3-dimethyloxiran-2-yl]-3-[(5R,8S,9S,10S,11S,14R)-11-hydroxy-4,4,8,10,14-pentamethyl-3-oxo-1,2,5,6,7,9,11,12,15,16-decahydrocyclopenta[a]phenanthren-17-yl]butyl] acetate*	*Alisma*	138	MOL004957	*HMO*	*Radix Glycyrrhizae*
48	MOL001439	*arachidonic acid*	*Purslane*	139	MOL004959	*1-Methoxyphaseollidin*	*Radix Glycyrrhizae*
49	MOL003578	*Cycloartenol*	*Purslane*	140	MOL004961	*Quercetin der.*	*Radix Glycyrrhizae*
50	MOL002773	*beta-carotene*	*Purslane*	141	MOL004966	*3'-Hydroxy-4'-O-Methylglabridin*	*Radix Glycyrrhizae*
51	MOL006657	*isobetanidin*	*Purslane*	142	MOL000497	*licochalcone a*	*Radix Glycyrrhizae*
52	MOL006662	*isobetanin_qt*	*Purslane*	143	MOL004974	*3'-Methoxyglabridin*	*Radix Glycyrrhizae*
53	MOL005399	*alexandrin_qt*	*Radix Sanguisorbae*	144	MOL004978	*2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol*	*Radix Glycyrrhizae*
54	MOL005853	*methyl-2,3,6-tri-O-galloyl-β-D-glucopyranoside*	*Radix Sanguisorbae*	145	MOL004980	*Inflacoumarin A*	*Radix Glycyrrhizae*
55	MOL005858	*3,7,8-Tri-O-methylellagic acid*	*Radix Sanguisorbae*	146	MOL004985	*icos-5-enoic acid*	*Radix Glycyrrhizae*
56	MOL005864	*methyl-6-O-galloyl-β-D-glucopyranoside*	*Radix*	147	MOL004988	*Kanzonol F*	*Radix Glycyrrhizae*

			Sanguisorbae				
57	MOL005869	*daucostero_qt*	*Radix Sanguisorbae*	148	MOL004989	*6-prenylated eriodictyol*	*Radix Glycyrrhizae*
58	MOL010813	*Benzo[a]carbazole*	*Radix Aucklandiae*	149	MOL004990	*7,2',4'-trihydroxy□5-methoxy-3□arylcoumarin*	*Radix Glycyrrhizae*
59	MOL010828	*cynaropicrin*	*Radix Aucklandiae*	150	MOL004991	*7-Acetoxy-2-methylisoflavone*	*Radix Glycyrrhizae*
60	MOL001689	*acacetin*	*Scutellaria*	151	MOL004993	*8-prenylated eriodictyol*	*Radix Glycyrrhizae*
61	MOL000173	*wogonin*	*Scutellaria*	152	MOL004996	*gadelaidic acid*	*Radix Glycyrrhizae*
62	MOL000228	*(2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one*	*Scutellaria*	153	MOL000500	*Vestitol*	*Radix Glycyrrhizae*
63	MOL002714	*baicalein*	*Scutellaria*	154	MOL005000	*Gancaonin G*	*Radix Glycyrrhizae*
64	MOL002909	*5,7,2,5-tetrahydroxy-8,6-dimethoxyflavone*	*Scutellaria*	155	MOL005001	*Gancaonin H*	*Radix Glycyrrhizae*
65	MOL002910	*Carthamidin*	*Scutellaria*	156	MOL005003	*Licoagrocarpin*	*Radix Glycyrrhizae*
66	MOL002913	*Dihydrobaicalin_qt*	*Scutellaria*	157	MOL005007	*Glyasperins M*	*Radix Glycyrrhizae*
67	MOL002914	*Eriodyctiol (flavanone)*	*Scutellaria*	158	MOL005008	*Glycyrrhiza flavonol A*	*Radix Glycyrrhizae*
68	MOL002915	*Salvigenin*	*Scutellaria*	159	MOL005012	*Licoagroisoflavone*	*Radix Glycyrrhizae*
69	MOL002917	*5,2',6'-Trihydroxy-7,8-dimethoxyflavone*	*Scutellaria*	160	MOL005016	*Odoratin*	*Radix Glycyrrhizae*
70	MOL002925	*5,7,2',6'-Tetrahydroxyflavone*	*Scutellaria*	161	MOL005017	*Phaseol*	*Radix Glycyrrhizae*
71	MOL002927	*Skullcapflavone II*	*Scutellaria*	162	MOL005018	*Xambioona*	*Radix Glycyrrhizae*
72	MOL002928	*oroxylin a*	*Scutellaria*	163	MOL005020	*dehydroglyasperins C*	*Radix Glycyrrhizae*
73	MOL002932	*Panicolin*	*Scutellaria*	164	MOL002879	*Diop*	*Codonopsis Scutellaria*
74	MOL002933	*5,7,4'-Trihydroxy-8-methoxyflavone*	*Scutellaria*	165	MOL000449	*Stigmasterol*	*Codonopsis Scutellaria Coix Seed Radix Aucklandiae*
75	MOL002934	*NEOBAICALEIN*	*Scutellaria*	166	MOL003896	*7-Methoxy-2-methyl isoflavone*	*Codonopsis Radix Glycyrrhizae*
76	MOL002937	*DIHYDROOROXYLIN*	*Scutellaria*	167	MOL000006	*luteolin*	*Codonopsis Purslane*
77	MOL000525	*Norwogonin*	*Scutellaria*	168	MOL000211	*Mairin*	*Astragalus Radix SanguisorbaeRadix Aucklandiae Radix Glycyrrhizae*
78	MOL000552	*5,2'-Dihydroxy-6,7,8-trimethoxyflavone*	*Scutellaria*	169	MOL000239	*Jaranol*	*Astragalus Radix Glycyrrhizae*
79	MOL000073	*ent-Epicatechin*	*Scutellaria*	170	MOL000296	*hederagenin*	*Astragalus Poria cocos*
80	MOL001490	*bis[(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate*	*Scutellaria*	171	MOL000354	*isorhamnetin*	*Astragalus Radix Glycyrrhizae*
81	MOL008206	*Moslosooflavone*	*Scutellaria*	172	MOL000392	*formononetin*	*Astragalus Radix Glycyrrhizae*
82	MOL010415	*11,13-Eicosadienoic acid, methyl ester*	*Scutellaria*	173	MOL000417	*Calycosin*	*Astragalus Radix Glycyrrhizae*
83	MOL012245	*5,7,4'-trihydroxy-6-methoxyflavanone*	*Scutellaria*	174	MOL000422	*kaempferol*	*Astragalus Purslane Radix SanguisorbaeRadix Glycyrrhizae*
84	MOL012246	*5,7,4'-trihydroxy-8-methoxyflavanone*	*Scutellaria*	175	MOL000098	*quercetin*	*Astragalus Rhizoma Coptis PurslaneRadix SanguisorbaeRadix Glycyrrhizae*
85	MOL012266	*rivularin*	*Scutellaria*	176	MOL002897	*epiberberine*	*Rhizoma CoptisScutellaria*
86	MOL001484	*Inermine*	*Radix Glycyrrhizae*	177	MOL001458	*coptisine*	*Rhizoma CoptisScutellaria*
87	MOL001792	*DFV*	*Radix Glycyrrhizae*	178	MOL000359	*sitosterol*	*Tangerine Peel Coix Seed Alisma Radix Aucklandiae Scutellaria Radix*

							Glycyrrhizae
88	MOL002311	*Glycyrol*	*Radix Glycyrrhizae*	179	MOL004328	*naringenin*	*Tangerine Peel Radix Glycyrrhizae*
89	MOL002565	*Medicarpin*	*Radix Glycyrrhizae*	180	MOL005100	*5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one*	*Tangerine Peel Purslane*
90	MOL003656	*Lupiwighteone*	*Radix Glycyrrhizae*	181	MOL000358	*beta-sitosterol*	*Purslane Radix SanguisorbaeScutellaria*
91	MOL004805	*(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one*	*Radix Glycyrrhizae*				

active components and targets of action of JPQCHSR are summarized in Table 1.

Prediction of UC-related targets

Using the key word "ulcerative colitis", a total of 4622 UC-related targets were obtained in the GeneCards database.

"TCM drugs-Active Components-Targets-Diseases" network

Using the jvenn online analysis tool, after the intersection of the active component targets and the disease targets, a total of 205 potential targets of JPQCHSR in the treatment of UC were obtained (Figure 1). Then, a visual network of "TCM Drugs - Active Components - Targets - Diseases" was established using the Cytoscape version 3.7.2 (Figure 2). The network diagram contains 383 nodes, which included 205 target gene nodes, 165 active component nodes, 12 TCM drug nodes, and 1 disease node. With the help of the "Network analyzer" plug-in in the software, we analyzed the topological properties of the network nodes. The average node "degree" value of the compounds in the network was calculated to be 12.72. Table 2 shows the topological information of the active components with a "degree" value of ≥ 13. The degree of a node is the number of edges connected to the node. A higher degree means a more important role that a node plays in the network. As shown in Table 2, 77 compounds including quercetin (degree = 121), luteolin (degree = 52), kaempferol (degree = 46), calycosin (degree = 38), naringenin (degree = 32), nobiletin (degree = 30), baicalein (degree = 29), arachidonic acid (degree = 29), and formononetin (degree = 27) had degree values higher than the mean degree value. Thus, these components were predicted preliminarily as the core compounds of JPQCHSR for the treatment of UC.

The PPI network

In order to understand the interactions among the UC-related target proteins after JPQCHSR treatment, the effective targets were imported into the STRING database for further analysis. The species default was "Homo sapiens", and the minimum interaction score threshold was set to 0.900. After the isolated nodes were removed, a PPI network graph was constructed (Figure 3). The network graph contained a total of 182 nodes and 1021 edges, with the average node degree value being 11.22. Table 3 shows the information of targets with degree values of ≥ 12. A total of 72 targets including the signal transducer and activator of transcription 3 (STAT3, degree = 49), protein kinase B (AKT1, degree = 46), tumor protein p53 (TP53, degree = 46), mitogen-activated protein kinase 1 (MAPK1, degree = 44), mitogen-activated protein kinase 3 (MAPK3, degree = 43), Jun N-terminal kinase (JNK, degree = 42), and tumor necrosis factor (TNF, degree = 39) might be the core targets of JPQCHSR in the treatment of UC.

GO and KEGG enrichment analysis

The R 3.6.3 software was used to perform GO and KEGG enrichment analyses on 205 intersection targets, during which a total of 2861 GO terms and 171 KEGG pathways were obtained. The GO enrichment analysis was based on three aspects: Biological process (BP), cellular component (CC), and molecular function (MF). The enriched GO terms included 2681 BPs, 93 CCs, and 171 MFs. With P value set at < 0.05 and according to the number of enriched genes, the top 20 terms were used to draw a bubble chart (Figure 4), in which the vertical axis represents the function annotation, the horizontal axis represents the gene ratio, the bubble size represents the number of enriched genes, and the bubble color represents P value. BPs involved response to oxidative stress, response to lipopolysaccharide, response to molecule of bacterial

Table 2 Compound degree information (degree ≥ 13)

Name	Degree	Name	Degree
MOL000098	121	MOL004857	17
MOL000006	52	MOL004849	17
MOL000422	46	MOL004835	17
MOL000173	38	MOL004808	17
MOL004328	32	MOL003656	17
MOL005828	30	MOL012266	16
MOL002714	29	MOL004915	16
MOL001439	29	MOL004883	16
MOL000392	27	MOL004864	16
MOL003896	25	MOL004856	16
MOL000497	24	MOL004833	16
MOL000378	24	MOL004820	16
MOL000354	24	MOL004815	16
MOL002773	22	MOL002934	16
MOL004959	21	MOL005012	15
MOL000358	21	MOL004961	15
MOL008206	20	MOL004885	15
MOL005003	20	MOL004884	15
MOL004978	20	MOL004863	15
MOL004974	20	MOL004841	15
MOL004891	20	MOL004810	15
MOL004828	20	MOL002933	15
MOL001689	20	MOL000552	15
MOL000500	20	MOL005008	14
MOL004991	19	MOL004990	14
MOL004966	19	MOL004911	14
MOL004811	19	MOL004827	14
MOL002565	19	MOL002927	14
MOL008400	18	MOL002917	14
MOL005007	18	MOL000449	14
MOL004912	18	MOL005020	13
MOL004824	18	MOL005017	13
MOL002928	18	MOL004904	13
MOL000417	18	MOL004879	13
MOL005016	17	MOL004848	13
MOL005000	17	MOL004814	13
MOL004957	17	MOL000380	13
MOL004908	17	MOL000371	13
MOL004907	17		

origin and response to antibiotics; CCs involved membrane raft, membrane microdomain, membrane region, vesicle lumen, and cytoplasmic vesicle lumen; and

Table 3 The degree information of targets in the protein-protein interaction network (degree ≥ 12)

Name	Degree	Name	Degree	Name	Degree
STAT3	49	CDKN1A	20	AR	14
AKT1	46	PRKCA	19	HIF1A	14
TP53	46	CASP3	19	ALB	14
MAPK1	44	TIMP1	19	PTGS2	14
MAPK3	43	FN1	19	PPARA	14
JUN	42	CASP8	19	PPARG	13
TNF	39	STAT1	19	GSK3B	13
RELA	35	PRKCD	18	IGF2	13
HSP90AA1	32	IL2	18	CCNA2	13
MAPK14	32	BCL2	18	TNFRSF1A	13
IL6	31	TGFB1	18	MMP2	13
MAPK8	30	IL4	18	ERBB2	13
VEGFA	28	IL1B	18	F2	12
FOS	28	BCL2L1	17	CXCL2	12
EGFR	25	NFKBIA	17	RAF1	12
RB1	24	MMP9	17	NOS3	12
CTNNB1	24	PRKCB	16	E2F1	12
MYC	24	CDK1	16	CHUK	12
CCND1	22	IL10	16	XIAP	12
ESR1	22	CREB1	15	IGFBP3	12
RXRA	21	CCL2	15	CCNB1	12
CXCL8	21	CDK2	15	CDK4	12
NR3C1	20	IFNG	15	PCNA	12
EGF	20	MDM2	14	MMP3	12

MFs involved transcription factor activity, preceptor ligand activity, cytokine receptor binding, protein serine/threonine kinase activity, and phosphatase binding.

The results of the KEGG pathway enrichment are displayed as a bar graph, in which the length of the bars represents the number of enriched genes and the color depth refers to *P* values. As shown in Figure 4, the results of KEGG metabolic pathway enrichment involved infection, apoptosis, nutrition, immunity, inflammation, and other pathways, which included AGE-RAGE signaling pathway, Kaposi sarcoma-associated herpesvirus infection, IL-17 signaling pathway, TNF signaling pathway, and human cytomegalovirus infection.

Molecular docking

Molecular docking is a computer-aided virtual screening technology that predicts the binding mode and affinities between ligands and their receptors, in accordance with geometric matching, energy matching, and other principles of interaction. It is generally believed that the docking score > 4.0 indicates that the docking molecules have certain binding activity with the target, the docking score > 5.0 indicates good binding activity, and the docking score > 7.0 indicates strong binding activity[21].

We selected compounds with the top ten "degree" values in Section 2.3 and target proteins with top five "degree" values in Section 2.4 for molecular docking. Except for baicalein, the remaining nine compounds had certain binding activity with AKT1, TP53, MAPK1, and MAPK3; among them, quercetin, wogonin, and naringenin had a docking score higher than 5.0 with AKT1, TP53, MAPK1, and MAPK3, suggesting good binding activity; nobiletin had a docking score higher than 7.0 with AKT1, MAPK1, and MAPK3, showing strong binding activity; all the docking scores of

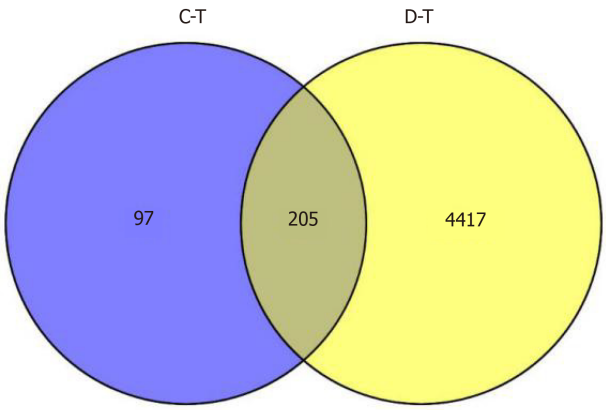


Figure 1 Potential targets of action of Jianpi Qingchang Huashi Recipe in the treatment of ulcerative colitis. C-T: Active component targets; D-T: Ulcerative colitis-related targets.

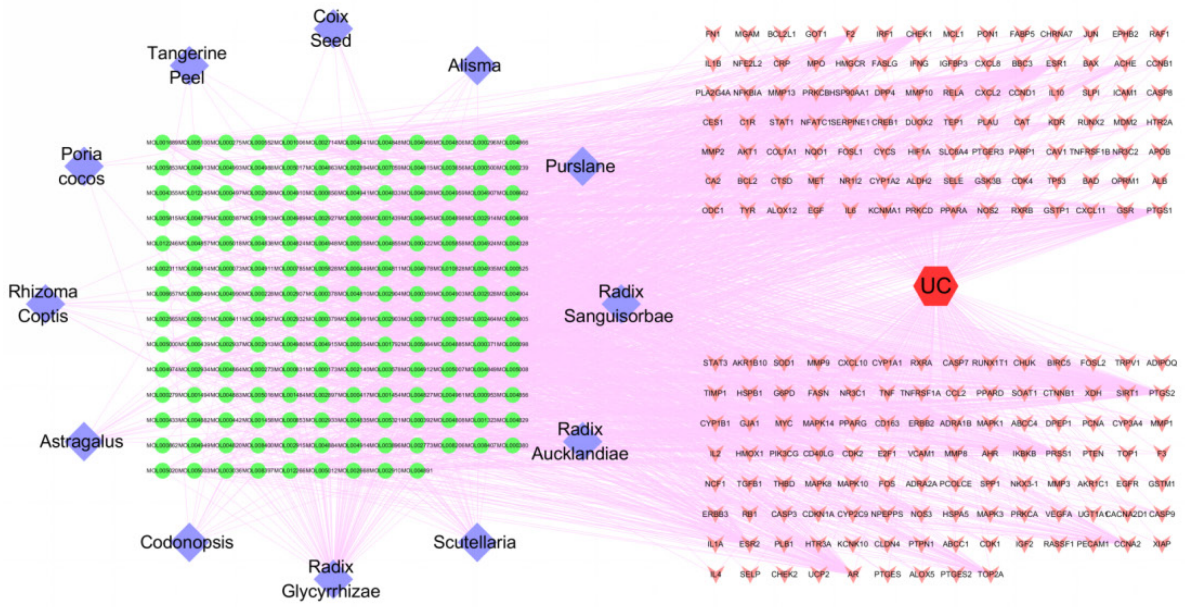


Figure 2 The visual network of "traditional Chinese medicine drugs-Active Components-Targets-Diseases". The circles represent the active component, the diamonds represent traditional Chinese medicine drugs, the arrows represent the disease targets, and the hexagons represent the diseases.

arachidonic acid with AKT1, TP53, MAPK1, and MAPK3 were higher than 7.0, indicating strong binding activity. As shown in the molecular docking pattern diagram (Figure 5), wogonin stably bound to the active site of STAT3 through hydrogen bonding interactions with amino acids including ARG609, GLU612, SER613, THR620, and VAL637 on the STAT3 target protein; through hydrogen bond interactions with LYS14, GLU17, ASN54, ARG86 and GLN79 on the AKT1 target protein, quercetin bound to the active site of AKT1 stably; luteolin stably bound to the active site of TP53 through SER1503, ASP1520, and MET1584 on the TP53 target protein; naringenin stably bound to the active site of MAPK1 through TYR36, GLU71, and GLN105 on the MAPK1 target protein; and kaempferol stably bound to the active site of MAPK3 through ILE48, MET125, LYS131, ASN171, and ASP184 on MAPK3 target protein.

DISCUSSION

The incidence of UC has been increasing over the past years. It is characterized by a long disease course and complex pathogenic mechanisms. Western medicine-based treatments rely mainly on hormones and biological agents[22-25]. Although these treatments may achieve short-term therapeutic effects, they may cause severe adverse reactions with long-term use. Based on the combination of the data mining method

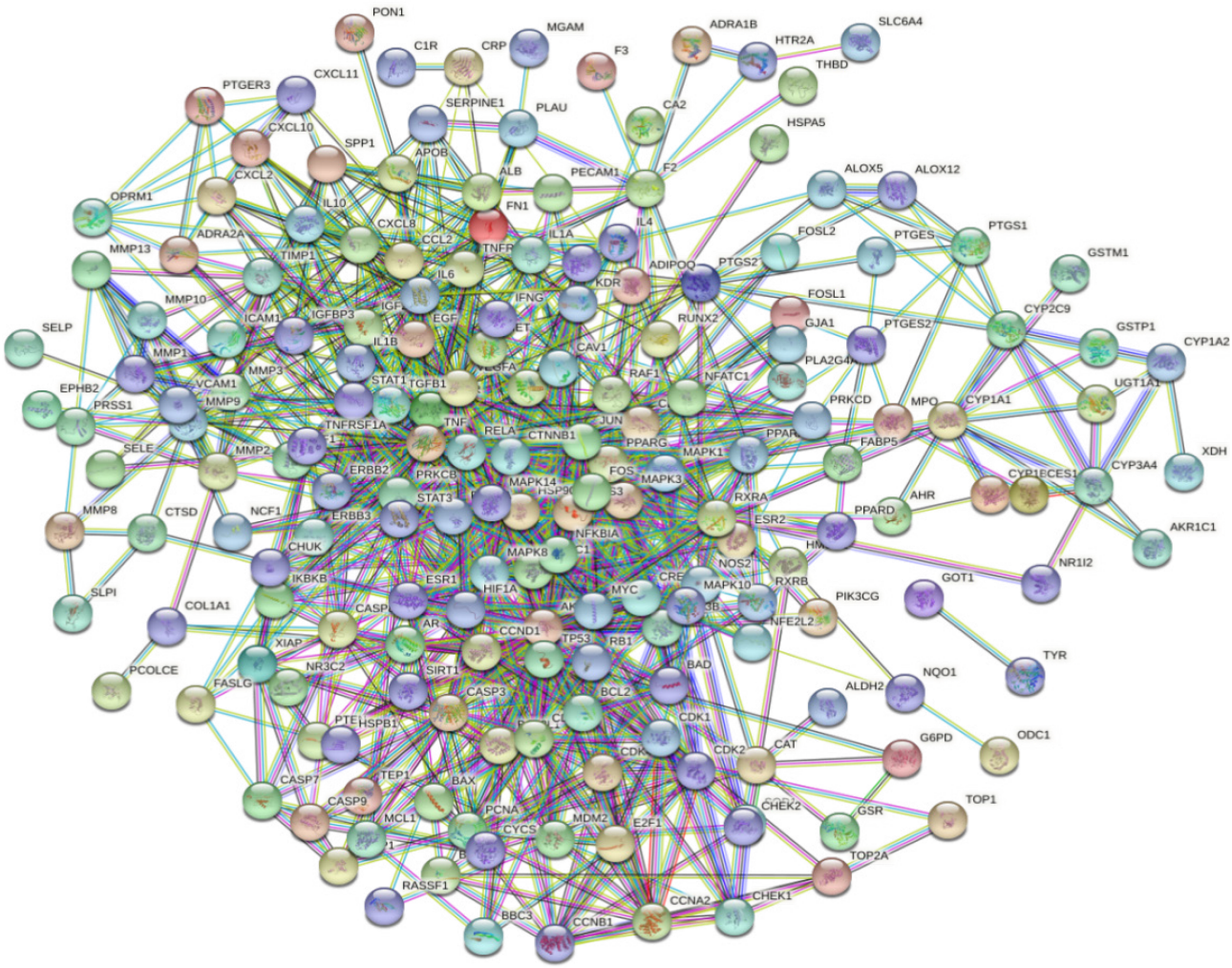
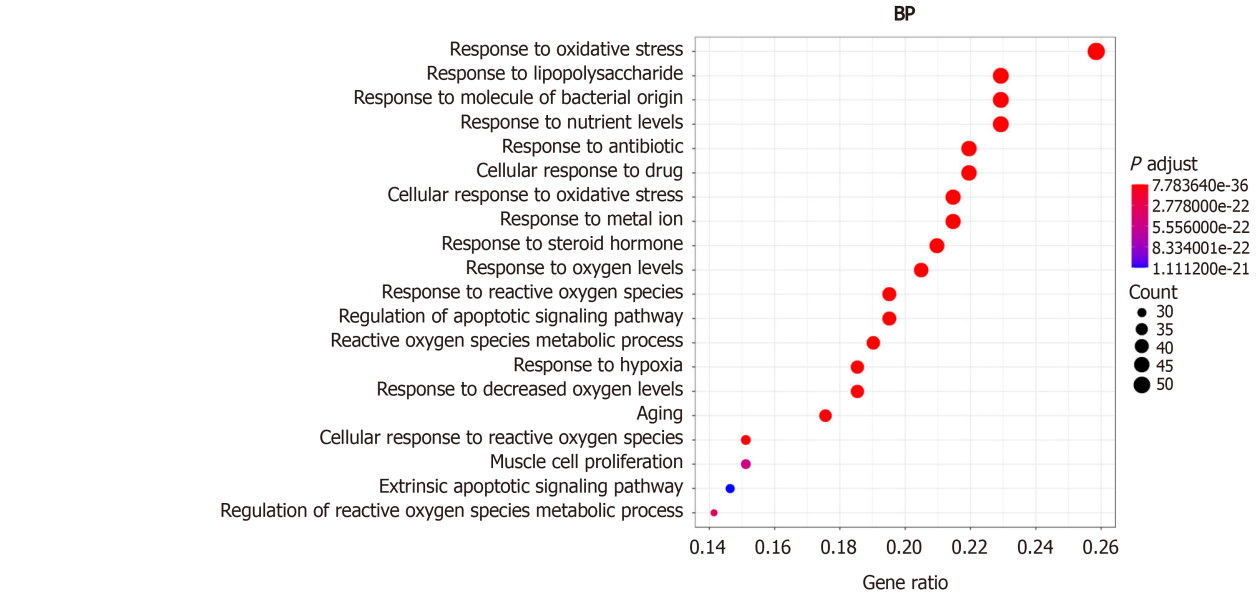


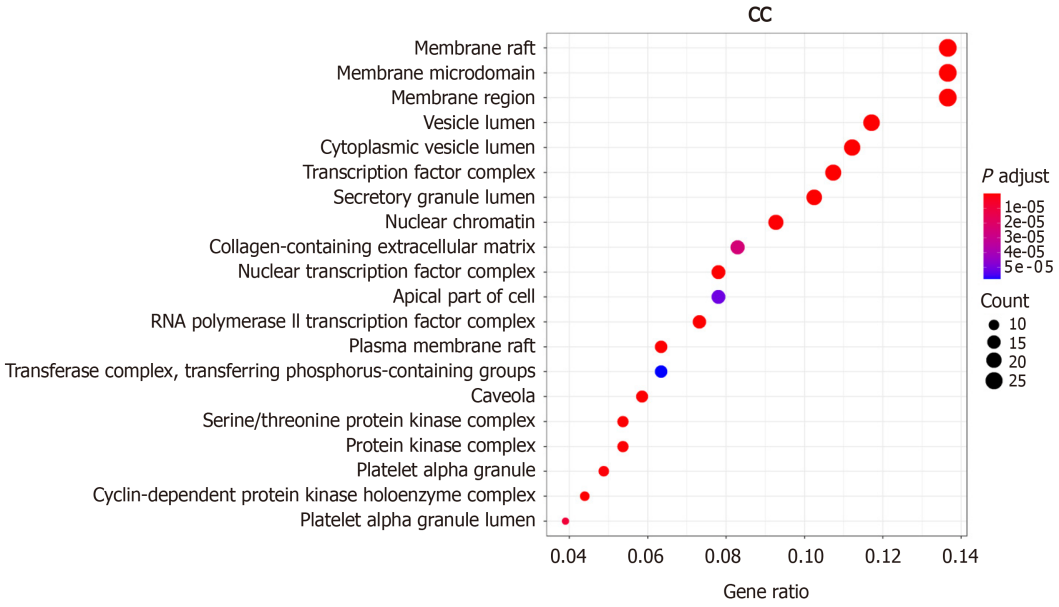
Figure 3 Diagram of protein–protein interactions.

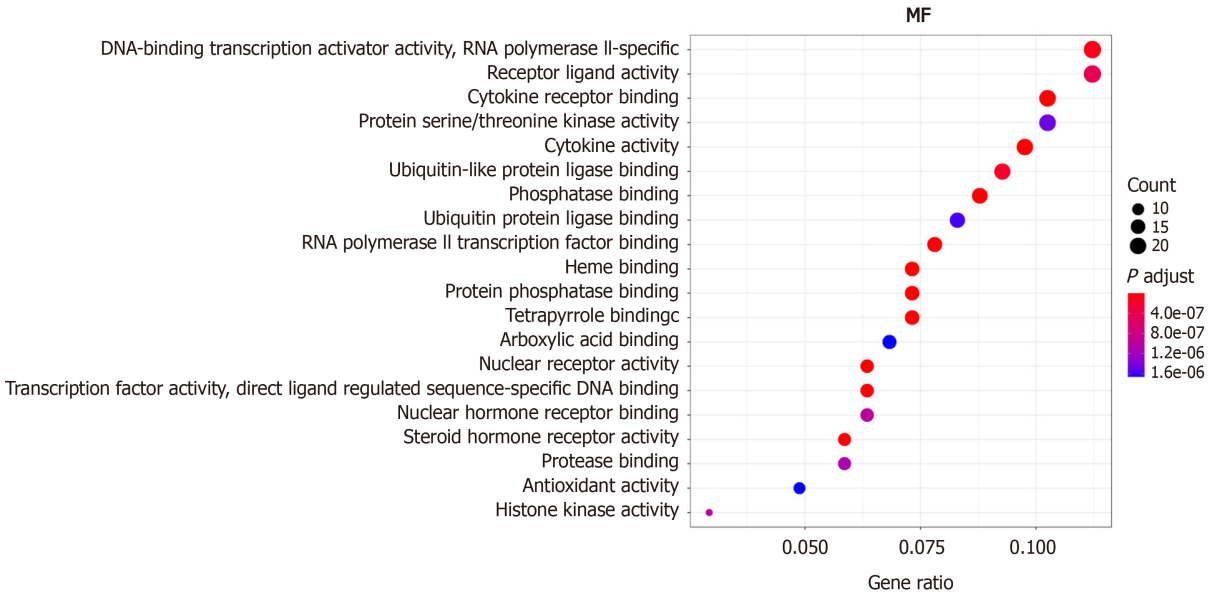
and network pharmacology approach[26-28], we performed comprehensive and systematic prediction for the effect of JPQCHSR in treating UC, which has provided some new insights into future basic research and clinical application of JPQCHSR.

Using network pharmacology approach, we obtained 181 active components and 302 corresponding targets, among which there were 205 UC-related targets. As shown in the visual network of "TCM Drugs-Active Components-Targets-Diseases", the key components of JPQCHSR in treating UC included quercetin, luteolin, kaempferol, calycosin, naringenin, nobiletin, baicalein, arachidonic acid, and formononetin. Quercetin is a plant flavonoid that is found in many types of fruits and vegetables[29, 30]. It has anti-inflammatory, anti-oxidant, and anti-cancer activities[31-34]. Studies have shown that quercetin can lower the expressions of MMP2, MMP9, TLR4, NF-κBp65, and cadherin E; by suppressing the migration and invasion of Caco-2 cells *via* inhibiting the Toll-like Receptor 4/NF-κB pathway, quercetin may be effective in treating colitis[35]. Luteolin is a natural antioxidant and has the functions of scavenging oxygen free radicals and protecting cells. Li *et al*[36] found that luteolin could significantly reduce the expressions of inflammatory factors such as iNOS, TNF-α and IL-6 and increase the activities of superoxide dismutase and catalase in colon tissues; it was expected that luteolin might suppress experimental colitis *via* the Nrf2 pathway. In addition, luteolin can also exert its anti-inflammatory, anti-apoptotic, and anti-autophagy effects by inhibiting JNK1/2, p38, PI3K/AKT, NF-κB, and STAT3 pathways and inducing ERK1/2, thereby playing a role in the treatment of colitis[37]. Kaempferol is a flavonoid compound with anti-apoptosis, anti-inflammatory, and other pharmacological activities. It can play an anti-osteoarthritis role by down-regulating the expression of miR-146a[38].

As shown in the PPI network, 72 targets including STAT3, AKT1, TP53, MAPK1, MAPK3, JUN, and TNF may be the core targets of JPQCHSR in treating UC. Signal Transducer and Activator of Transcription (STAT) pathway is essential for cell prolif-


BP
Response to oxidative stress
Response to lipopolysaccharide
Response to molecule of bacterial origin
Response to nutrient levels
Response to antibiotic
Cellular response to drug
Cellular response to oxidative stress
Response to metal ion
Response to steroid hormone
Response to oxygen levels
Response to reactive oxygen species
Regulation of apoptotic signaling pathway
Reactive oxygen species metabolic process
Response to hypoxia
Response to decreased oxygen levels
Aging
Cellular response to reactive oxygen species
Muscle cell proliferation
Extrinsic apoptotic signaling pathway
Regulation of reactive oxygen species metabolic process
0.14
0.16
0.18
0.20
0.22
0.24
0.26
Gene ratio
P adjust
7.783640e-36
2.778000e-22
5.556000e-22
8.334001e-22
1.111200e-21
Count
30
35
40
45
50


CC
Membrane raft
Membrane microdomain
Membrane region
Vesicle lumen
Cytoplasmic vesicle lumen
Transcription factor complex
Secretory granule lumen
Nuclear chromatin
Collagen-containing extracellular matrix
Nuclear transcription factor complex
Apical part of cell
RNA polymerase II transcription factor complex
Plasma membrane raft
Transferase complex, transferring phosphorus-containing groups
Caveola
Serine/threonine protein kinase complex
Protein kinase complex
Platelet alpha granule
Cyclin-dependent protein kinase holoenzyme complex
Platelet alpha granule lumen
0.04
0.06
0.08
0.10
0.12
0.14
Gene ratio
P adjust
1e-05
2e-05
3e-05
4e-05
5e-05
Count
10
15
20
25


MF
DNA-binding transcription activator activity, RNA polymerase II-specific
Receptor ligand activity
Cytokine receptor binding
Protein serine/threonine kinase activity
Cytokine activity
Ubiquitin-like protein ligase binding
Phosphatase binding
Ubiquitin protein ligase binding
RNA polymerase II transcription factor binding
Heme binding
Protein phosphatase binding
Tetrapyrrole bindingc
Arboxylic acid binding
Nuclear receptor activity
Transcription factor activity, direct ligand regulated sequence-specific DNA binding
Nuclear hormone receptor binding
Steroid hormone receptor activity
Protease binding
Antioxidant activity
Histone kinase activity
0.050
0.075
0.100
Gene ratio
Count
10
15
20
P adjust
4.0e-07
8.0e-07
1.2e-06
1.6e-06

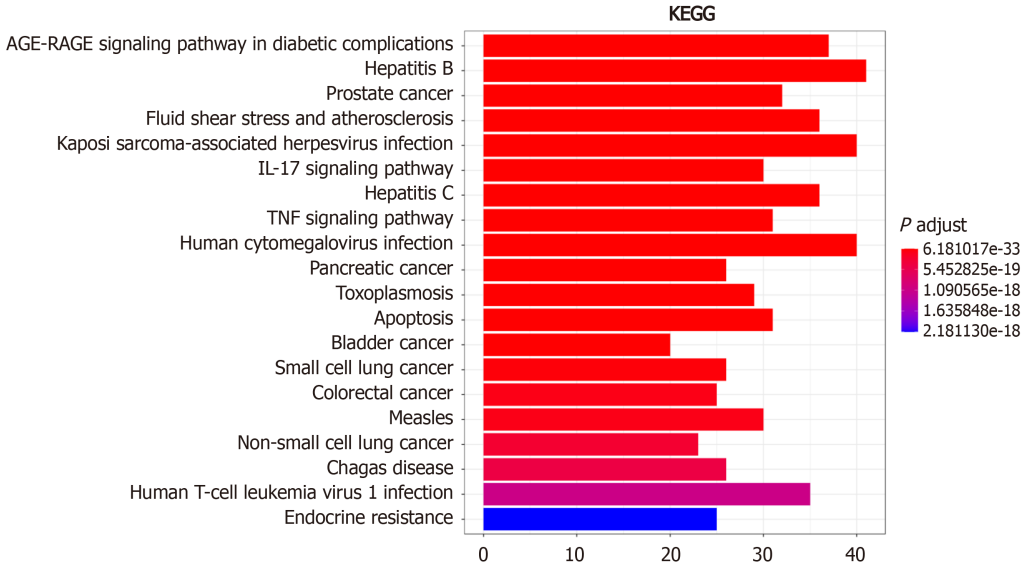


Figure 4 Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis of the potential targets of action of Jianpi Qingchang Huashi Recipe in the treatment of ulcerative colitis. BP: Biological process; CC: Cellular component; KEGG: Kyoto Encyclopedia of Genes and Genomes; MF: Molecular function.

eration and differentiation[39] and is involved in the pathogenesis of colorectal cancer. Research has shown that STAT3 expression in T cells, macrophages, and epithelial cells in patients with colitis is directly related to the severity of inflammation[40]. TP53, a tumor suppressor gene, is closely related to the occurrence of colon cancer and may serve as a key target for UC prevention and treatment[41,42].

Our enrichment analyses showed that the effective targets were involved in many BPs including response to oxidative stress, response to lipopolysaccharide, molecular response to bacterial origin, and response to antibiotics; they also participated in membrane rafts, membrane microdomains, membrane region, vesicle lumen, cytoplasmic vesicle lumen, and other CCs; finally, they were involved in transcription factor activity, preceptor ligand activity, cytokine receptor binding, protein serine/threonine kinase activity, phosphatase binding, and other MFs. The 205 effective targets exerted their effects in treating UC mainly through AGE-RAGE signaling pathway, Kaposi sarcoma-associated herpesvirus infection, IL-17 signaling pathway, TNF signaling pathway, and human cytomegalovirus infection, which also reflected the mechanisms of TCM drugs in treating diseases *via* multiple components, multiple targets, and multiple pathways. The IL-17 pathway is involved in autoimmune diseases, self-defense, and regulation of autoimmune balance[43-46]. As a strong proinflammatory cytokine, IL-17 can increase cell permeability and promote the production of other pro-inflammatory factors and chemokines, thus playing an important role in the pathogenesis of UC[47-52].

Molecular docking showed that the active compounds of JPQCHSR for treating UC had certain affinities with the core targets. The active compounds interacted with the amino acids of the target proteins through hydrogen bonding, thereby stably binding to the active sites of the target proteins.

CONCLUSION

In summary, using the network pharmacology and molecular docking technology, we predicted that the active components such as quercetin, luteolin, and kaempferol in JPQCHSR act on targets including STAT3, AKT1, TP53, MAPK1, MAPK3, JUN, and TNF *via* IL-17, TNF, and other signaling pathways to reduce the expressions of inflammatory factors and repair intestinal mucosal damage, thereby exerting their roles in the treatment UC.

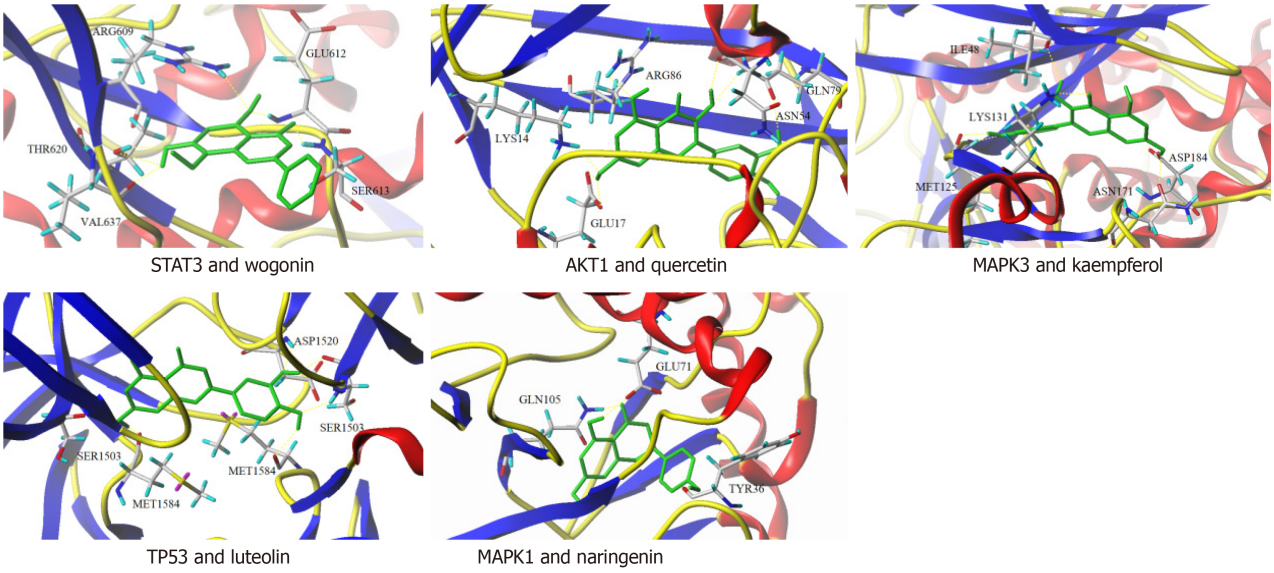


Figure 5 Molecular docking patterns between AKT1, TP53, MAPK1 and MAPK3 and quercetin, luteolin, naringenin and kaempferol.

ARTICLE HIGHLIGHTS

Research background

Traditional Chinese medicine has played an important role in the treatment of ulcerative colitis (UC), but the specific mechanism of action has not been clarified, which needs further research.

Research motivation

To provide objective basis for the treatment of UC with traditional Chinese medicine.

Research objectives

To investigate the potential mechanism of Jianpi Qingchang Huashi Recipe (JPQCHSR) for the treatment of UC based on network pharmacology and molecular docking.

Research methods

Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform was used to extract the active components and action targets of JPQCHSR.

Research results

Through database analysis, a total of 181 active components, 302 targets and 205 therapeutic targets were obtained for JPQCHSR. The key compounds include quercetin, luteolin, kaempferol, *etc*. The core targets involved STAT3, AKT1, TP53, MAPK1, MAPK3, JUN, TNF, *etc*. Total 2861 items were obtained by GO enrichment analysis, and 171 items were obtained by KEGG pathway enrichment analysis. The results of molecular docking showed that the key active components in JPQCHSR had certain affinity with the core target.

Research conclusions

The treatment of UC with JPQCHSR is a complex process of multi-component, multi-target and multi-pathway regulation.

Research perspectives

Traditional Chinese medicine has a huge potential mechanism in the treatment of UC.

REFERENCES

1 **Gajendran M**, Loganathan P, Jimenez G, Catinella AP, Ng N, Umapathy C, Ziade N, Hashash JG. A comprehensive review and update on ulcerative colitis. *Dis Mon* 2019; **65**: 100851 [PMID: 30837080

DOI: 10.1016/j.disamonth.2019.02.004]
2 **Koning M**, Ailabouni R, Gearry RB, Frampton CM, Barclay ML. Use and predictors of oral complementary and alternative medicine by patients with inflammatory bowel disease: a population-based, case-control study. *Inflamm Bowel Dis* 2013; **19**: 767-778 [PMID: 23429459 DOI: 10.1097/MIB.0b013e31827f27c8]
3 **Ungaro R**, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2017; **389**: 1756-1770 [PMID: 27914657 DOI: 10.1016/S0140-6736(16)32126-2]
4 **Porter RJ**, Kalla R, Ho GT. Ulcerative colitis: Recent advances in the understanding of disease pathogenesis. *F1000Res* 2020; **9** [PMID: 32399194 DOI: 10.12688/f1000research.20805.1]
5 **Weizman AV**, Ahn E, Thanabalan R, Leung W, Croitoru K, Silverberg MS, Steinhart AH, Nguyen GC. Characterisation of complementary and alternative medicine use and its impact on medication adherence in inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; **35**: 342-349 [PMID: 22176478 DOI: 10.1111/j.1365-2036.2011.04956.x]
6 **Limketkai BN**, Gordon M, Mutlu EA, De Silva PS, Lewis JD. Diet Therapy for Inflammatory Bowel Diseases: A Call to the Dining Table. *Inflamm Bowel Dis* 2020; **26**: 510-514 [PMID: 31819987 DOI: 10.1093/ibd/izz297]
7 **Opheim R**, Hoivik ML, Solberg IC, Moum B; IBSEN Study Group. Complementary and alternative medicine in patients with inflammatory bowel disease: the results of a population-based inception cohort study (IBSEN). *J Crohns Colitis* 2012; **6**: 345-353 [PMID: 22405172 DOI: 10.1016/j.crohns.2011.09.007]
8 **Dossett ML**, Davis RB, Lembo AJ, Yeh GY. Complementary and alternative medicine use by US adults with gastrointestinal conditions: Results from the 2012 National Health Interview Survey. *Am J Gastroenterol* 2014; **109**: 1705-1711 [PMID: 25001257 DOI: 10.1038/ajg.2014.108]
9 **Zheng L**, Zhang YL, Dai YC, Chen X, Chen DL, Dai YT, Tang ZP. Jianpi Qingchang decoction alleviates ulcerative colitis by inhibiting nuclear factor-κB activation. *World J Gastroenterol* 2017; **23**: 1180-1188 [PMID: 28275298 DOI: 10.3748/wjg.v23.i7.1180]
10 **Chen YL**, Zheng YY, Dai YC, Zhang YL, Tang ZP. Systems pharmacology approach reveals protective mechanisms of Jian-Pi Qing-Chang decoction on ulcerative colitis. *World J Gastroenterol* 2019; **25**: 2603-2622 [PMID: 31210713 DOI: 10.3748/wjg.v25.i21.2603]
11 **Dai YC**, Zheng L, Zhang YL, Chen X, Chen DL, Wang LJ, Tang ZP. Jianpi Qingchang decoction regulates intestinal motility of dextran sulfate sodium-induced colitis through reducing autophagy of interstitial cells of Cajal. *World J Gastroenterol* 2017; **23**: 4724-4734 [PMID: 28765693 DOI: 10.3748/wjg.v23.i26.4724]
12 **Wu M**, Li P, An Y, Ren J, Yan D, Cui J, Li D, Li M, Wang M, Zhong G. Phloretin ameliorates dextran sulfate sodium-induced ulcerative colitis in mice by regulating the gut microbiota. *Pharmacol Res* 2019; **150**: 104489 [PMID: 31689519 DOI: 10.1016/j.phrs.2019.104489]
13 **Zhang R**, Zhu X, Bai H, Ning K. Network Pharmacology Databases for Traditional Chinese Medicine: Review and Assessment. *Front Pharmacol* 2019; **10**: 123 [PMID: 30846939 DOI: 10.3389/fphar.2019.00123]
14 **Saikia S**, Bordoloi M. Molecular Docking: Challenges, Advances and its Use in Drug Discovery Perspective. *Curr Drug Targets* 2019; **20**: 501-521 [PMID: 30360733 DOI: 10.2174/1389450119666181022153016]
15 **Kataria R**, Khatkar A. Molecular Docking of Natural Phenolic Compounds for the Screening of Urease Inhibitors. *Curr Pharm Biotechnol* 2019; **20**: 410-421 [PMID: 30963969 DOI: 10.2174/1389201020666190409110948]
16 **Liu CX**, Lui R, Fan HR, Xiao XF, Chen XP, Xu HY, Lin YP. Network Pharmacology Bridges Traditional Application and Modern Development of Traditional Chinese Medicine. *Chin Herb Med (English)* 2015; **7**: 3-17
17 **Ferreira LG**, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. *Molecules* 2015; **20**: 13384-13421 [PMID: 26205061 DOI: 10.3390/molecules200713384]
18 **Ru J**, Li P, Wang J, Zhou W, Li B, Huang C, Guo Z, Tao W, Yang Y, Xu X, Li Y, Wang Y, Yang L. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *J Cheminform* 2014; **6**: 13 [PMID: 24735618 DOI: 10.1186/1758-2946-6-13]
19 **Bardou P**, Mariette J, Escudié F, Djemiel C, Klopp C. jvenn: an interactive Venn diagram viewer. *BMC Bioinformatics* 2014; **15**: 293 [PMID: 25176396 DOI: 10.1186/1471-2105-15-293]
20 **Yu G**, Wang LG, Han Y, He QY. clusterProfiler: an R package for comparing biological themes among gene clusters. *OMICS* 2012; **16**: 284-287 [PMID: 22455463 DOI: 10.1089/omi.2011.0118]
21 **Lohning AE**, Levonis SM, Williams-Noonan B, Schweiker SS. A Practical Guide to Molecular Docking and Homology Modelling for Medicinal Chemists. *Curr Top Med Chem* 2017; **17**: 2023-2040 [PMID: 28137238 DOI: 10.2174/1568026617666170130110827]
22 **Li S**, Zhang B. Traditional Chinese medicine network pharmacology: theory, methodology and application. *Chin J Nat Med* 2013; **11**: 110-120 [PMID: 23787177 DOI: 10.1016/S1875-5364(13)60037-0]
23 **Wu CW**, Lu L, Liang SW, Chen C, Wang SM. [Application of drug-target prediction technology in network pharmacology of traditional Chinese medicine]. *Zhongguo Zhong Yao Za Zhi* 2016; **41**: 377-382 [PMID: 28868850 DOI: 10.4268/cjcmm20160303]
24 **Yang M**, Chen JL, Xu LW, Ji G. Navigating traditional chinese medicine network pharmacology and computational tools. *Evid Based Complement Alternat Med* 2013; **2013**: 731969 [PMID: 23983798

DOI: 10.1155/2013/731969]

25 **Huo MQ**, Peng S, Ren Y, Shu Z, Zhang YL, Qiao YJ. [Discovery and application of traditional Chinese medicine efficacy markers based on systematic traditional Chinese medicine]. *Zhongguo Zhong Yao Za Zhi* 2020; **45**: 3245-3250 [PMID: 32726036 DOI: 10.19540/j.cnki.cjcmm.20200210.402]

26 **Hua Z**, Zhai FT, Tian J, Gao CF, Xu P, Zhang F, Liu SJ, Dong K, Du XF, Zhang Z, Yang G. Effectiveness and safety of oral Chinese patent medicines as adjuvant treatment for unstable angina pectoris on the national essential drugs list of China: a protocol for a systematic review and network meta-analysis. *BMJ Open* 2019; **9**: e026136 [PMID: 31542734 DOI: 10.1136/bmjopen-2018-026136]

27 **Zhou J**, Wang Q, Xiang Z, Tong Q, Pan J, Wan L, Chen J. Network Pharmacology Analysis of Traditional Chinese Medicine Formula *Xiao Ke Yin Shui* Treating Type 2 Diabetes Mellitus. *Evid Based Complement Alternat Med* 2019; **2019**: 4202563 [PMID: 31583009 DOI: 10.1155/2019/4202563]

28 **Hao da C**, Xiao PG. Network pharmacology: a Rosetta Stone for traditional Chinese medicine. *Drug Dev Res* 2014; **75**: 299-312 [PMID: 25160070 DOI: 10.1002/ddr.21214]

29 **Zhou C**, Liu L, Zhuang J, Wei J, Zhang T, Gao C, Liu C, Li H, Si H, Sun C. A Systems Biology-Based Approach to Uncovering Molecular Mechanisms Underlying Effects of Traditional Chinese Medicine Qingdai in Chronic Myelogenous Leukemia, Involving Integration of Network Pharmacology and Molecular Docking Technology. *Med Sci Monit* 2018; **24**: 4305-4316 [PMID: 29934492 DOI: 10.12659/MSM.908104]

30 **Jarrell JT**, Gao L, Cohen DS, Huang X. Network Medicine for Alzheimer's Disease and Traditional Chinese Medicine. *Molecules* 2018; **23** [PMID: 29751596 DOI: 10.3390/molecules23051143]

31 **Luo TT**, Lu Y, Yan SK, Xiao X, Rong XL, Guo J. Network Pharmacology in Research of Chinese Medicine Formula: Methodology, Application and Prospective. *Chin J Integr Med* 2020; **26**: 72-80 [PMID: 30941682 DOI: 10.1007/s11655-019-3064-0]

32 **Yuan H**, Ma Q, Cui H, Liu G, Zhao X, Li W, Piao G. How Can Synergism of Traditional Medicines Benefit from Network Pharmacology? *Molecules* 2017; **22** [PMID: 28686181 DOI: 10.3390/molecules22071135]

33 **Granato M**, Rizzello C, Gilardini Montani MS, Cuomo L, Vitillo M, Santarelli R, Gonnella R, D'Orazi G, Faggioni A, Cirone M. Quercetin induces apoptosis and autophagy in primary effusion lymphoma cells by inhibiting PI3K/AKT/mTOR and STAT3 signaling pathways. *J Nutr Biochem* 2017; **41**: 124-136 [PMID: 28092744 DOI: 10.1016/j.jnutbio.2016.12.011]

34 **Tang SM**, Deng XT, Zhou J, Li QP, Ge XX, Miao L. Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects. *Biomed Pharmacother* 2020; **121**: 109604 [PMID: 31733570 DOI: 10.1016/j.biopha.2019.109604]

35 **Han M**, Song Y, Zhang X. Quercetin Suppresses the Migration and Invasion in Human Colon Cancer Caco-2 Cells Through Regulating Toll-like Receptor 4/Nuclear Factor-kappa B Pathway. *Pharmacogn Mag* 2016; **12**: S237-S244 [PMID: 27279714 DOI: 10.4103/0973-1296.182154]

36 **Li Y**, Shen L, Luo H. Luteolin ameliorates dextran sulfate sodium-induced colitis in mice possibly through activation of the Nrf2 signaling pathway. *Int Immunopharmacol* 2016; **40**: 24-31 [PMID: 27569028 DOI: 10.1016/j.intimp.2016.08.020]

37 **Vukelić I**, Detel D, Batičić L, Potočnjak I, Domitrović R. Luteolin ameliorates experimental colitis in mice through ERK-mediated suppression of inflammation, apoptosis and autophagy. *Food Chem Toxicol* 2020; **145**: 111680 [PMID: 32783997 DOI: 10.1016/j.fct.2020.111680]

38 **Jiang R**, Hao P, Yu G, Liu C, Yu C, Huang Y, Wang Y. Kaempferol protects chondrogenic ATDC5 cells against inflammatory injury triggered by lipopolysaccharide through down-regulating miR-146a. *Int Immunopharmacol* 2019; **69**: 373-381 [PMID: 30776646 DOI: 10.1016/j.intimp.2019.02.014]

39 **Oda K**, Hamanishi J, Matsuo K, Hasegawa K. Genomics to immunotherapy of ovarian clear cell carcinoma: Unique opportunities for management. *Gynecol Oncol* 2018; **151**: 381-389 [PMID: 30217369 DOI: 10.1016/j.ygyno.2018.09.001]

40 **Kasembeli MM**, Bharadwaj U, Robinson P, Tweardy DJ. Contribution of STAT3 to Inflammatory and Fibrotic Diseases and Prospects for its Targeting for Treatment. *Int J Mol Sci* 2018; **19** [PMID: 30081609 DOI: 10.3390/ijms19082299]

41 **Lu X**, Yu Y, Tan S. p53 expression in patients with ulcerative colitis - associated with dysplasia and carcinoma: a systematic meta-analysis. *BMC Gastroenterol* 2017; **17**: 111 [PMID: 29070013 DOI: 10.1186/s12876-017-0665-y]

42 **Elmashad NM**, Ziada DH, Hasby EA, Mohamed AEM. Immunohistochemical expression of proinflammatory enzyme COX-2 and p53 in ulcerative colitis and its associated dysplasia and colorectal carcinoma. *J Microsc Ultrastruct* 2016; **4**: 195-202 [PMID: 30023227 DOI: 10.1016/j.jmau.2016.03.003]

43 **Singh S**, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018; **47**: 162-175 [PMID: 29205406 DOI: 10.1111/apt.14422]

44 **Yang H**, Li Y, Shen S, Gan D, Han C, Wu J, Wang Z. Network Pharmacology-Based Investigation into the Mechanisms of Quyushengxin Formula for the Treatment of Ulcerative Colitis. *Evid Based Complement Alternat Med* 2019; **2019**: 7870424 [PMID: 31976001 DOI: 10.1155/2019/7870424]

45 **Tao W**, Xu X, Wang X, Li B, Wang Y, Li Y, Yang L. Network pharmacology-based prediction of the active ingredients and potential targets of Chinese herbal Radix Curcumae formula for application to cardiovascular disease. *J Ethnopharmacol* 2013; **145**: 1-10 [PMID: 23142198 DOI:

10.1016/j.jep.2012.09.051]

46 **Wang ZY**, Liu JG, Li H, Yang HM. Pharmacological Effects of Active Components of Chinese Herbal Medicine in the Treatment of Alzheimer's Disease: A Review. *Am J Chin Med* 2016; **44**: 1525-1541 [PMID: 27848250 DOI: 10.1142/S0192415X16500853]

47 **Pan Y**, Kong LD. High fructose diet-induced metabolic syndrome: Pathophysiological mechanism and treatment by traditional Chinese medicine. *Pharmacol Res* 2018; **130**: 438-450 [PMID: 29471102 DOI: 10.1016/j.phrs.2018.02.020]

48 **Xin P**, Kuang HX, Li XL, Wang Y, Zhang BM, Bu H, Wang ZB, Meng YH, Wang YH, Wang QH. [Proteomics and its application to determine mechanism of action of traditional Chinese medicine]. *Zhongguo Zhong Yao Za Zhi* 2018; **43**: 904-912 [PMID: 29676086 DOI: 10.19540/j.cnki.cjcmm.20180118.002]

49 **Yoo M**, Shin J, Kim H, Kim J, Kang J, Tan AC. Exploring the molecular mechanisms of Traditional Chinese Medicine components using gene expression signatures and connectivity map. *Comput Methods Programs Biomed* 2019; **174**: 33-40 [PMID: 29650251 DOI: 10.1016/j.cmpb.2018.04.002]

50 **Su M**, Gong XJ, Zhou X. [Research progress in mechanism of traditional Chinese medicine active ingredients against cervical cancer]. *Zhongguo Zhong Yao Za Zhi* 2019; **44**: 675-684 [PMID: 30989879 DOI: 10.19540/j.cnki.cjcmm.20181220.002]

51 **Li L**, Liu H, Shi W, Yang J, Xu D, Huang H, Wu L. Insights into the Action Mechanisms of Traditional Chinese Medicine in Osteoarthritis. *Evid Based Complement Alternat Med* 2017; **2017**: 5190986 [PMID: 28203259 DOI: 10.1155/2017/5190986]

52 **Huo X**, Lu F, Qiao L, Li G, Zhang Y. A Component Formula of Chinese Medicine for Hypercholesterolemia Based on Virtual Screening and Biology Network. *Evid Based Complement Alternat Med* 2018; **2018**: 1854972 [PMID: 30050582 DOI: 10.1155/2018/1854972]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com