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Mechanisms of *Paeonia lactiflora* in Treatment of Ulcerative Colitis: A Network Pharmacological Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: *Paeonia lactiflora* is the main active ingredient of peony decoction, which is used to treat ulcerative colitis (UC) in traditional Chinese medicine (TCM). Network pharmacology indicates the multiple interactions among genes, proteins, and metabolites associated with diseases and drugs from the network perspective, which shows the multi-component and multi-target attributes of TCM. This study predicted the pharmacological mechanism of *Paeonia lactiflora* in the treatment of UC by network pharmacological method.

Material/Methods: Chemical constituents of *Paeonia lactiflora* were searched from TCMSP data, gene names of target sites were extracted from UniProt database, and disease targets of ulcerative colitis were obtained from the CTD disease database. Use Venny online tools to obtain common targets for drugs and diseases. The DAVID database was used to enrich GO and KEGG for the common target, and the related functions and pathways were obtained. Cytoscape 3.7.1 was used to construct the 'drug-compound-target-disease' network.

Results: There are 70 common target genes between *Paeonia lactiflora* and UC. GO analysis showed that the biological functions of the common target genes of *Paeonia lactiflora* and UC include response to lipopolysaccharide, response to estradiol, response to drug, positive regulation of nitric oxide biosynthetic process, and steroid hormone-mediated signaling pathway. Enrichment of the KEGG signaling pathway mainly involves signaling pathways, including Pathways in cancer, TNF signaling pathway, Tuberculosis, Hepatitis B, and Toxoplasmosis.

Conclusions: The network pharmacology intuitively shows the multi-component, multi-target, and multi-channel pharmacological effects of *Paeonia lactiflora* on UC, and provides a scientific basis for studying the mechanism of the effect of *Paeonia lactiflora* on UC.

MeSH Keywords: **Colitis, Ulcerative • Medicine, Chinese Traditional • Pharmacologic Actions**

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Background

Peony decoction (Baishao) is composed of *Paeonia lactiflora*, Betelang, Rhubarb, *Scutellaria baicalensis*, *Coptis chinensis*, *Angelica sinensis*, first-class cinnamon, licorice, and banksia rose. It can effectively relieve abdominal pain, fecal pus and blood, and tenesmus [1]. Experimental studies and clinical application show that peony decoction has obvious therapeutic effects on ulcerative colitis [2,3]. *Paeonia lactiflora* is one of the main active ingredients of peony decoction. The pathogenesis of ulcerative colitis is complex and *Paeonia lactiflora* contains many ingredients; therefore, its mechanism in treatment of ulcerative colitis needs to be further clarified. It is important to explore the mechanism of *Paeonia lactiflora* in the treatment of ulcerative colitis from the perspective of systems biology by using the method of network pharmacology.

Network pharmacology is a research method for designing multi-target drug molecules based on the theory of systems biology and network analysis of biological systems by selecting specific signal nodes (Nodes). Network pharmacology emphasizes multi-channel regulation of signaling pathways in order to improve the therapeutic effect of drugs, reduce toxic and adverse effects, enhance the success rate of clinical trials of new drugs, and reduce the cost of drug research and development [4,5]. After thousands of years of clinical practice, traditional Chinese medicine has accumulated rich experience. Traditional Chinese medicine and its prescriptions are multi-component, multi-channel, and multi-target, and show advantages in the treatment and prevention of diseases [6]. However, because the mechanism of traditional Chinese medicine is difficult to quantify, its scientific nature has been questioned. At present, network pharmacology has been applied in the field of traditional Chinese medicine, which provides a basis for revealing the mechanism of action of traditional Chinese medicine [7]. For example, Yu et al. found that in the progression of asthma, 8 major putative targets of Yin-Huang-Qing-Fei capsule were associated with the inflammatory process [8]. Chen et al. reported that 34 proteins and 28 related pathways of YXST may explain the mechanism by which Yangxinshi tablet acts on heart failure and myocardial infarction [9]. Zhang et al. found 66 QiXueHe Capsule candidate targets that may be used to treat menstrual disorders [10]. The purpose of the present study was to use network pharmacology to analyze the mechanism by which *Paeonia lactiflora* is effective in treating ulcerative colitis, and to provide a reference for further experimental verification.

Material and Methods

Major compounds and related targets of Paeonia lactiflora were obtained from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database. The screening criteria were: oral bioavailability (OB) >30% and drug-like (DL) properties >0.15. The genes corresponding to the target were queried through the UniProt database. With 'Ulcerative colitis' as the key word, the CTD disease database was used to search for disease target genes of ulcerative colitis. The Venny online tool was used to obtain common target genes for drugs and diseases. GO and KEGG enrichment analysis of common target genes were performed using the DAVID database to obtain the related functions and pathways. The screening criterion was FDR <0.05. Cytoscape 3.7.1 was used to construct the 'drug-compound-target gene-disease' network.

Results

Drug target prediction

The chemical constituents and targets of *Paeonia lactiflora* were predicted in the TCMSP database. A total of 13 compounds of *Paeonia lactiflora* were obtained, as shown in Table 1. We could not obtain related targets from 5 of them (11alpha, 12alpha-epoxy-3beta-23-dihydroxy-30-norolean-20-en-28, 12beta-olide, albiflorin_qt, benzoyl paeoniflorin, Lactiflorin, and paeoniflorin_qt). We entered the target name and selected "person" as the species in the UniProt database. As a result, 71 genes corresponding to the target were identified.

Disease target prediction

By searching the keyword 'ulcerative colitis' in the CTD disease database, 14 775 disease targets were obtained.

Intersection target

A total of 70 common targets for drugs and diseases are obtained using the Venny online tools, as shown in Figure 1.

GO analysis of drug-disease intersection target gene

We imported 70 common target genes into the DAVID database and selected "person" as the species and set FDR at <0.05, yielding 41 enrichment results. The enrichment of biological processes is shown in Table 2. The ggplot2.R package was used for visualization, and the results are shown in Figure 2. The biological processes include response to lipopolysaccharide, response to estradiol, response to drug, positive regulation of nitric oxide biosynthetic process, and steroid hormone mediated signaling pathway.

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Table 1. Compounds in *Paeonia lactiflora*.

Mol ID	Molecule name	OB (%)	DL
MOL000492	(+)-catechin	54.83	0.24
MOL001919	(3S,5R,8R,9R,10S,14S)-3,17-dihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9-hexahydro-1H-cyclopenta[a]phenanthrene-15,16-dione	43.56	0.53
MOL001910	11alpha,12alpha-epoxy-3beta-23-dihydroxy-30-norolean-20-en-28,12beta-olide	64.77	0.38
MOL001928	Albiflorin_qt	66.64	0.33
MOL001930	Benzoyl paeoniflorin	31.27	0.75
MOL000358	beta-sitosterol	36.91	0.75
MOL000422	Kaempferol	41.88	0.24
MOL001921	Lactiflorin	49.12	0.8
MOL000211	Mairin	55.38	0.78
MOL001918	Paeoniflorgenone	87.59	0.37
MOL001924	Paeoniflorin	53.87	0.79
MOL001925	Paeoniflorin_qt	68.18	0.4
MOL000359	Sitosterol	36.91	0.75

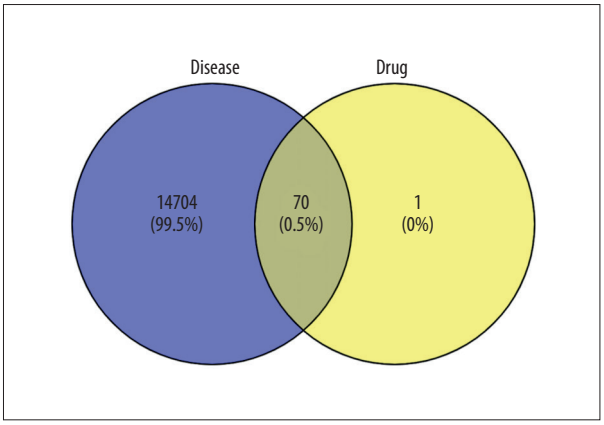

Figure 1. Venn diagram of disease and drug targets.

Analysis of KEGG pathway enrichment

We imported 70 common target genes into the DAVID database, selected "person" as the species, and set FDR as <0.05, producing 41 enrichment results. The enrichment of biological processes is shown in Table 3. The ggplot2.R (3.2.0 Version) package was used for visualization and the results are shown in Figure 3. The target gene network of Paeonia lactiflora-ulcerative colitis is mainly related to Pathways in cancer, TNF signaling pathway, Tuberculosis, Hepatitis B, and Toxoplasmosis.

Drug-compound-target-disease network

Cytoscape 3.7.1 software was used to construct the 'drug-compound-target-disease' network of *Paeonia lactiflora*, and the interaction among drugs, compounds, diseases, and targets was obtained. The results are shown in Figure 4.

Discussion

The occurrence of ulcerative colitis (UC) involves genetic, biochemical, psychological, social, and environmental factors [11]. Many scholars have studied the pathogenesis of UC in terms of infection factors, immune factors, and genetic factors [12,13]. In view of the complex pathogenesis of ulcerative colitis, it is difficult for a single target drug to have a better therapeutic effect, and multi-target combination drug therapy has become the trend of UC treatment in the future [14]. Scholars regard traditional Chinese medicine as a library of combinatorial compounds [15,16]. Because of the multi-target effect of TCM, it has become an important source of UC therapeutic drugs [17,18]. By exploring the relationship between drugs and diseases from a holistic perspective, network pharmacology is holistic and systematic, which provides a new strategy for the study of traditional Chinese medicine.

Paeonia lactiflora is an important traditional Chinese medicine, which has been widely used in anti-inflammatory, analgesic,

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Table 2. GO functional enrichment analysis of common targets (top 10).

Biological processes	GO ID	Related targets	FDR
Response to lipopolysaccharide	0032496	OPRM1, VCAM1, CASP3, CYP1A1, CASP9, PTGS2, JUN, CASP8, SLPI, CYP1A2, LBP, SELE	9.99E-08
Response to estradiol	0032355	CASP3, CASP9, PTGS2, SLC6A4, CASP8, ESR1, F7, CAT, CYP1A2, GSTP1	1.90E-07
Response to drug	0042493	ICAM1, CASP3, IL6, CYP1A1, PTGS2, SLC6A2, JUN, BCL2, RELA, SLC6A4, PPARG, ADRA1A, CAT, STAT1	4.40E-07
Positive regulation of nitric oxide biosynthetic process	0045429	OPRM1, AKT1, ICAM1, IL6, PTGS2, ESR1, INSR	3.38E-05
Steroid hormone mediated signaling pathway	0043401	PGR, NR1I3, NR1I2, RXRA, PPARG, NR3C2, ESR1	1.93E-04
Aging	0007568	VCAM1, AKT1, IL6, CYP1A1, CASP9, RELA, JUN, ADRA1A, CAT	5.98E-04
Cellular response to lipopolysaccharide	0071222	ICAM1, IL6, RELA, MAPK8, LBP, NOS2, CD14, GSTP1	6.43E-04
Xenobiotic metabolic process	0006805	CYP3A4, NR1I2, CYP1B1, PTGS1, CYP1A2, GSTP1, AHR	4.00E+00
Response to toxic substance	0009636	CYP1B1, BAX, BCL2, SLC6A4, PON1, GSTP1, AHR	1.00E+00
Positive regulation of transcription from RNA polymerase II promoter	0045944	AR, IL6, RXRA, RELA, PPARG, ESR1, STAT1, AHR, PGR, AKT1, ADRB2, NR1I3, NR1I2, NCOA2, JUN, PPP3CA, IKBKB	3.00E+00

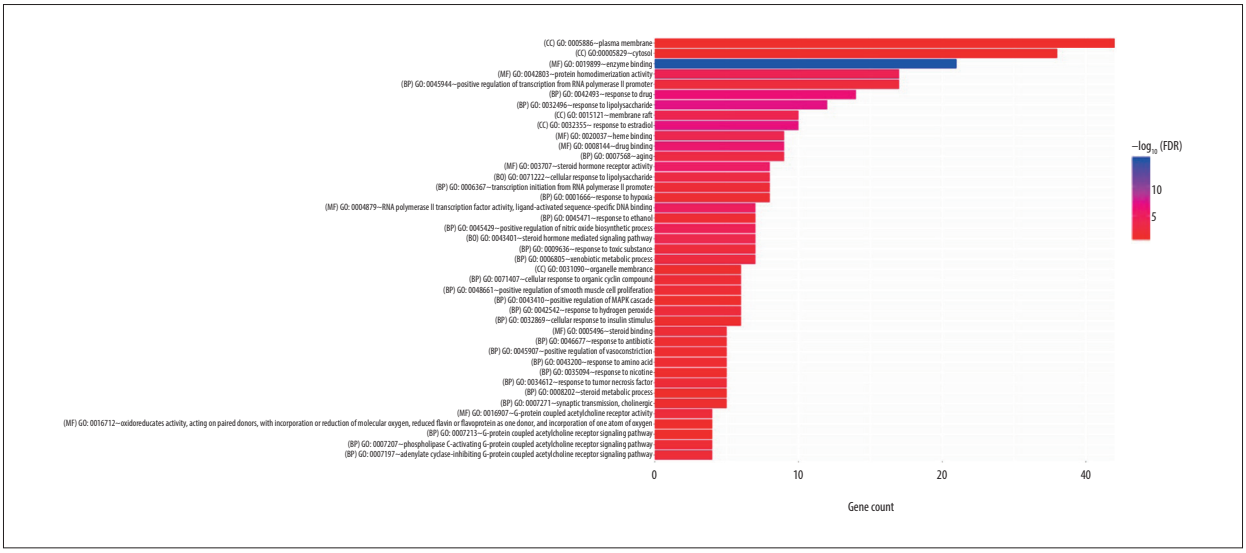

Figure 2. GO functional enrichment. The X-axis represents the number of genes enriched in function, the y-axis GO function annotation, and the color represents the significance of enrichment. The bluer the color, the higher the significance.

and immune regulation for hundreds of years [19]. In this study, the TCMSP database was used to predict the chemical composition and targets of *Paeonia lactiflora*. A total of 13 compounds of *Paeonia lactiflora* were found, of which 5 compounds had no corresponding target. Further target prediction indicated that 71 targets were related to 8 active ingredients. UC disease targets were analyzed using the CTD network online analysis platform, and 70 common target genes between drug and disease were obtained using the Venny online tool.

Our exploration of the biological function of target genes of *Paeonia lactiflora* in the treatment of UC showed that the common target genes between *Paeonia lactiflora* and UC included OPRM1, VCAM1, CASP3, CYP1A1, CASP9, IL6, BCL2, AKT1, PTGS2, JUN, CASP8, SLPI, and CYP1A2. These target genes are involved in biological processes, including response to lipopolysaccharide, response to estradiol, response to drug, positive regulation of nitric oxide biosynthetic process, steroid hormone-mediated signaling pathway, aging, cellular response to

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Table 3. KEGG functional enrichment analysis of common targets (top 10).

Term	Fold enrichment	Related targets	FDR
hsa05200: Pathways in cancer	5.739	PRKCA, AR, IL6, PTGS2, RXRA, RELA, PPARG, STAT1, MMP1, AKT1, CASP3, CASP9, JUN, BAX, BCL2, CASP8, MAPK8, NOS2, IKBKB, GSTP1	4.45E-07
hsa04668: TNF signaling pathway	12.647	VCAM1, AKT1, ICAM1, CASP3, IL6, PTGS2, RELA, JUN, CASP8, MAPK8, IKBKB, SELE	1.69E-06
hsa05152: Tuberculosis	8.9197	AKT1, CASP3, IL6, CASP9, BCL2, RELA, BAX, CASP8, MAPK8, LBP, PPP3CA, NOS2, STAT1, CD14	3.06E-06
hsa05161: Hepatitis B	10.11	PRKCA, IL6, RELA, STAT1, AKT1, CASP3, CASP9, BCL2, BAX, JUN, CASP8, MAPK8, IKBKB	3.49E-06
hsa05145: Toxoplasmosis	11.277	AKT1, CASP3, CASP9, RELA, BCL2, CASP8, MAPK8, ALOX5, NOS2, IKBKB, STAT1	3.40E-05
hsa04620: Toll-like receptor signaling pathway	10.639	AKT1, IL6, RELA, JUN, CASP8, MAPK8, LBP, IKBKB, STAT1, CD14	3.26E-04
hsa04932: Non-alcoholic fatty liver disease (NAFLD)	8.2151	AKT1, CASP3, IL6, RELA, JUN, RXRA, BAX, CASP8, MAPK8, IKBKB, INSR	6.91E-04
hsa04210: Apoptosis	14.551	AKT1, CASP3, CASP9, RELA, BAX, BCL2, CASP8, IKBKB	0.001105
hsa05164: Influenza A	7.1292	PRKCA, AKT1, ICAM1, IL6, CASP9, RELA, JUN, PRSS1, MAPK8, IKBKB, STAT1	0.002545
hsa05204: Chemical carcinogenesis	11.277	GSTM1, CYP3A4, GSTM2, CYP1B1, CYP1A1, PTGS2, CYP1A2, GSTP1	0.006317

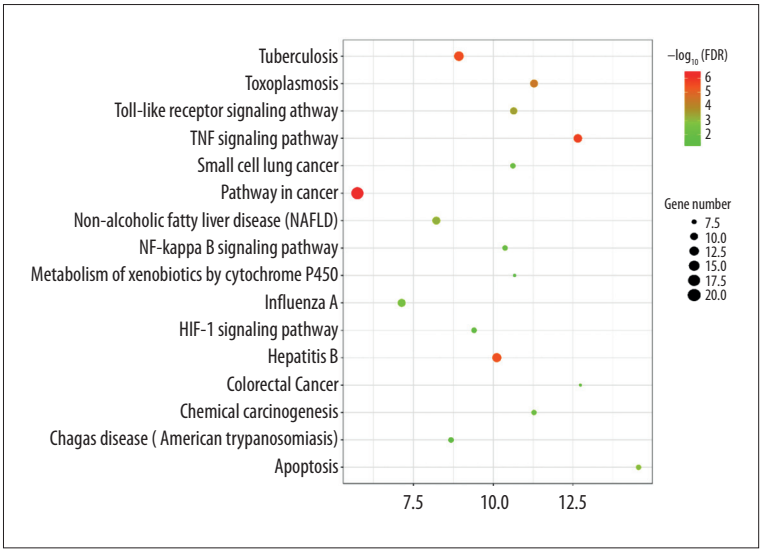

Figure 3. KEGG pathway enrichment.

lipopolysaccharide, xenobiotic metabolic process, response to toxic substance, and positive regulation of transcription from RNA polymerase II promoter. This also indicates that UC involves abnormalities in many biological processes *in vivo*, similar to the results of previous pathological studies of UC. For example, Obana et al. reported ulcerative colitis was related to a promoter polymorphism of the lipopolysaccharide receptor gene, CD14 [20]. Crotty reported ulcerative colitis resulted from a reactive xenobiotic metabolite that is conjugated before excretion into the bile [21]. Principi et al. reviewed the estrogen receptors had been reported to have anti-inflammatory and anti-tumor roles in the colon, suggesting a translational potential that could prevent and/or treat UC [22]. These results suggest that *Paeonia lactiflora* could be used in the treatment of UC by improving these biological processes.

KEGG pathway enrichment analysis results were mainly related to Pathways in cancer, TNF signaling pathway, Tuberculosis,

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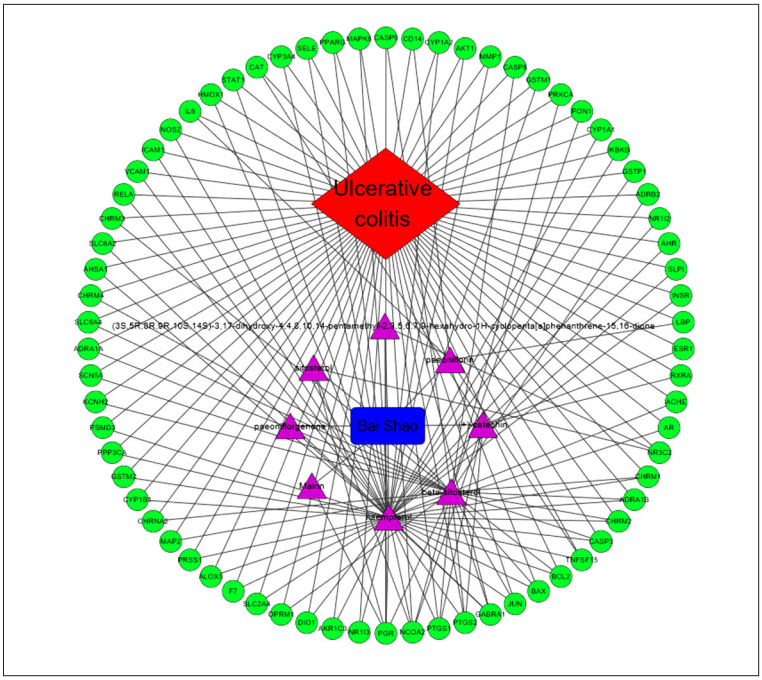

Figure 4. Drug-compound-target-disease network map.

Hepatitis B, Toxoplasmosis, Toll-like receptor signaling pathway, Non-alcoholic fatty liver disease (NAFLD), Apoptosis, Influenza A, and Chemical carcinogenesis. This is consistent with the previous research results of UC molecular biology. For example, TNF-α, as a pro-inflammatory and regulatory factor, plays an important role in the development of UC and disease progression because TNF promotes the release of pro-inflammatory factors [23]. In addition, it can work with interferon to change the barrier function of intestinal epithelial cells, enhance the permeability of intestinal mucosa and vascular wall, destroy the integrity of intestinal mucosa, and form ulcers [24]. Toll-like receptors are important mediators of innate defense of intestinal mucosa and play an important role in maintaining intestinal mucosa and intestinal microecology. Published research confirmed there is a relationship between nonsynonymous variants in the TLR1, TLR2, and TLR6 genes and extensive colonic disease in UC [25]. Therefore, it is speculated that *Paeonia lactiflora* exerts its pharmacodynamic effects by affecting the related signaling pathways by acting on the related targets. Previous studies have confirmed the role of *Paeonia lactiflora* in ulcerative colitis, as well as our results. For example, Liu et al. has confirmed that *Paeonia lactiflora* can treat UC by reducing the expression of pro-inflammatory factors, increasing the body's antioxidant effect, and reducing intestinal mucosal permeability in mice [26]. Fang et al. found that paeoniflorin significantly reduced the levels of TNF-alpha, IL-1, IL-10, 5-HT, TLR4, MyD 88, and NF-kappa B p65, and upregulated the expression of Tollip in ulcerative colon by significantly reducing the levels of TNF-alpha, IL-1, IL-10, and 5-HT [27].

The present study focused on inflammation-related signaling pathways, including the TNF signaling pathway and Toll-like receptor signaling pathway. These pathways mainly involve the genes VCAM1, AKT1, ICAM1, CASP3, IL6, PTGS2, RELA, JUN, CASP8, MAPK8, IKBKB, SELE, LBP, STAT1, and CD14. These genes have also been reported to be involved in the mechanism of UC. For example, PTGS2 participates in inflammatory regulation and antioxidant response [28]. IL6 gene expression is closely related to the progression of IBD [29]. JUN is a proto-oncogene and plays a key role in inflammation. Many inflammatory factors activate JUN directly or indirectly. Activated JUN further regulates the expression and regulation of related inflammatory factors, and then participates in the inflammatory response [30]. Therefore, *Paeonia lactiflora* has anti-inflammatory and immune effects by acting on these genes.

Although the present research revealed the mechanism of *Paeonia lactiflora* in the treatment of ulcerative colitis from the perspective of network pharmacology, it still has some limitations. The main limitation of this study is the lack of experimental verification, which will be further expanded in future research.

Conclusions

The results of this analysis show that *Paeonia lactiflora* acts on multiple targets and plays a therapeutic role on UC through multiple pathways. These predicted targets and pathways are consistent with the pharmacological effects reported in the literature. In addition, there are few reports about some targets

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in the results, which could provide clues for further study of the molecular mechanism of potential targets of *Paeonia lactiflora* in the treatment of UC. This study confirmed the therapeutic effect of the traditional Chinese medicine *Paeonia lactiflora* on UC by use of network pharmacological method, which embodies the multi-component, multi-target and integrated regulation of traditional Chinese medicine prescriptions, and provides a basis for further study of the pharmacological mechanism of *Paeonia lactiflora* in treatment of UC.

Conflict of interests

None.

Appendix

Access to resources:
TCMSP: *http://lsp.nwu.edu.cn/tcmsp.php*
CTD: *http://ctdbase.org/*
DAVID: *https://david.ncifcrf.gov/*
UniProt: *https://www.uniprot.org/*
Venny: *http://bioinfogp.cnb.csic.es/tools/venny/*
ggplot2.R(3.2.0 Version): *https://cran.r-project.org/web/packages/ggplot2/*
Cytoscape 3.7.1: *https://cytoscape.org/*

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