

Research Article

Revealing mechanism of *Caulis Sargentodoxae* for the treatment of ulcerative colitis based on network pharmacology approach

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Objective: The traditional Chinese medicine *Caulis Sargentodoxae* is widely used in the treatment of ulcerative colitis (UC), but the mechanism remains unknown. The present study aims to reveal its effective components, targets and pathways through network pharmacology and bioinformatics approaches.

Materials and methods: Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) was used to identify effective components. The ligand-based targets prediction was achieved through SwissTargetPrediction and Target-Net. UC-related targets were identified using Gene Expression Omnibus (GEO) data and DisGeNET. The common targets of disease and components were constructed and analyzed by PPI network. Lastly, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses are used to explain the functions of these common targets. Components-Targets-Pathways network was visualized and analyzed to further reveal the connection between the components and targets.

Results: Eight active components and 102 key targets were identified to play an important role in UC. These targets were related to regulation of protein serine/threonine kinase activity, positive regulation of cell motility, response to molecule of bacterial origin, response to toxic substance, ERK1 and ERK2 cascade, peptidyl-tyrosine modification, inositol lipid-mediated signaling, cellular response to drug, regulation of inflammatory response and leukocyte migration. Moreover, HIF-1 signaling pathway and PI3K-Akt signaling pathway were the key targets involved in UC-related signaling pathways.

Conclusion: The eight active components of *Caulis Sargentodoxae* mainly play a therapeutic role for UC through synergistic regulation of HIF-1 signaling pathway and PI3K-Akt signaling pathway.

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Introduction

Ulcerative colitis (UC) is a disease caused by a genetically predisposed host's immune disorder to antigens in the intestine, and its incidence and prevalence are increasing globally [1,2]. The disease has the characteristics of remission and flare, and in most cases drugs are used to induce and maintain remission. However, up to 15% of cases require surgery due to medical treatment failure or inflammation that develops into dysplasia [3]. The primary treatment goal of UC is to achieve disease remission, prevent disease-related complications, surgery and tumor, and maintain

the quality of life of patients [4]. The currently available data indicated that UC is an intestinal barrier disease, which is caused by epithelial cells or structural intestinal epithelial dysfunction, or strong inflammatory mediators and cells in the lamina propria to produce an inflammatory cascade. Therefore, treatment strategies can target epithelial cells or inflammatory cells to restore the intestinal barrier function and achieve clinical remission [5]. Currently, drugs used for UC include 5-aminosalicylic acid, steroids and immunosuppressants. However, long-term use of these drugs may cause a variety of side effects, such as liver and kidney toxicity, drug resistance and allergic reactions [6].

The use of herbs to treat various diseases has a long history. In addition, traditional Chinese medicine shows obvious advantages in the treatment of UC, such as low recurrence rate and fewer side effects [6]. Some natural active compounds have good therapeutic effects on experimental UC models. SM934 is a water-soluble artemisinin analog with anti-inflammatory and immunomodulatory effects. It was found to improve DSS-induced UC in mice by inhibiting neutrophils and macrophages [7]. Indigo Naturalis has been proven effective in a randomized, placebo-controlled trial [8]. However, there were potential adverse effects, including pulmonary hypertension [8]. This also reflects the complexity of Chinese herbal medicine.

Network pharmacology methods are rapidly evolving and applied to find new treatment opportunities and repositioning of approved drugs. They can also effectively map the unexplored targets of natural products, thereby providing drug space for proteins related to various complex diseases [9]. The purpose of constructing the network is to realize the interaction between bioactive compounds and target proteins and the interaction between various target proteins, and then to identify and verify the key nodes through network analysis and verification [10]. Network pharmacology has been successfully used to reveal the active ingredients and mechanisms of indigo naturalis in the treatment of UC [11]. *Caulis Sargentodoxae* is also a high-frequency herb used in the treatment of UC. As a heat-clearing and detoxifying Chinese medicine, it has been found to have significant anti-inflammatory, anti-thrombotic, anti-tumor and anti-bacterial effects [12]. However, its active ingredients and targets are still unclear. The present study is based on the network pharmacology approaches and bioinformatics technologies to clarify the mechanism of *Caulis Sargentodoxae* in the treatment of UC, and to provide new candidate compounds for the treatment of UC. The entire workflow is shown in Figure 1.

Materials and methods

Components acquisition and screening

Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) is a manually curated database containing 12144 herbal compounds and related pharmacokinetic properties (<https://tcmsp.com/tcmssp.php>) [13]. Oral bioavailability (OB), Drug-likeness (DL), Caco-2 permeability and other parameters information can be obtained from it. The components and characteristics of *Caulis Sargentodoxae* were retrieved from TCMSP. According to its suggested drug screening criteria, the components were screened. Finally, the compounds with molecular weight (MW) from 180 to 500 Dalton, $OB \geq 20\%$, $DL \geq 0.1$ were retained.

Targets collection of components in *Caulis Sargentodoxae*

Drug-targets prediction technology, which can predict component targets with high throughput and quickly, has been widely used in the preliminary research of drug development. The current prediction technologies mainly include ligands-based prediction methods (such as chemical similarity search, pharmacophore models etc.), targets-based prediction methods (such as reverse molecular docking) and machine learning methods. SwissTargetPrediction is a ligand-based targets prediction tool for bioactive small molecules (<http://www.swisstargetprediction.ch/>). The principle is to train the prediction model by multivariate logistic regression fitting of various size related subsets of known active molecules to weighted 2D and 3D similarity parameters [14]. TargetNet builds a large number of QSAR models based on current chemical and genomics data for molecular target prediction (<http://targetnet.scbdd.com/calcnnet/index/>). Its server will predict the activity of user-submitted molecules in 623 human proteins by building a high-quality QSAR model for each human protein [15]. The structures and SMILES of each component were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). Subsequently, the SMILES of each component were uploaded to two databases for targets prediction.

Acquisition of UC disease targets

Gene Expression Omnibus (GEO) is an ever-increasing platform for storing high-throughput sequencing data. Integrating sequencing information from different centers and performing gene differential expression analysis will facilitate the identification of disease treatment targets. We identified three series from GEO that all came from GPL6244,

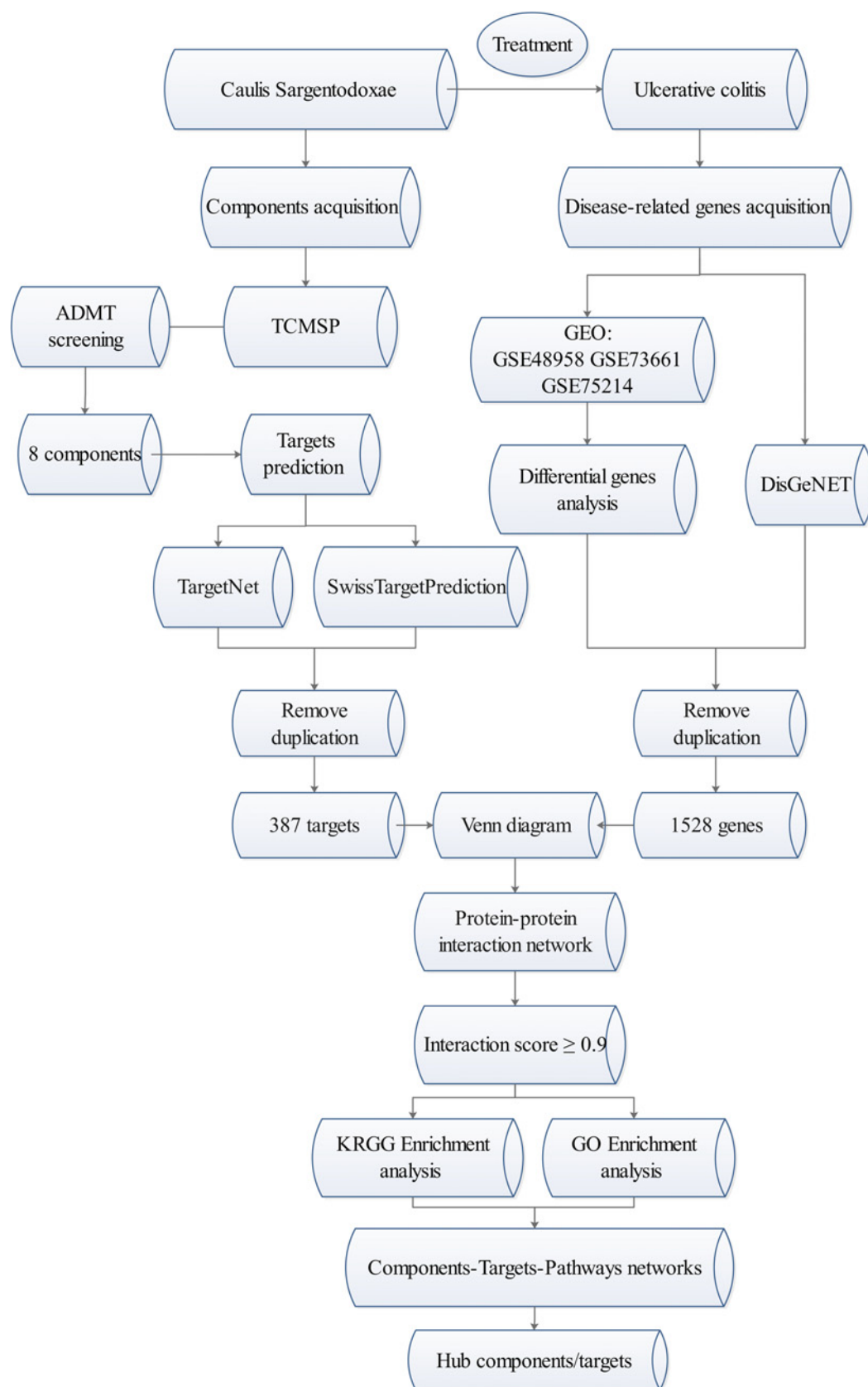


Figure 1. Work flow of the present study

among which GSE73661 contains 23 active UC tissues and 12 normal tissues, GSE75214 contains 74 active UC tissues and 11 normal tissues, GSE48958 contains 7 active UC tissues and 8 normal tissues. Genes with adjusted $P < 0.05$ and \log_2 (fold change) > 2 or \log_2 (fold change) < -2 were considered as differential genes, they have played an important role in the development of UC.

DisGeNET integrated data from public databases, GWASs, animal models and scientific literature, and collected a large number of variants and genes associated with human diseases (<https://www.disgenet.org/>). It currently covers more than 24000 diseases and traits, 17000 genes and 117000 genomic variants [16]. UC-related genes were also obtained via using 'ulcerative colitis' as the keyword to retrieve relevant genes in DisGeNET.

Construction and analysis of target protein-protein interaction network

STRING (<https://string-db.org/>) can carry out direct (physical) and indirect (functional) interactions of proteins to achieve a comprehensive and objective network [17]. The targets were uploaded in the form of gene symbol, the species was selected as '*Homo sapiens*', and the minimum required interaction score threshold 'highest confidence (≥ 0.9)' was set to obtain protein interaction information. Cytoscape v3.7.2 was used for visualization and in-depth analysis of the network. The hub nodes were identified in each network by calculating the size of the degree.

Gene ontology and Kyoto Encyclopedia of Genes and Genomes signal pathway enrichment analysis

Gene ontology (GO) is a gene function classification system that comprehensively describes the attributes of genes and gene products of various species through dynamically updated GO terms. It is used to describe the biological process (BP), the cellular component (CC) and molecular function (MF) of gene sets of interest. Kyoto Encyclopedia of Genes and Genomes (KEGG) is a knowledge base for systematic analysis of gene function, which can describe pathway data involved in genes of interest, including connection of metabolism, membrane transport, signal transduction and cell cycle, etc. We used WebGestalt (<http://www.webgestalt.org/#>), a network enrichment analysis tool, for GO and KEGG enrichment analyses. The reference set was selected as human genome protein encoding. And the enrichment method was selected as over-representation analysis.

Construction and analysis of components-targets-pathways network

Components-Targets-Pathways network was constructed and visualized via Cytoscape v3.7.2 to identify key molecules and targets. The degrees of each component and target were calculated using CytoHubba.

Toxicity prediction of components in *Caulis Sargentodoxae*

AdmetSAR 2.0 was a free tool and continually updated database for the prediction of ADMET properties, and has been widely used in chemical and pharmaceutical fields [18,19]. Each molecule's SMILES was input to obtain organ toxicity and other toxic properties.

Results

Components of *Caulis Sargentodoxae*

Nine eligible valid results were screened through TCMSP database, with $OB \geq 20\%$, $DL \geq 0.1$ and $500 \geq MW \geq 180$ Dalton. These molecules have good OB and DL properties (Table 1 and Supplementary Figure S1). We have also made a toxicity prediction for compounds with SMILES. Analysis found that they have no carcinogenicity, but emodin and physcion may have hepatotoxicity. And physcion and (-)-catechin were positive in Ames mutagenesis (Supplementary Table S1).

Putative targets of components

In both SwissTargetPrediction and TargetNet, we selected targets with a probability greater than 0 for subsequent analysis. Due to the lack of structural information and SMILES, we failed to obtain the targets of syringaresinol diglucoside-qt. The other 8 components get 396 targets through SwissTargetPrediction, and 719 targets through TargetNet. A total of 387 unique targets of 8 components were obtained after removal of the repeats. The relationship among the 8 components and the 387 targets was shown in Figure 2.

UC-related targets

GSE73661, GSE75214 and GSE48958 were respectively analyzed for differential genes. Through the Venn diagram, we obtained 87 common up-regulated genes and 42 common down-regulated genes from three series (Figure 3A,B).

Table 1 Parameter information of molecules in Caulis Sargentodoxae

TCMSP ID	Molecule name	Pubchem Cid	MW	OB (%)	DL
MOL000358	β-sitosterol	222284	414.79	36.91	0.75
MOL000359	Sitosterol	12303645	414.79	36.91	0.75
MOL000472	Emodin	3220	270.25	24.4	0.24
MOL000476	Physcion	10639	284.28	22.29	0.27
MOL007920	Meso-dihydroguaiaretic acid	476856	330.46	31.32	0.26
MOL007923	3-(4-Hydroxyphenyl)acrylic acid 4-hydroxyphenethyl ester	16119626	284.33	93.36	0.21
MOL007925	Glucosyringic acid	10383888	360.35	24.29	0.3
MOL000096	(-)-Catechin	73160	290.29	49.68	0.24
MOL007922	Syringaresnol diglucoside_qt	Not available	418.48	29.84	0.72

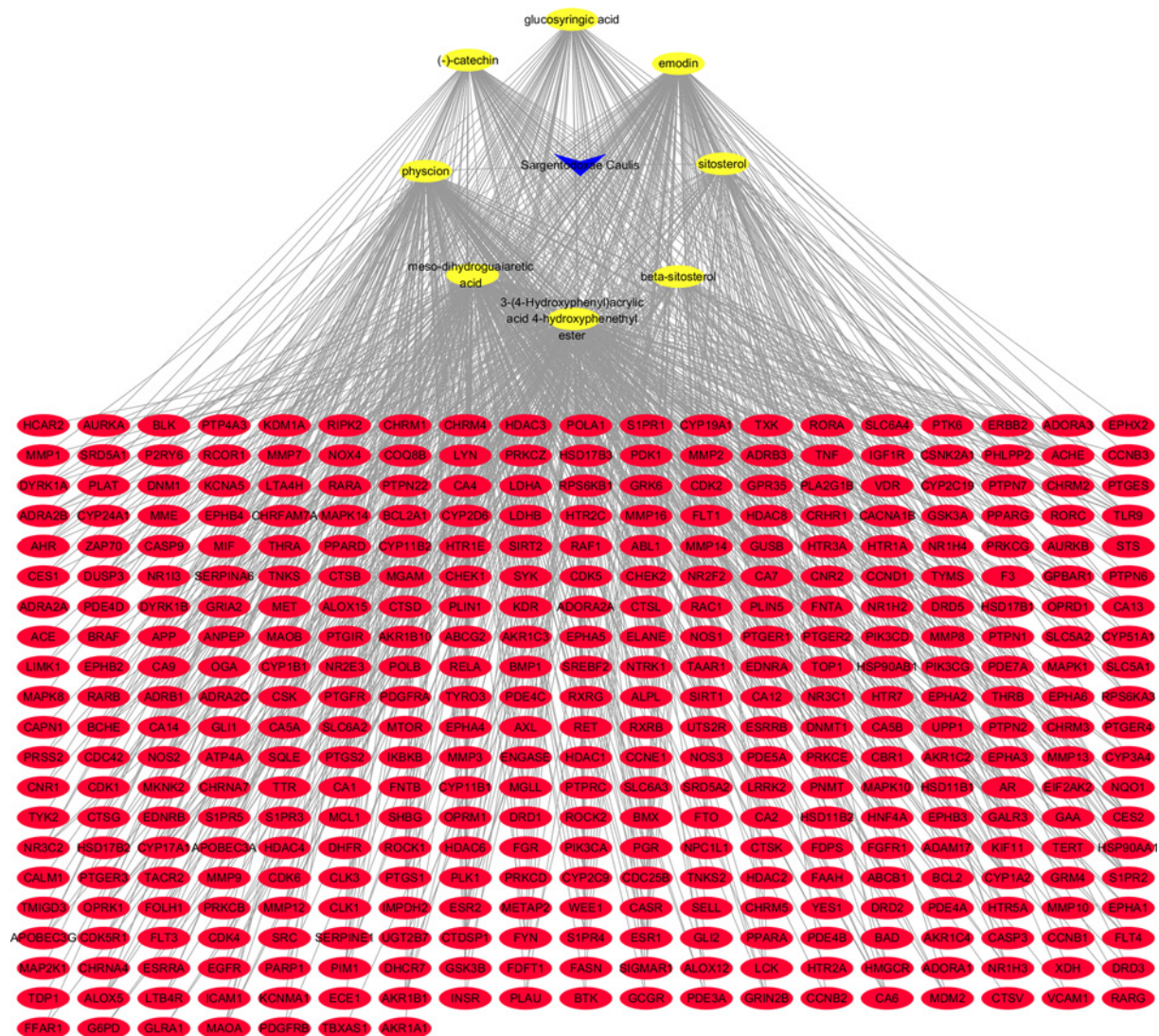


Figure 2. Components-targets-network of Caulis Sargentodoxae
The yellow ellipses represent the components, and the red ellipses represent the targets of components in Caulis Sargentodoxae.

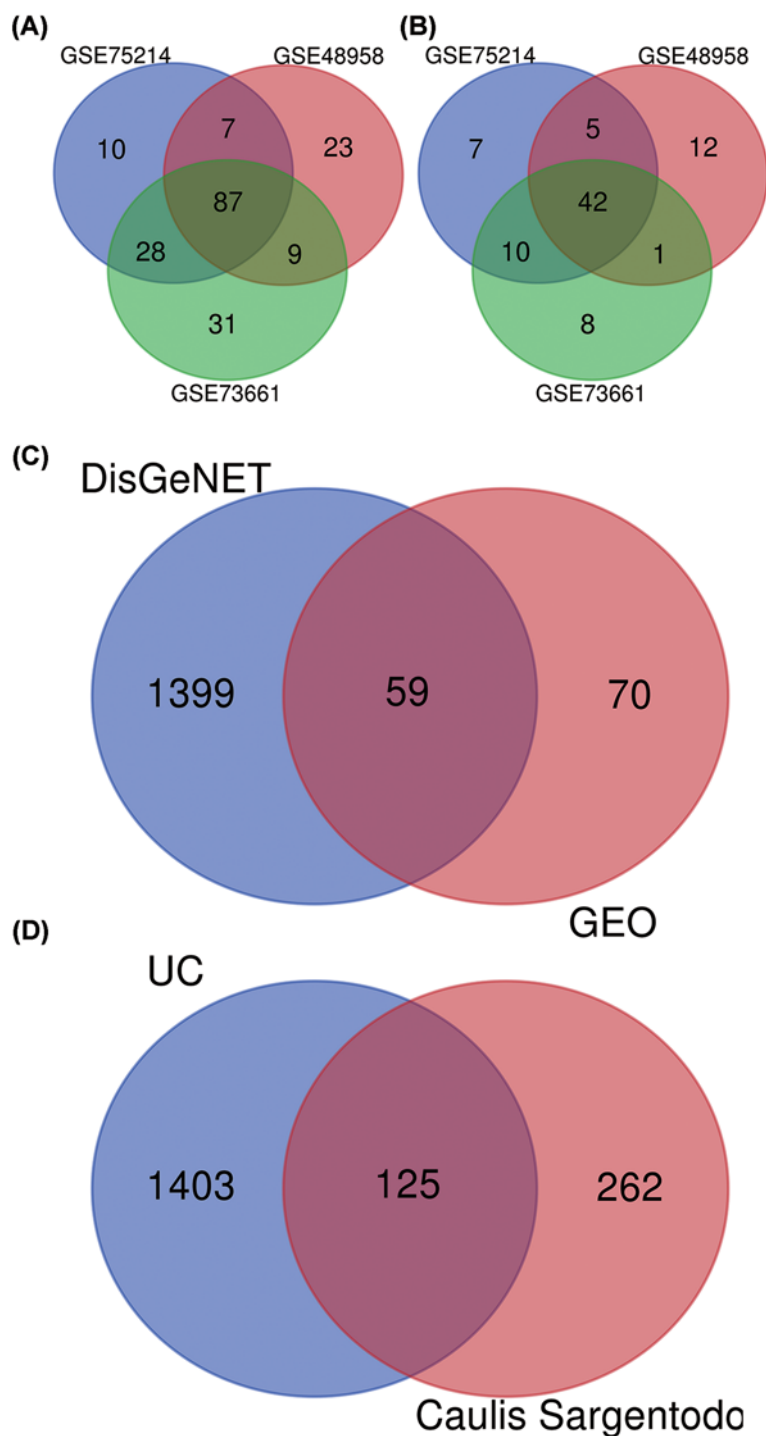


Figure 3. Work flow of targets screening

(A) Venn diagram of up-regulated genes in UC from three GEO series. (B) Venn diagram of down-regulated genes in UC from three GEO series. (C) Venn diagram of targets of UC from differential genes (GEO) and DisGeNET. (D) Venn diagram of targets from UC and *Caulis Sargentodoxae*.

Table 2 Hub genes in PPI network

Rank	Name	Score
1	<i>SRC</i>	56
2	<i>PIK3CA</i>	54
3	<i>MAPK1</i>	48
4	<i>HSP90AA1</i>	36
5	<i>MAPK8</i>	34
5	<i>ESR1</i>	34
7	<i>EGFR</i>	30
7	<i>LYN</i>	30
7	<i>RAC1</i>	30
10	<i>RELA</i>	28
11	<i>TNF</i>	24
11	<i>MAPK14</i>	24
13	<i>S1PR1</i>	22
14	<i>MMP2</i>	20
14	<i>MMP9</i>	20
14	<i>PRKCB</i>	20

In addition, we obtained 1458 UC-related targets from DisGeNET. A total of 1528 unique targets of UC were obtained after removal of the repeats (Figure 3C). By comparing the components targets and the disease targets through the Venn diagram, 125 targets for the treatment of UC were identified (Figure 3D). These targets may be the key proteins of *Caulis Sargentodoxae* in the treatment of UC.

PPI network of 125 common targets

We constructed PPI networks with threshold ‘highest confidence (≥ 0.9)’ in STRING. A network with 102 nodes and 618 edges was obtained (Figure 4). Based on the degree, we identified the key targets among them, including SRC, PIK3CA, MAPK1, HSP90AA1, MAPK8, ESR1, EGFR, LYN, RAC1, RELA, TNF, MAPK14, S1PR1, MMP2, MMP9, PRKCB (Table 2).

GO and KEGG enrichment analyses

Using WebGestalt to conduct bioinformatics analysis of the above key targets. We identified the top ten GO terms and pathways that were significantly enriched, respectively (Figures 5 and 6). In UC, the BPs mainly regulated by *Caulis Sargentodoxae* were regulation of protein serine/threonine kinase activity, positive regulation of cell motility, response to molecule of bacterial origin, response to toxic substance, ERK1 and ERK2 cascade, peptidyl-tyrosine modification, inositol lipid-mediated signaling, cellular response to drug, regulation of inflammatory response and leukocyte migration (Table 3).

In UC, the pathways mainly regulated by *Caulis Sargentodoxae* were Pathways in cancer, Proteoglycans in cancer, Endocrine resistance, Prostate cancer, AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway, MicroRNAs in cancer, Fluid shear stress and atherosclerosis, PI3K-Akt signaling pathway and EGFR tyrosine kinase inhibitor resistance (Table 4). Among them, the changes of HIF-1 signaling pathway and PI3K-Akt signaling pathway are most closely related to UC.

Components-targets-pathways network

The key targets of *Caulis Sargentodoxae* enriched to HIF-1 signaling pathway were BCL2, EGFR, ERBB2, FLT1, IGF1R, INSR, MAPK1, MKNK2, NOS2, NOS3, PIK3CA, PIK3CD, PRKCB, RELA, RPS6KB1 and SERPINE1 (Supplementary Figure S2). The key targets of *Caulis Sargentodoxae* enriched to PI3K-Akt signaling pathway were BCL2, CASP, CCND1, CCNE1, EGFR, ERBB2, FGFR1, FLT1, HSP90AA1, IGF1R, INSR, KDR, MAPK1, MCL1, MDM2, MET, NOS3, NTRK1, PIK3CA, PIK3CD, PIK3CG, RAC1, RELA, RPS6KB1 (Supplementary Figure S3). In the PPI network, EGFR, PRKCB, MAPK1, HSP90AA1, RELA, RAC1, PIK3CA were also identified as hub genes.

Moreover, we constructed components-targets-pathways network with 8 components, 102 hub targets and HIF-1 signaling pathway and PI3K-Akt signaling pathway (Figure 7). The network showed that these eight molecules were involved in regulating HIF-1 signaling pathway and PI3K-Akt signaling pathway. In this network, we further identified key molecules and targets using degrees (Table 5). Physcion, emodin, 3-(4-Hydroxyphenyl)acrylic acid

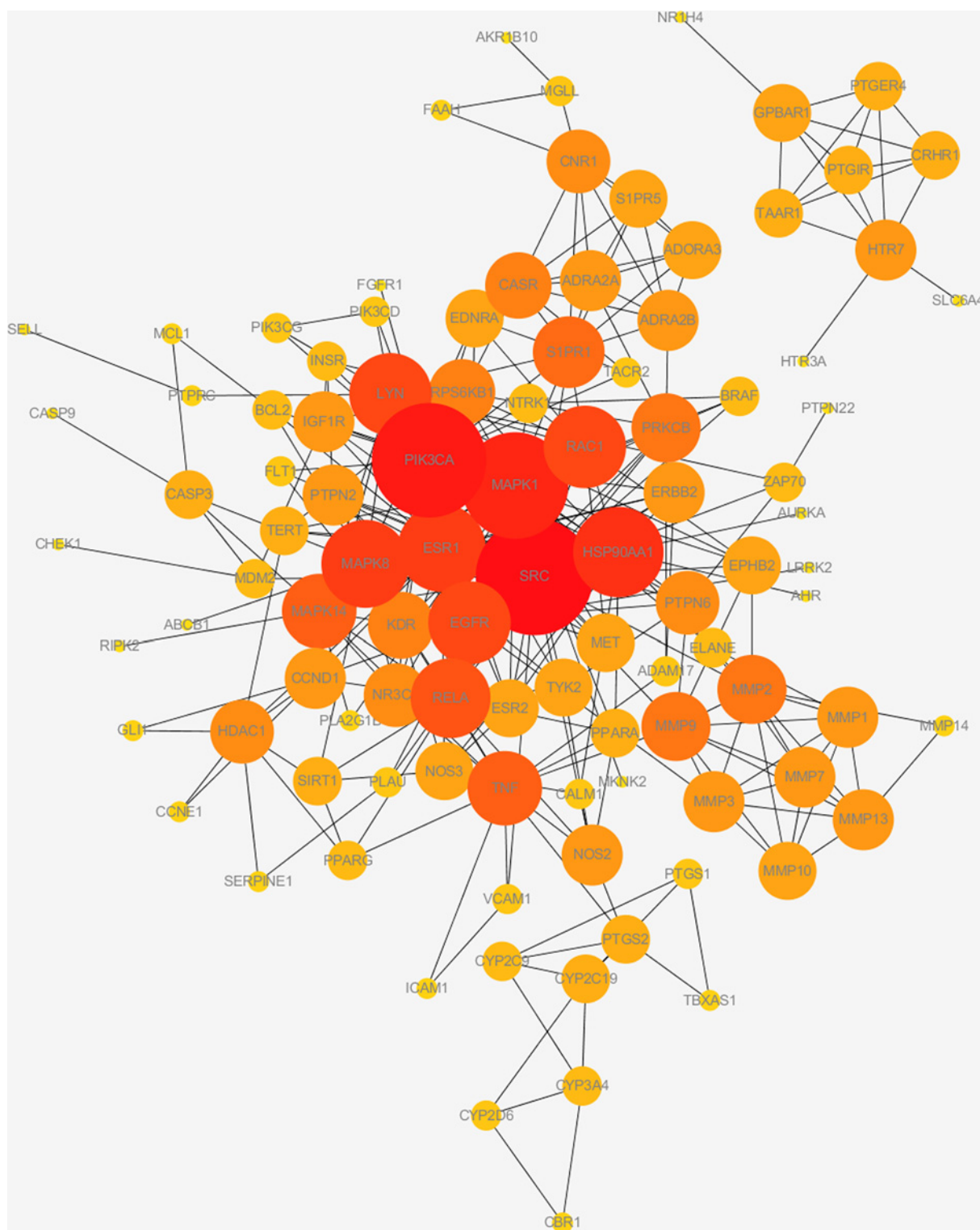


Figure 4. PPI network of common targets in UC and *Caulis Sargentodoxae* (interaction score ≥ 0.9)
The darker nodes represent higher degrees.

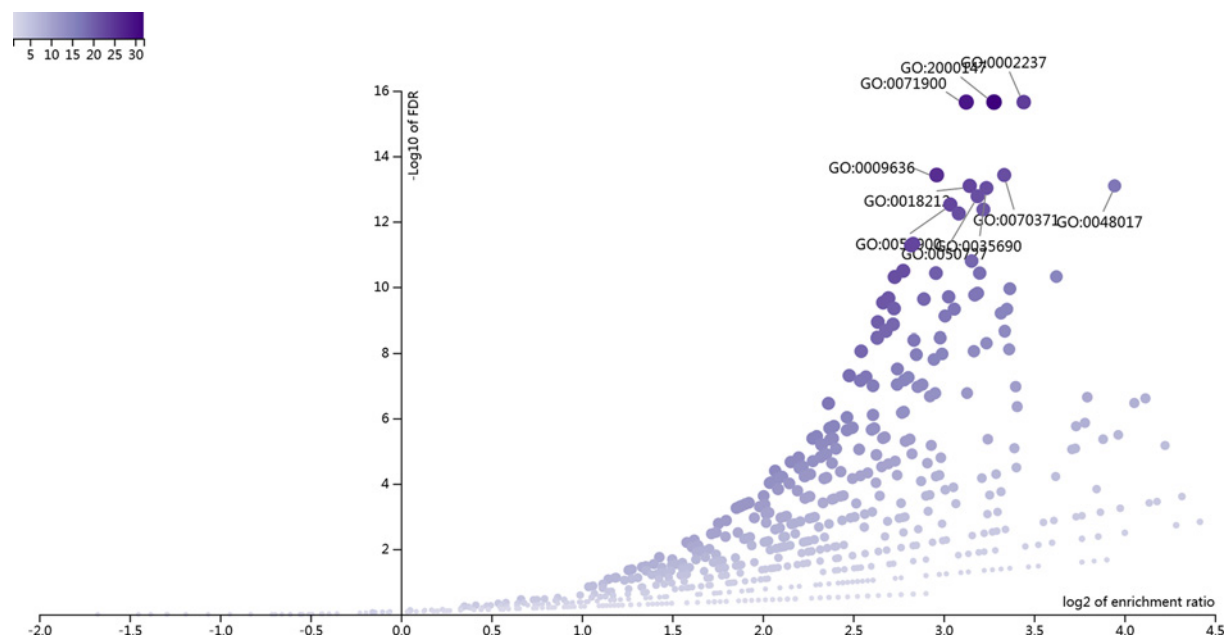


Figure 5. Volcano plot of the top ten significantly enriched GO terms of the common targets in UC and *Caulis Sargentodoxae*

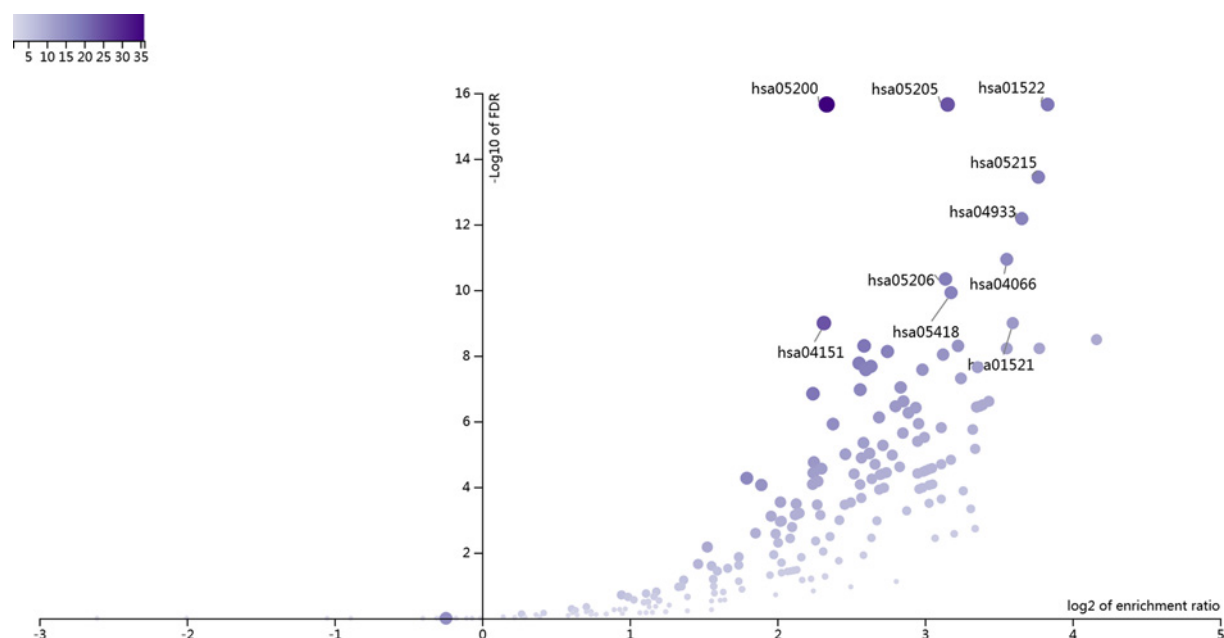


Figure 6. Volcano plot of the top ten significantly enriched pathways of the common targets in UC and *Caulis Sargentodoxae*

4-hydroxyphenethyl ester and meso-dihydroguaiaretic acid were the most important components that regulates the above two pathways.

Discussion

Although drugs such as aminosaliclate, glucocorticoids, antibiotics and anti-TNF α play a good role in the treatment of UC, they still fail to achieve healing results and often cause side effects [20]. In China, traditional Chinese medicine prescriptions are widely used to treat recurrent UC. The mechanism of these drug combination based on the basic theory of traditional Chinese medicine is often difficult to elucidate due to the complexity of the components. The holistic view of Chinese medicine has a lot in common with the key ideas of network pharmacology and systems

Table 3 Top ten significantly enriched GO terms of key targets

Gene set	Description	Size	Expect	Ratio	P-value	FDR
GO:0071900	Regulation of protein serine/threonine kinase activity	497	3.323	8.7272	0	0
GO:2000147	Positive regulation of cell motility	493	3.2962	9.7081	0	0
GO:0002237	Response to molecule of bacterial origin	330	2.2064	10.878	0	0
GO:0009636	Response to toxic substance	499	3.3363	7.793	2.22E-16	3.77E-14
GO:0070371	ERK1 and ERK2 cascade	326	2.1796	10.093	2.22E-16	3.77E-14
GO:0018212	Peptidyl-tyrosine modification	389	2.6009	8.8432	6.66E-16	8.09E-14
GO:0048017	Inositol lipid-mediated signaling	165	1.1032	15.41	6.66E-16	8.09E-14
GO:0035690	Cellular response to drug	349	2.3334	9.4282	8.88E-16	9.44E-14
GO:0050727	Regulation of inflammatory response	361	2.4137	9.1148	1.78E-15	1.68E-13
GO:0050900	Leukocyte migration	419	2.8014	8.21	3.55E-15	3.02E-13

Table 4 Top ten significantly enriched pathways of key targets

Gene set	Description	Size	Expect	Ratio	P-value	FDR
hsa05200	Pathways in cancer	524	7.1346	5.0458	0	0
hsa05205	Proteoglycans in cancer	198	2.6959	8.9024	0	0
hsa01522	Endocrine resistance	98	1.3343	14.239	0	0
hsa05215	Prostate cancer	97	1.3207	13.629	4.44E-16	3.62E-14
hsa04933	AGE-RAGE signaling pathway in diabetic complications	99	1.348	12.612	1.02E-14	6.66E-13
hsa04066	HIF-1 signaling pathway	100	1.3616	11.751	2.13E-13	1.16E-11
hsa05206	MicroRNAs in cancer	150	2.0424	8.8133	9.90E-13	4.61E-11
hsa05418	Fluid shear stress and atherosclerosis	138	1.879	9.0475	2.93E-12	1.20E-10
hsa04151	PI3K-Akt signaling pathway	354	4.82	4.9793	3.10E-11	1.02E-09
hsa01521	EGFR tyrosine kinase inhibitor resistance	79	1.0756	12.086	3.11E-11	1.02E-09

biology. This network-based approach can explain the combination rules and network regulation effects of herbal formulas [21]. Network pharmacology strategies were successfully used to reveal mechanism of Lang Chuang Wan in treating systemic lupus erythematosus [22] and Yizhiqingxin formula on Alzheimer's disease [23].

Combined with the bioinformatics research on diseases, we can more clearly define the targets and specific mechanisms of Chinese medicine on the diseases, and identify key active molecules. This is of great significance to the development of natural medicines and the treatment of diseases. In our study, we successfully identified eight active molecules and two important pathways related to UC through network pharmacology and bioinformatics. They played a synergistic role in regulating HIF-1 signaling pathway and PI3K-Akt signaling pathway. Current evidences showed that Treg/Th17 imbalance is closely related to UC. The mTOR-HIF-1 α -Th17 and STAT3-HIF-1 α -Th17 pathways play an important role in the development of Th17 and the activation of IL-17. In addition, HIF-1 α can bind to Foxp3, thereby affecting the development and function of Treg [24]. PI3K can respond to LPS and TNF- α , thereby activating Akt and affecting NF- κ B to produce anti-apoptotic and pro-inflammatory effects [25]. Therefore, *Caulis Sargentodoxae* can improve UC by regulating them.

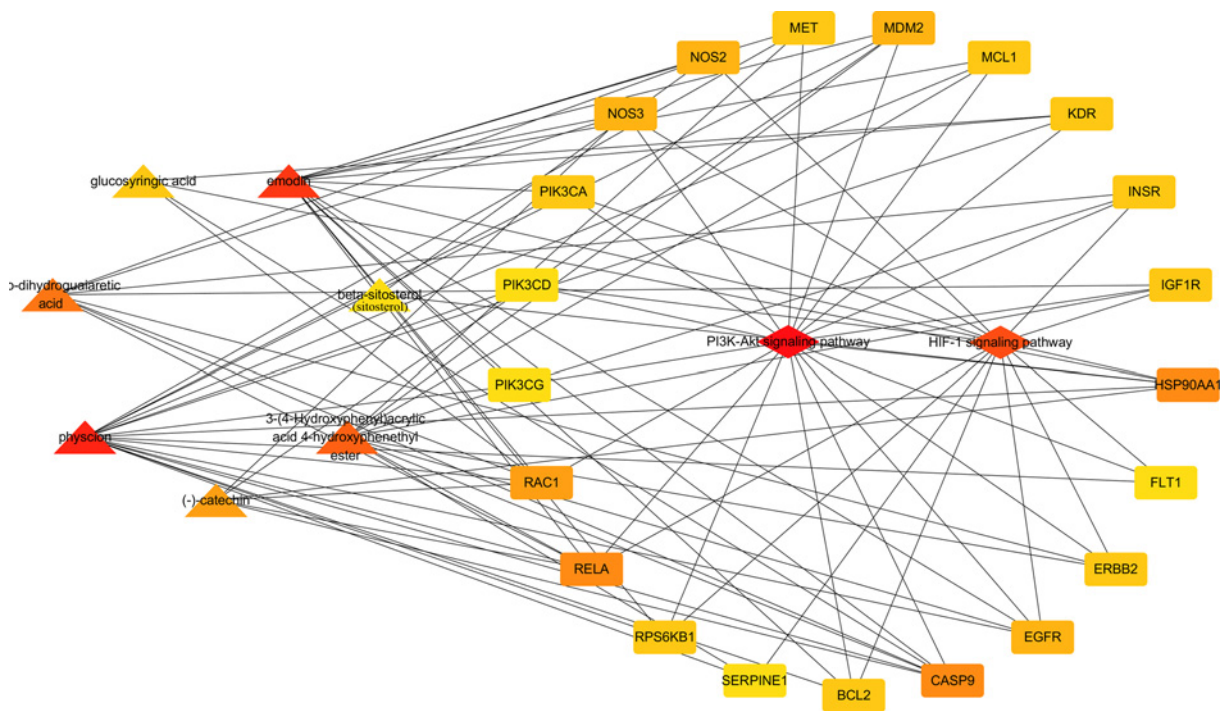


Figure 7. Components-targets-pathways network of *Caulis Sargentodoxae*
The triangles represent the components, the quadrangles represent the pathways, and the squarenesses represent the targets that can be regulated by the components and are in the pathways. The darker nodes represent higher degrees.

Table 5 Hub genes/molecules in components-targets-pathways network

Rank	Name	Score
1	Physcion	18
2	Emodin	17
3	3-(4-Hydroxyphenyl)acrylic acid 4-hydroxyphenethyl ester	12
4	Meso-dihydroguaiaretic acid	9
5	CASP9	7
5	RELA	7
5	HSP90AA1	7
8	(-)-Catechin	6
8	RAC1	6
10	MDM2	5
10	NOS3	5
10	NOS2	5
10	EGFR	5
14	MET	4
14	BCL2	4
14	PIK3CA	4
14	Glucosyringic acid	4
14	RPS6KB1	4
14	ERBB2	4
14	KDR	4
14	MCL1	4
14	INSR	4
14	IGF1R	4
24	β-sitosterol	3
24	PIK3CG	3
24	PIK3CD	3
24	SERPINE1	3
24	FLT1	3

According to Components-Targets-Pathways network, the degrees of physcion, emodin, 3-(4-Hydroxyphenyl)acrylic acid 4-hydroxyphenethyl ester and meso-dihydroguaiaretic acid were the highest. Physcion is an anthraquinone compound commonly found in various plants, and shows anti-cancer properties in a variety of tumors. It can significantly inhibit the production of LPS/IFN- γ -induced NO in various cells via attenuating iNOS [26]. It can also reduce the gene expression of TNF- α , IL-6 and IL-1 β in hepatocellular carcinoma cells induced by LPS in a dose-dependent manner by regulating p38 [27]. This indicated that it has good anti-inflammatory ability. And in our study, it was also identified as the most critical component for the treatment of UC. Emodin is a natural anthraquinone derivative with a wide range of pharmacological properties, including anticancer, liver protection, anti-inflammatory, antioxidant and antibacterial activities [28]. Emodin was found to induce autophagy in L02 human hepatocytes by inhibiting PI3K/AKT/mTOR signaling pathway [29]. Emodin was found to protect mice from DSS-induced colitis via the regulation of TLR5/NF- κ B signaling pathway [30], and significantly inhibit LPS-mediated NF- κ B activation and DNA binding activity in RAW264.7 cells [31]. This is consistent with our computer-based research, and indicates that emodin can regulate PI3K-Akt signaling pathway to exert anti-inflammatory effects. Meso-dihydroguaiaretic acid was found can attenuate airway inflammation and mucus hypersecretion in an ovalbumin-induced murine model of asthma via inhibiting the activation of NF- κ B, ERK1/2 and p38 [32]. However, the pharmacological activity of 3-(4-Hydroxyphenyl)acrylic acid 4-hydroxyphenethyl ester has not been reported yet, and further experiments are needed.

Overall, our results suggested that *Caulis Sargentodoxae* can treat UC through regulating HIF-1 signaling pathway and PI3K-Akt signaling pathway, but this effect is a synergistic effect of eight active components. It is necessary to further compare the therapeutic effects of *Caulis Sargentodoxae* and its different components in animal models, and further evaluate these molecules in terms of safety and higher efficacy. Analyzing and verifying the effective dose and toxicity of different molecules by using pharmacology and toxicology experiments will also have important significance for clinical applications.

Data Availability

The data used to support the findings of the present study are included within the article and the supplementary files.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution

G.Z. and B.L. designed the present study. B.L., X.Z., J.Y. and W.L. collected and organized the data. B.L., X.Z., J.L., X.L. and R.W. completed the data analysis and chart processing. B.L. and X.Z. wrote the manuscript. G.Z. reviewed the manuscript.

Abbreviations

BP, biological process; DL, drug-likeness; DSS, dextran sulphate sodium; EGFR, epidermal growth factor receptor; GEO, gene expression omnibus; GO, gene ontology; GWAS, genome-wide association studies; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; KEGG, Kyoto Encyclopedia of Genes and Genomes; LPS, lipopolysaccharide; MW, molecular weight; OB, oral bioavailability; PPI, protein-protein interaction; TCMS, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; Th17, T helper cell 17; TLR5, toll like receptor 5; Treg, regulatory T cell; UC, ulcerative colitis.

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