Original Article

Network pharmacology to explore the mechanism of traditional Chinese medicine in the treatment of ground glass nodules

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Background: Ground glass nodules (GGNs) in the lung are considered to be a high-risk factor of lung adenocarcinoma. Immediate surgery is not recommended for GGNs patients, and low-dose computed tomography (CT) is often used for observation and follow-up, which brings high psychological and economic burden to the patient.

Methods: Three traditional Chinese medicine (TCM) prescriptions for the treatment of GGNs were found through database including PubMed, Google Scholar, and China National Knowledge Infrastructure (CNKI), Scopus and so on. The possible targets of the active ingredients of the TCM preparations and the gene targets of GGNs were screened out from Traditional Chinese Medicine Systems Pharmacology (TCMSP), UniProt and GeneCards. Network visualization was realized via STRING, Cytoscape 3.7.2, Evenn, DAVID and Hiplot. Finally, molecular docking Vina and PyMOL software were performed to further explore the possibility of drug-target interactions using PubChem compounds, protein data bank (PDB) database, Autodocktools and Autodock.

Results: Three TCM preparations could target the same 13 potential therapeutic targets in GGNs. From network pharmacology, 14 signaling pathways, the functions of the significant targets, an effective ingredient in TCM prescriptions and its functions were obtained.

Conclusions: Chinese herbal formulas containing quercetin could be a potential treatment for GGNs, targeting C-reactive protein (*CRP*), tumor necrosis factor (*TNF*), interferon gamma (*IFN-γ*), intercellular adhesion molecule 1 (*ICAM-1*), and vascular endothelial growth factor A (*VEGFA*) through the hypoxia-inducible factor 1 (HIF-1) pathway, mitogen-activated protein kinase (MAPK) signaling pathway, and leukocyte transendothelial migration.

Keywords: Ground glass nodules (GGNs); traditional Chinese medicine (TCM); network pharmacology

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Introduction

According to the 2020 global cancer statistics report released by the International Agency for Research on Cancer, lung cancer accounts for 11.4% of new cancer cases and is the leading cause of death among all cancers. About 1.8 million people died of lung cancer, accounting for 18% of all cancer deaths (1). The emergence of ground glass nodules (GGNs) often suggests that it is related to lung cancer (2), which refers to the slightly increased density of the inner bronchus and vascular texture on high resolution computed tomography (CT), and most of them are early non-invasive or minimally invasive adenocarcinoma. Timely detection and intervention to prevent GGNs from developing into lung cancer may be a feasible way to reduce the prevalence of lung cancer.

The treatment of GGNs is still controversial in clinic. In the study of prognosis modeling, it is suggested that there may not be changed without surgery. Therefore, clinically, it is inclined to perform surgical resections for patients with certain symptoms or pathological changes, but the proportion of these patients is not high. The financial and emotional stress for patients increases gradually as the patient needs to pay attention to the size of the nodule with regular low-dose CT scans. In the treatment of lung cancer, people begin to prefer traditional Chinese medicine (TCM), and the use of TCM is more and more accepted. Therefore, we wondered whether TCM also had a certain therapeutic effect on GGNs and what its possible mechanism would be. In our initial investigation, we found that previous studies have indicated the use of Chai Hu Shu Gan San (CHSGS) and Si Ni San He Sheng Jiang San (SNSHSJS) in cancer treatment (3-6). Additionally, the main component in CHSGS, bupleurum, has been shown to have antioxidant, anticancer, and apoptotic properties (7,8). Li Shi Jian Zhi Shu Fang (LSJZSF) was developed by the renowned Chinese medicine expert Kongding Li and has been widely employed in treating interstitial pneumonia. Additionally, network modeling for simulating TCM has been extensively utilized, offering new insights into the rationale behind herb classifications and facilitating the exploration of TCM pharmacology (9,10). In this research, we searched multiple databases, sorted out the researches on the intervention treatment of TCM on GGNs, and analyzed their possible mechanisms. We present this article in accordance with the STREGA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1492/rc).

Highlight box

Key findings

- Traditional Chinese medicinal prescriptions can be deployed to treat ground glass nodules, focusing on multiple targets.

What is known and what is new?

- Traditional Chinese medicine has discovered potential treatments for ground glass nodules, as well as the mechanisms behind them.
- All Chinese herbal formulas in the database used to treat ground glass nodules contain quercetin and have the same targets.

What is the implication, and what should change now?

- This investigation could provide more potential drug targets for treating ground glass nodules.

Methods

Establishing and analysing network pharmacology is an important approach to explore the mechanism of TCM. The process begins with identifying potential targets and active ingredients, predicting their functions through network analysis, and then exploring their relationship. The procedure of this research is shown in *Figure 1*.

Search of TCM in the treatment of GGNs

We searched multiple database [PubMed, China National Knowledge Infrastructure (CNKI), Google Scholar, Scopus and so on] with "ground glass nodules" and "treatment" or "traditional Chinese medicine" as keywords without language restriction. Finally, we found three TCM prescriptions in CNKI for treating GGNs, namely, CHSGS (11), LSJZSF (12) and SNSHSJS (13).

Screening of action targets of components of CHSGS, LSJZSF, and SNSHSJS

To identify the action targets associated with CHSGS, LSJZSF, and SNSHSJS, a thorough search and screening process was carried out for all active components derived from the respective herbs (see *Table 1*). The identified ingredients include a variety of herbs such as Chaihu, Baishao, Ezhu, Danggui, Chuanxiong, Yujin, Xiangfu, Dihuang, Zhimu, Mihoutaogen, Baihuasheshecao, Shanzhuyu, Suanzao, Tusizi, Baiziren for CHSGS; Gancao, Zhike, Yuxingcao, Lianqiao, Huangqin, Huangjing, Nanshashen, Zhebeimu, Chishao for LSJZSF; and Chaihu,

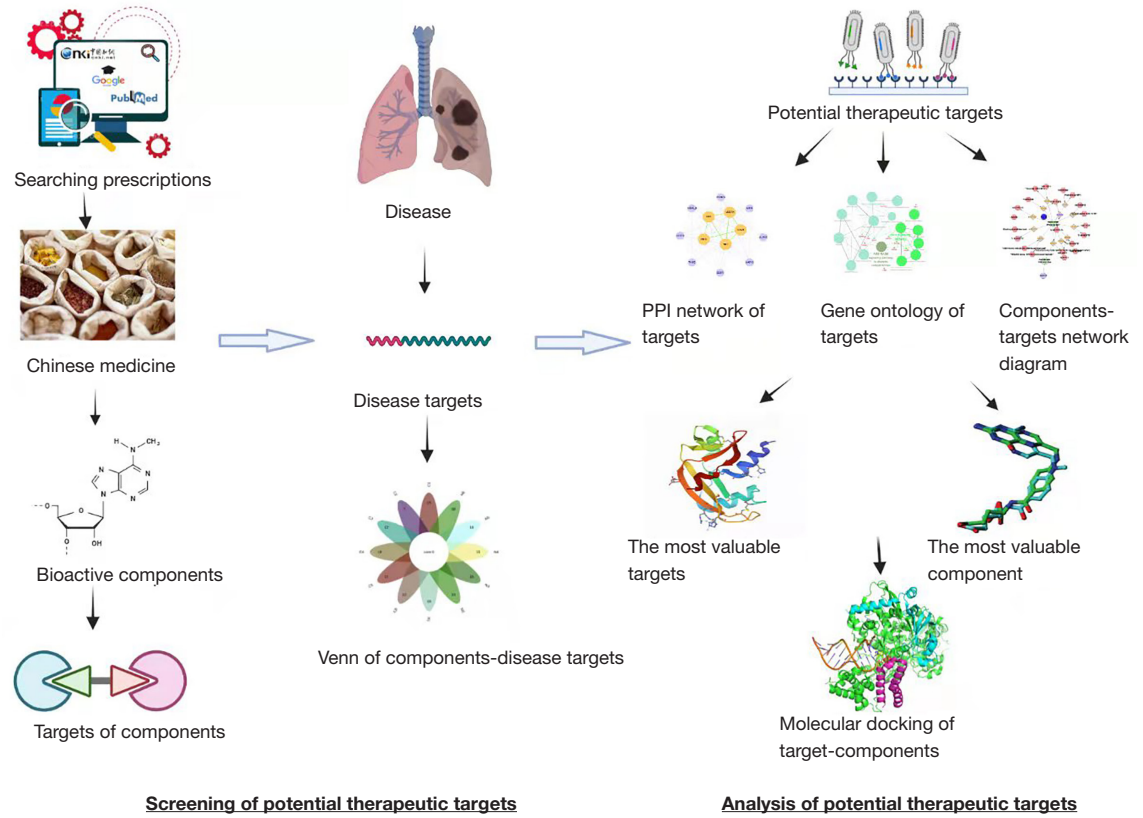

Figure 1 Workflow of the study. The figure indicates the mechanism of traditional Chinese medicine for the treatment of ground glass nodules using the network pharmacology and computational bioinformatics analysis approach. PPI, protein-protein interaction.

Table 1 The herbs of three TCM prescriptions

Prescription	TCM
CHSGS	Chaihu, Baishao, Ezhu, Danggui, Chuanxiong, Yujin, Xiangfu, Dihuang, Zhimu, Mihoutaogen, Baihuasheshecao, Shanzhuyu, Suanzao, Tusizi, Baiziren
LSJZSF	Gancao, Zhike, Yuxingcao, Lianqiao, Huangqin, Huangjing, Nanshashen, Zhebeimu, Chishao
SNSHSJS	Chaihu, Baishao, Jiangcan, Jianghuang, Chantui, Zhike, Gancao

TCM, traditional Chinese medicine; CHSGS, Chai Hu Shu Gan San; LSJZSF, Li Shi Jian Zhi Shu Fang; SNSHSJS, Si Ni San He Sheng Jiang San.

Baishao, Jiangcan, Jianghuang, Chantui, Zhike, Gancao for SNSHSJS. The active components meeting strict research criteria were carefully selected based on oral bioavailability (OB ≥30%) and drug-likeness (DL ≥0.18) using the Traditional Chinese Medicine Systems Pharmacology (TCMSP, http://tcmsp-e.com) (14), Subsequently, the targets corresponding to these selected active ingredients from TCMSP were further refined using standardized gene names according to UniProt (https://www.uniprot.org/) for simplification and consistency in the subsequent analysis (15).

Acquisition of GGNs targets

The keyword "ground glass nodules" in GeneCards (https://www.genecards.org/) was searched to screen the target genes of GGNs in the database.

Screening of common targets of TCM prescriptions—GGNs

The targets of components of CHSGS, LSJZSF, and SNSHSJS and GGNs were arranged into a two-column matrix mode and imported into the Flower plot model in Evenn (http://www.ehbio.com/test/venn) (16). Then, the Venn diagram of the three prescriptions and GGNs was respectively drawn, and the table of interactive genes was exported.

Visualization of Gene Ontology (GO) analysis of GGNs targets and potential targets

To further confirm the relationship between the genes identified from screening the common targets of TCM prescriptions (GGNs) and the genes related to the treatment of GGNs, we imported the GGN genes into the STRING database (https://cn.string-db.org) to create a preliminary protein-protein interaction (PPI) network model. This model was then exported in tab separated values (TSV) text format. We used the Maximal Clique Centrality (MCC) method in Cytohubba, a Cytoscape plugin, to identify the top ten targets of GGNs and the five hub genes associated with the common targets of TCM prescriptions—GGNs (17). This approach allowed us to assess the importance of these genes within the PPI network. We obtained the results of GO analysis through DAVID (https://david.ncifcrf.gov), and then visualized them through Hiplot (https://hiplot.com.cn).

Construction and analysis of TCM prescriptions—GGNs network model

GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) function enrichment were carried out through the ClueGo plug-in of Cytoscape to analyze the common targets of medicines and disease. The analysis of GO includes three parts: cellular component, molecular function and biological process. After being introduced into ClueGo for analysis, the relevant enrichment pathway was derived. A component-target-pathway network was established by Cytoscape to visually expressed the connections.

PPI network analysis of TCM prescription—GGNs common targets

The common targets of TCM prescriptions—GGNs were imported into the STRING. The preliminary model of PPI network was constructed and later exported to the TSV text format. Visual network of the PPI network was obtained by Cytoscape, and each node represents the target of the intersection of the two. Then, the most valuable component is obtained through the data of components-targets.

Visualization of KEGG the most valuable component

Before molecular docking, to further verify the effectiveness of the most valuable component, we obtained the results of KEGG analysis of all TCM including this component through BATAM-TCM (http://bionet.ncpsb.org/batman-tcm/) and visualized them.

GGNs target docking with molecules of the most valuable component

The 3D structures of the five hub genes of the common targets of TCM prescriptions—GGNs were obtained from protein data bank (PDB) (http://www.rcsb.org/) database, and the 3D structures of the most valuable component were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) database (18). Then, molecular docking was performed. The component and targets were converted from their native format to pdbqt format through Autodocktools 1.5.6, and the structures were optimized by deleting water molecules and adding hydrogen atoms. Next, Autodock Vina was used for molecular docking, and the docking process was calculated by genetic algorithm (19). All docking operation options were the default values. Finally, the docking results with the highest score were visualized through PyMoL (20).

Statistical analysis

The Fisher's Exact test evaluated gene enrichment in annotation terms in DAVID, while ClueGo integrated GO terms and KEGG pathways to construct a functionally structured network of TCM prescriptions-GGNs. ClueGo's network employs kappa statistics to analyze the similarity of genes connected to different pathways, revealing their intricate interactions. The hypergeometric cumulative distribution test by BATAM-TCM was utilized to conduct the enrichment analysis of the most valuable component. A P value that is 0.05 or lower is typically regarded as statistically significant.

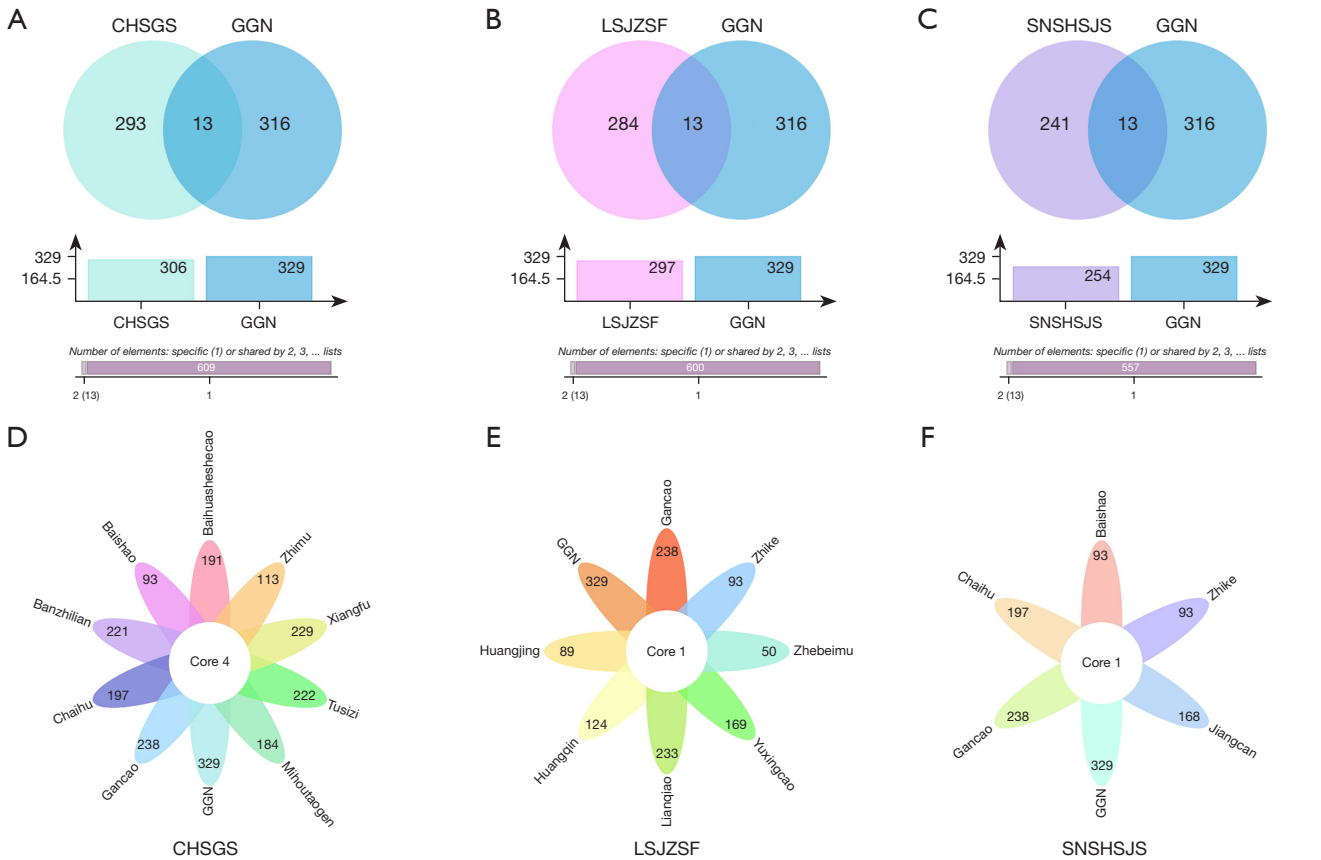

Figure 2 Analysis of intersecting genes in GGNs and the three traditional Chinese medicine prescriptions. (A-C) The Venn diagram is interactive and shows the intersection of genes between GGNs and CHSGS, LSJZSF, and SNSHSJS. The x-axis represents the different groups, while the y-axis shows the total number of genes. (D-F) Flow plot depicting the crossover genes of each important herb in CHSGS, LSJZSF, SNSHSJS and GGNs respectively. GGN, ground glass nodule; CHSGS, Chai Hu Shu Gan San; LSJZSF, Li Shi Jian Zhi Shu Fang; SNSHSJS, Si Ni San He Sheng Jiang San.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Results of active ingredients and targets

According to the requirements, 252 active ingredients were screened out in the CHSGS (Table S1), 216 active ingredients in the LSJZSF (Table S2), and 133 active ingredients in the SNSHSJS (Table S3), whilst no active ingredients were screened out from Chantui.

Potential target genes of TCM prescriptions in the treatment of GGNs

All targets of CHSGS intersect with GGNs. Similarly, the remaining two prescriptions also intersected with those of GGNs, the target genes of which were all 13 and the same (*Figure 2A-2C*). They were thrombomodulin (*THBD*), myeloperoxidase (*MPO*), peroxisome proliferator activated receptor gamma (*PPARG*), epidermal growth factor receptor (*EGFR*), vascular endothelial growth factor A (*VEGFA*), tumor necrosis factor (*TNF*), intercellular adhesion molecule 1 (*ICAM-1*), interferon gamma (*IFN-γ*), arachidonate 5-lipoxygenase (*ALOX5*), C-reactive protein

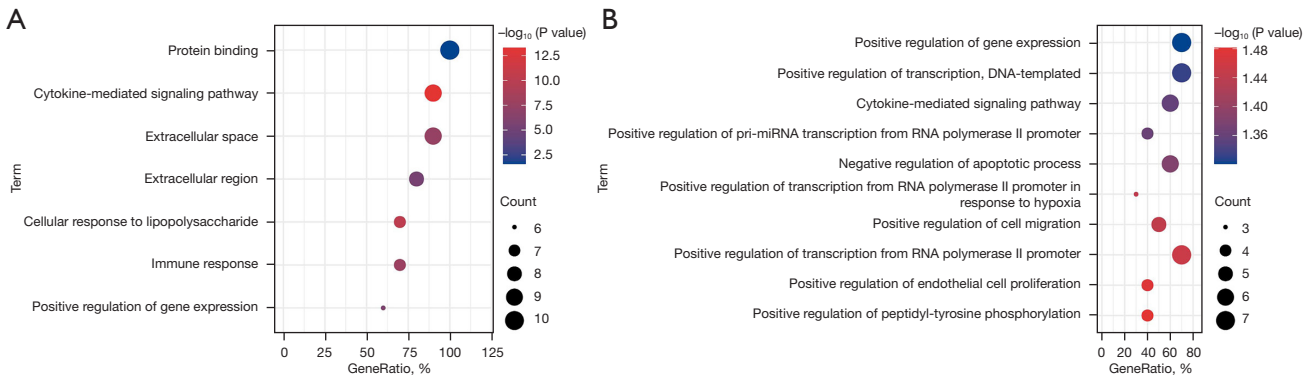

Figure 3 GO analysis of GGNs targets and potential therapeutic targets. (A) The GO analysis of the top 10 genes in GGNs and (B) GO analysis of the top 5 potential therapeutic targets with TCM against GGNs. The y-axis shows significantly enriched categories of the targets and the x-axis shows the GeneRatio, which is calculated as the number of differentially expressed genes divided by the total number of genes associated with the GO term. GO, Gene Ontology; GGN, ground glass nodule; TCM, traditional Chinese medicine.

(*CRP*), CD40 ligand (*CD40LG*), mitogen-activated protein kinase 3 (*MAPK3*) and signal transducer and activator of transcription 3 (*STAT3*). In order to further explore the potential therapeutic targets, we intersected the more important targets of TCM in the three prescriptions with the targets of GGNs respectively. Four intersection genes were identified among the significant TCM targets of CHSGS and GGN (*Figure 2D*), which include *PPARG*, *TNF*, *ICAM-1*, and *ALOX5*. Furthermore, LSJZSF and SNSHSJS share 1 interactive gene which is *PPARG* (*Figure 2E,2F*). To explore the potential therapeutic mechanisms fully, we use the 13 potential therapeutic targets that in three formulations to intersect with GGNs as analysis data in the following analysis.

The results of visualization of GO of GGNs genes and the potential therapeutic genes

According to the GO analysis of GGNs and the potential therapeutic targets, dot plot (*Figure 3A*) showed the top three in GGNs genes were protein binding, cytokine-mediated signaling pathway and extracellular space, while the top three in the potential therapeutic genes analysis were positive regulation of gene expression, positive regulation of transcription, DNA-templated and cytokine-mediated signaling pathway (*Figure 3B*). In addition to the anti-cancer-related pathways such as positive regulation of transcription, and DNA-templated, negative regulation of apoptotic process, positive regulation of cell migration and so on, potential drug targets of TCM and GGNs all had cytokines mediated signaling pathway and positive regulation of gene expression, indicating that the direct pathways for TCM treating GGNs may be these and prevented GGNs from developing into lung cancer.

ClueGo analysis of potential target genes of the three TCM prescriptions in the treatment of GGNs

We performed ClueGo analysis on the 13 potential therapeutic targets of components of CHSGS, LSJZSF, and SNSHSJS to show the functional grouping of potential genes and their role in biological processes. The size of the nodes in the network indicated the enrichment significance, and the functional related groups overlap. The result suggested that potential therapeutic targets associated with tyrosine phosphorylation of STAT protein, acute inflammatory response, superoxide metabolic process and astrocyte differentiation (*Figure 4A*). Also, it showed that potential therapeutic targets were more related to hypoxia-inducible factor 1 (HIF-1) signaling pathway and advanced glycation end product (AGE)-the receptor of advanced glycation end product (RAGE) signaling pathway (*Figure 4B,4C*). Further enrichment analysis of up-regulated genes showed that there were at least three genes involved in each of the 14 related pathways. HIF-1 signaling pathway and AGE-RAGE signaling pathway ranked higher. AGE-RAGE signaling pathway promoted the survival pathway of cancer cells through the negative feedback regulation of apoptosis and the positive regulation of survival promoting mechanism, and inhibiting AGE-RAGE signaling may help to counteract the progress of inflammatory cascade leading to various pathological conditions (21). Moreover,

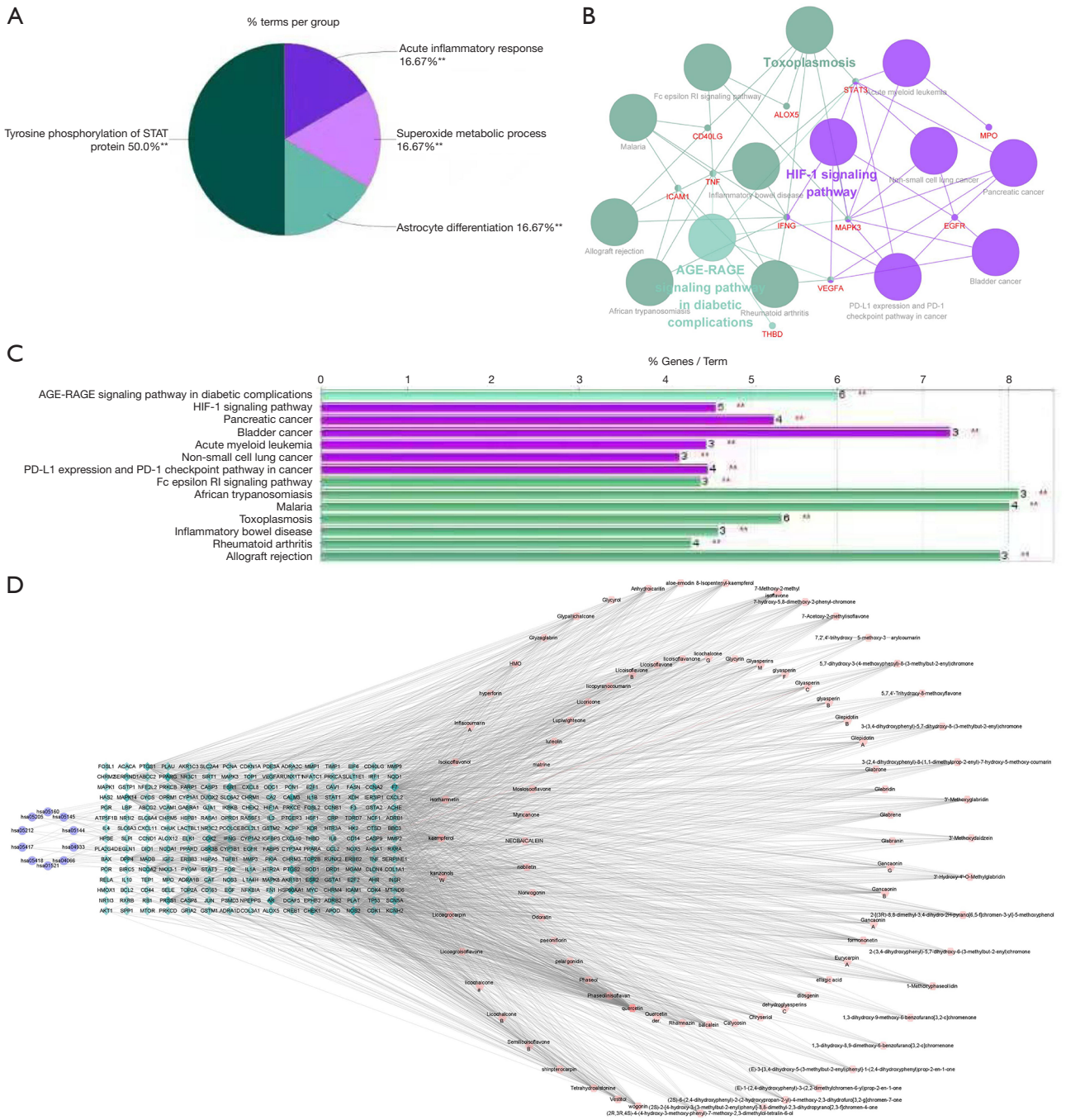

Figure 4 Functional characterization of 13 potential therapeutic targets with TCM against GGNs. (A) GO analysis of intersecting genes of TCM and GGNs, including cellular component, molecular function and biological process. **, P<0.01. (B,C) KEGG pathway of potential therapeutic targets. (D) The component-target-pathway network. The purple nodes represent pathways associated with targets, the green nodes represent target genes and the pink nodes are main components. PD-L1, programmed death-ligand 1; PD-1, programmed cell death 1; TCM, traditional Chinese medicine; GGN, ground glass nodule; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

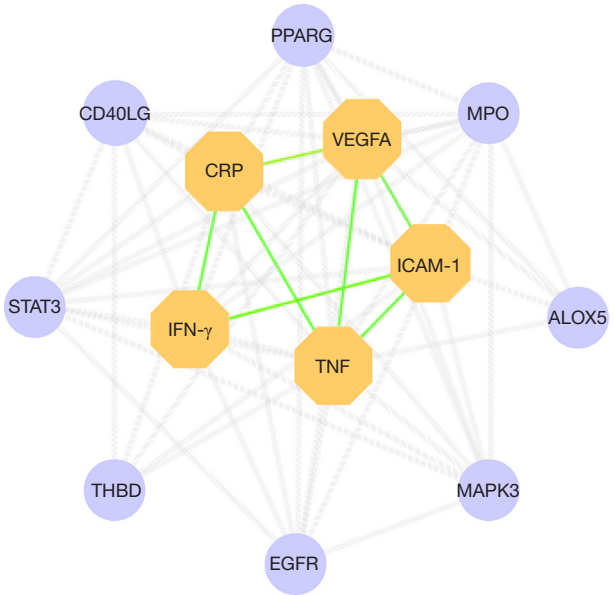

Figure 5 The PPI network related to the action of TCM against GGNs. Five core targets—*CRP*, *IFN-γ*, *TNF*, *ICAM-1* and *VEGFA*—are in yellow. *CRP*, C-reactive protein; *IFN-γ*, interferon gamma; *TNF*, tumor necrosis factor; *ICAM-1*, intercellular adhesion molecule 1; *VEGFA*, vascular endothelial growth factor A; PPI, protein-protein interaction; TCM, traditional Chinese medicine; GGN, ground glass nodule.

some studies have shown that therapeutic targeting HIF has the potential to improve the therapeutic effect in the treatment of cancer (22-24). Therefore, we speculated that TCM can prevent GGNs lesions from becoming malignant tumors through these two pathways, so as to achieve the effect of treating GGNs. Moreover, we illustrated the network of major components from CHSGS, LSJZSF, and SNSHSJS, their associated gene targets, and pathways. This comprehensive depiction provides a visual representation of the intricate connections within our study (*Figure 4D*).

PPI network of TCM prescription in the treatment of GGNs

The protein interaction network of potential targets was drawn in Cytohubba. The results revealed that 61 nodes were interacting among the 13 nodes, which included *ALOX5*, *MPO*, *ICAM-1*, *PPARG*, *VEGFA*, *TNF*, *CD40LG*, *IFN-γ*, *CRP*, *STAT3*, *THBD*, *EGFR*, and *MAPK3* (*Figure 5*). Based on the MCC scores, the top five target proteins were identified as hub genes, with *CRP*, *TNF*, *IFN-γ*, *ICAM-1*, and *VEGFA* being the most significant. The MCC scores for these hub genes can be found in Table S4. Upon analyzing these data, it was determined that quercetin was the most valuable component, meeting the criteria of OB ≥30% and DL ≥0.18.

The result of KEGG of quercetin

Based on the visualization of KEGG analysis of all TCM including quercetin through BATAM-TCM (*Figure 6A*), we learned that quercetin was wildly associated with HIF-1 signaling pathway, MAPK signaling pathway and leukocyte transendothelial migration according to the coverage, in which HIF-1 signaling pathway also appeared in the KEGG result of potential therapeutic genes. As is known to us, MAPK signaling pathway is more important than other pathways in cell proliferation, differentiation, apoptosis, angiogenesis and tumor metastasis. Continuous activation of MAPK signaling pathway can transform normal cells into tumor cells, while inhibition of this pathway can restore tumor cells to a non-transformed state *in vitro* and inhibit the growth of tumors *in vivo*, suggesting that the increase of activation of MAPK signaling pathway may be closely related to the occurrence and development of tumors (25). In lung cancer, tumor cells secrete cytokines stimulate leukocyte transendothelial migration and enhance tumor progression to affect angiogenesis (26). Therefore, quercetin may prevent cancer by influencing these three processes.

Target molecular docking of TCM prescriptions in the treatment of GGNs

The five most valuable genes, namely *CRP*, *TNF*, *IFN-γ*, *ICAM-1* and *VEGFA*, were reversely searched for the active components corresponding to the target for molecular docking. The docking mode of the two was shown from the binding position and the interaction of key residues. The active substance formed an ionic bond with the amino acid residues TYR-49 and SER-44 of CRP protein (*Figure 6B*); the interaction between the active substance and TNF protein (the amino acid residues were LEU-51 and HIS-52) was an ionic bond (*Figure 6C*); the active substance formed an ionic bond with the amino acid residue ASP-34 of VEGFA protein (*Figure 6D*); the active substance formed an ionic bond with the amino acid residues ASN-1091, ASP-1095 and SER-3 of ICAM-1 protein (*Figure 6E*); the active substance formed an ionic bond with the amino

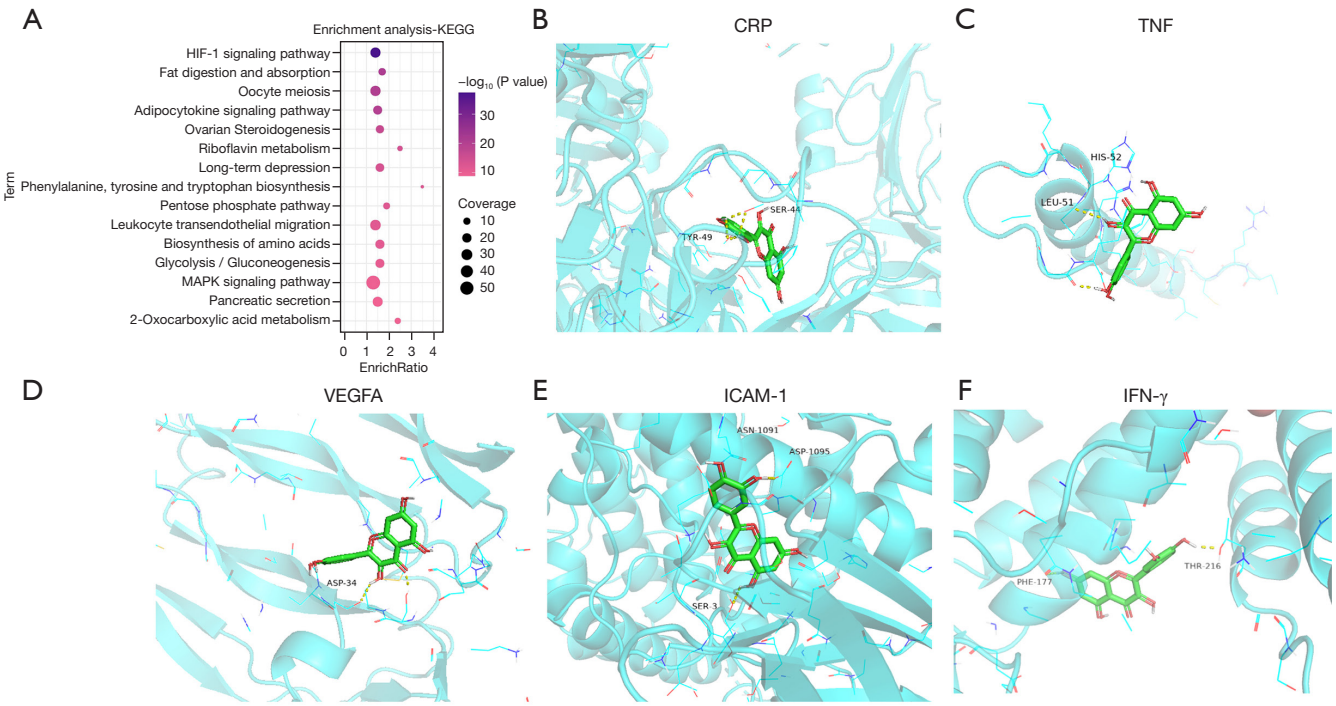

Figure 6 Network of active ingredient quercetin and further molecular docking. (A) KEGG pathway of quercetin. Molecular models of quercetin binding to the predicted target proteins (B) CRP, (C) TNF, (D) VEGFA, (E) ICAM-1 and (F) IFN-γ. KEGG, Kyoto Encyclopedia of Genes and Genomes; CRP, C-reactive protein; TNF, tumor necrosis factor; VEGFA, vascular endothelial growth factor A; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon gamma.

acid residues PHE-177 and THR-216 of IFN-γ protein (*Figure 6F*). All of them locked the binding orientation through hydrogen bonding. The binding energies of quercetin to CPR, TNF, VEGFA, ICAM-1 and IFN-γ were −9.2, −5.2, −6.2, −8.5 and −7.3 kcal·mol^{-1} respectively. The smaller the value, the greater the binding energy was, indicating that quercetin had a strong binding ability to CPR, TNF, VEGFA, ICAM-1 and IFN-γ.

Discussion

At present, for the management of GGNs, the best practice is to carefully monitor patients through follow-up CT. Due to the high-risk malignant tumor of GGNs, malignant tumor is likely to occur once new solid components or solid components increase in follow-up CT. When malignant tumor is suspected, surgical biopsy should be performed to determine pulmonary parenchymal resection (27). During the follow-up process, there is no treatments, which will bring some psychological pressure to the patients. Therefore, we hope to find a breakthrough in the treatment of GGNs in TCM prescriptions.

In China, many people use TCM to treat various diseases including pulmonary nodules. There are related researches on GGNs treatment with TCM in CNKI, which proves that TCM is effective. The treatment mechanism based on TCM is characterized by multiple targets and multiple systems. We assumed that the mechanisms of different TCM prescriptions were different. Interestingly, common potential therapeutic targets were found in these three TCM preparations. In the results of the Cytoscape analysis, we found that the active ingredient quercetin was responsible for the emergence of common potential therapeutic targets, and it was presented in multiple components of these three TCM formulations. Quercetin may be a potential drug in GGNs treatment. Studies have confirmed that quercetin can delay the progression of lung adenocarcinoma by reducing cell proliferation, migration, and invasion, ultimately achieving anticancer effects (28,29).

Through our network pharmacological analysis of TCM, we found that the most extensive coverage treatment pathway in quercetin were HIF-1 signaling pathway,

MAPK signaling pathway and leukocyte transendothelial migration. Hypoxia is one of the most common conditions encountered within the tumor microenvironment that drives tumor progression. As one of the transcriptional family regulating hypoxic adaptation in cancer, the upregulation of HIF-1 signaling pathway could activate various hallmarks of cancer such as leukocyte transendothelial migration; MAPK signaling pathway is associated with cancer progression (30). Progression could be regulated by targeting these pathways. Among the potential targets *CRP*, *TNF*, *IFN-γ*, *ICAM-1* and *VEGFA* involved in these pathways, *CRP* can induce *TNF* secretion by MAPK signaling pathway, which has a definite impact on tumor cell proliferation, transendothelial-neutrophil migration, invasion and chemical resistance (31). The *ICAM-1* on the surface of endothelial cells mediates the adhesion and extravasation of leukocytes and plays a key role in the inflammatory response (32). Inadequate vasculature causes pockets of low oxygen, which exerts a pro-apoptotic response in some cancer cells, *VEGFA* is considered to be the main stimulatory signal of angiogenesis *in vivo*, promoting endothelial cell survival and mediate angiogenesis, which is very important for tumor progression (33). Therefore, inhibition of VEGFA signaling pathway is a common therapeutic strategy in oncology. TCM targets the HIF-1 signaling pathway, thereby preventing the transcription of the HIF target gene, such as *VEGFA* (34). *IFN-γ* inhibits the expression of several phosphatase involved in MAPK pathway, related to various inflammatory or immune stimuli, which plays a dual and opposite role in cancer. IFN-γ signaling pathway inhibits tumor growth by preventing tumor cell cycle, inducing tumor ischemia and activating antigen—preserving cells and effector cells, while damaging and inhibiting immune cells (35). At the same time, *IFN-γ* promotes tumor growth by promoting tumorigenesis and angiogenesis, upregulation of tolerance molecules and inducing homeostasis (36). Consequently, in this study, we not only demonstrate the potential of Chinese medicines in addressing pulmonary nodules but also suggest that quercetin could be utilized as a new treatment formula for GGNs.

However, there are still some deficiencies in the articles. There are few articles collected based on the database, and the number of patients enrolled in these clinical researches is small. Additionally, this study lacks experimental data to support the findings, and the pharmacological mechanism of network pharmacological analysis of drugs still requires further analysis.

Conclusions

This research discovered that TCM can be utilized as a method for treating GGNs, and quercetin, a common component found in CHSGS, LSJZSF, and SNSHSJS, may have a crucial role in the treatment process. Quercetin could activate the HIF-1 signaling pathway and the MAPK signaling pathway, targeting *CRP*, *TNF*, *IFN-γ*, *ICAM-1*, and *VEGFA*, which leads to apoptosis of cancer cells and produces anti-cancer effects. Although this study provides new ideas for clinical treatment of GGNs, further research is still needed.

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Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1492/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1492/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Table S1 The active components of CHSGS

TCM	Mol ID	Molecule Name
Chaihu	MOL001645	Linoleyl acetate
Chaihu	MOL002776	Baicalin
Chaihu	MOL000449	Stigmasterol
Chaihu	MOL000354	isorhamnetin
Chaihu	MOL000422	kaempferol
Chaihu	MOL004598	3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl)chromone
Chaihu	MOL004609	Areapillin
Chaihu	MOL013187	Cubebin
Chaihu	MOL004624	Longikaurin A
Chaihu	MOL004628	Octalupine
Chaihu	MOL004644	Sainfuran
Chaihu	MOL004648	Troxerutin
Chaihu	MOL004653	(+)-Anomalin
Chaihu	MOL004702	saikosaponin c_qt
Chaihu	MOL004718	α-spinasterol
Chaihu	MOL000490	petunidin
Chaihu	MOL000098	quercetin
Baishao	MOL001910	11alpha,12alpha-epoxy-3beta-23-dihydroxy-30-norolean-20-en-28,12beta-olide
Baishao	MOL001918	paeoniflorgenone
Baishao	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
Baishao	MOL001921	Lactiflorin
Baishao	MOL001924	paeoniflorin
Baishao	MOL001925	paeoniflorin_qt
Baishao	MOL001928	albiflorin_qt
Baishao	MOL001930	benzoyl paeoniflorin
Baishao	MOL000211	Mairin
Baishao	MOL000358	beta-sitosterol
Baishao	MOL000359	sitosterol
Baishao	MOL000422	kaempferol
Baishao	MOL000492	(+)-catechin
Ezhu	MOL000296	hederagenin
Ezhu	MOL000906	wenjine
Ezhu	MOL000940	bisdemethoxycurcumin
Danggui	MOL000358	beta-sitosterol
Danggui	MOL000449	Stigmasterol
Chuanxiong	MOL002135	Myricanone
Chuanxiong	MOL002140	Perlolyrine
Chuanxiong	MOL002151	senkyunone
Chuanxiong	MOL002157	wallichilide
Chuanxiong	MOL000359	sitosterol
Chuanxiong	MOL000433	FA
Yujin	MOL000358	beta-sitosterol
Yujin	MOL000359	sitosterol
Yujin	MOL004241	curcolactone
Yujin	MOL004244	(4aR,5R,8R,8aR)-5,8-dihydroxy-3,5,8a-trimethyl-6,7,8,9-tetrahydro-4aH-benzo[f]benzofuran-4-one
Yujin	MOL004253	Curcumenolactone C
Yujin	MOL004260	(E)-1,7-Diphenyl-3-hydroxy-1-hepten-5-one
Yujin	MOL004263	(E)-5-Hydroxy-7-(4-hydroxyphenyl)-1-phenyl-1-heptene
Yujin	MOL004291	Oxycurcumenol
Yujin	MOL004305	Zedoalactone A
Yujin	MOL004306	Zedoalactone B
Yujin	MOL004309	zedoalactone E
Yujin	MOL004311	Zedoarolide A
Yujin	MOL004313	Zedoarolide B
Yujin	MOL004316	1,7-Diphenyl-3-acetoxy-6(E)-hepten
Yujin	MOL004328	naringenin
Xiangfu	MOL003044	Chryseriol
Xiangfu	MOL000354	isorhamnetin
Xiangfu	MOL003542	8-Isopentenyl-kaempferol
Xiangfu	MOL000358	beta-sitosterol
Xiangfu	MOL000359	sitosterol
Xiangfu	MOL004027	1,4-Epoxy-16-hydroxyheneicos-1,3,12,14,18-pentaene
Xiangfu	MOL004053	Isodalbergin
Xiangfu	MOL004058	Khell
Xiangfu	MOL004059	khellol glucoside
Xiangfu	MOL010489	Resivit
Xiangfu	MOL004068	rosenonolactone
Xiangfu	MOL004071	Hyndarin
Xiangfu	MOL004074	stigmasterol glucoside_qt
Xiangfu	MOL004077	sugeonyl acetate
Xiangfu	MOL000422	kaempferol
Xiangfu	MOL000449	Stigmasterol
Xiangfu	MOL000006	luteolin
Xiangfu	MOL000098	quercetin
Dihuang	MOL000359	sitosterol
Dihuang	MOL000449	Stigmasterol
Zhimu	MOL001677	asperglaucide
Zhimu	MOL003773	Mangiferolic acid
Zhimu	MOL000422	kaempferol
Zhimu	MOL004373	Anhydroicaritin
Zhimu	MOL004489	Anemarsaponin F_qt
Zhimu	MOL004492	Chrysanthemaxanthin
Zhimu	MOL004497	Hippeastrine
Zhimu	MOL004514	Timosaponin B III_qt
Zhimu	MOL000449	Stigmasterol
Zhimu	MOL004528	Icariin I
Zhimu	MOL004540	Anemarsaponin C_qt
Zhimu	MOL004542	Anemarsaponin E_qt
Zhimu	MOL000483	(Z)-3-(4-hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl)ethyl]acrylamide
Zhimu	MOL000546	diosgenin
Zhimu	MOL000631	coumaroyltyramine
Banzhilian	MOL001755	24-Ethylcholest-4-en-3-one
Banzhilian	MOL002714	baicalein
Banzhilian	MOL002719	6-Hydroxynaringenin
Banzhilian	MOL002915	Salvigenin
Banzhilian	MOL000351	Rhamnazin
Banzhilian	MOL000359	sitosterol
Banzhilian	MOL005190	eriodictyol
Banzhilian	MOL005869	daucostero_qt
Banzhilian	MOL000006	luteolin
Banzhilian	MOL008206	Moslosooflavone
Banzhilian	MOL000098	quercetin
Mihoutaogen	MOL000358	beta-sitosterol
Mihoutaogen	MOL000359	sitosterol
Mihoutaogen	MOL000471	aloe-emodin
Mihoutaogen	MOL000492	(+)-catechin
Mihoutaogen	MOL000073	ent-Epicatechin
Mihoutaogen	MOL000098	quercetin
Baihuasheshecao	MOL001646	2,3-dimethoxy-6-methyanthraquinone
Baihuasheshecao	MOL001659	Poriferasterol
Baihuasheshecao	MOL001663	(4aS,6aR,6aS,6bR,8aR,10R,12aR,14bS)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid
Baihuasheshecao	MOL001670	2-methoxy-3-methyl-9,10-anthraquinone
Baihuasheshecao	MOL000449	Stigmasterol
Baihuasheshecao	MOL000358	beta-sitosterol
Baihuasheshecao	MOL000098	quercetin
Shanzhuyu	MOL001494	Mandenol
Shanzhuyu	MOL001495	Ethyl linolenate
Shanzhuyu	MOL001771	poriferast-5-en-3beta-ol
Shanzhuyu	MOL002879	Diop
Shanzhuyu	MOL002883	Ethyl oleate (NF)
Shanzhuyu	MOL003137	Leucanthoside
Shanzhuyu	MOL000358	beta-sitosterol
Shanzhuyu	MOL000359	sitosterol
Shanzhuyu	MOL000449	Stigmasterol
Shanzhuyu	MOL005360	malkangunin
Shanzhuyu	MOL005481	2,6,10,14,18-pentamethylicosa-2,6,10,14,18-pentaene
Shanzhuyu	MOL005486	3,4-Dehydrolycopen-16-al
Shanzhuyu	MOL005489	3,6-Digalloylglucose
Shanzhuyu	MOL005503	Cornudentanone
Shanzhuyu	MOL005530	Hydroxygenkwanin
Shanzhuyu	MOL005531	Telocinobufagin
Shanzhuyu	MOL008457	Tetrahydroalstonine
Shanzhuyu	MOL000554	gallic acid-3-O-(6'-O-galloyl)-glucoside
Shanzhuyu	MOL005552	gemin D
Shanzhuyu	MOL005557	lanosta-8,24-dien-3-ol,3-acetate
Suanzaoren	MOL001521	ceanothic acid
Suanzaoren	MOL001522	(S)-Coclaurine
Suanzaoren	MOL001525	Daucosterol
Suanzaoren	MOL001527	jujuboside A_qt
Suanzaoren	MOL001532	phytosterol
Suanzaoren	MOL001539	sanjoinenine
Suanzaoren	MOL001542	swertisin
Suanzaoren	MOL001546	zizyphusine
Suanzaoren	MOL000211	Mairin
Tusizi	MOL001558	sesamin
Tusizi	MOL000184	NSC63551
Tusizi	MOL000354	isorhamnetin
Tusizi	MOL000358	beta-sitosterol
Tusizi	MOL000422	kaempferol
Tusizi	MOL005043	campest-5-en-3beta-ol
Tusizi	MOL005440	Isofucosterol
Tusizi	MOL005944	matrine
Tusizi	MOL006649	sophranol
Tusizi	MOL000953	CLR
Tusizi	MOL000098	quercetin
Baiziren	MOL001439	arachidonic acid
Baiziren	MOL002211	11,14-eicosadienoic acid
Baiziren	MOL000359	sitosterol
Baiziren	MOL003927	Dihomolinolenic acid
Baiziren	MOL008153	5Z-eicosenoic acid
Gancao	MOL001484	Inermine
Gancao	MOL001792	DFV
Gancao	MOL000211	Mairin
Gancao	MOL002311	Glycyrol
Gancao	MOL000239	Jaranol
Gancao	MOL002565	Medicarpin
Gancao	MOL000354	isorhamnetin
Gancao	MOL000359	sitosterol
Gancao	MOL003656	Lupiwighteone
Gancao	MOL003896	7-Methoxy-2-methyl isoflavone
Gancao	MOL000392	formononetin
Gancao	MOL000417	Calycosin
Gancao	MOL000422	kaempferol
Gancao	MOL004328	naringenin
Gancao	MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one
Gancao	MOL004806	euchrenone
Gancao	MOL004808	glyasperin B
Gancao	MOL004810	glyasperin F
Gancao	MOL004811	Glyasperin C
Gancao	MOL004814	Isotrifoliol
Gancao	MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one
Gancao	MOL004820	kanzonols W
Gancao	MOL004824	(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one
Gancao	MOL004827	Semilicoisoflavone B
Gancao	MOL004828	Glepidotin A
Gancao	MOL004829	Glepidotin B
Gancao	MOL004833	Phaseolinisoflavan
Gancao	MOL004835	Glypallichalcone
Gancao	MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol
Gancao	MOL004841	Licochalcone B
Gancao	MOL004848	licochalcone G
Gancao	MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin
Gancao	MOL004855	Licoricone
Gancao	MOL004856	Gancaonin A
Gancao	MOL004857	Gancaonin B
Gancao	MOL004860	licorice glycoside E
Gancao	MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone
Gancao	MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone
Gancao	MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone
Gancao	MOL004879	Glycyrin
Gancao	MOL004882	Licocoumarone
Gancao	MOL004883	Licoisoflavone
Gancao	MOL004884	Licoisoflavone B
Gancao	MOL004885	licoisoflavanone
Gancao	MOL004891	shinpterocarpin
Gancao	MOL004898	(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one
Gancao	MOL004903	liquiritin
Gancao	MOL004904	licopyranocoumarin
Gancao	MOL004905	3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid
Gancao	MOL004907	Glyzaglabrin
Gancao	MOL004908	Glabridin
Gancao	MOL004910	Glabranin
Gancao	MOL004911	Glabrene
Gancao	MOL004912	Glabrone
Gancao	MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone
Gancao	MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone
Gancao	MOL004915	Eurycarpin A
Gancao	MOL004917	glycyroside
Gancao	MOL004924	(-)-Medicocarpin
Gancao	MOL004935	Sigmoidin-B
Gancao	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one
Gancao	MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one
Gancao	MOL004948	Isoglycyrol
Gancao	MOL004949	Isolicoflavonol
Gancao	MOL004957	HMO
Gancao	MOL004959	1-Methoxyphaseollidin
Gancao	MOL004961	Quercetin der.
Gancao	MOL004966	3'-Hydroxy-4'-O-Methylglabridin
Gancao	MOL000497	licochalcone a
Gancao	MOL004974	3'-Methoxyglabridin
Gancao	MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol
Gancao	MOL004980	Inflacoumarin A
Gancao	MOL004985	icos-5-enoic acid
Gancao	MOL004988	Kanzonol F
Gancao	MOL004989	6-prenylated eriodictyol
Gancao	MOL004990	7,2',4'-trihydroxy-5-methoxy-3-arylcoumarin
Gancao	MOL004991	7-Acetoxy-2-methylisoflavone
Gancao	MOL004993	8-prenylated eriodictyol
Gancao	MOL004996	gadelaidic acid
Gancao	MOL000500	Vestitol
Gancao	MOL005000	Gancaonin G
Gancao	MOL005001	Gancaonin H
Gancao	MOL005003	Licoagrocarpin
Gancao	MOL005007	Glyasperins M
Gancao	MOL005008	Glycyrrhiza flavonol A
Gancao	MOL005012	Licoagroisoflavone
Gancao	MOL005013	18α-hydroxyglycyrrhetic acid
Gancao	MOL005016	Odoratin
Gancao	MOL005017	Phaseol
Gancao	MOL005018	Xambioona
Gancao	MOL005020	dehydroglyasperins C
Gancao	MOL000098	quercetin

CHSGS, Chai Hu Shu Gan San; TCM, traditional Chinese medicine.

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Table S2 The active components of LSJZSF

TCM	Mol ID	Molecule Name
Chishao	MOL001002	ellagic acid
Chishao	MOL001918	paeoniflorgenone
Chishao	MOL001921	Lactiflorin
Chishao	MOL001924	paeoniflorin
Chishao	MOL001925	paeoniflorin_qt
Chishao	MOL002714	baicalein
Chishao	MOL002776	Baicalin
Chishao	MOL000358	beta-sitosterol
Chishao	MOL000359	sitosterol
Chishao	MOL004355	Spinasterol
Chishao	MOL000449	Stigmasterol
Chishao	MOL000492	(+)-catechin
Chishao	MOL006990	(1S,2S,4R)-trans-2-hydroxy-1,8-cineole-B-D-glucopyranoside
Chishao	MOL006992	(2R,3R)-4-methoxyl-distylin
Chishao	MOL006994	1-o-beta-d-glucopyranosyl-8-o-benzoylpaeonisuffrone_qt
Chishao	MOL006996	1-o-beta-d-glucopyranosylpaeonisuffrone_qt
Chishao	MOL006999	stigmast-7-en-3-ol
Chishao	MOL007003	benzoyl paeoniflorin
Chishao	MOL007004	Albiflorin
Chishao	MOL007005	Albiflorin_qt
Chishao	MOL007008	4-ethyl-paeoniflorin_qt
Chishao	MOL007012	4-o-methyl-paeoniflorin_qt
Chishao	MOL007014	8-debenzoylpaeonidanin
Chishao	MOL007016	Paeoniflorigenone
Chishao	MOL007018	9-ethyl-neo-paeoniaflorin A_qt
Chishao	MOL007022	evofolinB
Chishao	MOL007025	isobenzoylpaeoniflorin
Chishao	MOL002883	Ethyl oleate (NF)
Chishao	MOL005043	campest-5-en-3beta-ol
Zhebeimu	MOL001004	pelargonidin
Zhebeimu	MOL000358	beta-sitosterol
Zhebeimu	MOL004440	Peimisine
Zhebeimu	MOL004443	Zhebeiresinol
Zhebeimu	MOL004444	Ziebeimine
Zhebeimu	MOL004446	6-Methoxyl-2-acetyl-3-methyl-1,4-naphthoquinone-8-O-beta-D-glucopyranoside
Zhebeimu	MOL004450	Chaksine
Nanshashen	MOL002883	Ethyl oleate (NF)
Nanshashen	MOL000358	beta-sitosterol
Nanshashen	MOL001494	Mandenol
Nanshashen	MOL003479	cycloartenol acetate
Nanshashen	MOL003485	Phthalic acid, isobutyl undecyl ester
Huangjing	MOL001792	DFV
Huangjing	MOL002714	baicalein
Huangjing	MOL002959	3'-Methoxydaidzein
Huangjing	MOL000358	beta-sitosterol
Huangjing	MOL000359	sitosterol
Huangjing	MOL003889	methylprotodioscin_qt
Huangjing	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one
Huangjing	MOL000546	diosgenin
Huangjing	MOL006331	4',5-Dihydroxyflavone
Huangjing	MOL009760	sibiricoside A_qt
Huangjing	MOL009763	(+)-Syringaresinol-O-beta-D-glucoside
Huangjing	MOL009766	zhonghualiaoine 1
Huangqin	MOL001689	acacetin
Huangqin	MOL000173	wogonin
Huangqin	MOL000228	(2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one
Huangqin	MOL002714	baicalein
Huangqin	MOL002908	5,8,2'-Trihydroxy-7-methoxyflavone
Huangqin	MOL002909	5,7,2,5-tetrahydroxy-8,6-dimethoxyflavone
Huangqin	MOL002910	Carthamidin
Huangqin	MOL002911	2,6,2',4'-tetrahydroxy-6'-methoxychaleone
Huangqin	MOL002913	Dihydrobaicalin_qt
Huangqin	MOL002914	Eriodyctiol (flavanone)
Huangqin	MOL002915	Salvigenin
Huangqin	MOL002917	5,2',6'-Trihydroxy-7,8-dimethoxyflavone
Huangqin	MOL002925	5,7,2',6'-Tetrahydroxyflavone
Huangqin	MOL002926	dihydrooroxylin A
Huangqin	MOL002927	Skullcapflavone II
Huangqin	MOL002928	oroxylin a
Huangqin	MOL002932	Panicolin
Huangqin	MOL002933	5,7,4'-Trihydroxy-8-methoxyflavone
Huangqin	MOL002934	NEOBAICALEIN
Huangqin	MOL002937	DIHYDROOROXYLIN
Huangqin	MOL000358	beta-sitosterol
Huangqin	MOL000359	sitosterol
Huangqin	MOL000525	Norwogonin
Huangqin	MOL000552	5,2'-Dihydroxy-6,7,8-trimethoxyflavone
Huangqin	MOL000073	ent-Epicatechin
Huangqin	MOL000449	Stigmasterol
Huangqin	MOL001458	coptisine
Huangqin	MOL001490	bis[(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate
Huangqin	MOL001506	Supraene
Huangqin	MOL002879	Diop
Huangqin	MOL002897	epiberberine
Huangqin	MOL008206	Moslosooflavone
Huangqin	MOL010415	11,13-Eicosadienoic acid, methyl ester
Huangqin	MOL012245	5,7,4'-trihydroxy-6-methoxyflavanone
Huangqin	MOL012246	5,7,4'-trihydroxy-8-methoxyflavanone
Huangqin	MOL012266	rivularin
Lianqiao	MOL000173	wogonin
Lianqiao	MOL003281	20(S)-dammar-24-ene-3β,20-diol-3-acetate
Lianqiao	MOL003283	(2R,3R,4S)-4-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-2,3-dimethylol-tetralin-6-ol
Lianqiao	MOL003290	(3R,4R)-3,4-bis[(3,4-dimethoxyphenyl)methyl]oxolan-2-one
Lianqiao	MOL003295	(+)-pinoresinol monomethyl ether
Lianqiao	MOL003305	PHILLYRIN
Lianqiao	MOL003306	ACon1_001697
Lianqiao	MOL003308	(+)-pinoresinol monomethyl ether-4-D-beta-glucoside_qt
Lianqiao	MOL003315	3beta-Acetyl-20,25-epoxydammarane-24alpha-ol
Lianqiao	MOL000211	Mairin
Lianqiao	MOL003322	FORSYTHINOL
Lianqiao	MOL003330	(-)-Phillygenin
Lianqiao	MOL003344	β-amyrin acetate
Lianqiao	MOL003347	hyperforin
Lianqiao	MOL003348	adhyperforin
Lianqiao	MOL003365	Lactucasterol
Lianqiao	MOL003370	Onjixanthone I
Lianqiao	MOL000358	beta-sitosterol
Lianqiao	MOL000422	kaempferol
Lianqiao	MOL000522	arctiin
Lianqiao	MOL000006	luteolin
Lianqiao	MOL000791	bicuculline
Lianqiao	MOL000098	quercetin
Yuxingcao	MOL003851	Isoramanone
Yuxingcao	MOL000422	kaempferol
Yuxingcao	MOL004345	1-methyl-2-nonacosyl-4-quinolone
Yuxingcao	MOL004350	Ruvoside_qt
Yuxingcao	MOL004351	C09747
Yuxingcao	MOL004355	Spinasterol
Yuxingcao	MOL000098	quercetin
Zhike	MOL013381	Marmin
Zhike	MOL002341	Hesperetin
Zhike	MOL000358	beta-sitosterol
Zhike	MOL004328	naringenin
Zhike	MOL005828	nobiletin
Gancao	MOL001484	Inermine
Gancao	MOL001792	DFV
Gancao	MOL000211	Mairin
Gancao	MOL002311	Glycyrol
Gancao	MOL000239	Jaranol
Gancao	MOL002565	Medicarpin
Gancao	MOL000354	isorhamnetin
Gancao	MOL000359	sitosterol
Gancao	MOL003656	Lupiwighteone
Gancao	MOL003896	7-Methoxy-2-methyl isoflavone
Gancao	MOL000392	formononetin
Gancao	MOL000417	Calycosin
Gancao	MOL000422	kaempferol
Gancao	MOL004328	naringenin
Gancao	MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one
Gancao	MOL004806	euchrenone
Gancao	MOL004808	glyasperin B
Gancao	MOL004810	glyasperin F
Gancao	MOL004811	Glyasperin C
Gancao	MOL004814	Isotrifoliol
Gancao	MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one
Gancao	MOL004820	kanzonols W
Gancao	MOL004824	(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one
Gancao	MOL004827	Semilicoisoflavone B
Gancao	MOL004828	Glepidotin A
Gancao	MOL004829	Glepidotin B
Gancao	MOL004833	Phaseolinisoflavan
Gancao	MOL004835	Glypallichalcone
Gancao	MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol
Gancao	MOL004841	Licochalcone B
Gancao	MOL004848	licochalcone G
Gancao	MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin
Gancao	MOL004855	Licoricone
Gancao	MOL004856	Gancaonin A
Gancao	MOL004857	Gancaonin B
Gancao	MOL004860	licorice glycoside E
Gancao	MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone
Gancao	MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone
Gancao	MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone
Gancao	MOL004879	Glycyrin
Gancao	MOL004882	Licocoumarone
Gancao	MOL004883	Licoisoflavone
Gancao	MOL004884	Licoisoflavone B
Gancao	MOL004885	licoisoflavanone
Gancao	MOL004891	shinpterocarpin
Gancao	MOL004898	(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one
Gancao	MOL004903	liquiritin
Gancao	MOL004904	licopyranocoumarin
Gancao	MOL004905	3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid
Gancao	MOL004907	Glyzaglabrin
Gancao	MOL004908	Glabridin
Gancao	MOL004910	Glabranin
Gancao	MOL004911	Glabrene
Gancao	MOL004912	Glabrone
Gancao	MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone
Gancao	MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone
Gancao	MOL004915	Eurycarpin A
Gancao	MOL004917	glycyroside
Gancao	MOL004924	(-)-Medicocarpin
Gancao	MOL004935	Sigmoidin-B
Gancao	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one
Gancao	MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one
Gancao	MOL004948	Isoglycyrol
Gancao	MOL004949	Isolicoflavonol
Gancao	MOL004957	HMO
Gancao	MOL004959	1-Methoxyphaseollidin
Gancao	MOL004961	Quercetin der.
Gancao	MOL004966	3'-Hydroxy-4'-O-Methylglabridin
Gancao	MOL000497	licochalcone a
Gancao	MOL004974	3'-Methoxyglabridin
Gancao	MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol
Gancao	MOL004980	Inflacoumarin A
Gancao	MOL004985	icos-5-enoic acid
Gancao	MOL004988	Kanzonol F
Gancao	MOL004989	6-prenylated eriodictyol
Gancao	MOL004990	7,2',4'-trihydroxy-5-methoxy-3-arylcoumarin
Gancao	MOL004991	7-Acetoxy-2-methylisoflavone
Gancao	MOL004993	8-prenylated eriodictyol
Gancao	MOL004996	gadelaidic acid
Gancao	MOL000500	Vestitol
Gancao	MOL005000	Gancaonin G
Gancao	MOL005001	Gancaonin H
Gancao	MOL005003	Licoagrocarpin
Gancao	MOL005007	Glyasperins M
Gancao	MOL005008	Glycyrrhiza flavonol A
Gancao	MOL005012	Licoagroisoflavone
Gancao	MOL005013	18α-hydroxyglycyrrhetic acid
Gancao	MOL005016	Odoratin
Gancao	MOL005017	Phaseol
Gancao	MOL005018	Xambioona
Gancao	MOL005020	dehydroglyasperins C
Gancao	MOL000098	quercetin

LSJZSF, Li Shi Jian Zhi Shu Fang; TCM, traditional Chinese medicine.

Table S3 The active components of SNSHSJS

TCM	Mol ID	Molecule name
Chaihu	MOL001645	Linoleyl acetate
Chaihu	MOL002776	Baicalin
Chaihu	MOL000449	Stigmasterol
Chaihu	MOL000354	isorhamnetin
Chaihu	MOL000422	kaempferol
Chaihu	MOL004598	3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl)chromone
Chaihu	MOL004609	Areapillin
Chaihu	MOL013187	Cubebin
Chaihu	MOL004624	Longikaurin A
Chaihu	MOL004628	Octalupine
Chaihu	MOL004644	Sainfuran
Chaihu	MOL004648	Troxerutin
Chaihu	MOL004653	(+)-Anomalin
Chaihu	MOL004702	saikosaponin c_qt
Chaihu	MOL004718	α-spinasterol
Chaihu	MOL000490	petunidin
Chaihu	MOL000098	quercetin
Baishao	MOL001910	11alpha,12alpha-epoxy-3beta-23-dihydroxy-30-norolean-20-en-28,12beta-olide
Baishao	MOL001918	paeoniflorgenone
Baishao	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
Baishao	MOL001921	Lactiflorin
Baishao	MOL001924	paeoniflorin
Baishao	MOL001925	paeoniflorin_qt
Baishao	MOL001928	albiflorin_qt
Baishao	MOL001930	benzoyl paeoniflorin
Baishao	MOL000211	Mairin
Baishao	MOL000358	beta-sitosterol
Baishao	MOL000359	sitosterol
Baishao	MOL000422	kaempferol
Baishao	MOL000492	(+)-catechin
Jiangcan	MOL000098	quercetin
Jiangcan	MOL000422	kaempferol
Jiangcan	MOL000359	sitosterol
Jianghuang	MOL000449	Stigmasterol
Jianghuang	MOL000493	campesterol
Jianghuang	MOL000953	CLR
Zhike	MOL013381	Marmin
Zhike	MOL002341	Hesperetin
Zhike	MOL000358	beta-sitosterol
Zhike	MOL004328	naringenin
Zhike	MOL005828	nobiletin
Gancao	MOL001484	Inermine
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Gancao	MOL004856	Gancaonin A
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Gancao	MOL004882	Licocoumarone
Gancao	MOL004883	Licoisoflavone
Gancao	MOL004884	Licoisoflavone B
Gancao	MOL004885	licoisoflavanone
Gancao	MOL004891	shinpterocarpin
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Gancao	MOL004948	Isoglycyrol
Gancao	MOL004949	Isolicoflavonol
Gancao	MOL004957	HMO
Gancao	MOL004959	1-Methoxyphaseollidin
Gancao	MOL004961	Quercetin der.
Gancao	MOL004966	3'-Hydroxy-4'-O-Methylglabridin
Gancao	MOL000497	licochalcone a
Gancao	MOL004974	3'-Methoxyglabridin
Gancao	MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol
Gancao	MOL004980	Inflacoumarin A
Gancao	MOL004985	icos-5-enoic acid
Gancao	MOL004988	Kanzonol F
Gancao	MOL004989	6-prenylated eriodictyol
Gancao	MOL004990	7,2',4'-trihydroxy-5-methoxy-3-arylcoumarin
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Gancao	MOL004993	8-prenylated eriodictyol
Gancao	MOL004996	gadelaidic acid
Gancao	MOL000500	Vestitol
Gancao	MOL005000	Gancaonin G
Gancao	MOL005001	Gancaonin H
Gancao	MOL005003	Licoagrocarpin
Gancao	MOL005007	Glyasperins M
Gancao	MOL005008	Glycyrrhiza flavonol A
Gancao	MOL005012	Licoagroisoflavone
Gancao	MOL005013	18α-hydroxyglycyrrhetic acid
Gancao	MOL005016	Odoratin
Gancao	MOL005017	Phaseol
Gancao	MOL005018	Xambioona
Gancao	MOL005020	dehydroglyasperins C
Gancao	MOL000098	quercetin

SNSHSJS, Si Ni San He Sheng Jiang San; TCM, traditional Chinese medicine.

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Table S4 Top 5 hub genes with MCC scores

Genes	MCC
TNF	85920
ICAM-1	85920
VEGFA	85920
CRP	85800
IFN-γ	85680

MCC, Maximal Clique Centrality; *TNF*, tumor necrosis factor; *ICAM-1*, intercellular adhesion molecule 1; *VEGFA*, vascular endothelial growth factor A; *CRP*, C-reactive protein; *IFN-γ*, interferon gamma.

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