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

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).

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,

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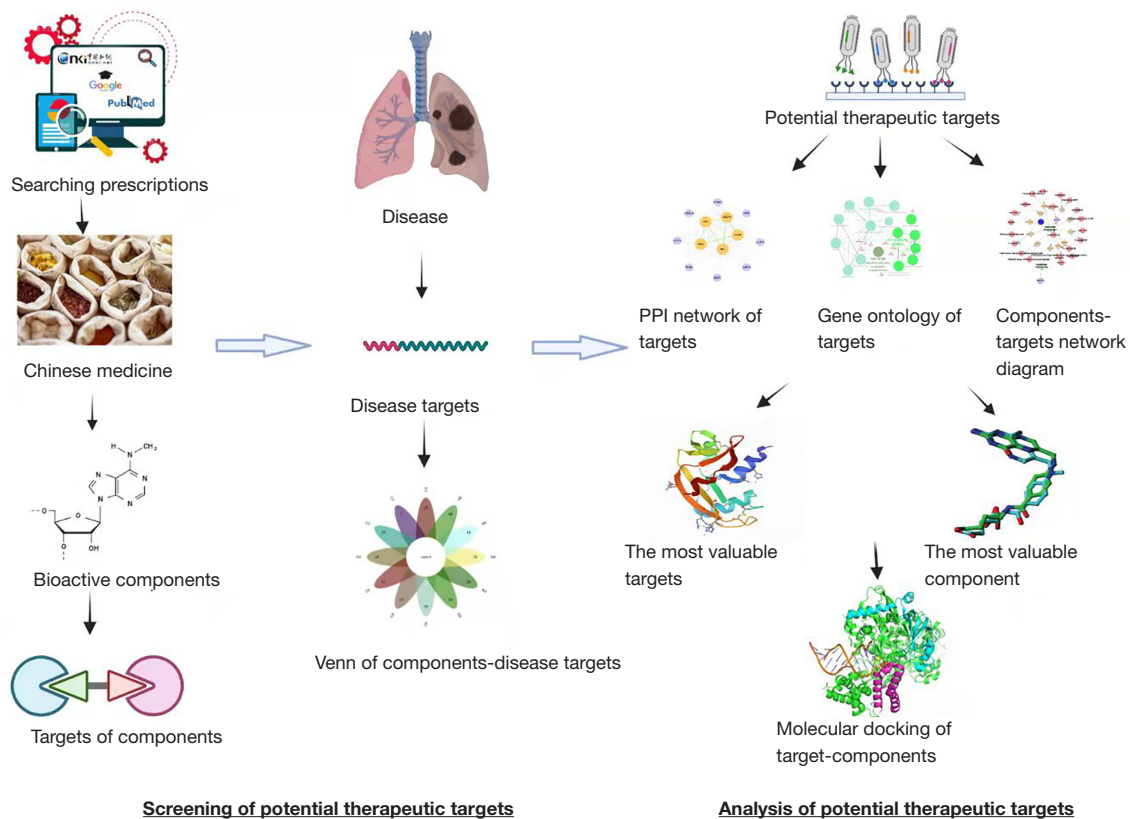
Figure 1 Workflow of the study. The figure indicates the mechanism of traditional Chinese medicine for the treatment of ground glass nodules using the network pharmacology and computational bioinformatics analysis approach. PPI, protein-protein interaction.

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.
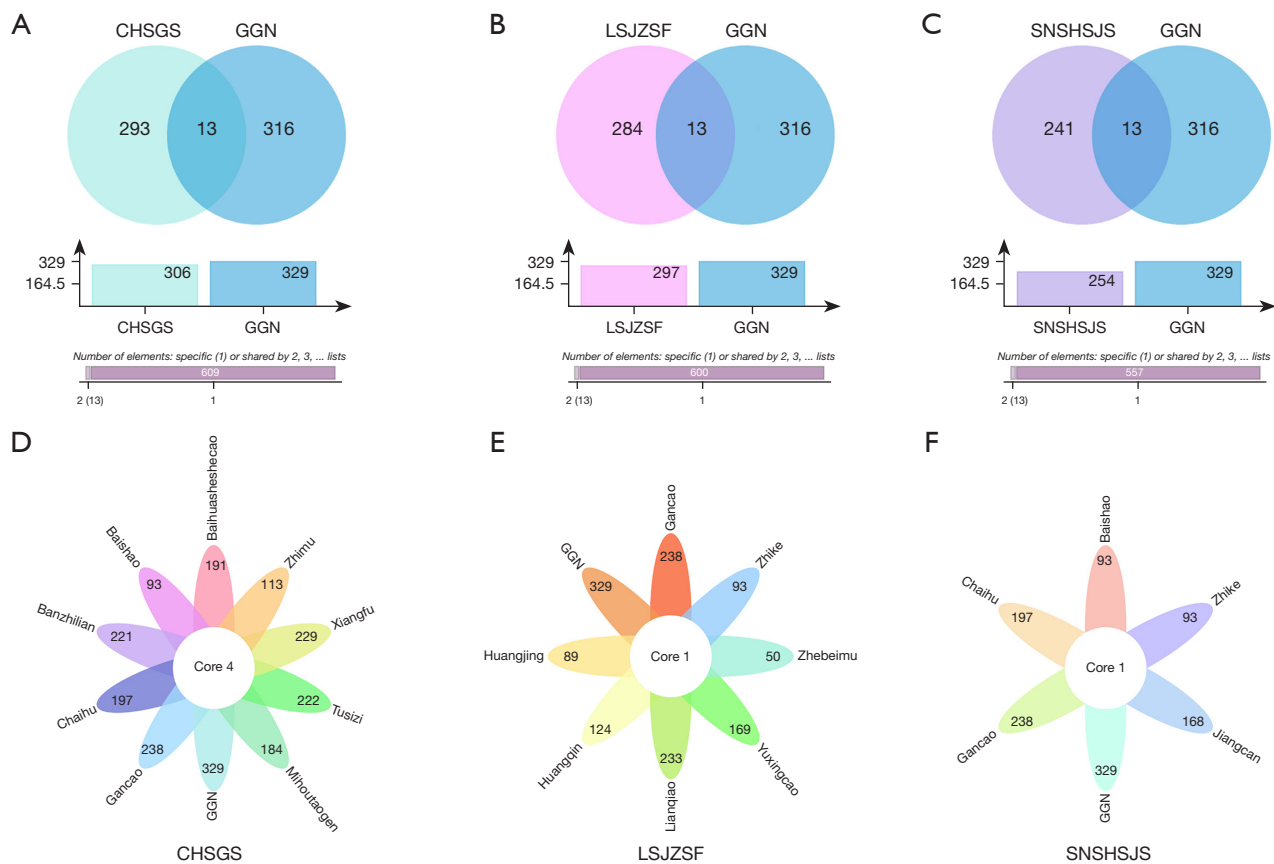
Figure 2 Analysis of intersecting genes in GGNs and the three traditional Chinese medicine prescriptions. (A-C) The Venn diagram is interactive and shows the intersection of genes between GGNs and CHSGS, LSJZSF, and SNSHSJS. The x-axis represents the different groups, while the y-axis shows the total 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
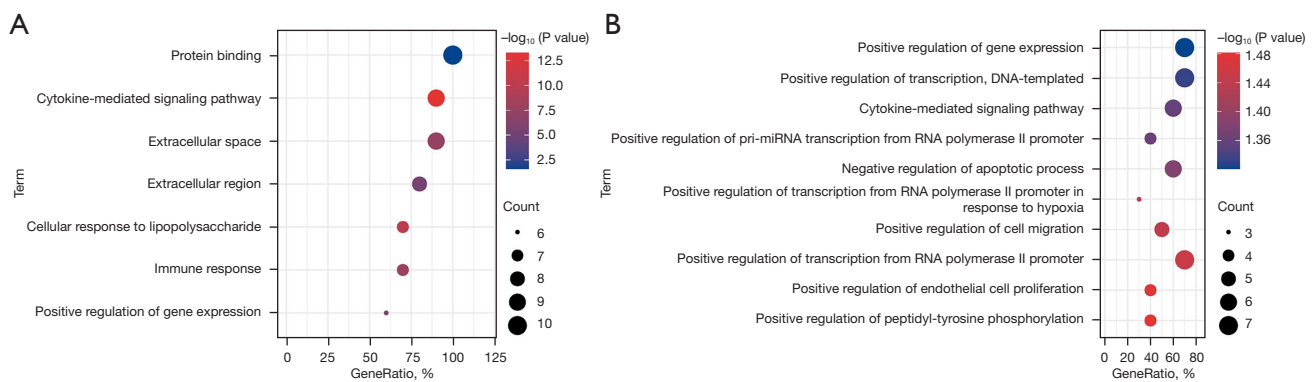
Figure 3 GO analysis of GGNs targets and potential therapeutic targets. (A) The GO analysis of the top 10 genes in GGNs and (B) GO analysis of the top 5 potential therapeutic targets with TCM against GGNs. The y-axis shows significantly enriched categories of the targets and the x-axis shows the GeneRatio, 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,
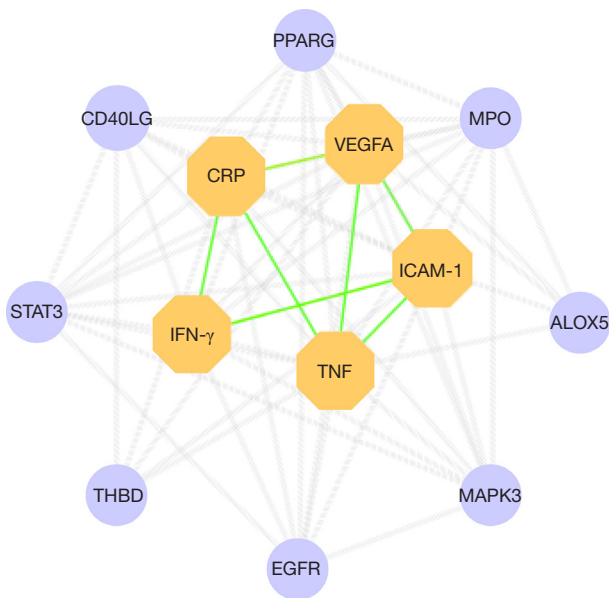
Figure 4 Functional characterization of 13 potential therapeutic targets with TCM against GGNs. (A) GO analysis of intersecting genes of TCM and GGNs, including cellular component, molecular function and biological process. **, P<0.01. (B,C) KEGG pathway of potential therapeutic targets. (D) The component-target-pathway 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
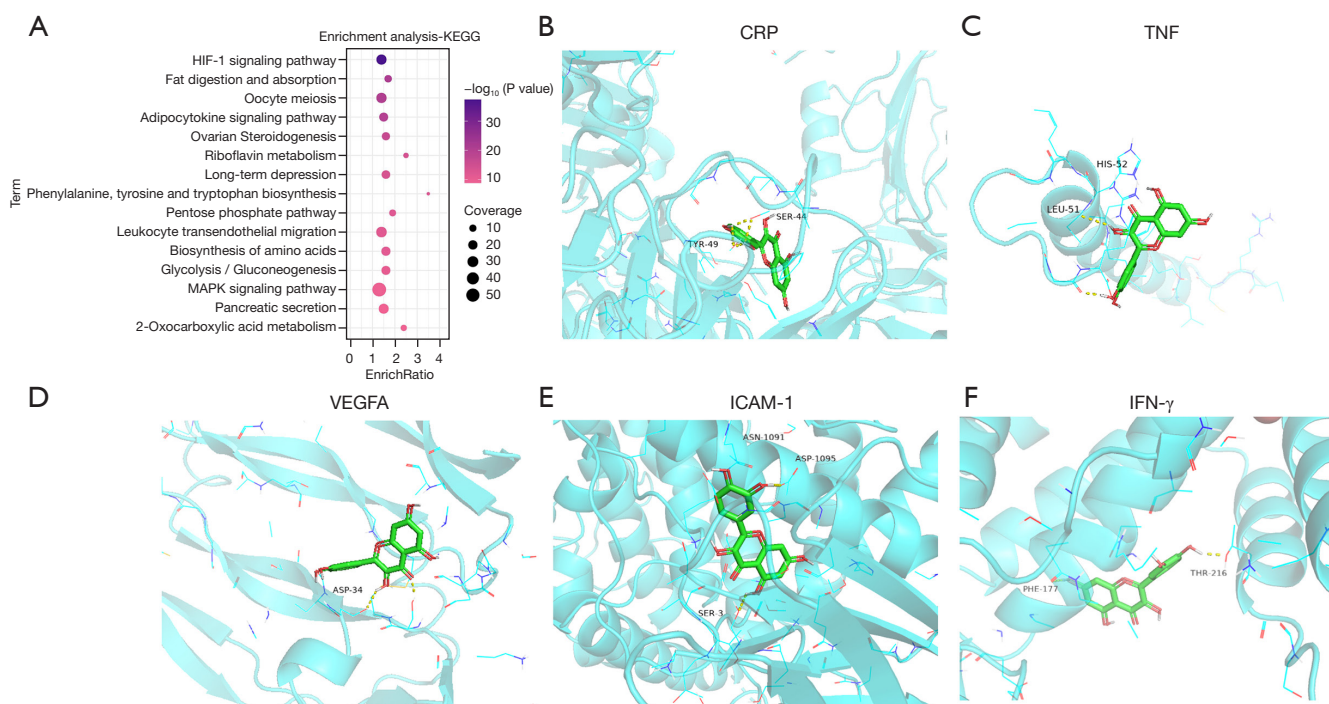
Figure 6 Network of active ingredient quercetin and further molecular docking. (A) KEGG pathway of quercetin. Molecular models of quercetin binding to the predicted target proteins (B) CRP, (C) TNF, (D) VEGFA, (E) ICAM-1 and (F) IFN-γ. KEGG, Kyoto Encyclopedia of Genes and Genomes; CRP, C-reactive protein; 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.

Acknowledgments

Footnote

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