ISSN 2618-1584 Vol. 5, Issue 2: 13-23, DOI: 10.25236/FMSR.2023.050203

Network-Based Pharmacology to Explore the Mechanism of Chaihu Shugan Powder's Intervention in Pulmonary Nodules

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Abstract: *Objective: Based on the results of drug mining for lung nodules in a real-world study, we investigated the mechanism of action of Chaihu Shugan powder in lung nodules using network pharmacology and molecular docking techniques, and provided a basis for clinical and basic research. METHODS: The main chemical components and corresponding targets of Chaihu Shugan powder were obtained in the TCMSP platform, the relevant targets of pulmonary nodules were obtained using GeneCards and OMIM databases, and the intersection targets of both were taken; the protein interaction network (PPI) was established using String database and mapped using Cytoscape software, while the CytoNCA plug-in was used to The core targets were screened by topological analysis; the GO biofunctional analysis and KEGG pathway analysis of the intersecting targets were carried out by R language software; the GO and KEGG gene enrichment analysis of the core targets were then carried out by the ClueGO plug-in in Cytoscape software to obtain the potential pathways of action of Chaihu Shugan powder in interfering with lung nodules; finally, the molecular docking between the active ingredients and the core targets was verified by Autodock software. Finally, the molecular docking of active ingredients and core targets was verified by Autodock software. The results showed that the main active compounds in Chaihu Shugan powder were able to bind well to the important targets in the core network. The results of KEGG enrichment analysis showed that the key targets were mainly enriched in small cell lung cancer, non-small cell lung cancer, TNF signaling pathway, IL-17 signaling pathway and other related pathways, involving multiple biological processes such as oxidative stress, inflammatory response and immune regulation. CONCLUSION: Chaihu Shugan powder intervenes in lung nodules with multi-component, multi-target and multi-pathway action characteristics. It is predicted that its main components, quercetin, lignan, kaempferol, naringenin and Chuan Chen Piin, may act on small cell lung cancer, non-small cell lung cancer, MAPK, PI3K/Akt, TNF, etc. through STAT3, MAPK3, MAPK1, JUN, TP53 and other targets This provides a more reliable theoretical basis for further research on the mechanism of Chaihu Shugan powder interfering with lung nodules.*

Keywords: *Network Pharmacology; Molecular Docking; Chaihu Shugan Powder; Pulmonary Nodule; Action Mechanism*

1. Introduction

A lung nodule is a lung lesion ≤3cm in diameter, with an opaque image, well-defined borders and completely surrounded by air-containing lung tissue, without manifestations such as pulmonary atelectasis, enlarged hilar lymph nodes or pleural effusion. Early stage lung cancer can present as purely ground glass nodules, partially solid nodules, mixed ground glass nodules or solid nodules. The detection rate of lung nodules is increasing with the popularity of health screening and the impact of the new coronary epidemic. The current guidelines for the management of pulmonary nodules, both domestic and international, still recommend follow-up [1-2] with limited intervention. Through clinical practice, we have found that the detection of pulmonary nodules often brings about greater negative emotions in patients, which are more harmful than the nodules themselves. Therefore, how to intervene in pulmonary nodules at an early stage to alleviate the negative emotions of patients and avoid the progression of the disease has become an urgent problem to be solved. In recent years, Chinese medicine has gained experience in intervening in pulmonary nodules and has gradually become an

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important tool for early intervention of pulmonary nodules [3-5].

By compiling and digging into the results of previous real-world studies, we found that Dr Ma Zhanping, the chief physician of our division, believes that pulmonary nodules belong to the category of "phlegm, lung accumulation and accumulation", which is located in the lung but is closely related to the liver and spleen. At the same time, according to the current situation in modern society, "yu" is an important pathogenic mechanism of the disease, and the basic formula for treating pulmonary nodules is Chaihu Shugan powder [6]. The formula consists of Chai Hu, Bai Shao, Chuan Xiong, Xiang Fu, Zhi Qiao, Chen Pi and Gan Cao, and is used to relieve depression, regulate qi and promote blood circulation. For example, Chen Zhicheng et al. [7] found that Chaihu Shugan powder combined with Sorafenib significantly reduced the levels of tumour markers and improved liver function in patients with hepatocellular carcinoma; Li Libing [8] et al. found that Chaihu Shugan powder could induce apoptosis in human breast cancer MCF-7 cells by inhibiting the levels of Bcl-2 protein and VEGF factor.

Network pharmacology and molecular docking techniques can provide a more scientific description of the molecular mechanism of action of Chinese herbal medicine compound for the treatment of diseases, and illustrate the multi-component, multi-target and multi-pathway characteristics of Chinese medicine for the treatment of diseases [9]. Therefore, in this paper, based on network pharmacology and molecular docking techniques, we investigate the mechanism of action of Chai Hu Shu Hep Shaan in the treatment of pulmonary nodules, and provide a relevant basis for subsequent real-world studies,The research process is shown in Figure 1.

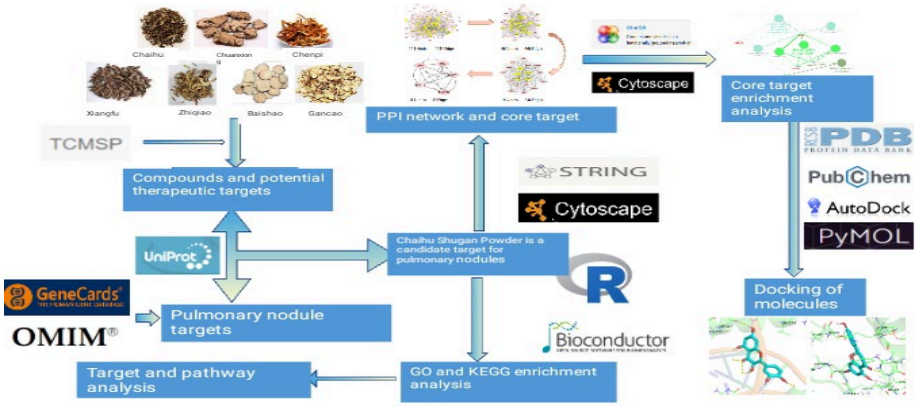

Figure 1: Research flow chart.

2. Materials and Methods

2.1. Access to Key Compounds

The TCMSP (http://tcmspw.com/tcmsp.php) platform was used to obtain the main compounds of Chaihu Shugan powder. Based on the ADEM characteristics, the screening conditions of oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 were set to obtain the compounds that met the conditions.

2.2. Access to Potential Targets for Chaihu Shugan Powder Intervention in Pulmonary Nodules

Searches were conducted in the GeneCards (https://www.genecards.org/) and OMIM (https://www.genecards.org/) databases using "Pulmonary nodule" as the search term. To obtain targets for lung nodule-related diseases. The TCMSP (http://tcmspw.com/tcmsp.php) platform was then used to obtain the relevant targets for the major compounds, and all the targets were converted to GeneSymbol IDs using the Uniprot database. The intersecting genes were identified as the potential therapeutic targets of Chaihu Shugan powder for the intervention of pulmonary nodules.

2.3. Drug-Component-Target Network Mapping

The key compounds ofChaihu Shugan powder and the potential therapeutic targets obtained were

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imported into Cytoscape software for drug-component-target network mapping. The top ten key compounds in the network were screened according to their Degree values for subsequent molecular docking validation.

2.4. Mapping of PPI networks and Selection of core Networks

The obtained potential therapeutic targets were imported into the STRING (https://string-db.org/) platform and a minimum action threshold (>0.9) was set to delete free genes and construct a protein interaction network (PPI); the network was then imported into Cytoscape software for visualisation and upgrading, and then the CytoNCA plugin was used for core network mining.

2.5. GO Biology Enrichment analysis and KEGG Pathway Enrichment Analysis

GO enrichment and KEGG enrichment analysis of potential therapeutic targets were carried out using R language software, with P value (pvalue) < 0.05 and corrected P value (qvalue) < 0.05 set as screening conditions. The enrichment analysis of the core targets in the PPI core network was then performed using the ClueGO plug-in in Cytoscape software and visualized.

2.6. Molecular Docking Assessment

The small molecule 2D structures of the core compounds were obtained from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) database and imported into Chemm Office software for conversion to 3D structures and structural optimization at the minimum free energy. The core protein receptor structures were obtained from the PPI network using the RCSB PDB (. org/) platform, and the water molecules and small molecule ligands were removed using Pymol software and then imported into AutoDockTools software for hydrogenation and other pre-processing; finally, molecular docking was performed using Vina software to assess the binding activity.

3. Result

3.1. Access to the Main Compounds and Potential Therapeutic Targets for Intervention in Pulmonary Nodules

A total of 118 major compounds were obtained after screening by oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 in the TCMSP platform. A total of 2747 disease targets were obtained from GeneCards and 147 from OMIM; after the removal of duplicates, a total of 2768 disease targets were obtained by combining the two databases. After integrating and screening the targets obtained from the first two databases, the R language software was used to obtain intersecting targets, and a total of 167 intersecting targets were obtained, i.e., 167 potential therapeutic targets forChaihu Shugan powder to intervene in lung nodules (see Figure 2).

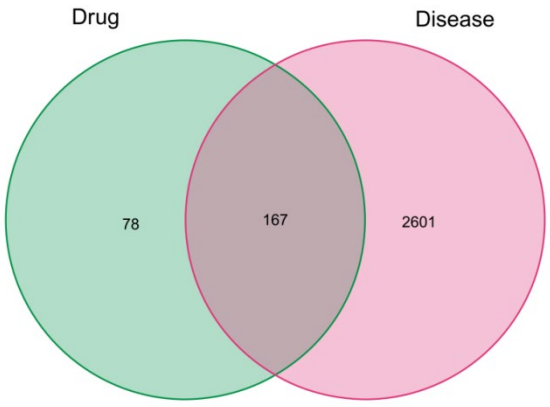

Figure 2: Venn diagram of drug targets and disease targets.

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3.2. Drug-COMPONENT-Target Modulation Network Diagram

The main compounds and potential therapeutic targets obtained above were imported into Cytoscape software, and the "drug-component-target" regulatory network was mapped out (see Figure 3), and the drug components were filtered according to Degree value to obtain the top 10 compounds (see Table 1) for subsequent Molecular docking validation.

Table 1: Degree values and sources of major compounds.

Coding	Compound name	Degree	Source
MOL000098	quercetin	112	Radix bupleuri, rhizoma cyperi, liquorice
MOL000422	Kaempferol	40	Radix bupleuri, Radix paeoniae alba, rhizoma cyperi, liquorice
MOL004328	naringenin	30	pericarpium citri reticulatae, Fructus Aurantii,liquorice
MOL005828	nobiletin	26	pericarpium citri reticulatae, Fructus Aurantii
MOL000497	licochalcone a	22	liquorice
MOL002135	Myricanone	21	Rhizoma chuanxiong
MOL000354	Isorhamnetin	19	Radix bupleuri, rhizoma cyperi, liquorice
MOL000392	Formononetin	19	liquorice
MOL003542	8-Isopentenyl kaempferol	19	rhizoma cyperi

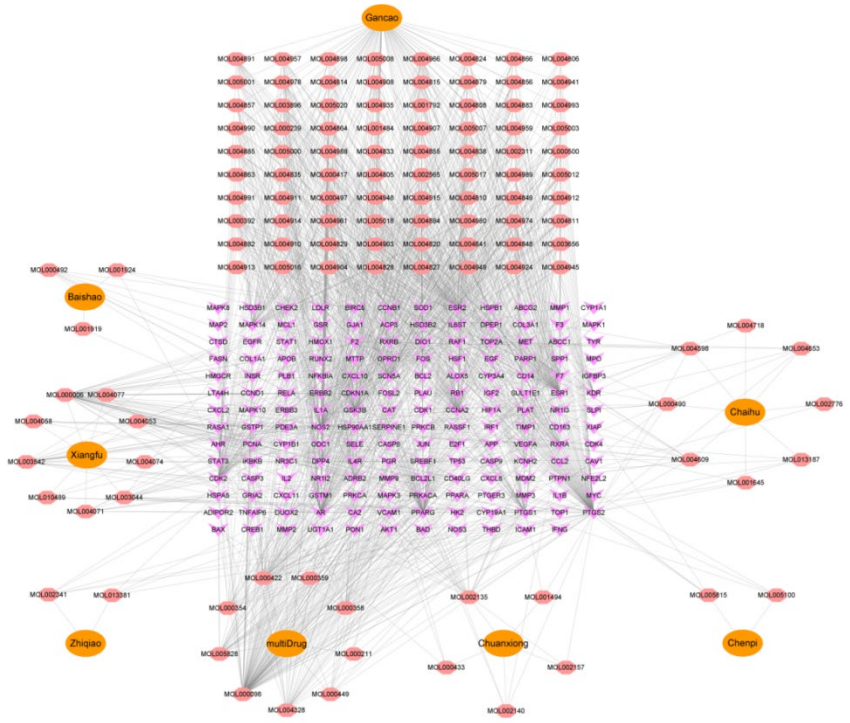

Figure 3: "Drug-component-target" regulatory network.

3.3. PPI networks and Core Targets

The obtained potential therapeutic targets were imported into the STRING network platform to build the PPI network, and the obtained networks were imported into Cytoscape software (Figure 4). Arranged according to Degree, the darker the color, the larger the node, indicating the greater role of this node in the network. Then, CytoNCA plug-in is used to calculate the values of DC, BC, CC, EC, NC, and LAC of network nodes, and the median of the above values is obtained. Targets less than the median are removed. After topological analysis, it was concluded that the core genes (Figure 5) were STAT3, MAPK3, MAPK1, JUN and TP53, which were receptor proteins for subsequent molecular docking verification

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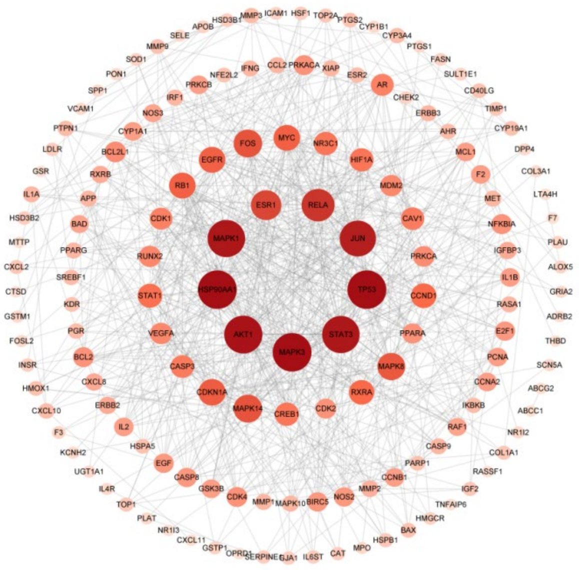

Figure 4: PPI protein interactions network.

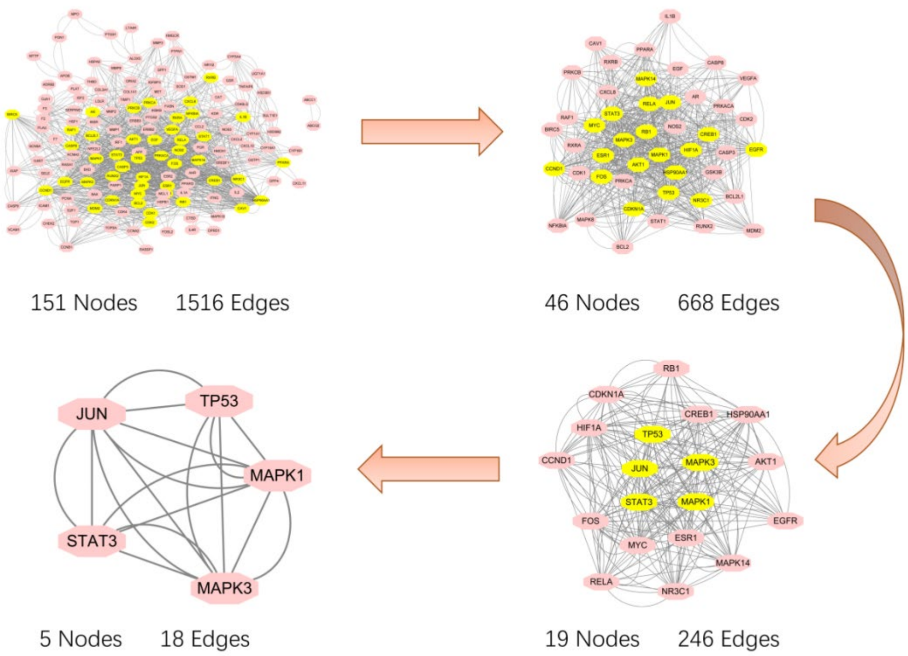

Figure 5: PPI core network diagram.

3.4. GO Biology Enrichment Results and KEGG Pathway Enrichment Results

The results of the GO biology enrichment analysis (Figure 6) showed that a total of 2666 results were obtained, of which biological processes (BP) mainly involved responses to antibiotics, cellular responses to oxidative stress, responses to nutrient levels, etc.; cellular components (CC) mainly involved serine/threonine protein kinase complexes, protein kinase complexes, RNA polymerase II transcriptional regulatory complexes, etc.; molecular functions (MF A total of 181 pathways were obtained from KEGG enrichment analysis, mainly involving non-small cell lung cancer, small cell lung cancer, MAPK signaling The results of KEGG enrichment analysis showed that 181 pathways were obtained, mainly involving non-small cell lung cancer, small cell lung cancer, MAPK signaling pathway, PI3K-Akt signaling pathway, IL-17 signaling pathway and tumor necrosis factor (TNF) signaling pathway.

Enrichment analysis of the core targets STAT3, MAPK3, MAPK1, JUN and TP53 by the ClueGO

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plug-in in Cytoscape software showed that the results (Figure 7) showed that the main biological processes involved in the core targets were the cellular response to cadmium ions, RNA-directed DNA polymerase activity, regulation of telomerase activity, telomerase activity, RNA polymerase II positive regulation of pri-miRNA transcription, pri-miRNA transcription by RNA polymerase II, and regulation of pri-miRNA transcription by RNA polymerase, with the more significant ones being RNA-directed DNA polymerase activity and positive regulation of pri-miRNA transcription by RNA polymerase II. The main pathways involved were AGE-RAGE signaling pathways in non-small cell lung cancer, pancreatic cancer, endometrial cancer, colorectal cancer, acute myeloid leukemia, and diabetic complications, among which the more significant ones were non-small cell lung cancer and pancreatic cancer pathways.

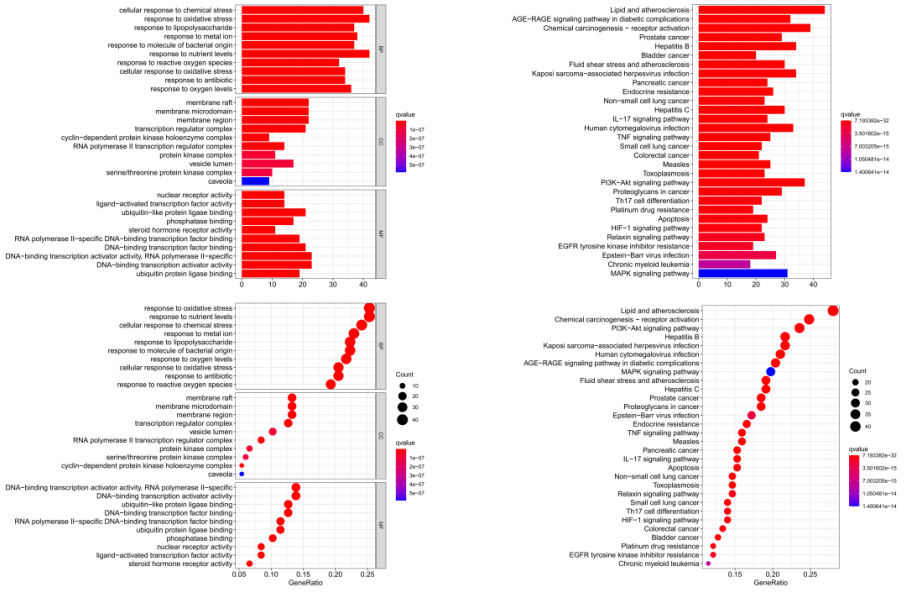

Figure 6: Potential target enrichment analysis.

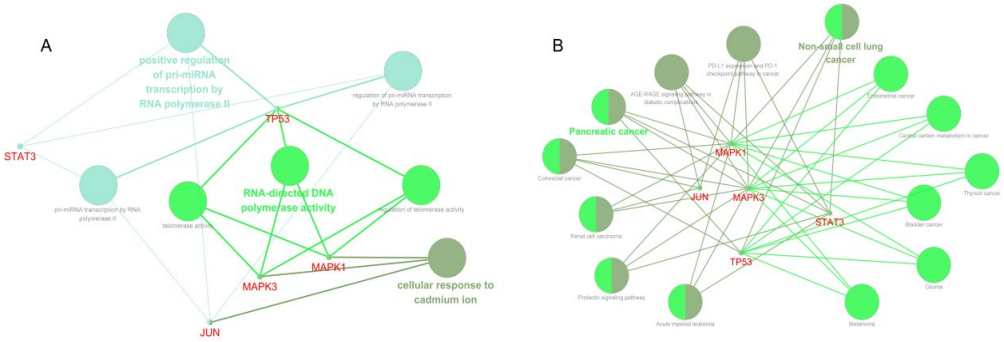

Figure 7: Core target enrichment analysis.

3.5. Molecular Docking Results

Table 2: Binding energy between active compound and core target.

Drug composition	Combined energy/kcal-mol-1				
	Stat3	Mapk3	Mapk1	Jun	Tp53
Quercetin	-7.6	-8.3	-8.9	-9.5	-7.2
Lignocaine	-7.1	-9.0	-8.9	-9.1	-7.3
Kaempferol	-7.3	-8.6	-8.6	-9.2	-7.0
Naringenin	-6.9	-8.1	-8.6	-8.7	-7.0
Szechuan chenopodium	-6.0	-7.8	-7.5	-7.1	-6.6

Molecular docking of the important compounds quercetin, lignan, kaempferol, naringenin and trichothecene with the obtained core targets STAT3, MAPK3, MAPK1, JUN and TP53 was carried out,

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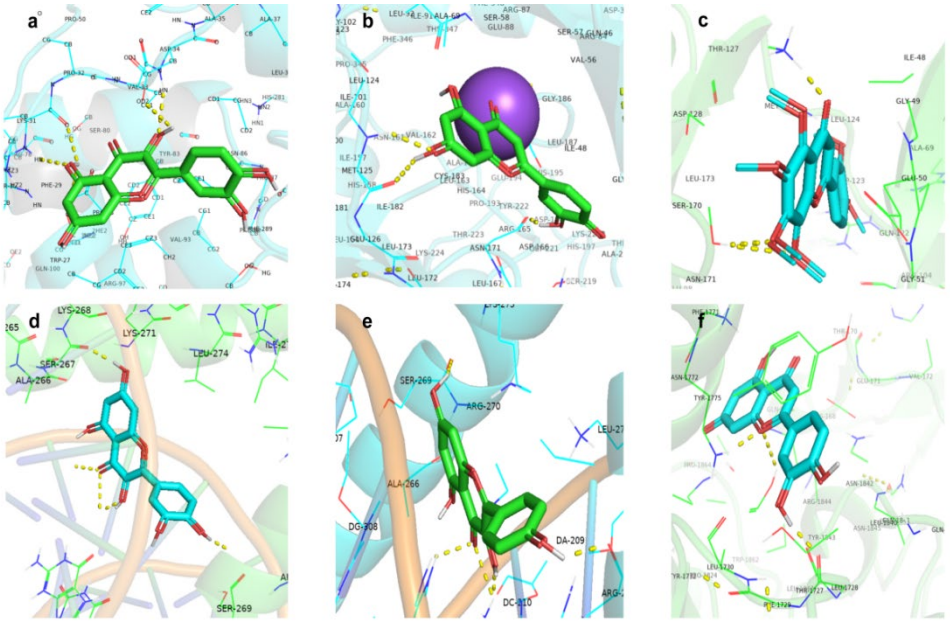
and the results are shown in Table 2, respectively; the literature reports that a general binding energy score of ≤ -5.0 kcal-mol-1 indicates a good binding effect [10]The results showed that quercetin, lignan, kaempferol, naringenin and trichothecene all had binding energies less than -5.0 kcal-mol-1 to the core targets STAT3, MAPK3, MAPK1, JUN and TP53, suggesting that they have good docking ability. (Figure 8).



(a: quercetin and STAT3; b: lignan and MAPK3; c: lignan and TP53; d: naringenin and STAT3; e: naringenin with MAPK1; f: Kawaricetin with MAPK3)

Figure 8: Molecular docking diagram of main active ingredients and protein.

4. Discussion

The name "pulmonary nodules" is not recorded in ancient Chinese medical texts, but through a review of recent Chinese medicine papers on pulmonary nodules, it can be categorized as "phlegm, lung accumulation and accumulation" and its pathogenesis is mostly related to qi deficiency and phlegm stasis [11-12]. However, based on many years of clinical experience, my teacher Ma Zhanping suggested that "yu" is the fundamental pathogenesis of pulmonary nodules, and that if the qi flow is not smooth and qi transformation is not possible, then phlegm and blood stasis will remain in the lung and form nodules[6]. Chaihu Shugan powder, as a commonly used formula in clinical practice for the treatment of lung nodules detected without obvious symptoms or with anxiety and depression, has the effect of de-stressing the liver and relieving depression and regulating qi and blood, and has good intervention effects on a variety of cancers in reality[13-14] , so Chaihu Shugan powder was chosen as the intervention formula for this study, with a view to leading the way for later real-world studies.

4.1. Analysis of Potential Active Ingredients

The analysis of the drug-component-target network revealed that quercetin, lignan, kaempferol, naringenin and Chuan Chen Piin may be the key compounds of Chaihu Shugan powder to intervene in lung nodules. Modern pharmacological studies have shown that quercetin, lignan, kaempferol, naringenin and Chuan Chen Piin all have good anti-cancer effects, and their anti-cancer effects are mostly closely related to antioxidant, anti-inflammatory, immunomodulation and induction of apoptosis [15-19]. Quercetin can inhibit the proliferation and growth of lung cancer cells, promote apoptosis and block their invasion and metastasis through various mechanisms[15]; naringenin can enhance the sensitivity of lung cancer cells to radiotherapy drugs by inhibiting Akt expression and inducing apoptosis[20]; lignan can regulate NF-κB signaling pathway by inhibiting NF-κB activation, thereby inhibiting pro-inflammatory gene expression[21]; in conclusion The intervention of Chaihu Shugan powder in pulmonary nodules is the result of the combined action of multiple compounds, showing the multi-component and multi-target properties of the herbal compound.

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4.2. PPI core network Analysis

After topological analysis, five core targets were extracted, namely STAT3, MAPK3, MAPK1, JUN and TP53. Among them, MAPK3 and MAPK1 are both mitogen-activated protein kinases, which are involved in cell differentiation, apoptosis and proliferation [22] and are important targets for tumor induction. For example, Mu Mingchen et al [23] found that urinary polypeptide (CDA-II) can enhance the radio sensitivity of lung cancer cells by inhibiting tissue factor expression, a mechanism that may be closely related to the MAPK pathway. STAT3 has an important regulatory role in lung cancer cells and is strongly associated with the occurrence, development and prognosis of lung cancer [24], and some studies have shown that STAT3 is an important target of inflammatory-cancer transformation, which can be activated by inflammatory cell surface receptors such as IL-6, which can promote tumour cell proliferation, differentiation and metastasis through binding to downstream target genes [25]. TP53 is a tumour suppressor that can participate in apoptosis and proliferation by regulating the cell cycle, but mutations in TP53 can promote tumour cell proliferation, migration and invasion and enhance tumour cell metabolism [26]. In summary, the above core targets are important nodes involved in the process of tumorigenesis and development, so we further speculate that Chaihu Shugan powder may intervene in lung nodules through the above targets, which are involved in apoptosis, inhibiting inflammatory response and improving the tumor microenvironment.

4.3. Analysis of Bioconcentration Results

After biological analysis of the potential therapeutic targets and the analyzed core targets separately and validated against each other, we obtained the results of GO biological enrichment analysis mainly involving the response to antibiotics, cellular response to oxidative stress, response to nutrient levels, protein kinase complexes, RNA polymerase II transcriptional regulatory complexes, biological processes involving RNA polymerase II- The analysis of the KEGG pathway enrichment results allowed us to infer that the signaling pathways involved in Chaihu Shugan powder's intervention in lung nodules are mainly related to inflammatory response, immune response, oxidative stress, and apoptosis. Such as MAPK signaling pathway, PI3K-Akt signaling pathway, tumor necrosis factor signaling (TNF) pathway, etc.

MAPK signaling pathways are involved in cell inflammation, differentiation, proliferation, transformation, apoptosis and stress[27] .There are four main subfamilies: extracellular signal-regulated protein kinase (ERK), p38MAPK, c-Jun amino-terminal kinase (JNK) and ERK5, which are aberrantly expressed in a variety of cancers[28-29]. Zhang Yue et al.[30] found that naringenin may induce oxidative stress in lung cancer A549 cells through the P38 MAPK pathway, thereby contributing to apoptosis; Ming Mao et al.[31] found that the long-stranded non-coding RNA colon cancer-associated transcript 1 (lncRNA CCAT1)/mi R-181a-5p axis may regulate lung cancer cell proliferation and metastasis through the MAPK signaling pathway.

The PI3K/AKT pathway is one of the major cancer pathways and is currently one of the most common regulatory pathways in lung cancer. It plays an important role in the proliferation, invasion and metastasis of tumor cells, inhibition of apoptosis, promotion of angiogenesis and chemoresistance. [32]. For example, Fang Chuanzhi et al. [33] found that sodium zebranate injection could inhibit the invasion and metastasis of lung cancer A549 cells by inhibiting PI3K/AKT/mTOR signaling pathway activation and angiogenesis; Sun Hui et al. [34] found that dihydroartemisinin could down-regulate PI3K protein expression, reduce Akt phosphorylation level and inhibit PI3K/AKT signaling pathway, promote apoptosis to reverse the effects of cisplatin on lung cancer A549/DDP cell lines. Chen Chao et al.[35] found that microRNA (miR)-15b could increase CD4+ and CD4+/CD8+ levels through MET-PI3K-Akt signaling pathway, improve immune function, and induce apoptosis and inhibit proliferation of lung cancer cells in a lung cancer model mouse.

TNF-α, as a classical inflammatory factor, also plays an important role in tumor development[36], which is a key mediator of inflammatory cancer transformation and is aberrantly expressed in a variety of tumor patients[37], making it an emerging key biomarker for lung cancer diagnosis[38]. The study by Yanmei Cha et al.[39] found that TNF-α could improve the malignant biological behavior of lung cancer by influencing the NF-κB signaling pathway to regulate lung cancer cell proliferation and apoptosis; and TNF-α could play an anti-tumor role by promoting the proliferation and differentiation of B cells and producing tumor-specific antibodies.

Taken together, the results of the relevant studies suggest that Chaihu Shugan powder may exert anti-inflammatory, immunomodulatory, anti-oxidative stress, inhibition of cell proliferation,

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differentiation and induction of apoptosis in lung cancer cells through MAPK signaling pathway, PI3K-Akt signaling pathway, tumor necrosis factor (TNF) signaling pathway and various targets to further interfere with lung nodule development The aim is to further interfere with the development of lung nodules and their progression.

5. Conclusions

In this study, network pharmacology and molecular docking techniques were used to investigate the mechanism of action of Chaihu Shugan powder in interfering with pulmonary nodules. The main compounds screened were quercetin, lignan, kaempferol and naringenin, which interfered with most of the targets. Biological enrichment analysis predicted that Chaihu Shugan powder may intervene in lung nodules through non-small cell lung cancer, PI3K-Akt signalling pathway, MAPK signalling pathway, tumour necrosis factor (TNF) signalling pathway and their interactions as anti-inflammatory, immunomodulatory, regulating apoptosis proliferation and improving tumour microenvironment, reflecting the multi-component, multi-targeting nature of Chinese medicine. In this paper, we predicted that the effects of Chai Chai on the lung nodules would be more effective than those of other Chinese medicines. In conclusion, this paper predicts the relevant compounds, pathways and targets of Chaihu Shugan powder to intervene in pulmonary nodules for future real-world studies, and provides a certain method and basis for further deepening the data of real-world studies. However, the shortcoming is that the virtual validation was only performed through molecular docking, without considering the content of each component in the drug and the changes of the compounds when combined. It is hoped that further animal experiments or in vitro cellular experiments will be conducted to improve and validate the results.

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