A Network Pharmacology Approach to Investigating the Mechanism of Sophorae Flavescentis Radix for the Treatment of Lung Cancer

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Research

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Abstract

In this study, the bioactive components and predictive targets of *Sophorae Flavescentis Radix* were investigated by network pharmacology analysis, so as to further elucidate its potential biological mechanism in treating lung cancer. The targets corresponding to lung cancer were obtained by OMIM and Genecards. By intersecting with the targets of *Sophorae Flavescentis Radix* and lung cancer, the *Sophorae Flavescentis Radix*-lung cancer targets were obtained. Protein-protein interaction network was constructed by an online database STRING and hub genes were screened by Cytoscape 3.7.0 software. ClusterProfiler package was used to analyze Gene ontology (GO) and KEGG enrichment of the targets in R. A total of 45 bioactive components were screened from *Sophorae Flavescentis Radix*, corresponding to 482 *Sophorae Flavescentis Radix* targets and 25019 lung cancer targets. According to the GO and KEGG enrichment analysis, *Sophorae Flavescentis Radix* played a therapeutic role in treating lung cancer via proteoglycans lung cancer, human cytomegalovirus infection, microRNAs in cancer, PI3K-Akt signaling pathway, etc. Seven hub genes (IL6, CASP3, EGFR, VEGFA, MYC, CCND1 and ESR1) were screened by degree algorithm. In a word, the results of this study may provide novel insights into the mechanisms of *Sophorae Flavescentis Radix* in treatment of lung cancer.

1. Introduction

Lung cancer, as one of the most common malignancies, is a leading cause of cancer death. The overall survival rate of patients with advanced lung cancer is unsatisfactory ^[1-2]. Lung cancer can histologically be classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Nearly 85% of lung cancers are NSCLC. SCLC has following characteristics: aggressive metastasis and rapid cellular growth ^[3]. Despite advances in modern medical techniques, such as surgical resection, chemotherapy and radiotherapy, the results after treatment remain unsatisfactory ^[4-6]. Therefore, it is essential to develop more efficient therapies for lung cancer.

Typical traditional Chinese medicine (TCM) therapies, with a long history in treating diseases, mainly include acupuncture and Chinese herbal medicine ^[7]. TCM, with the advantages of remarkable curative effect and few adverse reactions, has been applied in clinic in China for thousands of years and has become an integral part of the health care system. Experimental studies of TCM on pulmonary fibrosis and lung cancer have confirmed its efficacy and unique advantages ^[8-11]. Herbal medicines are most frequently used because they may reduce side effects of conventional therapies and improve the effectiveness of treatments ^[12-13]. *Sophorae Flavescentis Radix*, known as Kushen in Chinese, has been used to treat lung diseases for hundreds, especially lung cancer. However, its mechanism in treating lung cancer remains unclear. TCM has a complex biological molecular mechanism because of its multiple components. ^[14]. It's difficult to further explore TCM's molecular mechanism through animal or cellular studies, because it requires considerable human and material resources ^[15]. Network pharmacology is proposed on the basis of systems biology and network analysis. As a result of the rapid development of various bio-informatics, systems pharmacology has been applied to discover active ingredients or

components of TCM and their molecular mechanisms^[16-21]. Therefore, the study of TCM based on network pharmacology is valuable, which provides an approach for further investigating the effect of Sophorae Flavescentis Radix in lung cancer alleviation and recovery.

In this study, systems pharmacology was used to investigate the targets and mechanisms of Sophorae Flavescentis Radix in preventing and treating lung cancer. Then, the results concluded from the network pharmacology prediction were validated and the mechanism of Sophorae Flavescentis Radix in treating lung cancer was explored. Fig. 1 is a flowchart of the whole study design. The study is the first to explore the mechanism of Sophorae Flavescentis Radix in treating lung cancer by network pharmacology.

2. Materials And Methods

2.1. Data preparation

2.1.1. Collection of Sophorae Flavescentis Radix bioactive compounds

All the bioactive components of Sophorae Flavescentis Radix were collected from Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, <http://tcmospw.com/tcmosp.php>)^[22]. Bioactive ingredients meeting criteria $OB \geq 30\%$ and $DL \geq 0.18$ were selected after screening was carried out based on adsorption, distribution, metabolism and excretion (ADME)^[23]. In addition, XLGB contained some bioactive compounds that were excluded because their OB and DL values were lower than the set criteria.

2.1.2. Collection predicted targets of bioactive compounds

The targets related to the selected bioactive compounds were collected from TCMSP (<http://tcmospw.com/tcmosp.php>). UniProt (<https://www.uniprot.org/>) was used to validate the information of predicted targets, including name and gene ID^[24].

2.1.3. Collection targets of lung cancer

The “lung cancer” was a keyword for retrieving lung cancer-related genes from the Online Mendelian Inheritance in Man (OMIM) (<http://www.omim.org/>)^[25] and GeneCards (<http://www.genecards.org>)^[26]. The lung cancer-related target information was confirmed by UniProt with “Homo sapiens” setting.

2.2. Construction of component-target-pathway-disease network

A bioactive component-predicted target network was constructed based on active components and predicted targets by Cytoscape 3.7.0 (<https://cytoscape.org/>). In the network, nodes represent genes, targets, proteins or molecules, and connections between nodes are interactions between them. The “degree” value of a node is indicated by the number of connections between nodes ^[27], and the larger the value, the more likely the target is to become the key target of a compound.

2.3. Protein-protein interaction network construction

A Venn analysis was conducted by a website at the following URL (<http://bioinformatics.psb.ugent.be/webtools/Venn/>) to overlap the selected targets of *Sophorae Flavescentis Radix* and lung cancer-related targets to elucidate the potential mechanism of *Sophorae Flavescentis Radix* on lung cancer. The *Sophorae Flavescentis Radix* potential targets and lung cancer-related common targets obtained were used for the construction of PPI network by STRING database (<https://string-db.org/>). Cytoscape 3.7.0 can be used to visualize and analyze the interconnection network, and plug-in network analysis was used for analyzing the network topology properties ^[28].

2.4. Gene ontology and pathway enrichment analyses

The GO database (<https://metascape.org/>) ^[29], including biological process (BP), cellular component (CC) and molecular function (MF), can analyze potential biological molecular mechanisms. The KEGG database (<https://metascape.org/>) ^[29] was for identifying biological functions and selecting targets. In this study, Cluster Profiler package in R (<https://bioconductor.org/>) ^[30] was used for GO functional annotation and KEGG pathway analysis, and the significance threshold of adjusted p-value was < 0.05.

3. Results

3.1. Identify potential targets of *Sophorae Flavescentis Radix*

The TCMSP database was used to select bioactive compounds of *Sophorae Flavescentis Radix*. 45 kinds of bioactive compounds with $OB \geq 30\%$ and $DL \geq 0.18$ were screened out. Details of bioactive compounds are shown in Table 1. Through TCMSP, 482 targets consistent with the bioactive compounds of *Sophorae Flavescentis Radix* were screened. 25019 targets associated with lung cancer were screened by GeneCards and OMIM databases and duplicate targets were excluded. The obtained bioactive compounds and targets laid a foundation for the construction of the subsequent network.

3.2. Compound-compound target network

To clarify the relationship between the bioactive components of *Sophora flavescens* and their predicted targets, a component-target-pathway-disease network was constructed (as shown in Fig.2). The network has 138 targets (45 bioactive compounds and 93 predicted targets) and 309 interaction edges. Through multi-compounds and multi-targets, the bioactive compounds of *Sophorae Flavescents Radix* act on the systematic biological network system. Among them, quercetin and luteolin have the most potential targets, indicating that these highly bioactive compounds are important for treating lung cancer.

3.3. PPI network for *Sophorae Flavescents Radix* on lung cancer

To explain the potential mechanism of *Sophorae Flavescents Radix* in lung cancer treatment, the lung cancer-related targets and compound predicted targets were intersected. The PPI network (Fig.3), with 93 nodes and 757 interaction edges, was constructed by introducing the obtained targets into STRING (PPI combined score > 0.7). In the network, genes interacted through known (from curated databases and determined experiments), predicted (gene neighborhood, fusions, and co-occurrence), and other (textmining, co-expression, and protein homology) interactions. Based on the degree principle, seven targets with the largest degree value, interleukin-6 (IL6), caspase-3 (CASP3), epidermal growth factor receptor (EGFR), vascular endothelial growth factor A (VEGFA), Myc proto-oncogene protein (MYC), estrogen receptor (ESR1) and G1/S-specific cyclin-D1 (CCND1) were selected as hub genes, as shown in Table 2.

Table 2
Hub genes of treating lung cancer of *Sophorae Flavescents Radix*.

Gene name	Uniprot ID	Target	Degree
IL6	P05231	Interleukin-6	51
CASP3	P42574	Caspase-3	50
EGFR	P00533	Epidermal growth factor receptor	49
VEGFA	P15692	Vascular endothelial growth factor A	49
MYC	P01106	Nyc proto-oncogene protein	48
ESR1	P03372	Estrogen receptor	46
CCND1	P24385	G1/S-specific cyclin-D1	45

3.4. Gene ontology (GO) and pathway analyses

GO and KEGG enrichment analysis of the targets was conducted by ClusterProfiler in R. Fig. 4 is the bubble chart of GO enrichment analysis linked to *Sophorae Flavescents Radix* against lung cancer, and top 10 terms in BP, CC and MF were selected. The BP results indicated that these targets respond to

steroid hormones, xenobiotic stimulus, radiation, metal ion, oxygen levels, ketone, antibiotic, hypoxia, decreased oxygen levels, etc. CC consisted of membrane raft, membrane microdomain, membrane region, transcription factor complex, nuclear chromatin, vesicle lumen, secretory granule lumen, cytoplasmic vesicle lumen, RNA polymerase II transcription factor complex and cyclin-dependent protein kinase holoenzyme complex. The MF results indicated that these targets were generally associated with binding, nuclear receptor activity, and RNA polymerase II-specific.

In Fig.5, KEGG enrichment analysis showed that targets were principally associated with proteoglycans in cancer, human cytomegalovirus infection, microRNAs in cancer, PI3K-Akt signalling pathway, hepatitis B, kaposi sarcoma-associated herpesvirus infection, prostate cancer, hepatocellular carcinoma, and Epstein-Barr virus infection.

4. Discussion

Lung cancer is a main cause of cancer death^[31]. Although the treatment of lung cancer has shifted from cytotoxic drugs to precise individualized therapies, such as small molecule tyrosine kinase inhibitors and immune checkpoint blockades, the 5-year survival rate is still low (approximately 15%) in the past 20 years^[32]. Most patients with advanced lung cancer continue to develop after receiving anticancer treatment and eventually fail to escape from death due to ineffective treatment^[33]. Sophorae Flavescentis Radix, developed by TCM, has been used in the treatment of parasites, viruses, bacteria, cancer, arrhythmia, but its mechanism is unclear. Therefore, a comprehensive understanding of its molecular mechanism is significant for preventing and treating lung cancer with Sophorae Flavescentis Radix.

45 bioactive components of Sophorae Flavescentis Radix were screened out, such as flavonoids, coumarins, alkaline, saponins. Compared with other bioactive compounds in Sophorae Flavescentis Radix, quercetin (OB = 46.43, DL = 0.28) and luteolin (OB = 36.16, DL = 0.25) have higher value degrees. Quercetin is a flavonoid compound easily found in daily diet. Previous studies indicated that quercetin has such effects as anti-inflammatory, anti-oxidation and anti-cancer^[34-35]. According to some in vivo and in vitro experiments, quercetin has an anti-tumor effect by altering cell cycle progression, inhibiting cell proliferation, promoting apoptosis, inhibiting angiogenesis and metastasis progression and affecting autophagy^[36-41]. Kun-ChiehChen et al. have demonstrated the attenuation mechanism of luteolin on epithelial-mesenchymal transition of A549 lung cancer cells induced by TGF- β 1^[42].

As the PPI network showed, the related targets of Sophorae Flavescentis Radix against lung cancer were composed of 93 nodes and 757 interaction edges. According to the results of GO enrichment analysis, the targets in the PPI network were mainly responded to steroid hormones, xenobiotic stimulus, radiation, metal ion, oxygen levels, ketone, antibiotic, hypoxia, decreased oxygen levels, etc. Jill M. Siegfried et al. suggested that lungs contain receptors for estrogen and progesterone and these hormones play a role in lung development, inflammation and canceration^[43]. The KEGG enrichment analysis suggested that proteoglycans in cancer, human cytomegalovirus infection, microRNAs in cancer, PI3K-Akt signaling

pathway, hepatitis B, kaposi sarcoma-associated herpesvirus infection, prostate cancer, hepatocellular carcinoma, and Epstein-Barr virus infection were the key signaling pathways related to lung cancer. Sun Jia suggested that proteoglycan is a gene related to tumor metastasis. Proteoglycan may maintain or inhibit cell growth, affect cell adhesion and regulate the mutual interaction between cell and matrix [44]. Human cytomegalovirus components are often found in tumors, and they rely on the recognition and killing of cancer cells.

Through the PPI network analysis of *Sophora flavescens* for lung cancer, 7 genes with the highest degree values were selected as the hub genes, namely IL6, CASP3, EGFR, VEGFA, MYC, CCND1 and ESR1. Interleukin-6 (IL-6) gene polymorphism has been demonstrated to be related to an increased risk of lung cancer [45]. Shin YupLee et al. suggested that caspase-3 (CASP3) is an important regulator and executor in apoptosis pathway and plays an essential role in the development and progression of lung cancer [46]. Several studies have demonstrated that EGFR and VEGFA contribute to increased risk of lung cancer [47-48].

5. Conclusions

According to this study, *Sophorae Flavescentis Radix* can be used to treat lung cancer because of its mechanism involving such hub genes as IL6, CASP3, EGFR, VEGFA, MYC, CCND1 and ESR1. The mechanism of *Sophorae Flavescentis Radix* in treating lung cancer needs to be proved by further in vivo and in vitro studies.

6. Declarations

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest:

The authors declare no conflict of interest.

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Authors' contributions

L.Y. and S.P. conceived of the project; L.Y., K.Y., and J.Z. conducted all experimental work and collected data; L.Y. and S.P. analysed and discussed the results; L.Y., J.Z. and K.L. drafted part of the manuscript; S.P. coordinated the study and drafted the manuscript in its present form.

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Flow chart of the pharmacology-based study of Sophorae Flavescentis Radix on lung cancer.

Figure 2

Compound-compound target network of targets of Sophorae Flavescentis Radix against lung cancer

Figure 4

Bubble charts of Gene ontology enrichment analyses linked to *Sophorae Flavescentis Radix* against lung cancer.

Figure 5

Bubble charts of KEGG enrichment analyses linked to Sophorae Flavescentis Radix against lung cancer.

Figure 5

Bubble charts of KEGG enrichment analyses linked to Sophorae Flavescentis Radix against lung cancer.

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