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To study the mechanism of Scutellariae Radix and Astragaloside in the treatment of lung cancer based on network pharmacology

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Abstract

The aim of the study wasto explore the target and potential mechanism of Scutellariae Radix and Astragaloside in the treatment of lung cancer infection by network pharmacology.

The target information of baicalein and flavonin was mined from CTD database and Swiss database. Genecards database, DRUGBANK database, and OMIM database were used to search for lung cancer related genes. The target protein network map (PPI) was drawn by using the STRING database analysis and Cytoscape3.7.1 software. With the help of Perl language, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis and gene function analysis (GO) enrichment analysis were carried out by using the biological program package of *R* language.

In total, 347 biological targets of Astragaloside and Scutellariae Radix were identified through the collection and analysis of multiple databases. In total, 1526 lung cancer targets were obtained from a multi-disease database. The "component-target" network of Astragaloside and Scutellariae Radix was constructed, and the protein interaction network (PPI) of the overlapping targets was analyzed to identify the key targets of drug-influenced diseases. In addition, KEGG pathway analysis and GO enrichment analysis were performed on the overlapping targets to explore the mechanism of Scutellariae Radix and Astragaloside in the treatment of lung cancer.

Scutellariae Radix and Astragaloside have the characteristics of multi-component, multi-target and multi-pathway in the treatment of lung cancer, which provides a new idea and scientific basis for further research on the molecular mechanism of the antilung cancer effect of Scutellariae Radix and Astragaloside.

Abbreviations: GO = gene function analysis, KEGG = Kyoto Encyclopedia of Genes and Genomes.

Key words: lung cancer, network pharmacology, KEGG, Scutellariae Radix and Astragaloside

1. Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and fatality rate in China, and the treatment of lung cancer is still the main research direction.[1] Chemotherapy is still the main treatment for middle and advanced lung cancer, but different degrees of myelosuppression occur after chemotherapy.[2] It is manifested as leukocyte, hemoglobin, and thrombocytopenia, which seriously affects the quality of life of patients and impeded the smooth progress of chemotherapy.[3] Currently, hematopoietic growth factor drugs are mainly used in clinical treatment, which leads to expensive treatment price, multiple adverse reactions, and slow onset time.[4] Traditional Chinese medicine has unique advantages, which can reduce the adverse reactions of internal medicine, reduce the economic burden of patients, and has the advantages of simple and reliable efficacy. Its treatment methods are varied.

The plants of genus *Scutellaria L.* (Lamiaceae) are perennial herbs. Many of these species have medicinal uses. Among them, the roots of *Scutellaria baicalensis* Georgi are used in China as Huang-Qin (*Scutellariae Radix*), one of the most popular traditional Chinese medicines.

ZW and LM contributed equally to this work.

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

Ethic statement: The current analysis does not require ethical approval, because our analysis only collects uploaded data information from the public database search. The article does not involve in any patient's personal data and will not cause any patient hurt.

The authors declared that they have no conflict of interest.

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The Traditional Chinese Medicine theory considers Scutellariae Radix has the functions of clearing heat, eliminating dampness, purging fire, detoxification, hemostasis, and preventing miscarriage. Scutellariae Radix is now listed officially in Chinese Pharmacopoeia. Modern medicine also shows that Scutellaria baicalensis can reduce oxidative stress and resist edema.

Inhibitory effects of apoptosis:[5] Chrysosperma is a genus of *Molygonatum* Mill in Liliaceae. It is mainly distributed in the northern temperate zone and northern subtropical zone, and widely distributed in a vast area except for the southern tropical zone[6] It has potential medicinal value in antiaging, immunity regulation, blood lipid regulation, memory improvement, antitumor, antibacterial, and so on.

This integration has been found, based on computer and bioinformation technology, to screen the corresponding targets of Scutellariae Radix and Scutellariae Radix saponin, to construct a "component-target" network model of Scutellariae Radix and Scutellariae Radix saponin by network analysis, and to study the effects of Scutellariae Radix and Scutellariae Radix saponin on lung cancer genes and related signaling pathways in combination with lung cancer disease targets, and to gain a preliminary understanding of the material basis and mechanism of action of Scutellariae Radix and Scutellariae Radix saponin in lung cancer therapy.

2. Material

Toxicological Genome Database (CTD) (http://ctdbase.org/); DRUGBANK database (https://go.drugbank.com/); GENECARDS database (https://www.GENECARDS.org/); STRING database (https://string-db.org/cgi/input.pl); OMIM database (https://omim.org/); KOBAS database (http://kobas.cbi.pku.edu.cn/kobas3); Cytoscape3.7.1 software; Swiss target prediction database (http://www.swisstargetprediction.ch/); *R* language

3. Methods

3.1. Prediction of drug action targets

The CTD database and Swiss Target Prediction database were combined to retrieve the corresponding targets of the drugs, and the chemical structures of Scutellariae Radix and Astragaloside were determined. Then, the corresponding target information of each compound component was continued to be mining in the Swiss database. After the target information was obtained, Perl language and Uniprot database were used to convert the target names of Scutellariae Radix and saponin into standard gene names.

3.2. Prediction of disease-related targets

Genecards database, drugbank database, and OMIM database were used to mine the disease genes of lung cancer, and the related genes of novel corona virus were obtained and summarized. The "VennDiagram" program package of *R* language was used to cross compare the disease targets with the related targets of Astragaloside and Scutellariae Radix to obtain the overlapping targets, and the topoisomerization screening analysis of the overlapping targets was carried out.

3.3. Construction of drug active ingredient-target network

The corresponding targets of Astragaloside and Scutellariae Radix obtained above were imported into Cytoscape3.7.1 software to construct the active component-target network map.

3.4. Construction of drug-disease overlapping target interaction network (PPI)

The STRING database analysis technology is a database that collects and collates information about protein-protein interactions and predicts protein-protein relationships. The obtained overlapping targets were input into the STRING database, and the PPI corresponding to Scutellariae Radix and Astragaloside was constructed based on the strength of the interaction relationship between the targets. Cytoscape3.7.1 software was used for network visualization analysis, visual analysis and *R* language statistics were used to obtain the active ingredient-target interaction network diagram.

3.5. KEGG enrichment analysis

Perl language combined with BioConductor biological information database will be used to convert all overlapping target names into Entrez Gene IDs for future use; Use *R* software to install the "Colorspace" and "String" packages, and download the *R* biological packages such as "Dose", "Clusterprofiler" and "Pathview". Enter the Entrez Gene ID of the converted overlapping target, and run the *R* language script for KEGG pass enrichment analysis.

3.6. Gene function analysis (GO)

Perl language combined with BioCunductor biological information database will be used to convert all overlapping target names into Entrez Gene IDs for future use; Use *R* software to install the "Colorspace" and "String" packages, and download the *R* biological packages such as "Dose", "Clusterprofiler," and "Pathview". Enter the Entrez Gene ID of the converted overlapping target, and run the *R* language script for GO pass enrichment analysis.

4. Result and Disscusion

4.1. Construction of active component-target network of baicalein and flavonin

According to the screened targets related to Astragaloside and Scutellariae Radix, Cytoscape3.7.1 software was used to establish the active ingredient-target network, as shown in Figure 1. The network contains a total of 349 nodes. In the figure, the green nodes represent the component nodes, and the circle represents the 347 related action targets. In network analysis, the degree value of nodes indicates the importance of nodes in the network.

4.2. PPI construction

A total of 1526 lung cancer targets were retrieved from Genecards database, Drugbank database and OMIM database. Then compared with 319 related targets of Astragaloside and Scutellariae Radix, 119 overlapping target information was obtained. Topological heterogeneity analysis was carried out on the overlapping targets to screen out the top 30 targets with Degree value, as shown in Figure 2. The targets with high connectivity were counted by topological analysis. The table shows the ranking of all overlapping targets of GeGREE. It can be seen from the table that the Degree values of Akt1, VEGFA, MAPK, and EGFR are relatively high, which may be the potential targets of Scutellariae Radix and Astragaloside affecting lung cancer.

4.3. KEGG enrichment analysis

Perl language was used to convert the overlapping 27 gene names into Entrez gene ID. Bioconductor operation of *R* package was

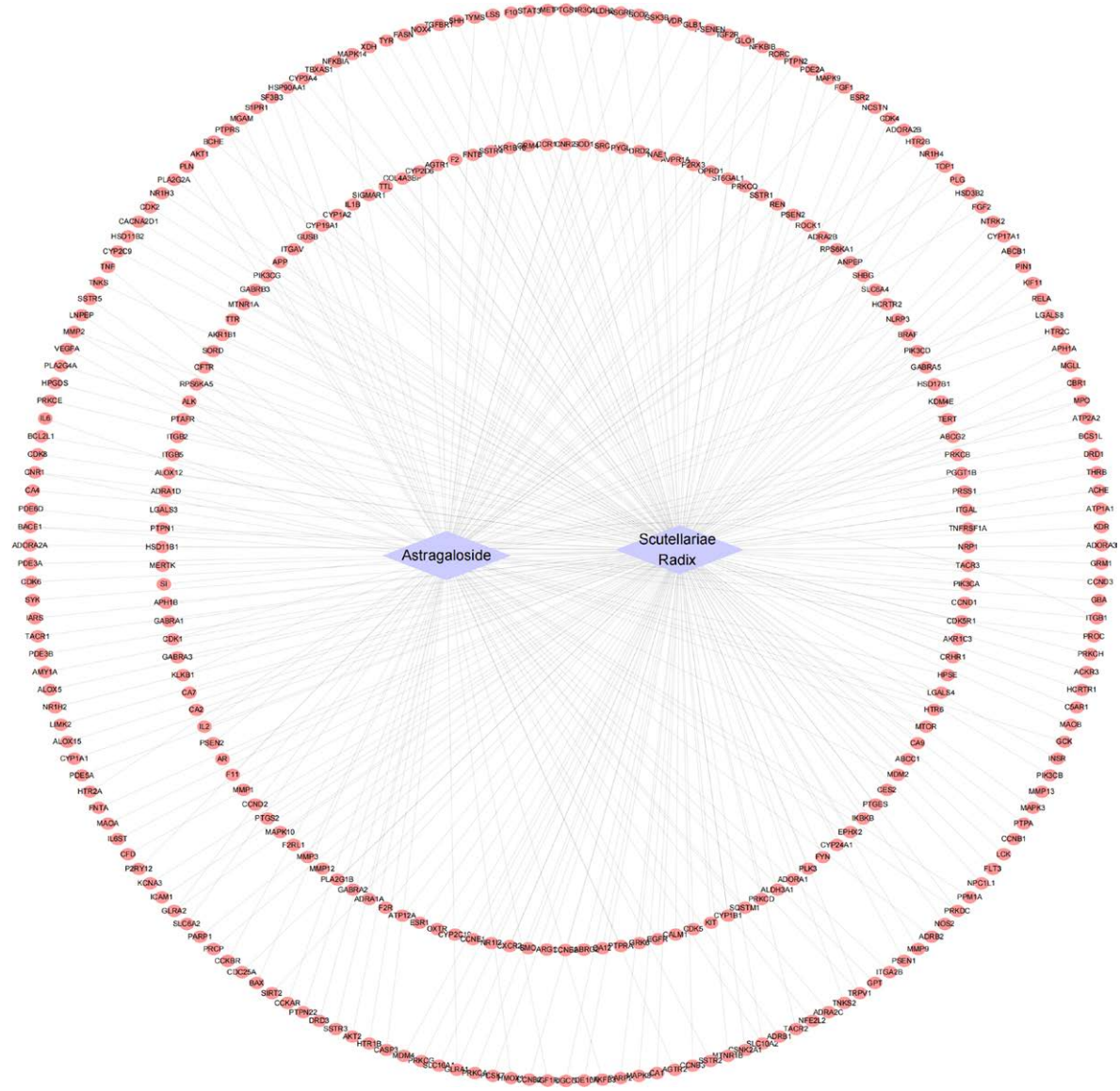

Figure 1. Composition-target network diagram.

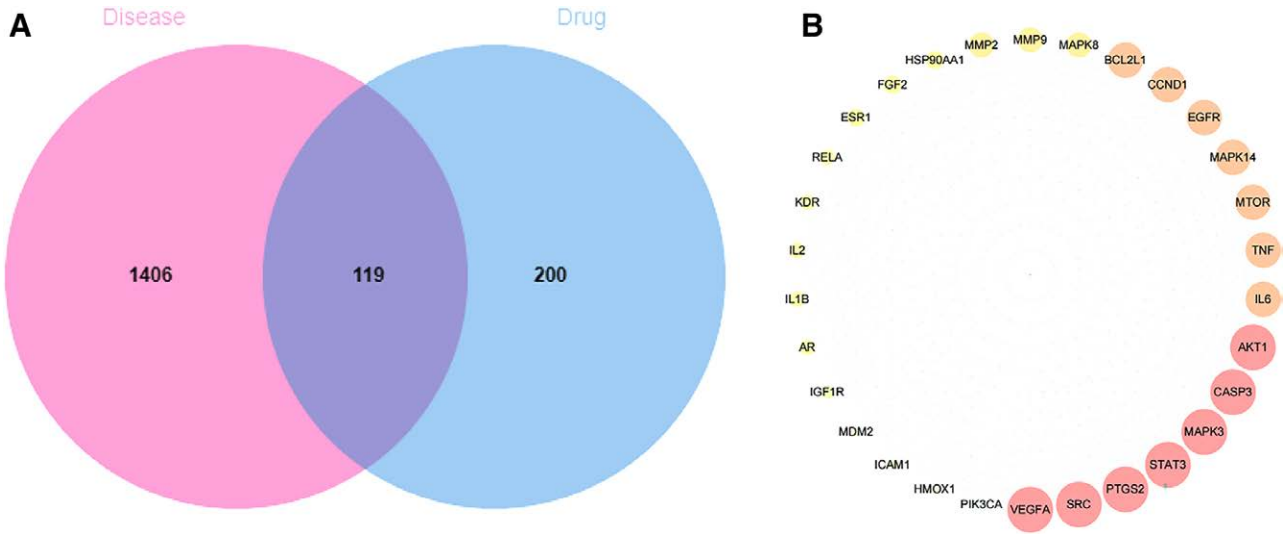

Figure 2. Information summary of overlapping targets.

used to derive KEGG pathway enrichment and screen, and 143($P \leq 0.01$) was obtained. The first 30 pathway information was selected to draw the map. The enrichment information is shown in Figure 3.

4.4. GO enrichment

Bioconductor operation of *R* package was used to derive KEGG pathway enrichment and screening, and 143($P \leq 0.01$) were obtained. The first 30 pathway information was selected to draw the map, and the screening value was set ($P \leq 0.01$). A total of 385 GO entries were obtained, and the first 30 pathway information was selected to draw the map. The enrichment information is shown in Figure 4.

Lung cancer is one of the malignant tumors with the fastest increase in morbidity and mortality and the biggest threat to people's health and life.[7] In the past 50 years, many countries have reported a significant increase in the incidence and mortality of lung cancer. The incidence and mortality of lung cancer are the first among all malignant tumors in males, the second among females, and the second among mortality. The etiology of lung cancer is still not completely clear.[8].

In this study, network pharmacological methods were used to preliminarily explore the mechanism of action of Scutellariae Radix and Astragaloside in the treatment of lung cancer. According to the compound target diagram, there were 347 targets of active ingredients, indicating that Scutellariae Radix and Astragaloside had multi-component and multi-target characteristics in their efficacy.

The PPI network diagram shows that there are multiple interactions among the targets, and the greater the degree of connectivity, the greater the possibility of treating lung cancer by this target. It was found that AKT1, VEGFA and MAPK had a high correlation in the network diagram. Akt protein kinase is an important signaling molecule in the PI3K-Akt signaling pathway and has a variety of biological activities.[9] Studies have shown that inhibition of Akt activity can induce cell apoptosis, and inhibit cell migration and proliferation.[10] In vitro experiments also found that AKT plays an important role in the formation of blood vessels, and AKT can promote intravascular whitening. Expression of Akt1 gene silenced by targeted siRNA and its inhibitory effect on endothelial cell migration induced by skin growth factor in lung cancer.[11] Akt signaling pathway plays an important role in the regulation of proliferation, apoptosis and migration of NSCLC cells. Phosphorylation of Akt activates endothelial nitric oxide synthase, leading to neovascularization and promoting endothelial cell migration induced by vascular endothelial growth factor.[12] VEGFA is a potent and specific endothelial cell mitosis agent, which can promote the division and proliferation of endodermal cells and increase microvascular permeability when it binds to the receptor[13] VEGFA plays an important role in tumor genesis and development. Studies have confirmed that VEGFA can promote tumor growth and proliferation.[14] Positive expression of VEGFA was found in various clinical trials in lung cancer patients.[15] There are experiments show VEGFA and its receptor 2 (VEGFAR - 2), in order to promote vascular endothelial cell proliferation, growth and survival, such as biological behavior, in malignant tumor cells, the expression of VEGFA increases, and raised VEGFAR - 2 expression level, so as to promote the growth of lung cancer cells.[16] MAPK kinase is one of the important pathways in eukaryotic signal transmission network and plays a key role in gene expression regulation and cytoplasmic functional activities.[17] Abnormal activation of MAPK pathway is closely related to tumor proliferation, metastasis, and invasion. Some researchers have proved that inhibition of MAPK signaling pathway can effectively promote apoptosis of cancer cells and affect the progression of cancer.[18]

The 30 overlapping targets were enriched through KEGG pathway, and the enrichment results showed that the AGE-Rage

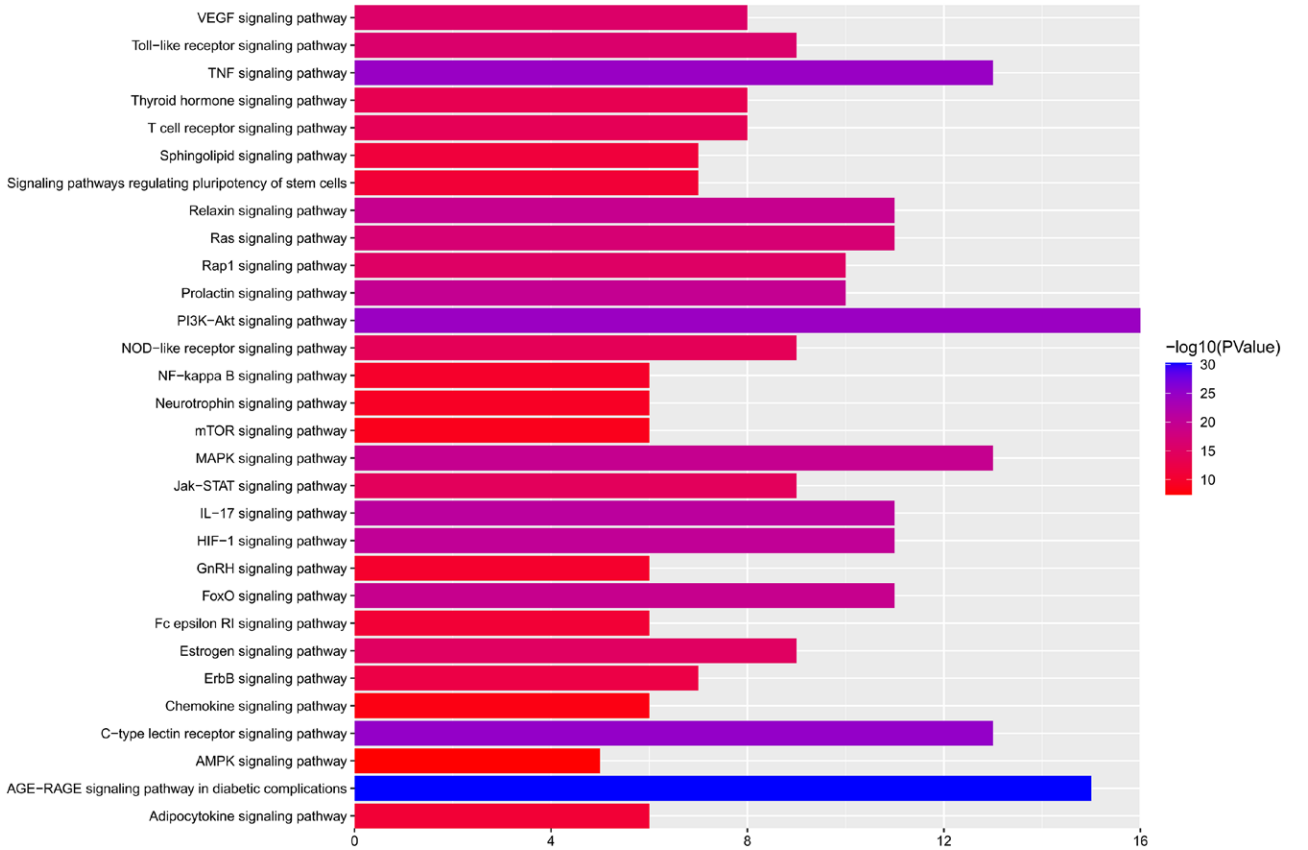

Figure 3. KEGG pathway enrichment.

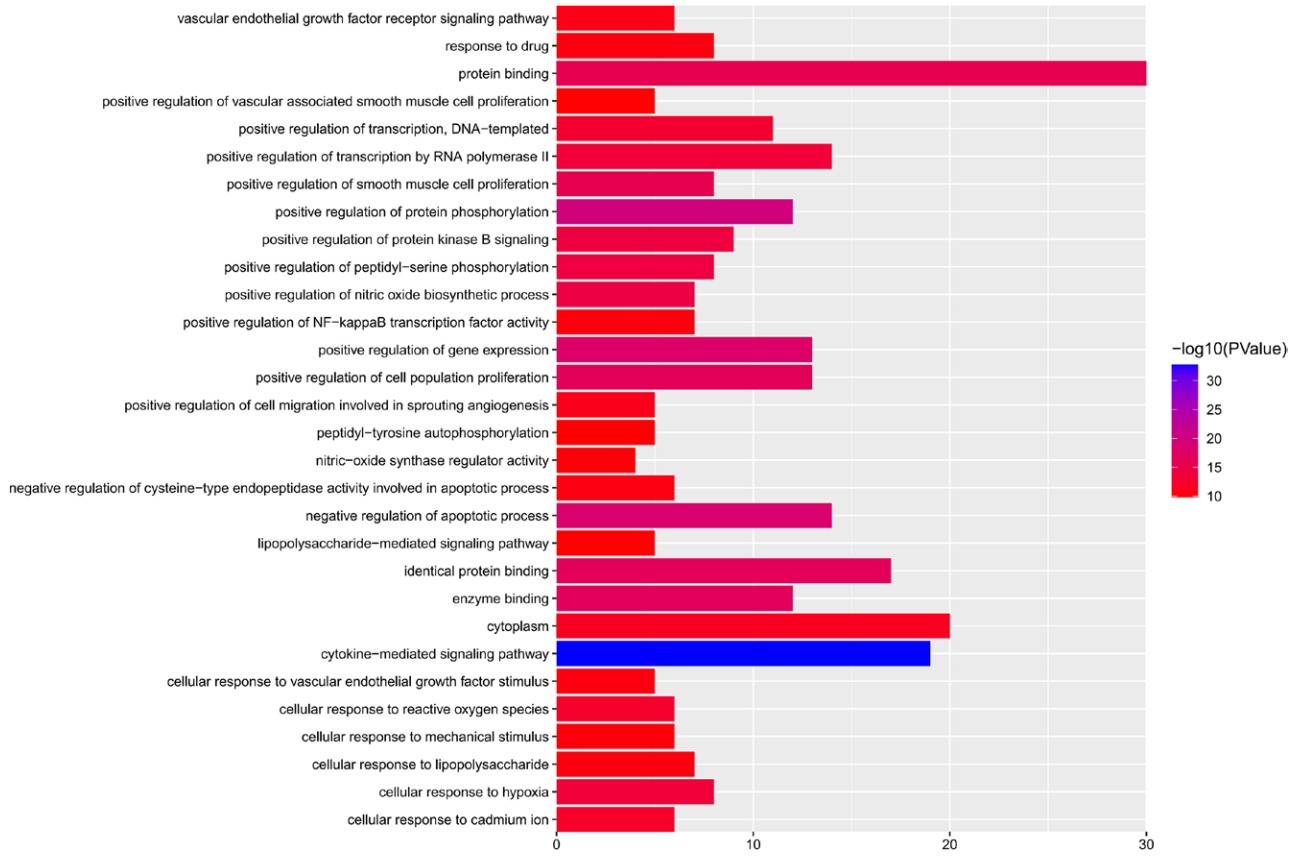

Figure 4. GO functional enrichment.

signaling pathway, TNF signaling pathway, PI3K-Akt signaling pathway, and other pathways were highly enriched.

These results suggest that Scutellariae Radix and Astragaloside may regulate the immune system of the body, reduce the inflammatory response, and play a role in intervening the progression of lung cancer by resisting and clearing invading pathogens and infected cells.

Twenty-seven overlapping targets were enriched through the GO pathway, and the results showed that most of them were biological processes, suggesting that Scutellariae Radix and flavonin may affect the progression of lung cancer by regulating cell apoptosis, cytokine conduction, cell proliferation, and other biological pathways.

5. Conclusions

In summary, this study, on the basis of network pharmacology, use all kinds of software and database, build the Scutellariae Radix methyl glucoside and yellow fine saponin "ingredients-targets" network diagram, and will fully correspond to the target and screening out the treatment of lung cancer in targets, the KEGG pathway enrichment analysis was carried on and GO gene function analysis, system to study the effect of the treatment of lung cancer pathway and pathways, for clinical Scutellariae Radix methyl glucoside and yellow fine saponin provide basis for treatment of lung cancer. However, the drawback of this study is that the network pharmacological analysis only provides a prediction, which needs to be validated by further experiments and clinical trials.

Author contributions

Zijuan Wang, Lingpeng Meng, Xian Gu, and Zhenye Xu contributed to the study conception and design. All authors collected the data and performed the data analysis. All authors contributed to the interpretation of the data and the completion of figures and tables. All authors contributed to the drafting of the article and final approval of the submitted version.

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