Network Pharmacological Analysis of Action Mechanism of Mongolian Medicine *Rhododendron micranthum* Turcz. in Treating Lung Cancer

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Abstract [**Objectives**] To explore the action mechanism of Mongolian medicine *Rhododendron micranthum* Turcz. on lung cancer by network pharmacology. [**Methods**] Based on the high-throughput experiment and reference database (HERB) of traditional Chinese medicine, component target database (Swiss ADME), small molecule drug target prediction online platform (SWISS Target Prediction), human gene business card database (GENECARD), the database of genes and mutation sites related to human diseases (DISGENET) and other databases, the target genes of drugs and diseases were screened out. Venny software was used for obtaining the target intersection of active components of the Mongolian medicine *R. micranthum* Turcz. and the lung cancer, a CytoNCA plug-in in cytoscape 3.10.0 software was used for screening candidate core target genes, and related effective components were obtained in a reverse direction. A drug-active ingredient-gene-disease regulation network was established, a protein-protein interaction (PPI) network was established by means of the STRING database to screen core genes, and common targets were screened by the David database. Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) were used for enrichment analysis. [**Results**] There were 13 effective components of Mongolian medicine *R. micranthum* Turcz. for treating lung cancer and 115 drug disease intersection target genes. Core genes affecting the disease included *SRC*, *HSP90AB1*, *EGFR*, *AKT1*, and *ERBB2*. GO functional enrichment analysis involved 462 items of biological processes, 64 items of cellular components and 126 items of molecular functions. Enrichment analysis of KEGG signaling pathways screened out cancer pathways, endocrine resistance, PI3K-Akt signaling pathways, proteoglycans in cancer and other signaling pathways. [**Conclusions**] Mongolian medicine *R. micranthum* Turcz. can inhibit the proliferation of lung cancer cells from multiple targets and pathways, and the results of network pharmaceutical analysis provide a theoretical basis for further experimental research.

Key words Network pharmacology, Mongolian medicine *Rhododendron micranthum* Turcz., Lung cancer, Action mechanism

1 Introduction

Lung cancer (LC) is a malignant tumor with the highest incidence and mortality rate worldwide, with a 5-year survival rate of 19.7% in China[1]. Histologically, lung cancer is divided into small cell lung cancer and non-small cell lung cancer, of which non-small cell lung cancer accounts for about 85%[2]. At present, the western medicine treatment of LC is mainly surgery, radiotherapy, chemotherapy, molecular targeted therapy and immunotherapy, but the gradual formation of drug resistance and drug toxicity bring trouble to clinical treatment. Therefore, it is urgent to find more efficient drugs to treat lung cancer. Therefore, it is urgent to find more efficient drugs to treat lung cancer.

Mongolian medicine *R. micranthum* Turcz. is a plant of the genus *Rhododendron* in family Ericaceae. It is pungent and bitter in taste and cold in nature. It has the effects of expelling wind, dredging collaterals, stopping bleeding and relieving pain[3-7]. It is used to treat acute and chronic bronchitis. In addition, Mongolian medicine *R. micranthum* Turcz. extract can inhibit the growth of a variety of cancer cells and induce apoptosis of cancer cells, but the pathway and molecular biological mechanism of its promotion of apoptosis are still not clear[8]. Network pharmacology is a novel bioinformatics technique for drug target prediction. By constructing a "drug-component-target" interaction network with holistic and systematic characteristics to explain the mechanism of TCM treatment from multiple aspects, this method is in line with the characteristics of "multiple prescriptions, multiple ways and multiple targets" of TCM, and can be used to analyze and clarify the material basis of TCM efficacy[9].

Therefore, on the basis of previous work, we intended to use network pharmacological methods to study the disease targets and the active component targets of Mongolian medicine *R. micranthum* Turcz., constructed the network of "Mongolian medicine *R. micranthum* Turcz.-active components of Mongolian medicine *R. micranthum* Turcz.-targets", to explore the anti-LC mechanism of Mongolian medicine *R. micranthum* Turcz., and provide a theoretical basis for the discovery of new pharmacodynamic targets, as well as the verification of pharmacodynamic substances of traditional Chinese medicine and the further study of pharmacodynamic substances.

2 Data and methods

2.1 Screening of active components and targets The high-throughput experiment- and reference-guided database of traditional Chinese medicine (HERB, http://herb.ac.cn/)[10] was used to search related chemical compounds of Mongolian medicine *R. micranthum* Turcz. According to Lipinski's five principles:

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molecular weight (MW≤500); logP≤5; hydrogen bond acceptor (nOH≤10) and hydrogen bond donor (nOHNH≤5), the standard linear symbol (SMILEname) was kept. Copying and pasting the pubchemID of the relevant components into an organic small molecule bioactivity database (PubChem, https://pubchem.ncbi.nlm.nih.gov/), wherein logP was less than or equal to 5 according to logP≤5 of Lipinski's five principles; nOHNH≤5, the relevant components were screened. In addition, the relevant chemical components of Mongolian medicine *R. micranthum* Turcz. were searched by literature, and the standard linear symbols of compounds were obtained by PubChem. The standard linear symbols of relevant chemical components found by the above two methods were uploaded to the Swiss ADME database (http://www.swissadme.ch/) for pharmacokinetic screening[11]. Components with (i) high gastrointestinal absorption and (ii) three or more "Yes" results from the drug-likeness evaluation methods (Lipinski, Ghose, Veber, Egan, and Muegge) were retained[12]. The targets related to the active components were screened from HERB and Swiss Target Prediction (http://www.swisstargetpredic-tion.ch/), and the targets with the probability value of target prediction >0 were included.

2.2 Screening of disease candidate targets Using the databases DisGeNET (https://www.disgenet.org/), GeneCards (https://www.genecards.org/), with the keyword "Lung cancer", LC related target points were obtained. After removing the duplicate, the LC corresponding target points were obtained. The online mapping tool Venny 2.1 was used to take the intersection of active ingredient targets and LC related targets, and then Mongolian medicine *R. micranthum* Turcz. Key anti-LC targets were obtained.

2.3 Construction of protein-protein interaction (PPI) network Venny 2.1 software was adopted to obtain the gene of the intersection of the active component target of the Mongolian medicine *R. micranthum* Turcz. and the gene target of the LC, namely the potential target, the network of "Mongolian medicine *R. micranthum* Turcz.-active components-targets" was constructed by Cytoscape 3.10.0 software. The potential targets were imported into the STRING database (https://string-db.org/)[13], the Multiple proteins tool was selected, and the species was "Homo sapiens" as the screening condition; the confidence level was set as 0.7; set the network display to Hide disconnected nodes in the network; set the number of clusters in Kmeans clustering to 3. The uncorrelated targets were deleted, and the obtained PPI network map output as a TSV file, which was optimized by Cytoscape 3.10.0 software, and screened according to the betweenness centrality (BC), closeness centrality (CC), degree centrality (DC) and eigenvector centrality (EC) calculated by CytoNCA plug-in. 16 PPI core gene targets were obtained by drawing a bar graph according to the degree.

2.4 GO biological function and KEGG pathway enrichment analysis The DAVID (https://david.ncifcrf.gov/)[14] database was used to select the species parameter as Homo sapiens, and the Biological Process (BP) was analyzed by GO (Gene Ontology) functional enrichment, Cellular Component (CC), Molecular Function (MF), KEGG (Kyoto Encyclopedia of Genes and Genomes, KEGG) pathway enrichment analysis was performed simultaneously, and the results were plotted as a bar graph and a bubble graph[15].

3 Results and analysis

3.1 Acquisition of active components With the conditions set in Section **2.1** as the screening conditions, 40 chemical components related to Mongolian medicine *R. micranthum* Turcz. were obtained by HERB database search, and 15 chemical components were selected by literature search. Finally, 13 relevant active components were obtained (Table 1). The active components were screened to the relevant targets, and 275 Mongolian medicine *R. micranthum* Turcz. related targets were finally obtained after de-duplication and summarization.

Table 1 Active components of Mongolian medicine *Rhododendron micranthum* Turcz. after screening

No.	Compound name	Standard linear symbol
1	Kaempferol	OC1=C2C(OC(C3=CC=C(O)C=C3)=C(O)C2=O)=CC(O)=C1
2	5-hydroxy-7, 4'-dimethoxy-6, 8-dimethyl flavone	O=C1C=C(C2=CC=C(OC)C=C2)OC3=C1C(O)=C(C)C(OC)=C3C
3	8-Demethyleucalyptin	COC1CCC(CC1)C1CC(=O)C2C(O1)CC(C(C2O)C)OC
4	Hirsutine	CO/C=C(/[C@H]1C[C@@H]2N(C[C@@H]1CC)CCC1C2[NH]C2C1CCCC2)\C(=O)OC
5	(+)-spathulenol	C1CCC2C(N1)C1CCC3C4C1C(C2)CCC4CCC3
6	Isocaryophyllene	C/C/1=C/CCC(=C)[C@H]2CC([C@@H]2CC1)(C)C
7	1, 4, 4-Trimethyl-8-methylene-1, 5-cycloundecadiene	C/C/1=C/CC(/C=C\CC(=C)CCC1)(C)C
8	4, 11, 11-Trimethyl-8-methylene-5-oxatricyclo (8.2.0.0(4, 6))dodecane	C[C@@]12CC[C@@H]3[C@@H](CC3(C)C)C(=C)CC[C@@H]1O2
9	3, 4', 5, 7-Tetrahydroxyflavone Hydrate	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
10	Myrcene	CC(=CCCC(=C)C=C)C
11	Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
12	Scopoletin	COC1=C(C=C2C(=C1)C=CC(=O)O2)O
13	Syringic acid	COC1=CC(=CC(=C1O)OC)C(=O)O

3.2 Construction of target network Using the databases of DisGeNET and GeneCards, 4 173 genes related to LC were found from DisGeNET database with the keyword of "Lung cancer". A total of 25 000 genes related to LC were found from the GeneCards database, and 2 422 LC corresponding target genes were screened out after the relevant targets of the two databases were obtained through summarization after de-duplication with Relevance scores >30 (median) as the limiting condition. The above results were used as the disease candidate genes in this experiment, and they were crossed with Mongolian medicine *R. micranthum* Turcz. candidate genes to obtain 115 potential targets (Fig. 1). The obtained Mongolian medicine *R. micranthum* Turcz. effective active components and potential target genes were visualized using CytoScape 3.10.0 software, and the attributes of the network, such as edges and endpoints, are set as shown in Fig. 2, and obtained a network diagram of that Mongolian medicine *R. micranthum* Turcz. -active components-targets. The analysis of the network shows that the network consists of 118 nodes and 333 edges, with light blue patterns representing the effective components and red patterns representing the Mongolian medicine *R. micranthum* Turcz. (EF), the target point was represented by a dark blue pattern, the node size represented the value size, and the larger the node, the larger the value (Fig. 2). Through network topology analysis, the average values of BC, CC, EC and degree (BC >220, CC >0.36, EC >0.06, degree >6) of the active components were used for screening. The Top five compounds were Hirsutine, (+)-spathulenol, β-humulene (1, 4, 4-Trimethyl-8-methylene-1, 5-cycloundecadiene), kaempferol (3, 4', 5, 7-tetrahydroxyflavone Hydrate) and syringic acid, suggesting that they were at the core of the network and were regarded as core components. Therefore, Mongolian medicine *R. micranthum* Turcz. has the characteristics of multi-component and multi-target in the prevention of LC.

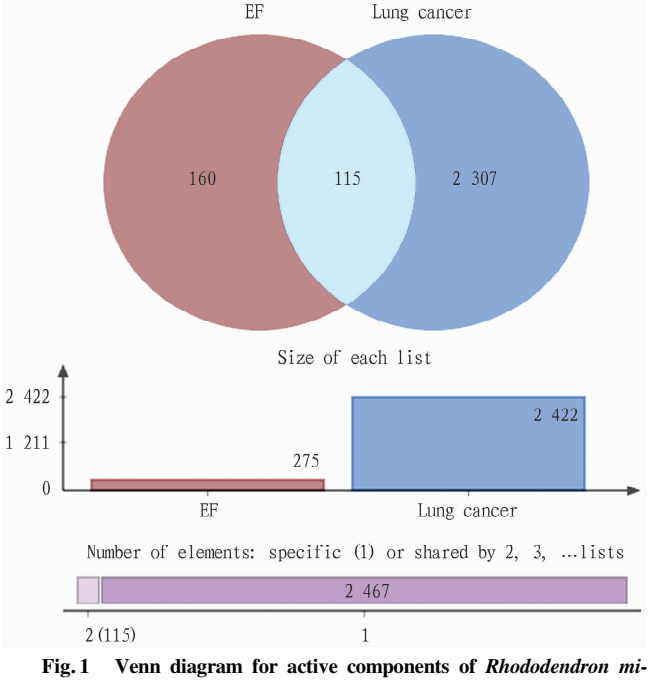

Fig. 1 Venn diagram for active components of *Rhododendron micranthum* Turcz. and LC disease targets

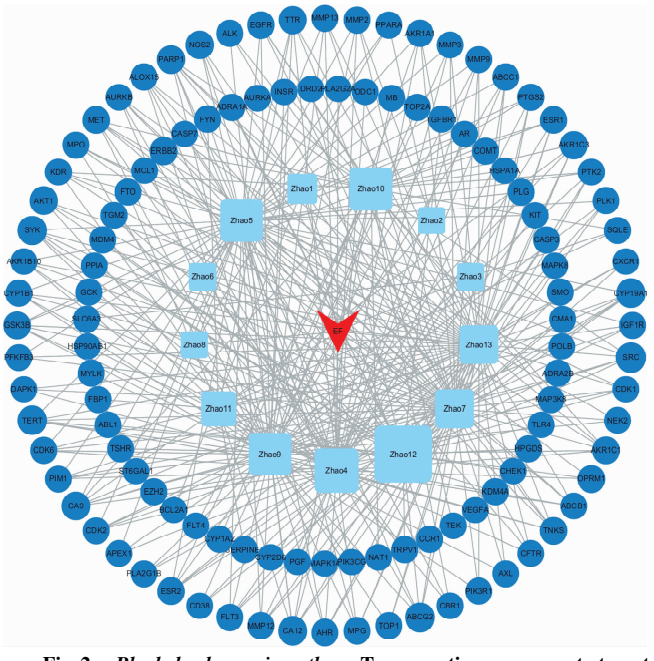

Fig. 2 *Rhododendron micranthum* Turcz. -active components-target network diagram

3.3 Construction of PPI network We imported the common targets of the Mongolian medicine *R. micranthum* Turcz. and LC into the String database to obtain a PPI network of the Mongolian medicine *R. micranthum* Turcz. and the LC, the connecting lines between the nodes in the graph indicate that there is interaction between them. Different colors indicate different types of interaction. The more connecting lines, the closer the interaction. The number of nodes was 115, the number of edges was 357, the average node degree was 6.21, and the average local clustering coefficient was 0.537 (Fig. 3A). Then, using the. tsv file downloaded from String to screen (according to the average value of BC, DC, EC, and CC) and plot a bar chart based on the degree (Fig. 3B). Through the bar plot, it can be seen more intuitively that the more nodes connected to each node, the more critical the role of the node in the network, and 16 PPI core gene targets were obtained. The top five nodes with the highest association values were SRC (28), HSP90AB1 (28), EGFR (28), AKT1 (27) and ERBB2 (25) (Fig. 3C). These results suggest that these genes may be potential targets for Mongolian medicine *R. micranthum* Turcz. in treating the lunge cancer.

3.4 GO biological function and KEGG pathway enrichment analysis The DAVID database was used to select Homo sapiens as the species parameter, and the GO function and KEGG signaling pathway enrichment analysis was performed on the intersection targets of Mongolian medicine *R. micranthum* Turcz. in treating the LC, and 462 entries of biological process were obtained, including vascular endothelial growth factor receptor signaling pathway, positive regulation of kinase activity, peptide-tyrosine phosphorylation, development of multicellular organisms, protein phosphorylation, cell surface receptor protein tyrosine kinase signaling pathway, positive regulation of MAPK cascade, protein phosphorylation, negative regulation of apoptosis, phosphorylation, *etc.* There

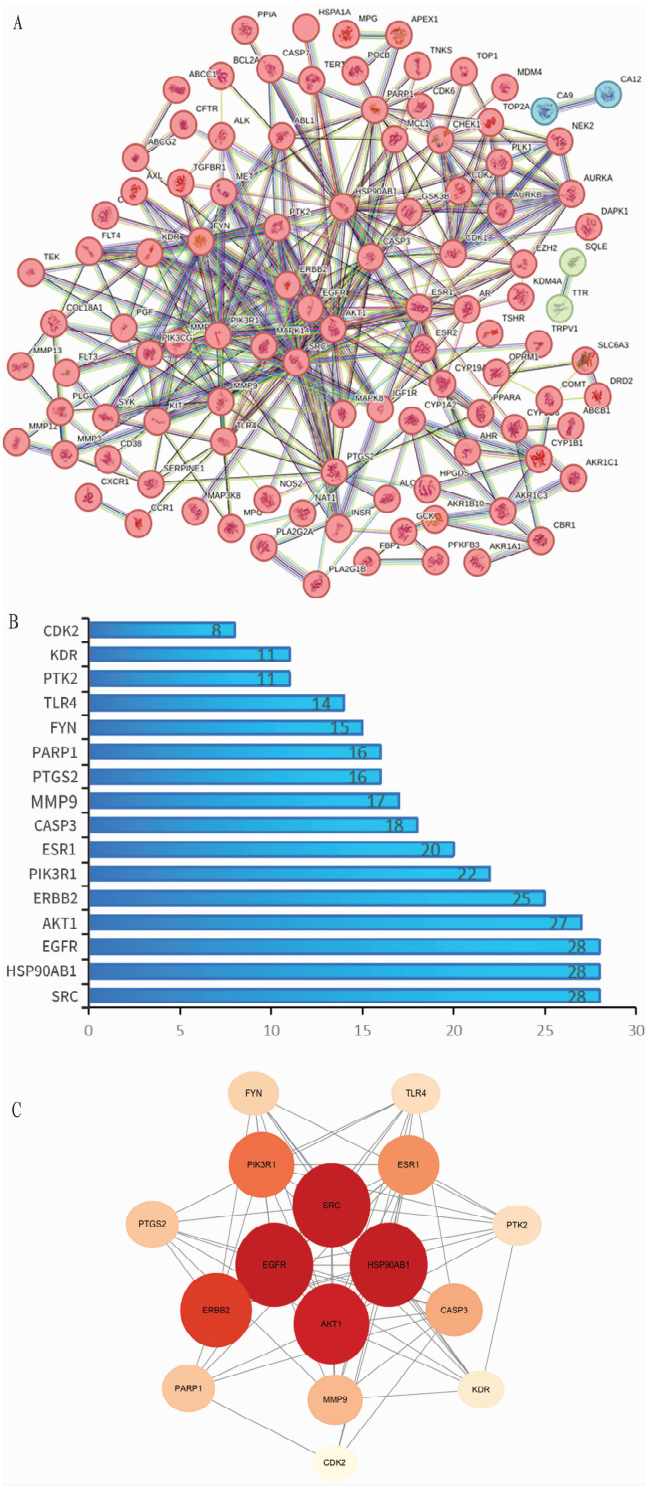

Fig. 3 PPI network of *Rhododendron micranthum* Turcz. and the lung cancer and core targets in treating the lung cancer

were 64 entries of cellular components, including receptor complex, chromosome, telomere region, protein-containing complex, cell surface, intracellular membrane binding organelle, nucleoplasm, cytoplasm, plasma membrane, cytoplasm, nucleus, *etc.* There were 126 entries of molecular functions, including membrane receptor protein tyrosine kinase activity, growth factor binding, protein tyrosine kinase activity, protein kinase activity, kinase activity, protein serine/threonine kinase activity, enzyme binding, protein serine kinase activity, ATP binding, protein binding, *etc.* According to the descending order of the number of enriched genes, the top 10 of each category were selected to plot a bar chart (Fig. 4).

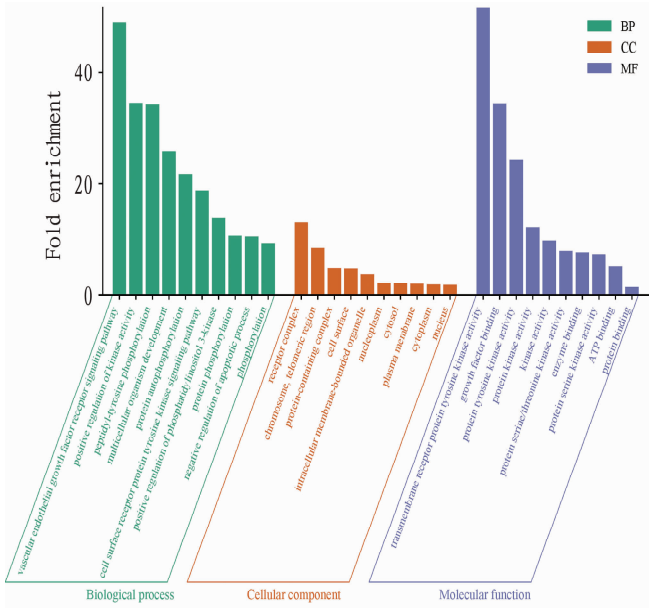

Fig. 4 GO functional enrichment analysis

Enrichment analysis of KEGG signaling pathways showed that there were 127 pathways, After deletion of unrelated pathways, they mainly included cancer pathways, endocrine resistance, PI3K-Akt signaling pathways, proteoglycans in cancer, chemical carcinogenesis-reactive oxygen species, MAPK signaling pathways, focal adhesion, Ras signaling pathways, EGFR tyrosine kinase inhibitor resistance, HIF-1 signaling pathways, *etc.* We selected the first 20 entries to plot a bubble diagram. The size of the bubble in the diagram represents the number of targets enriched by the item. The larger the bubble is, the more targets are enriched. The color of the bubble represents the *P* value. The redder the color is, the smaller the *P* value is (Fig. 5).

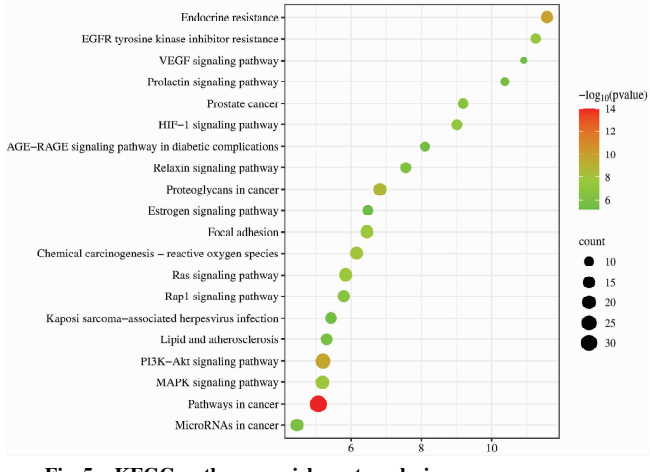

Fig. 5 KEGG pathway enrichment analysis

4 Discussion

According to the literature, the study of the chemical components of Mongolian medicine *R. micranthum* Turcz. started as early as 1972. Scopoletin, hyperin, astragaloside, quercetin, kaempferol, and rhodotoxin were isolated and identified from *R. micranthum* Turcz. Research results show that hyperoside and triterpenoids in *R. micranthum* Turcz. are the effective anti-tumor components[16-18]. Because of the difficulty of detecting some trace components, not all active components of *R. micranthum* Turcz. can be detected. For a long time, the bioactive components of Mongolian medicine *R. micranthum* Turcz. against LC and their mechanisms have not been clearly clarified. Further isolation of Mongolian medicine *R. micranthum* Turcz. and identification of bioactive components with potent therapeutic or adjuvant anti-LC effects are needed[19].

In this paper, the anti-LC mechanism of Mongolian medicine *R. micranthum* Turcz. was discussed based on network pharmacology, and the results showed that there were 13 potential active components and 115 potential targets in Mongolian medicine *R. micranthum* Turcz. It is suggested that Mongolian medicine *R. micranthum* Turcz. may be used to treat LC through the synergistic mechanism of multi-component and multi-target. Based on the PPI network, the effective components against LC were screened, and the effective components of LC (kaempferol, 5-hydroxy-7, 4'-dimethoxy-6, 8-dimethyl flavone, *etc.*) were obtained. According to the degree value calculated by the software, we selected 16 core targets, which play a key role in the PPI network and are the core targets for the treatment of LC by Mongolian medicine *R. micranthum* Turcz. SRC, HSP90AB1, EGFR, AKT1, ERBB2, are targets with higher significance. SRC, HSP90AB1 and EGFR have the largest nodes in PPI, which may be the important targets of Mongolian medicine *R. micranthum* Turcz. against the lung cancer. SRC (steroid receptor coactivator) is a non-receptor tyrosine kinase encoded by the SRC proto-oncogene and a core member of the SRC family of protein kinases[20]. SRC, widely distributed in human cells, can regulate cell division, motility, adhesion, angiogenesis and survival, and play an important role in maintaining normal physiological functions. SRC induces the transformation of various malignant cells, which has been found in a variety of tumor cells, and can be involved in tumor production, growth, metastasis, and so on. Abnormal activation or overexpression of SRC-related signaling pathways can lead to abnormalities in the body, accordingly leading to cancer.

The results of GO-pathway enrichment of Mongolian medicine *R. micranthum* Turcz. anti-LC targets showed that, for Mongolian medicine *R. micranthum* Turcz. in treating the lung cancer, the BP is mainly through the positive regulation of vascular endothelial growth factor receptor signaling pathway, kinase activity, peptide-tyrosine phosphorylation and so on. CC mainly includes receptor complex, chromosome, telomere region, *etc.* MF mainly includes membrane receptor protein tyrosine kinase activity, growth factor binding, protein tyrosine kinase activity and other pathways. Enrichment analysis of KEGG signaling pathways showed that they were mainly involved in cancer pathways, endocrine resistance, PI3K-Akt signaling pathways, proteoglycans in cancer and other pathways. The above pathway studies show that the main way for the active components of Mongolian medicine *R. micranthum* Turcz. to participate in the anti-LC effect is the regulatory pathway. The analysis and prediction data in this paper need to be verified by further experiments in future, and the research work will be based on these results to carry out in-depth research on component separation and identification, activity evaluation, serum pharmacochemistry and mechanism of action of *R. micranthum* in the treatment of LC[21].

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