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Analysis of the Mechanism of *Ophiopogon japonicus* in Treating Pneumonia Based on Network Pharmacology

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

This study explores the mechanism of Ophiopogon japonicus in treating pneumonia through network pharmacology, establishes a physiological and pharmacological relationship between the two based on targets, and emphasizes the interaction between signaling pathways and targets. By utilizing Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis, specific biological processes and signaling pathways are utilized to enhance the understanding of the medicinal properties of traditional Chinese medicine through the use of bioinformatics and biomedical tools. This method aims to identify the key targets and signaling pathways of Ophiopogon japonicus affecting pneumonia status, providing insights into its anti-inflammatory effect in the lungs. The active application of network pharmacology methods in the field of pneumonia is a new trend in the modernization of traditional Chinese medicine.

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Keywords: Network pharmacology; Ophiopogon japonicus; pneumonia; signal pathway.

1. INTRODUCTION

Pneumonia, characterized by inflammation in the terminal airways, alveoli, and lung interstitium, can result from various factors including microbial infections, physicochemical triggers, immune dysfunction, allergies, and medications. It affects individuals of all ages, with children, the elderly, and those with underlying health conditions being particularly vulnerable [1,2].

Different pathogenic factors categorize pneumonia into infectious, physicochemical, allergic, and other types. While treatment options encompass traditional Chinese medicine formulas, chemical drugs, and biological products, the effectiveness of these approaches in improving pneumonia outcomes remains limited. Hence, there's an urgent need to explore more effective therapeutic agents.

Ophiopogon japonicus, a traditional Chinese medicine native to Sichuan, is renowned for its significant anti-inflammatory and antioxidant properties. Traditional Chinese medicine relies on the synergistic interactions among multiple components, forming a cohesive "component structure" that enhances therapeutic effects. However, the synergistic effects and compatibility structures among *Ophiopogon japonicus* components contributing to its anti-inflammatory properties remain underexplored [3-8].

This project employs network pharmacology, leveraging its bioinformatics and biomedical advantages, to investigate the therapeutic effects of *Ophiopogon japonicus* on pneumonia. By analyzing its multifaceted components, targets, pathways, and systems, the study aims to uncover the biological mechanisms and signaling pathways underlying *Ophiopogon japonicus*' efficacy in treating pneumonia. Ultimately, this research seeks to provide insights into the interaction between *Ophiopogon japonicus*' active ingredients and pneumonia targets, elucidating relevant signaling pathways and laying the groundwork for advancing traditional Chinese medicine research in pneumonia treatment [9-12].

2. MATERIALS AND METHODS

Chemical composition and target acquisition of *Ophiopogon japonicus*: We employ the following methodologies to identify the effective ingredients of *Ophiopogon japonicus* unit medicine:

(1) ETCM Database:

- Accessed via http://www.tcmip.cn/ETCM/.
- Adhering to drug-like properties criteria, including MW (relative molecular weight) ≤ 500, ALogP (lipid-water distribution coefficient) ≤ 5, noHNH (number of H+ receptors) ≤ 10, and noH (number of H+ donors) ≤ 5.
- Effective ingredients are obtained based on these parameters.

(2) PubChem Database:

- Utilizing the PubChem database (https://pubchem.ncbi.nlm.nih.gov).
- MW (relative molecular weight) serves as the screening criterion.
- Obtaining the SMILES (Simplified Molecular Input Line Entry System) notation for the chemical formula of *Ophiopogon japonicus* unit medicine.

(3) SWISS Target Prediction:

- Accessible via http://swisstargetprediction.ch.
- Initially, utilizing the SMILES notation of individual ingredients of *Ophiopogon japonicus* to derive their corresponding chemical structural formulas.
- Predicting the target genes associated with each component.
- Conducting screening if the correlation between the components and target genes exceeds 0.

This systematic approach facilitates the identification of effective ingredients and prediction of potential target genes for *Ophiopogon japonicus* unit medicine, enhancing our understanding of its therapeutic mechanisms.

Acquisition of targets for pneumonia: We utilize GeneCards (http://www.genecards.org) to screen for genes associated with pneumonia. Additionally, DisGeNET (http://www.Disgene.org/home) is employed to identify genes related to pneumonia (under the name "Pneumonic Plague" with the CUI: C0524688).

Following this, we compile the disease genes obtained from both databases and eliminate duplicates to derive a comprehensive list of pneumonia-related genes.

Construction of the "Taste Component Target" Network: The filtered ingredient and target data should be saved as a network file, preferably in a format compatible with Cytoscape 3.7.2 Software (http://www.cytoscape.org/). Once saved, import the file into Cytoscape to construct a network of medicinal taste components and targets.

Construction and topological analysis of protein-protein interaction (PPI) networks: Perform an intersection analysis using bioinformatics mapping software available at www.bioinformatics.com.cn. Import the intersection genes of *Ophiopogon japonicus* and pneumonia into the STRING database (http://string-db.org/, 10th edition) to establish a Protein-Protein Interaction (PPI) network diagram. Set the threshold to "medium confidence ≥ 0.7" to obtain pairwise correlation scores.

Import the data from STRING into Cytoscape 3.7.2 for network graph construction and topology analysis. Utilize the Cytoscape plugin "Network Analyzer" to measure six topology parameters: betweenness centrality (BC), closeness centrality (CC), degree centrality (DC), eigenvector centrality (EC), local edge connectivity (LAC), and network centrality (NC). Select nodes that meet the median value of all six indicators as key targets and extract core targets to construct a network.

GO analysis and KEGG pathway analysis: Perform gene ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation analysis on the predicted key target information using DAVID 6 (https://david.ncifcrf.gov/) database. Utilize the obtained results to create visual representations using GraphPad Prism 5.

3. RESULTS

Composition and Target Screening of *Ophiopogon japonicus*: Utilizing the ETCM database, 18 main components were identified from *Ophiopogon japonicus*. To address the requirements for treating pneumonia, a network diagram titled "Pneumonia Major Components Targets" was constructed using Cytoscape 3.7.2 software.

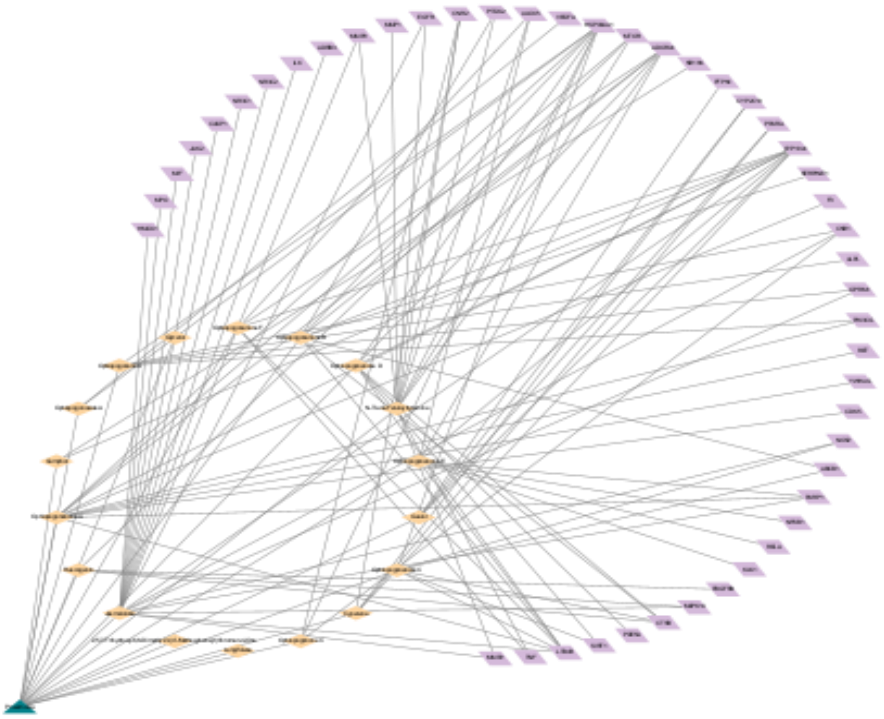

Fig. 1. "Pneumonia Component Target" Network

After integrating data from the SwissTargetPrediction database and removing duplicates, 555 prediction targets were identified for the components of *Ophiopogon japonicus*. Utilizing the GeneCards and DisGeNET databases, targets related to pneumonia were selected based on correlation coefficients ≥ 3.24 and a score of gda (database and literature support) ≥ 0.02. After removing duplicates, 780 pneumonia-related targets were obtained.

Using the online mapping software of Weishengxin, a Venn diagram was generated, revealing a total of 98 shared targets between *Ophiopogon japonicus* and pneumonia (refer to Fig. 1).

Subsequently, protein-protein interaction (PPI) analysis was conducted on the common targets of *Ophiopogon japonicus* and pneumonia. Initially, a PPI network was constructed using the STRING database, with a minimum required interaction score ≥ 0.7. This resulted in 98 nodes (excluding PDE4A and P4HTM, which did not participate in protein interactions) and 561 edges, highlighting the intricate relationship between protein interactions and regulation (refer to Fig. 2).

Utilizing Cytoscape 3.7.2 software for topology analysis, key target genes for treating pneumonia with *Ophiopogon japonicus* were identified. Targets with values of Degree, Betweenness Centrality (BC), and Closeness Centrality (CC) greater than the median were extracted, resulting in a total of 32 core targets.

From these core targets, the top ten were selected to construct the network, yielding 9 nodes and 28 edges. These targets are deemed to play a crucial role in the treatment of pneumonia with *Ophiopogon japonicus* (refer to Table 1 and Fig. 3).

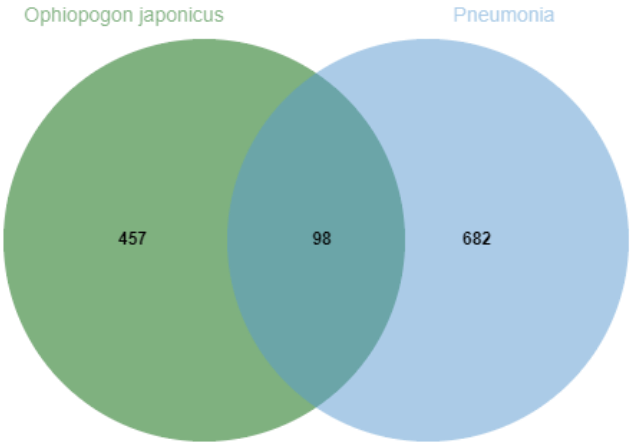

Fig. 2. Common targets

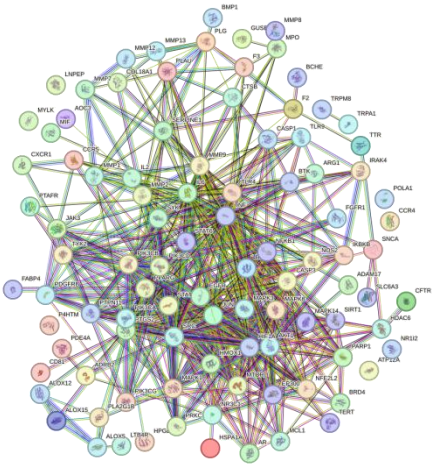

Fig. 3. Protein interaction analysis

Table 1. Top ten target points

Target Name	Degree Value
IL6	46
TNF	46
STAT3	43
AKT1	38
TLR4	33
EGFR	32
BCL2	31
NFKB1	31
SRC	31
JUN	29

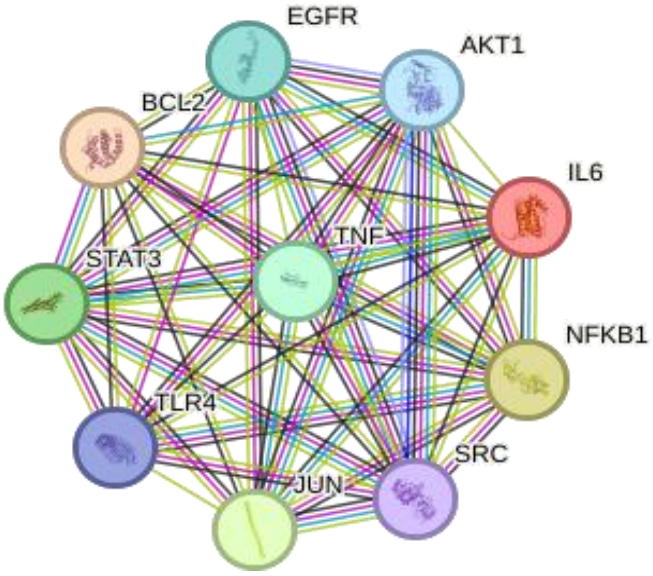

Fig. 4. Top Ten Target Protein Interactions

GO Function Analysis: GO functional analysis was conducted on the 10 targets within the core network using DAVID Bioinformatics Resources 6.7. Following the screening criteria of "Count ≥ 2" and "EASE scores ≤ 0.05", a total of 130 biological processes (BP), 14 cellular components (CC), and 9 molecular functions (MF) were identified.

The biological processes associated with the common targets encompassed positive regulation of smooth muscle cell proliferation, negative regulation of cell apoptosis, positive regulation of peptide serine phosphorylation, positive regulation of RNA polymerase II promoter transcription, positive regulation of transcription, DNA template, positive regulation of cytokine production in inflammatory response, inflammatory response, and cellular response to lipopolysaccharides.

Regarding cellular components, the identified categories included protein binding, transcriptional regulatory region sequence-specific DNA binding, enzyme binding, nitric oxide synthase regulatory activity, ubiquitin-protein ligase binding, among others.

Furthermore, molecular functions encompassed membrane rafts, transcription factor complexes, phagocytic cups, cytoplasm, mitochondria, cell surfaces, macromolecular complexes, cytoplasmic perinuclear regions, folded membranes, among others.

KEGG signaling pathway enrichment analysis: Further research on the anti-pneumonia pathway of *Ophiopogon japonicus* was conducted through KEGG pathway enrichment analysis. A total of 92 signaling pathways were identified from the 10 core targets, with a significance threshold of $P < 0.05$. Among these pathways, the top 20 significantly enriched pathways are depicted in Fig. 3.

These pathways include classic ones such as cocaine addiction, graft-versus-host disease, bladder cancer, African trypanosomiasis, Ras signaling pathway, regulation of actin cytoskeleton, cAMP signaling pathway, Rap1 signaling pathway, and cellular aging.

Based on the obtained results, all involved targets and their corresponding signaling pathways can be integrated to construct a "target signaling pathway" Sankey bubble diagram. This diagram will provide a visual representation of the relationships between the targets and the signaling pathways involved in the anti-pneumonia effects of *Ophiopogon japonicus*.

The results indicate that these potential targets exert their effects through multiple pathways, engaging in various regulatory mechanisms, and exhibiting significant potential value. Moreover, the observation of a small P value associated with the Rap1 signaling pathway, along with the presence of numerous enriched targets within it, suggests that *Ophiopogon japonicus* may exert its anti-pneumonia effect primarily through this particular signaling pathway.

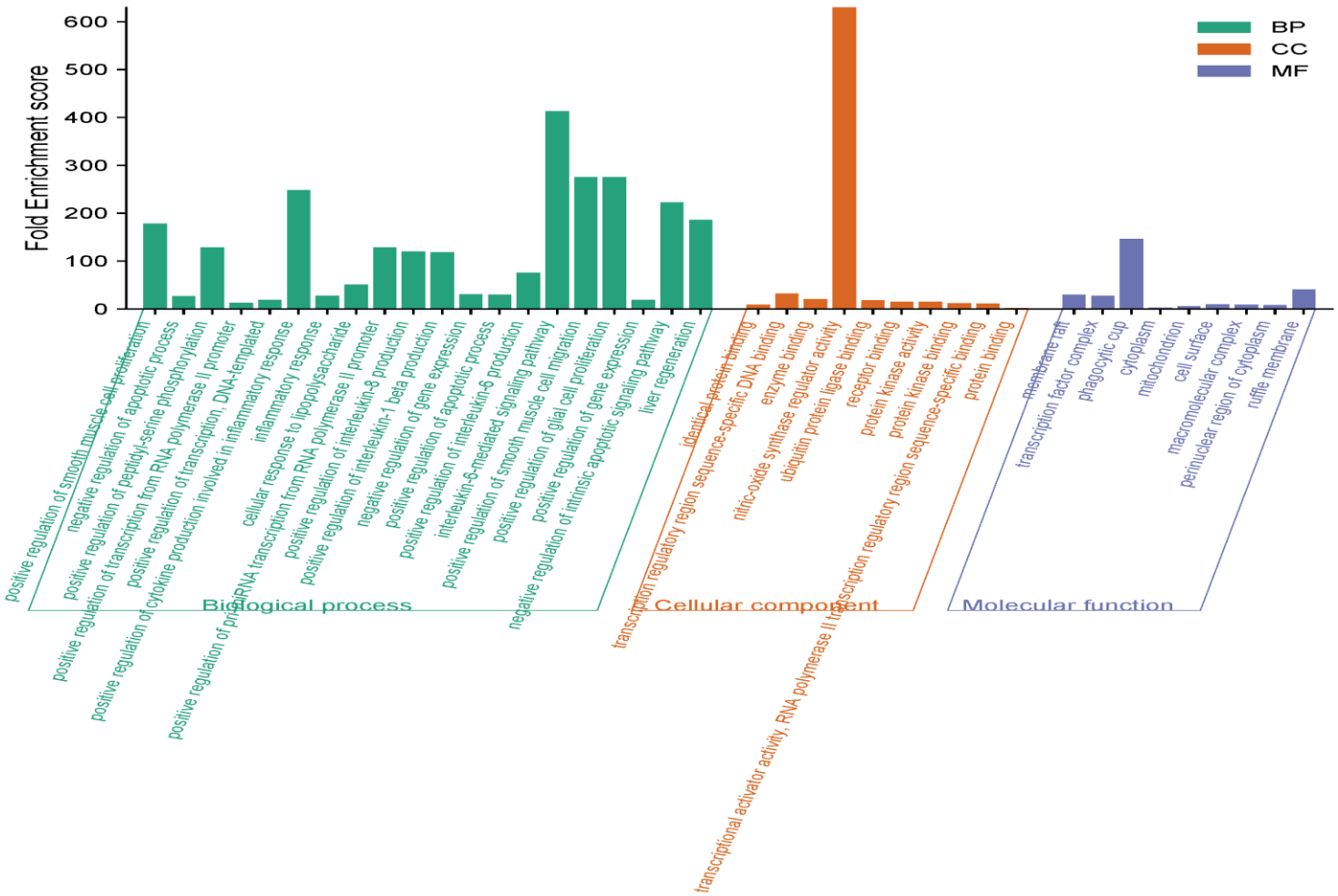

Fig. 5. GO Function Analysis

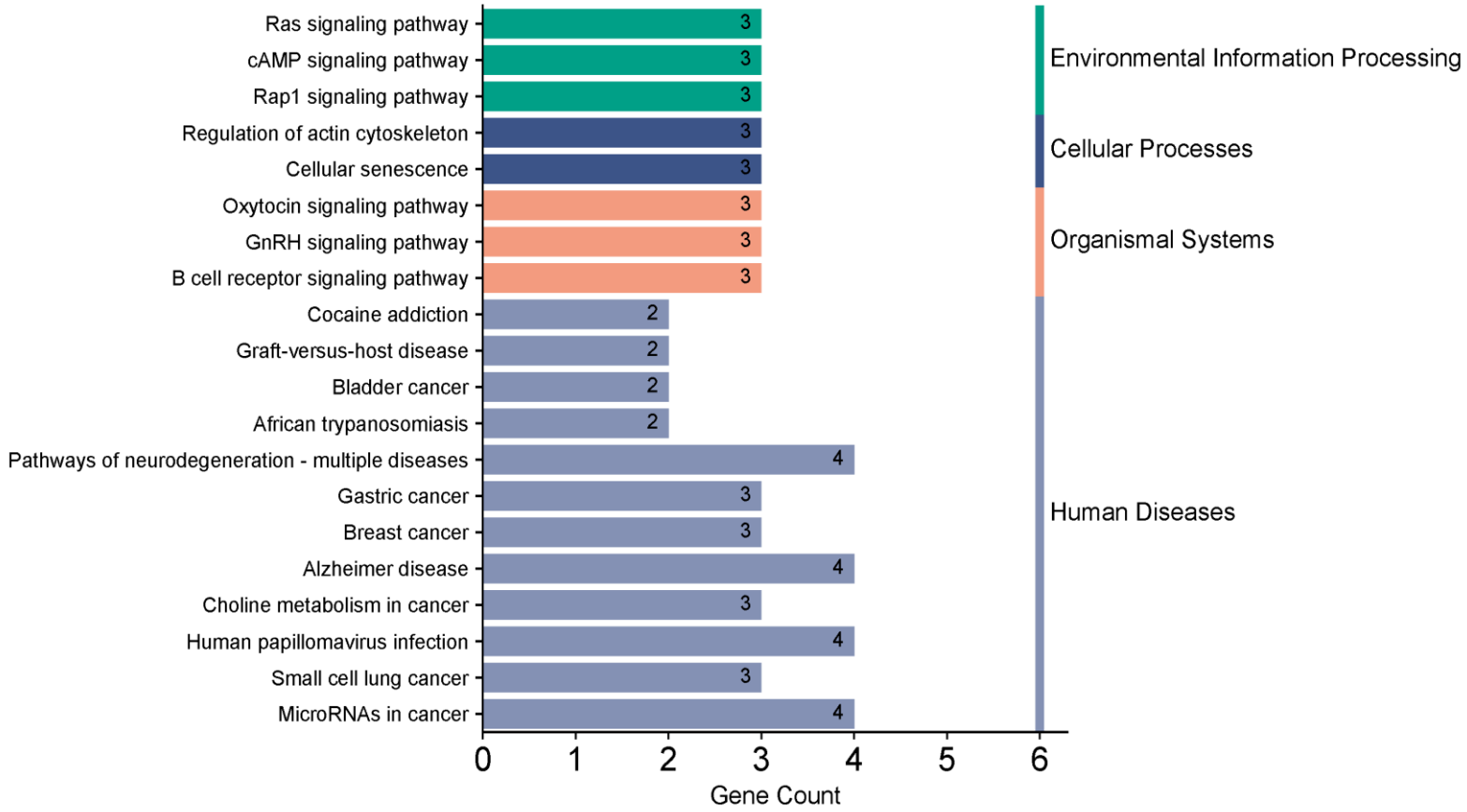

Fig. 6. Top 20 significantly enriched pathways

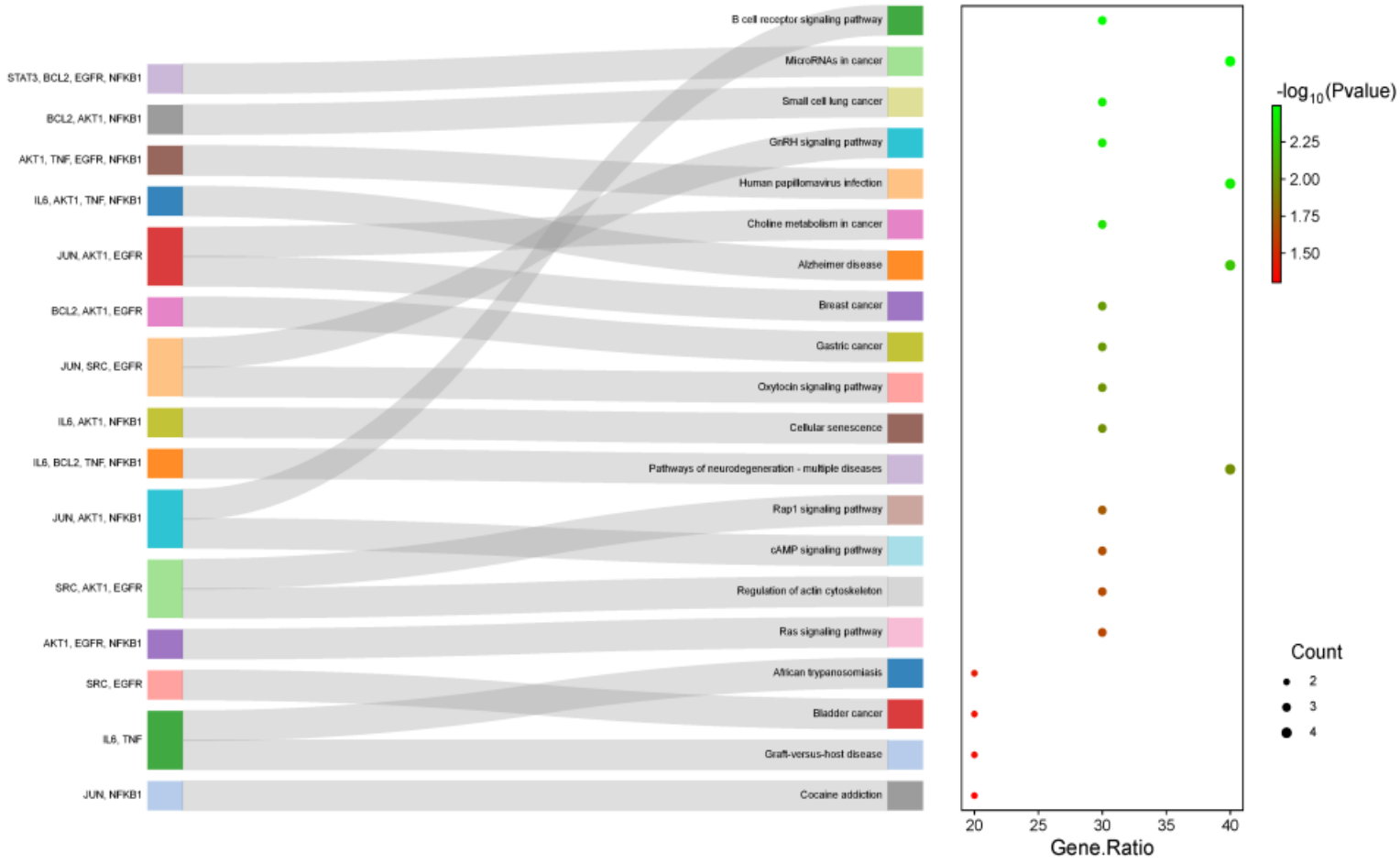

Fig. 7. "Target Signal Pathway" Sangi Bubble Diagram

4. DISCUSSION

Pneumonia represents a critical medical challenge as an acute respiratory infection affecting the lungs. The quest for more effective and safer treatments for pneumonia is imperative to maintain public health. Leveraging the innovative progress in traditional Chinese medicine, *Ophiopogon japonicus* has emerged as a promising therapeutic agent with anti-inflammatory and antioxidant properties, offering potential in diseases like pneumonia [13].

This project delves into the principal therapeutic targets and associated signaling pathways of *Ophiopogon japonicus* in pneumonia treatment, employing the advantages of network pharmacology and molecular docking technologies. The primary target of *Ophiopogon japonicus* in pneumonia treatment, along with its potential mode of action primarily through the Rap1 signaling pathway, was identified.

During drug therapy, the upregulation of TLR4 expression levels has been observed to enhance serum levels of IL-2, IL-4, and TNF-α, as well as the content of IgG and IgM, bolstering the body's immune response. Increased expression of STAT3 can mitigate pulmonary fibrosis and alleviate inflammatory response. Regulation to decrease TNF-α, IL-1β, IL-6 levels and inhibit the expression of iNOS and COX-2 proteins, significantly curtails the inflammatory response. Additionally, downregulating the expression of the IL-6 gene and proteins related to the JNK signaling pathway aids in alleviating the inflammatory response of lung cells. Regulation also reduces the apoptosis rate of pulmonary inflammatory cells, along with the expression of Cleaved caspase-3 protein and TNF-α, IL-6, IL-1α through horizontal inhibition of AKT1 and EGFR, among others. NF-κB plays a crucial role in intervening in pneumonia by regulating TNF-α expression and anti-apoptotic gene BCL2 [14-19].

Numerous studies have underscored the significance of the Rap1 signaling pathway in pneumonia development. Rap1, prevalent in animal cells, primarily regulates the MAPK signaling pathway and integrin function, influencing vital biological processes such as cell proliferation, differentiation, migration, and apoptosis. Dysregulation of Rap1 expression can lead to autoimmune diseases. Working in concert with other pathways, the Rap1 signaling pathway activates various cascades, ultimately reducing inflammatory factors' expression, delaying cell degeneration and death, and mitigating pulmonary vascular endothelial injury [20-24].

5. CONCLUSION

This study offers preliminary insights into the pathway and mechanism of using *Ophiopogon japonicus* to treat pneumonia, leveraging network pharmacology and molecular docking technologies. However, it is essential to acknowledge the limitations of network pharmacology, emphasizing the necessity for experimental verification of active ingredients, core targets, and pathways to facilitate drug development [25,26].

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

AII Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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