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Exploring the Therapeutic Effects of Codonopsis Pilosula on Heart Failure Based on Network Pharmacology

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Abstract: *This study explores the main active compounds and therapeutic targets of Codonopsis pilosula in treating heart failure through network pharmacology, aiming to elucidate its underlying mechanisms. The primary active ingredients and corresponding target genes of Codonopsis pilosula were obtained from the TCMSP network pharmacology database and the Uniprot protein database. Heart failure-related targets were identified using the Genecards database. A compound-target-disease network was constructed using Cytoscape software, and a protein-protein interaction (PPI) network was generated in the STRING database to calculate the degree values of the targets. GO (Gene Ontology) functional enrichment analysis and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis were performed on the targets using the DAVID database. A total of 21 main active compounds and 103 drug-related targets for Codonopsis pilosula were identified. From the Genecards database, 16,227 heart failure-related targets were obtained. After intersecting the targets, 103 potential therapeutic targets were identified, with key genes including AKT1, TNF, PTGS2, and TP53. GO and KEGG enrichment analysis revealed that Codonopsis pilosula primarily exerts its therapeutic effects on heart failure by regulating biological processes such as the cellular response to external stimuli, apoptosis, and miRNA transcription, while modulating pathways such as adipocytokine signaling, B cell receptor signaling, and the Apelin signaling pathway. Codonopsis pilosula shows therapeutic potential for heart failure, mainly through multi-target and multi-pathway regulation of cardiac metabolism.*

Keywords: *Codonopsis pilosula; heart failure; network pharmacology*

1. Introduction

Heart Failure (HF) is a syndrome characterized by circulatory disturbances due to cardiac systolic and diastolic dysfunctions, resulting in insufficient venous return being pumped from the heart, leading to venous congestion and inadequate arterial perfusion. Clinically, patients with heart failure often present with symptoms such as dyspnea upon exertion, fatigue, and edema. Current treatments primarily focus on symptomatic management, including the use of inotropes, diuretics, and vasodilators. Heart failure not only impairs the circulatory system but also damages respiratory, hepatic, and renal functions, potentially threatening the patient's life in severe cases. Among patients with chronic heart failure, the 5-year survival rate following the onset of clinical symptoms is typically less than 50% [1]. Therefore, the search for more effective treatments that can slow the progression of heart failure is of great clinical importance in improving long-term patient outcomes.

In recent years, with the increasing support for traditional Chinese medicine (TCM) research, the therapeutic effects of traditional herbal medicines on various diseases have been studied more comprehensively. Codonopsis pilosula, a herb included in the Chinese Pharmacopoeia, is derived from the dried roots of plants such as Codonopsis pilosula, Codonopsis tangshen, and Codonopsis pilosula var. modesta of the Campanulaceae family. It is neutral in nature and sweet in taste, and is traditionally used to quench thirst, tonify the middle, replenish qi, nourish the blood and fluids, and strengthen the spleen and lungs. Studies have shown that Codonopsis pilosula has therapeutic effects on various cardiovascular diseases. For instance, Dangshen Erling Decoction can reduce myocardial inflammatory injury by modulating the TLR4 signaling pathway, thereby inhibiting cardiac hypertrophy[2].

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Additionally, qi-tonifying herbs like Codonopsis pilosula and Astragalus can significantly enhance the rate of left ventricular pressure development and decay, ameliorating the symptoms of chronic heart failure in rats and slowing disease progression[3]. While existing research has demonstrated the efficacy of Codonopsis pilosula in treating heart failure, its molecular mechanisms remain incompletely understood.

Network pharmacology is a novel discipline based on systems biology that analyzes biological networks and selects specific signal nodes for multi-target drug molecule design. This approach emphasizes multi-pathway regulation of signaling pathways to enhance drug efficacy, reduce toxic side effects, and improve the success rate of clinical trials while reducing the cost of drug development. Therefore, this study aims to comprehensively investigate the molecular mechanisms underlying the therapeutic effects of Codonopsis pilosula on heart failure using network pharmacology, thereby providing theoretical support for its clinical application in the treatment of heart failure.

2. Materials and Methods

2.1 Identification of Active Components and Targets of Codonopsis pilosula

Codonopsis pilosula was entered into the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) to retrieve its chemical components. The active components were screened based on the criteria of oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. The corresponding target genes for the qualified active components were identified using the UniProt database (species limited to Homo sapiens). Duplicate targets were removed, resulting in a list of predicted targets for the effective active components of Codonopsis pilosula.

2.2 Identification of Heart Failure-Related Targets

"Heart failure" was used as the search term in the Genecards database (https://www.genecards.org/) to retrieve disease-related targets. The official gene names of these targets were obtained from the UniProt database (species limited to Homo sapiens). The predicted targets of Codonopsis pilosula's active components were mapped to heart failure-related targets using Venny2.1.0 to identify overlapping targets, thereby obtaining potential targets for Codonopsis pilosula in the treatment of heart failure.

2.3 Construction of the Codonopsis pilosula-Active Component-Target-Heart Failure Network

The active components of Codonopsis pilosula and the potential targets identified in Section 1.2 were imported into Cytoscape3.7.0 software to construct the "Codonopsis pilosula-active component-target-heart failure" network.

2.4 PPI Network Construction

The potential targets were imported into the STRING database (https://stringdb.org/) to construct a protein-protein interaction (PPI) network, with the species limited to Homo sapiens. The TSV file downloaded from the STRING database was then imported into Cytoscape3.7.0 software for visual analysis of the complex relationships between the potential targets. Topological parameters (degree) were used to describe the most critical nodes in the network, with higher degree values indicating greater importance. The key targets were analyzed based on their degree values.

2.5 GO Functional Enrichment and KEGG Pathway Enrichment Analysis

GO functional enrichment and KEGG pathway enrichment analyses of the targets of Codonopsis pilosula were performed using the DAVID database (http://david.ncifcrf.gov/). A threshold of $P < 0.05$ was set, and the top 10 or 20 items were plotted in statistical charts for visualization.

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3. Results

3.1 Active Components of Codonopsis pilosula

A total of 21 active components of Codonopsis pilosula that met the criteria of oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 were identified using the TCMSP platform, as shown in Table 1.

Table 1: Active Compounds of Codonopsis pilosula

Molecule Name	OB(%)	DL
3-beta-Hydroxymethyllenetanshiquinone	32.16103376	0.40894
5alpha-Stigmastan-3, 6-dione	33.1153996	0.79021
luteolin	36.16262934	0.24552
stigmast-7-enol	37.42312067	0.75133
7-(beta-Xylosyl)cephalomannine_qt	38.32745655	0.28646
Taraxerol	38.4025444	0.76677
Chrysanthemaxanthin	38.72398115	0.58352
methylicosa-11,14-dienoate	39.6670588	0.22908
SpinosideA	39.96685731	0.40288
11-Hydroxyrankinidine	40.002764	0.66203
7-Methoxy-2-methylisoflavone	42.56474148	0.19946
poriferasta-7,22E-dien-3beta-ol	42.97936552	0.75555
Spinasterol	42.97936552	0.75534
Diop	43.59332547	0.39247
ZINC03978781	43.82985158	0.75647
Stigmasterol	43.82985158	0.75665
(8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-1,2,4,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one	45.40461526	0.76174
Daturilin	50.36513472	0.76801
glycitein	50.47891366	0.23826
FrutinoneA	65.9037307	0.34184
Perlolyrine	65.94775259	0.2747

3.2 Targets of Active Components of Codonopsis pilosula

The target genes corresponding to the active components of Codonopsis pilosula were imported into the UniProt database for gene standardization. After removing duplicates, a total of 103 predicted targets for the active components of Codonopsis pilosula were identified.

3.3 Heart Failure-Related Targets

A total of 16,227 heart failure-related targets were retrieved from the Genecards database. By mapping the 103 predicted targets of Codonopsis pilosula's active components to the heart failure-related targets, a total of 103 overlapping targets were identified, as shown in Figure 1.

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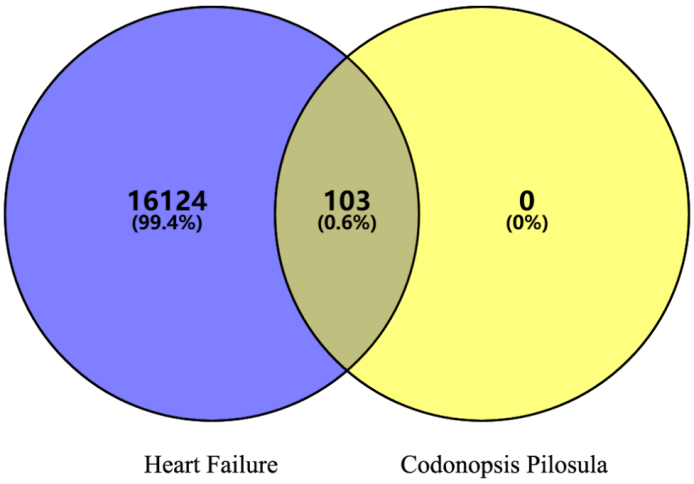

Figure 1: Screening Results of Heart Failure-Related Targets

3.4 Network of Codonopsis pilosula-Active Components-Targets-Heart Failure

Using Cytoscape 3.7.0 software, the "Codonopsis pilosula-active components-targets-heart failure" network was constructed, as shown in Figure 2. The network consists of 121 nodes and 213 edges. The top six compounds with the highest number of targets are luteolin (56 targets), 7-Methoxy-2-methyl isoflavone (41 targets), poriferasta-7,22E-dien-3beta-ol (40 targets), stigmasterol (28 targets), glycitein (22 targets), and 3-beta-Hydroxymethyllenetanshiquinone (16 targets). These compounds are likely the primary active components contributing to Codonopsis pilosula's therapeutic effects on heart failure.

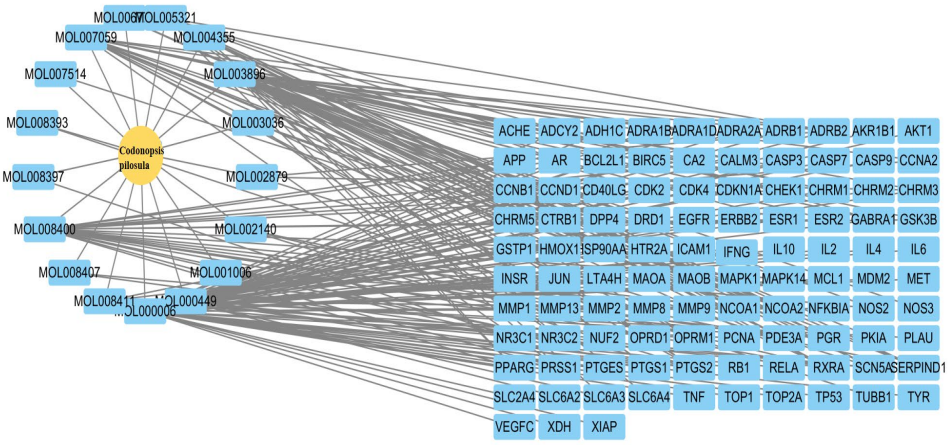

Figure 2: Network Results of Codonopsis pilosula-Active Components-Targets-Heart Failure

3.5 PPI Network

To further explore the mechanisms by which Codonopsis pilosula exerts its therapeutic effects on heart failure, a PPI network analysis was performed on the 103 predicted targets, and the network was visualized. The PPI network consists of 101 nodes and 1,441 edges, as shown in Figure 3.

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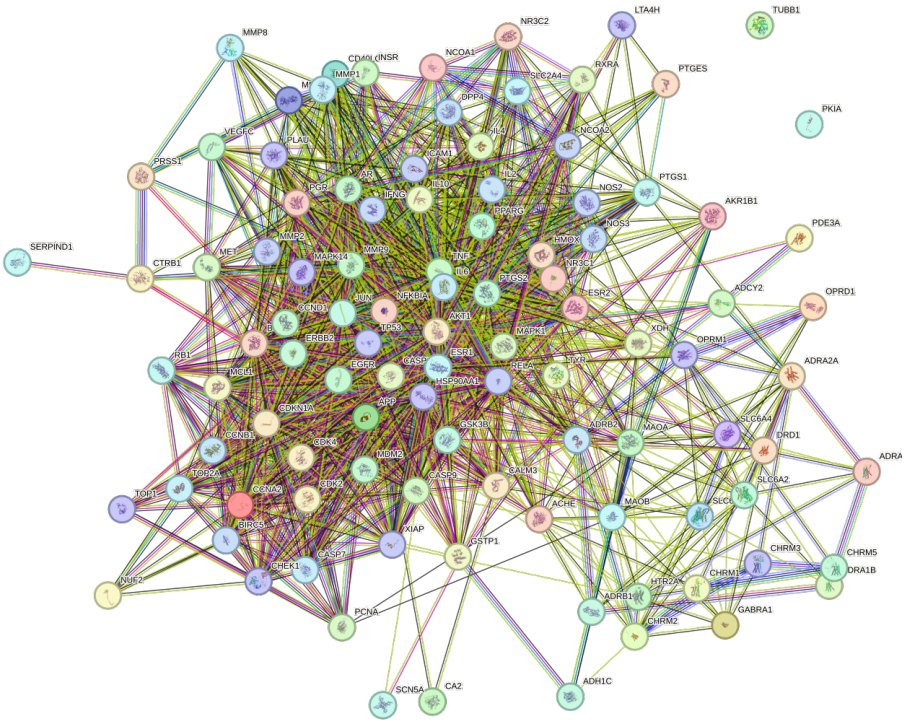

Figure 3: PPI Network

The TSV file from the STRING database was imported into Cytoscape, where the size of the nodes in the network represents the degree values of the targets. The nodes were arranged in a circular layout according to their degree values, from largest to smallest, as shown in Figure 4. The results of the study indicate that the genes AKT1, TNF, PTGS2, and TP53 rank highest in degree values, suggesting their central roles in the therapeutic mechanisms of Codonopsis pilosula for heart failure.

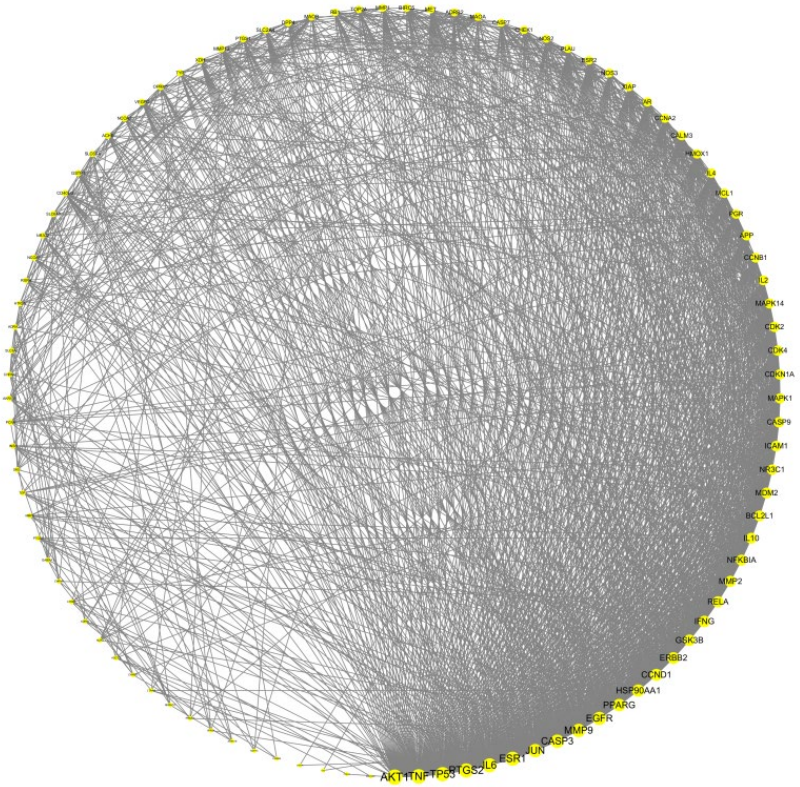

Figure 4: Degree Values of Predicted Targets

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3.6 GO Functional Enrichment Analysis and KEGG Pathway Enrichment Analysis Results

The 103 potential targets were subjected to GO functional enrichment analysis using the DAVID database. The top 10 enriched items in the categories of biological processes, cellular components, and molecular functions were selected and plotted in a bar chart, ranked by P-value in ascending order, as shown in Figure 5. Similarly, the results of the KEGG pathway enrichment analysis were ranked by P-value, and the top 20 pathways were plotted in a bar chart, also shown in Figure 5.

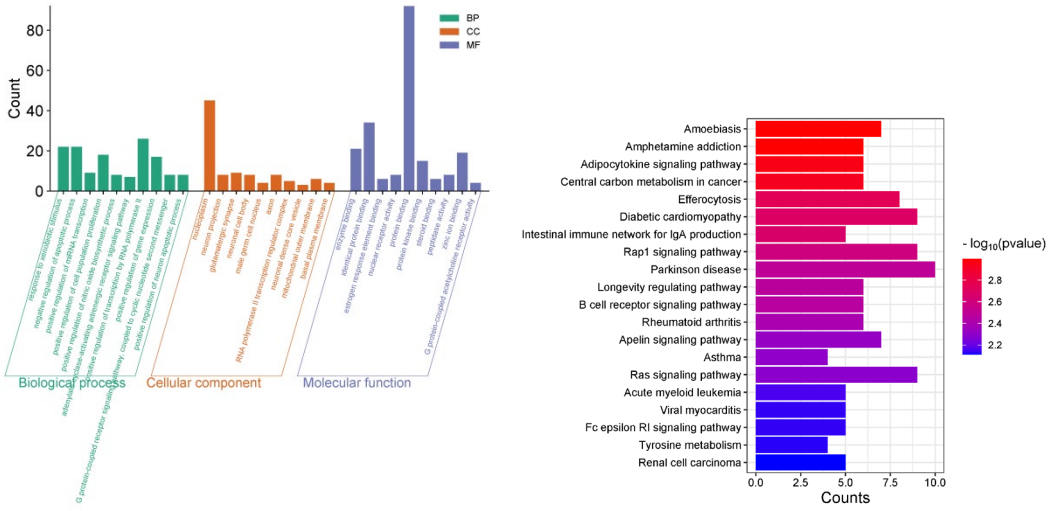

Figure 5: GO and KEGG Enrichment Analysis

4. Discussion

Heart failure is a pathological process characterized by reduced cardiac output and venous congestion due to systolic and diastolic dysfunction of the heart, which fails to meet the metabolic demands of the body. Despite symptomatic treatments, the prognosis for heart failure patients remains poor due to the lack of effective therapeutic drugs. Traditional Chinese medicine (TCM) adopts a holistic approach, emphasizing syndrome differentiation and treatment through multi-component, multi-target, and systemic regulation. Network pharmacology, which integrates systems biology, network analysis, and multi-efficacy drug research, offers a promising method for investigating these complex mechanisms. In this study, we employed network pharmacology to explore the mechanisms by which Codonopsis pilosula treats heart failure, demonstrating its potential as a therapeutic agent for clinical heart failure through multiple active components acting on various disease targets.

It is widely recognized that inflammation and cardiomyocyte apoptosis are critical pathological processes in the progression of heart failure. Codonopsis pilosula has been shown to possess multiple pharmacological properties, including immunomodulation, antioxidant, antitumor, anti-inflammatory, and gastrointestinal regulatory activities[4]. Our results indicate that luteolin, 7-Methoxy-2-methyl isoflavone,poriferasta-7,22E-dien-3beta-ol,stigmasterol,glycitein,and3-beta-Hydroxymethyllenetanshiquinone are the primary active components in Codonopsis pilosula. Previous research suggests that luteolin provides myocardial protection by mitigating mitochondrial damage and apoptosis in heart failure induced by isoproterenol[5]. Stigmasterol exhibits anti-inflammatory effects by regulating the glucocorticoid receptor[6]. These findings suggest that the polysaccharides and phenolic compounds in Codonopsis pilosula contribute to its anti-inflammatory and anti-apoptotic properties.

Our study identified key targets, including AKT1, TNF, PTGS2, and TP53, as mediators of the anti-inflammatory and anti-apoptotic effects of Codonopsis pilosula. AKT1, a serine/threonine protein kinase, plays multiple roles in the PI3K/Akt signaling pathway during heart failure, mediating inflammatory cytokine signaling and inhibiting apoptosis[7]. Tumor necrosis factor (TNF), an important cytokine in immune responses, drives the expression of inflammatory genes and indirectly promotes cell death[8]. Long non-coding RNA MALAT1 exacerbates inflammatory responses caused by myocardial ischemia-reperfusion injury by targeting miR-26b to regulate PTGS2[9]. Additionally, TP53 has been implicated in alleviating cardiac hypertrophy and inflammation in diabetic cardiomyopathy [10]. These findings highlight the role of Codonopsis pilosula's active components in regulating inflammation and apoptosis-related proteins, thereby providing cardiac protection in heart failure.

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Furthermore, our study found significant enrichment of the adipocytokine signaling pathway, autophagy signaling pathway, intestinal immune network for IgA production, Rap1 signaling pathway, B cell receptor signaling pathway, and Apelin signaling pathway in the therapeutic action of Codonopsis pilosula. The intestinal immune network for IgA production and B cell receptor signaling pathway are crucial for regulating inflammatory responses. The B cell receptor pathway recognizes foreign antigens and mediates complex biological effects, including B cell activation, proliferation, and differentiation [11]. Research by Yadava SM et al. indicated that miR-15b-5p promotes the expression of proinflammatory cytokines by inhibiting the Apelin signaling pathway [12]. Thus, Codonopsis pilosula's main active components may modulate these signaling pathways to regulate cardiac inflammation and improve heart failure outcomes.

In conclusion, this study employed network pharmacology to explore the potential mechanisms by which Codonopsis pilosula improves heart failure. The results suggest that Codonopsis pilosula exerts its therapeutic effects on heart failure through multiple active components acting on various targets and pathways. These findings provide important theoretical support for the clinical application of Codonopsis pilosula in treating heart failure.

Acknowledgments

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