Research Article

Screening of Active Components and Key Targets of Radix Codonopsis in the Treatment of Gastric Cancer

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Gastric cancer is the fifth most common cancer type in the world. The incidence and mortality of gastric cancer in China ranks second among malignant tumors in the country. At present, the main treatment method of gastric cancer is still surgical resection combined with chemotherapy. However, chemotherapy drugs will cause serious toxic and side effects on other normal tissues and cells. At the same time, chemotherapy drugs can make patients develop drug resistance and seriously affect the curative effect. By contrast, Chinese medicine has more advantages in the treatment of cancer. Dangshen (Radix Codonopsis), a traditional Chinese medicine, has been proved to be effective for the clinical treatment of gastric cancer. However, due to the complex components of Dangshen, the main active components and pharmacological mechanism for its treatment of gastric cancer are still unclear. In this study, the main active components and pharmacological mechanism of Radix Codonopsis in the treatment of gastric cancer were preliminarily explored based on network pharmacology and molecular docking. We obtained bioactive compounds and targets from Radix Codonopsis from the Chinese Medicine System Pharmacology Database (TCMSP) and constructed the active ingredient-target network of *Codonopsis pilosula*. We then obtained targets related to gastric cancer from the disease database. The common targets of Radix Codonopsis and gastric cancer were the key target of Radix Codonopsis for the treatment of gastric cancer. Then, we used Metascapedatabase to conduct functional enrichment analysis on the key targets of Radix Codonopsis for the treatment of gastric cancer to clarify the mechanism of Radix Codonopsis for the treatment of gastric cancer. We constructed a network to screen the main bioactive compounds and therapeutic targets, assessed the prognostic value of the main target genes by survival analysis, and finally assessed the binding affinity of the main target genes and main bioactive compounds of Radix Codonopsis for the treatment of gastric cancer by molecular docking. The results showed that the main active compounds of *Codonopsis pilosula* in treating gastric cancer were luteolin and cryptotanshinone, which played a role in the treatment of gastric cancer through the multitarget and multipathway mechanism.

1. Introduction

Gastric cancer is the fifth most common cancer type in the world and the third leading cause of cancer death in the world. Its incidence and mortality rate ranks second among malignant tumors in China, seriously affecting people's quality of life and social and economic development [1]. The occurrence of gastric cancer is mainly related to smoking [2], advanced age [3], heredity [4], and *Helicobacter pylori* [5]. At present, the main treatment methods of gastric cancer are still surgical resection and chemotherapy [6]. However, chemotherapy drugs will produce serious toxic and side

effects on other normal tissues and cells. At the same time, chemotherapy drugs can make patients develop drug resistance and seriously affect the curative effect [7]. By contrast, Chinese medicine has more advantages in the treatment of cancer due to its advantages of small toxicity and side effects. Studies have also shown that Chinese medicine not only has a unique advantage in the treatment of tumors but also plays an important role in promoting the recovery of tumor patients after tumor resection [8]. In China, Chinese medicine plays an important role in the comprehensive treatment of gastric cancer, among which *Codonopsis pilosula* plays an important role in the treatment

of gastric cancer. *Codonopsis pilosula*, as a traditional Chinese medicine, has many pharmacological activities and important medicinal value and can be used in combination with other traditional Chinese medicines to treat various diseases. The pharmacological activities of *Codonopsis pilosula* mainly include regulating immunity [9], cardiovascular protection [10], neuroprotection [11], regulation of gastrointestinal function [12], antibacterial [13], antiaging, and antioxidant effects [14]. At present, China's Food and Drug Administration has approved nearly 200 kinds of health food containing Radix Codonopsis. Radix Codonopsis has the efficacy of invigorating the spleen and tonifying the lung, which has a significant therapeutic effect on gastric cancer clinically. However, due to the complex components of Radix Codonopsis, the main active components and pharmacological mechanism of Radix Codonopsis in the treatment of gastric cancer are still unclear.

As the cutting edge of Chinese medicine research, network pharmacology technology integrated chemical, medical, and biological data and integrated the ideas of system biology and multidirectional pharmacology. Currently, it has been applied to many fields, such as target recognition of new drugs, discovery of lead compounds, research on action mechanism, and screening of material basis [15]. The network pharmacology combined with molecular docking provided a feasible method for elucidating the multicomponent and multitarget action mechanism of Chinese medicinal compound preparations [16]. In this study, network pharmacology and molecular docking were used to preliminarily explore the main active components and pharmacological mechanism of Radix Codonopsis in the treatment of gastric cancer, study the interaction between the chemical components of Radix Codonopsis and antigastric cancer targets, and establish the target network of chemical components, to provide the basis for elucidating the molecular mechanism of Radix Codonopsis antigastric cancer effect. This study provided a scientific basis for the treatment of gastric cancer with Radix Codonopsis, and it was of practical significance to guide its clinical medication.

2. Methods

2.1. Active Compounds and Targets of the Codonopsis pilosula.
We searched TCMSP (http://tcmspw.com/tcmsp.php) for the keyword "dangshen." Taking oral bioavailability (OB) ≥30% and drug-like property (DL) ≥0.18 as screening conditions, we screened the active components of *Codonopsis pilosula*. We collected the protein targets of the active ingredients of *Codonopsis pilosula* with the help of Herb database (http://herb.ac.cn/) and finally screened them through Excel to remove the duplicate targets, thus obtaining the final targets of the active compounds.

2.2. Targets of Codonopsis pilosula in Treating Gastric Cancer.
We used the keyword "gastric carcinoma" in GeneCards Database (https://www.genecards.org/) to search for gastric cancer-related targets. Then, using online Venny 2.1 Venn

diagram (http://www.bioinformatics.com.cn/static/others/jvenn/example.html), we matched and mapped the active component targets of Radix Codonopsis with disease-related targets. The intersection part was the key target of Radix Codonopsis for the treatment of gastric cancer, and the corresponding active component was the key component.

2.3. Functional Enrichment Analysis and Its Clustering Network Construction.
We used Metascape (https://metascape.org/gp/index.html#/main/step1) to conduct functional enrichment analysis on the target of Radix Codonopsis for the treatment of gastric cancer. The GO functional enrichment analysis mainly included biological process (BP), molecular function (MF), and cellular component (CC). The protein target was introduced into Metascape database, and GO analysis and KEGG pathway analysis are carried out on the action target of *Codonopsis pilosula*. Terms with a p value <0.01, a minimum count of 3, and an enrichment factor >1.5 (the enrichment factor is the ratio between the observed counts and the counts expected by chance) were collected and grouped into clusters based on their membership similarities; each color represents a group. p values were calculated based on the accumulative hypergeometric distribution. Kappa scores were used as the similarity metric when performing hierarchical clustering on the enriched terms, and subtrees with a similarity of >0.3 are considered a cluster. The final result showed the top 20 clusters, and the most statistically significant term within a cluster was chosen to represent the cluster.

2.4. Construction of Compound-Target Network and Protein-Protein Interaction Network.
In order to scientifically explain the therapeutic effect of Radix Codonopsis on gastric cancer by network pharmacology, we constructed a visual network to predict the relationship between compounds and targets. We constructed the compound-target network using Cytoscape 3.6.1 software. The node in the network represented the compound components and targets. If a compound might act on a potential target, they were connected by an edge. In addition, we used the Metascape (https://metascape.org/gp/index.html#/main/step1) to build an interaction network between proteins, in which each color represents a clustering module.

2.5. Construction of Network Modules and Screening of Core Targets.
The molecular complex detection (MCODE) algorithm has been applied to identify densely connected network components. Pathway and process enrichment analysis has been applied to each MCODE component independently, and the three best-scoring terms by p value have been retained as the functional description of the corresponding components. Finally, we chose a relatively important module from the seven modules to construct the target-component network, so as to find the key components and targets.

2.6. Survival Analysis of the Core Target Genes.
Kaplan–Meier plotter is a popular online site tool based on the databases of EGA, TCGA, and GEO for evaluating gene
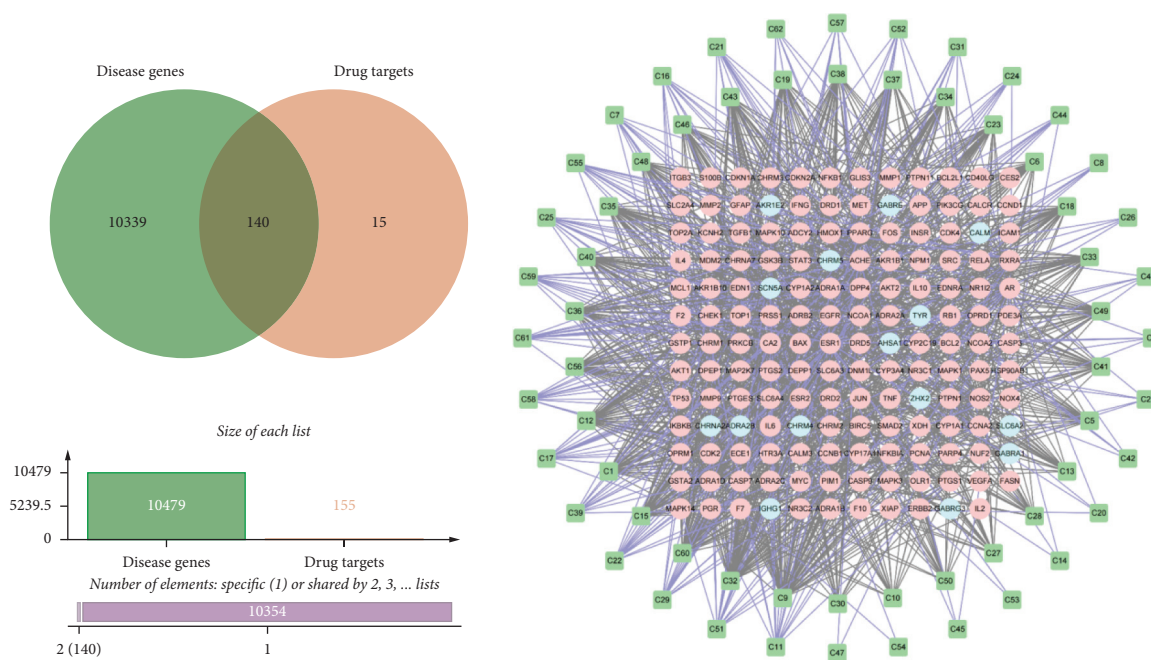
Figure 1: Screening of therapeutic targets and construction of its component network.

effects on survival [17]. The cancer species was set as "gastric carcinoma," and the key core target genes screened above were analyzed for survival by K–M plotter. Finally, we screened out genes that affected the overall survival of gastric cancer.

2.7. Molecular Docking Analysis.
We chose the MCODE2 network to construct the component-target network, found the targets and components with relatively high degree, and took them as docking objects. AutoDock Vina 1.1.2 software is used for docking, and PyMOL 2.4.1 software is used for visualization of docking results [18]. Finally, the results are further verified by docking score.

3. Results

3.1. Screening of Related Targets of Codonopsis pilosula in the Treatment of Gastric Cancer.
In TCMSP database, we searched 134 compounds in *Codonopsis pilosula*. In order to screen the potential active compounds, we evaluated the ADME properties of the compounds and screened out the compounds with OB value ≥30% and DL ≥0.18. A total of 62 potential active compounds were screened out. Through searching the action targets of these active compounds from the Herb database, 155 protein targets were collected. Then, in order to search for disease genes, we searched for the keyword "gastric cancer" in GeneCards database and found 10,479 gastric cancer-related targets. Finally, 140 common targets are obtained by mapping the disease targets with the component action targets (Figure 1), which we regard as the related targets of *Codonopsis pilosula* in treating gastric cancer.

3.2. Construction of Codonopsis pilosula Composition-Target Network.
After screening the common targets, we constructed a component-target network (Figure 1). In the network, the green squares on the periphery represent 62 active components, among which the degree value of the inner ring components is larger than that of the outer ring components, and the components in each ring are arranged clockwise according to the degree value. In order to show the target number of components more intuitively, we use two different-colored connecting lines to distinguish the action relationship between inner and outer ring components and target points. Circles in the network represent action targets, among which pink targets are 140 gastric cancer-related targets. From the network, we can see that compared with the outer ring component, the inner ring component has a higher degree of importance in the network. In addition, we can also find that most of the targets of *Codonopsis pilosula* are related to gastric cancer, suggesting that this medicine is more targeted for the treatment of gastric cancer.

3.3. Functional Enrichment Analysis of Therapeutic Targets for Gastric Cancer.
We analyzed the GO functional enrichment and KEGG pathway enrichment of the above 140 key targets by using Metascape database (http://metascape.org/) (Figures 2 and 3). GO analysis includes biological processes (BP), cellular components (CC), and molecular functions (MF), which together describe the functions of gene products. We will further cluster the obtained terms according to the similarity of members and show the first 20 clusters. Each cluster selects a term with the most statistical significance to represent the cluster.

KEGG enrichment analysis mainly involves pathways in cancer, AGE-RAGE signaling pathway in diabetic

- ■ Pathways in cancer
- ■ AGE-RAGE signaling pathway in diabetic complicatic
- ■ Endocrine resistance
- ■ Platinum drug resistance
- ■ foxo signaling pathway
- ■ Viral carcinogenesis
- ■ Jak-STAT signaling pathway
- ■ cGMP-PKG signaling pathway
- ■ Neuroactive ligand-receptor interaction
- ■ Inflammatory bowel disease (IBD)

- □ Transcriptional misregulation in cancer
- ■ Dopaminergic synapse
- ■ Adherens junction
- ■ Serotonergic synapse
- ■ AMPK signaling pathway
- ■ Chemical carcinogenesis
- ■ Alzheimer's disease
- ■ Mitophagy - animal
- ■ Ovarian steroidogenesis
- ■ Viral myocarditis

hsa05200: Pathways in cancer
hsa04933: AGE-RAGE signaling pathway in diabetic complications
hsa01522: Endocrine resistance
hsa01524: Platinum drug resistance
hsa04068: foxo signaling pathway
ko05203: Viral carcinogenesis
hsa04630: Jak-STAT signaling pathway
ko04022: cGMP-PKG signaling pathway
hsa04080: Neuroactive ligand-receptor interaction
ko05321: Inflammatory bowel disease (IBD)
hsa05202: Transcriptional misregulation in cancer
ko04728: Dopaminergic synapse
hsa04520: Adherens junction
hsa04726: Serotonergic synapse
hsa04152: AMPK signaling pathway
ko05204: Chemical carcinogenesis
hsa05010: Alzheimer's disease
ko04137: Mitophagy - animal
ko04913: Ovarian steroidogenesis
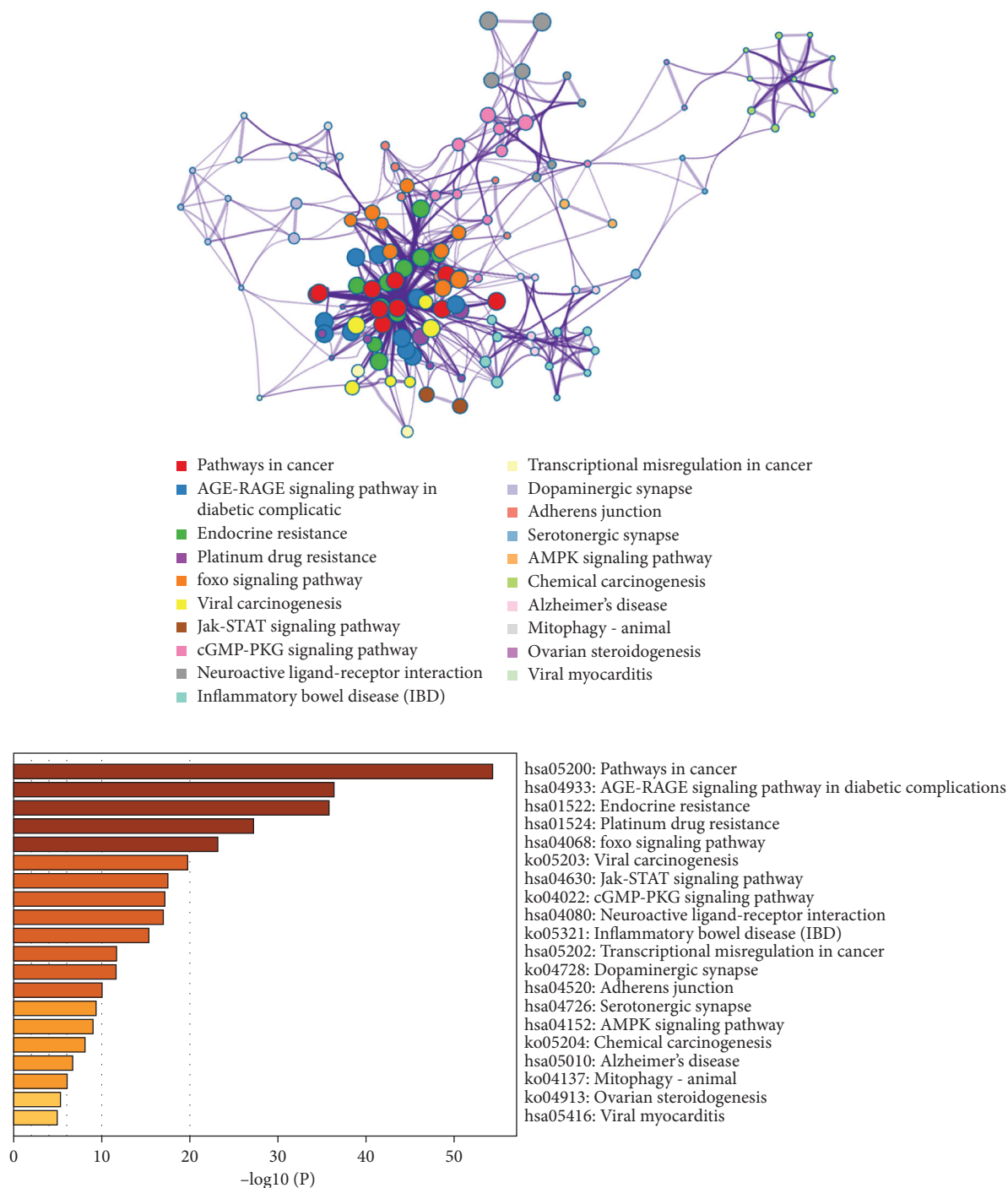hsa05416: Viral myocarditis

$-\log10 (P)$

Figure 2: The KEGG pathway enrichment analysis.

complications, endocrine resistance, platinum drug resistance, FOXO signaling pathway, viral carcinogenesis, JAK-STAT signaling pathway, cGMP-PKG signaling pathway, neuroactive ligand-receptor interaction, inflammatory bowel disease (IBD), and so on. GO analysis of *Codonopsis pilosula* in treating gastric cancer mainly involved cellular response to organic cyclic compound, response to drug, positive regulation of protein phosphorylation, response to inorganic substance, response to steroid hormone,

circulatory system process, response to radiation, response to oxygen levels, response to growth factor, aging, etc.

Enrichment analysis showed that 140 interaction targets between drugs and diseases were concentrated in cancer pathways, age-rage signaling pathways in diabetic complications, endocrine resistance, and other clusters. In addition, we also built an interaction network among terms, in which the cluster represented by "paths in cancer" is located in the center of the network. It is suggested that *Codonopsis*
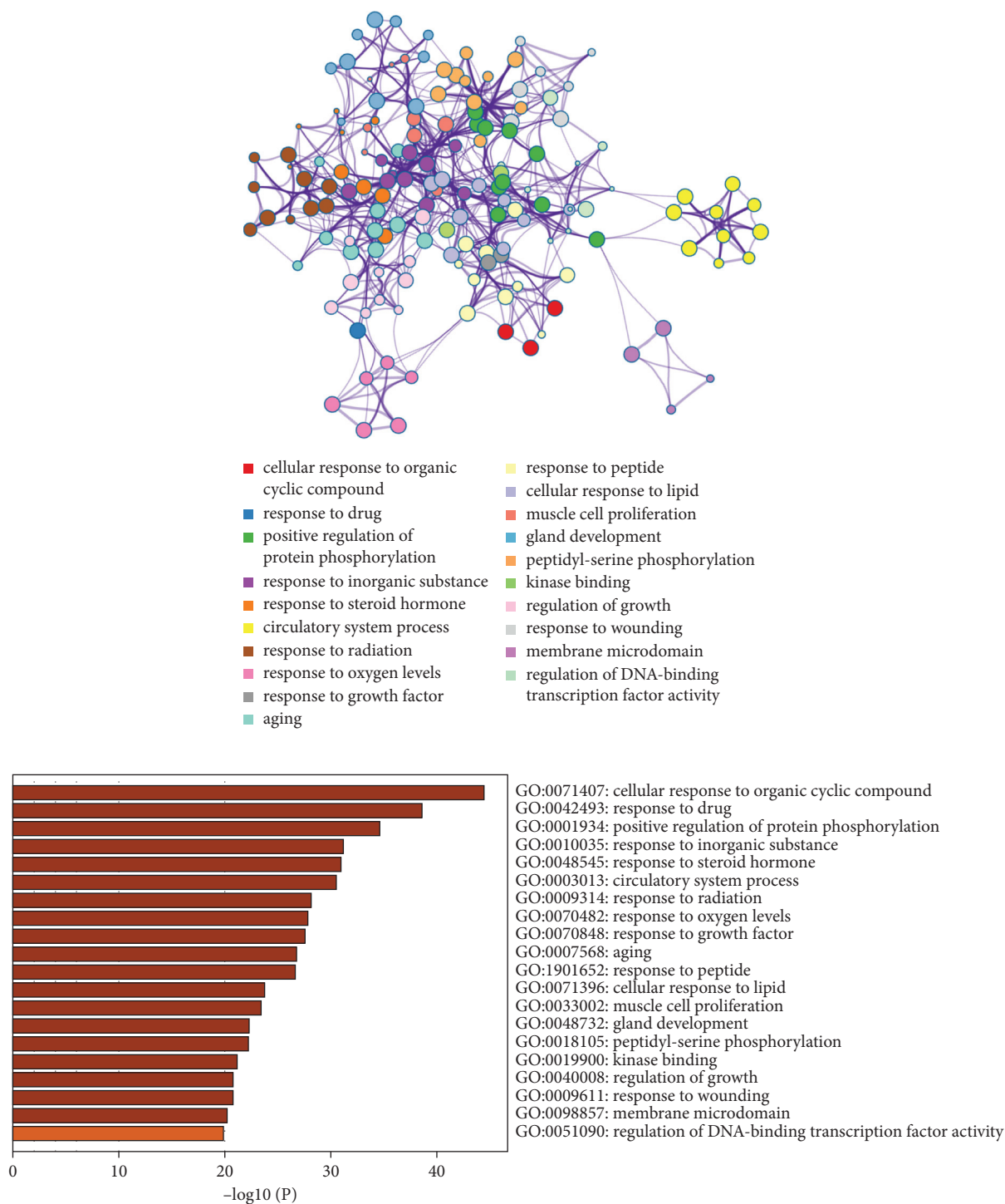
cellular response to organic cyclic compound

response to drug

positive regulation of protein phosphorylation

response to inorganic substance

response to steroid hormone

circulatory system process

response to radiation

response to oxygen levels

response to growth factor

aging

response to peptide

cellular response to lipid

muscle cell proliferation

gland development

peptidyl-serine phosphorylation

kinase binding

regulation of growth

response to wounding

membrane microdomain

regulation of DNA-binding transcription factor activity

GO:0071407: cellular response to organic cyclic compound
GO:0042493: response to drug
GO:0001934: positive regulation of protein phosphorylation
GO:0010035: response to inorganic substance
GO:0048545: response to steroid hormone
GO:0003013: circulatory system process
GO:0009314: response to radiation
GO:0070482: response to oxygen levels
GO:0070848: response to growth factor
GO:0007568: aging
GO:1901652: response to peptide
GO:0071396: cellular response to lipid
GO:0033002: muscle cell proliferation
GO:0048732: gland development
GO:0018105: peptidyl-serine phosphorylation
GO:0019900: kinase binding
GO:0040008: regulation of growth
GO:0009611: response to wounding
GO:0098857: membrane microdomain
GO:0051090: regulation of DNA-binding transcription factor activity

$-\log 10\,(P)$

FIGURE 3: The GO enrichment analysis.

pilosula may act on multiple targets through various signal pathways in this cluster and play a role in the treatment of gastric cancer. At the same time, it also provides reference value for further searching for key core targets and compounds.

3.4. Construction of Protein-Protein Interaction Network and Its Module Extraction.

In order to explore the relationship between action targets, we constructed a protein-protein interaction network and further carried out cluster analysis through modular extraction (Figure 4). We obtained seven types of modules from the target interaction network, representing each cluster with different colors. The size of the target in the network represents the degree of the target in the network, reflecting the number of targets interacting with it. The larger the target, the greater the weight of network participation and the more important it is in the network. It can be seen from the network that the targets in
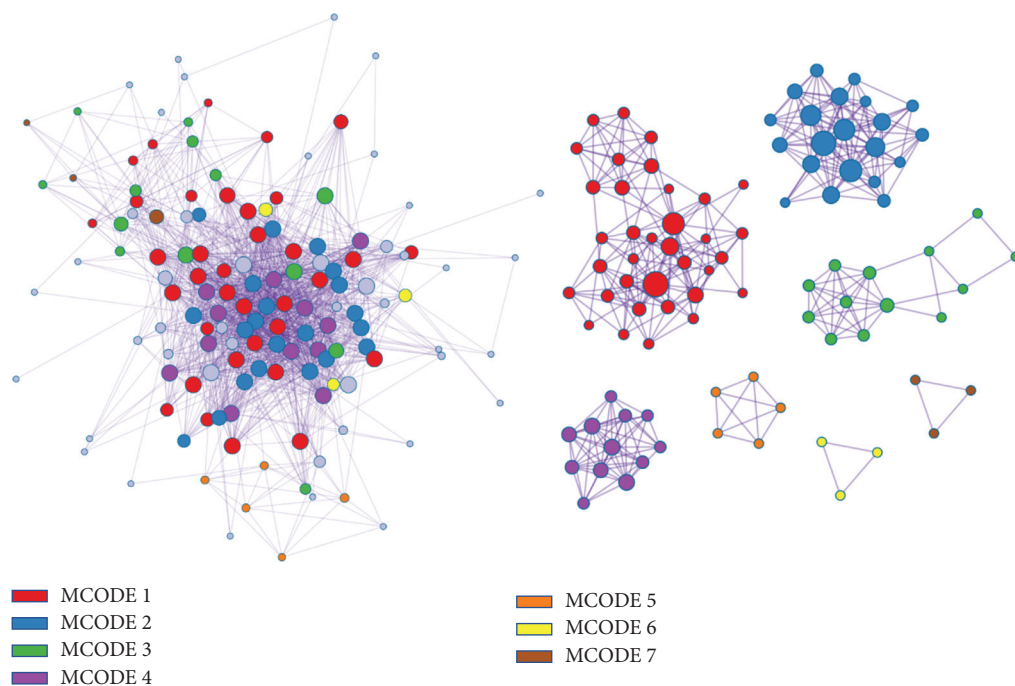
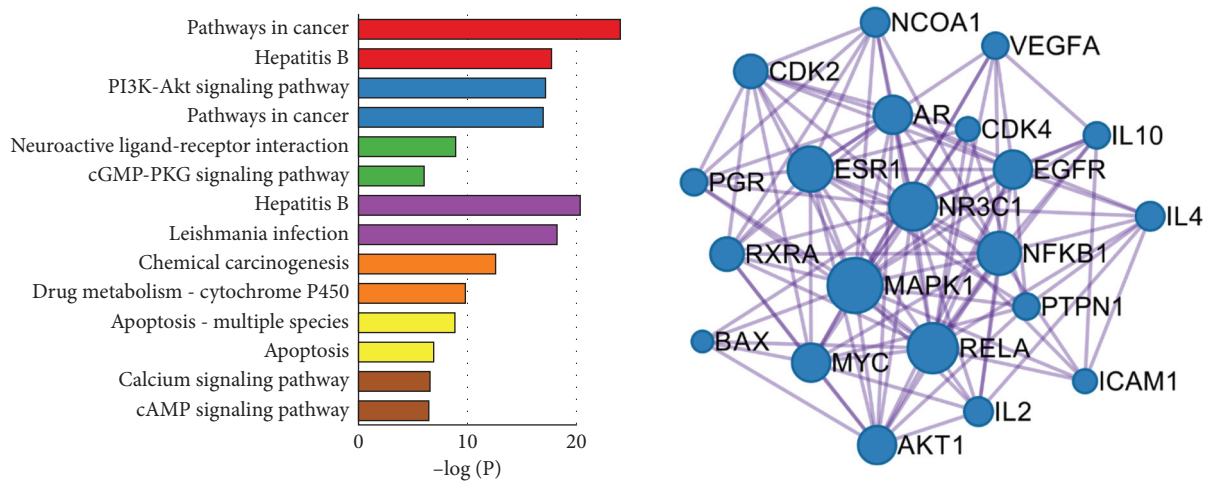Figure 4: Protein-protein interaction network.

Figure 5: Pathway enrichment analysis of MCODE2.

red MCODE1 and blue MCODE2 are relatively large, and the two modules are relatively located in the center of the PPI network, indicating that these two modules may play a leading role in the network.

In order to understand the pathways in which each module participated, we conducted enrichment analysis on seven clusters again (Figure 5) and found that the pathway in which the former two clusters participated involved the term "pathways in cancer," which occupied the largest weight in the pathway analysis network of the previous 140 related targets, indicating that compared with other modules, these two modules might play a more critical role. By comparing the other entries in the two modules (MCODE 1: Heptatitis B; MCODE2: PI3K-Akt signaling pathway), we focused on

the modules that were more related to gastric cancer and thus screened out MCODE2 as the core subnetwork.

3.5. Prognostic Analysis of Genes in Modules and Identification of Core Targets. We further used the K–M plotter to analyze the prognosis information of the core targets of MCODE 2. As shown in Figure 6, the results showed that VEGFA, IL10, AR, PGR, ESR1, EGFR, MAPK1, IL4, MYC, RELA, ICAM1, BAX, IL2, and AKT1 were correlated with the overall survival time of gastric cancer. Among these targets related to the total survival time of gastric cancer, MYC, MAPK1, and BAX have better prognosis, while other targets have poorer prognosis. In this modular network, most genes have
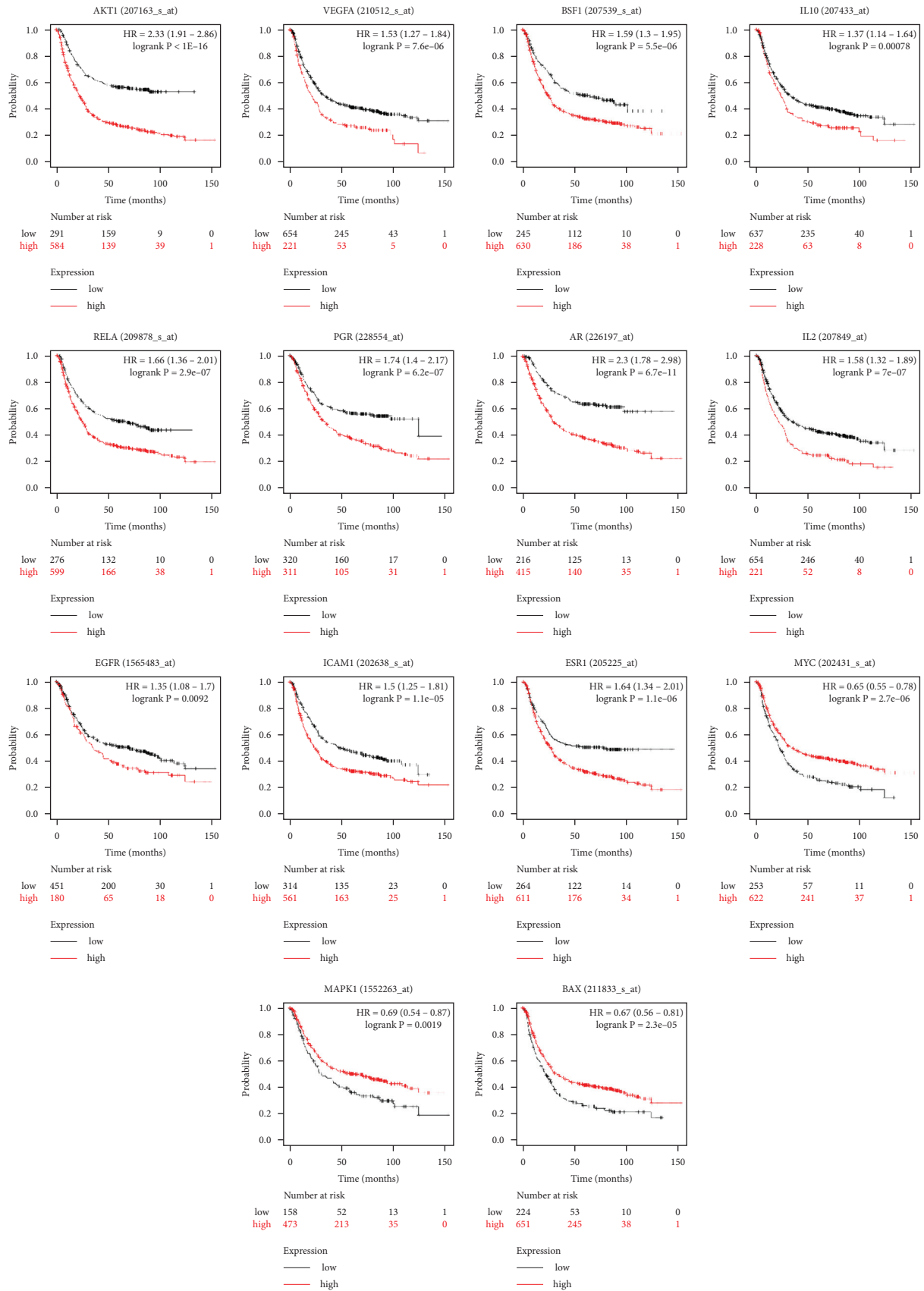
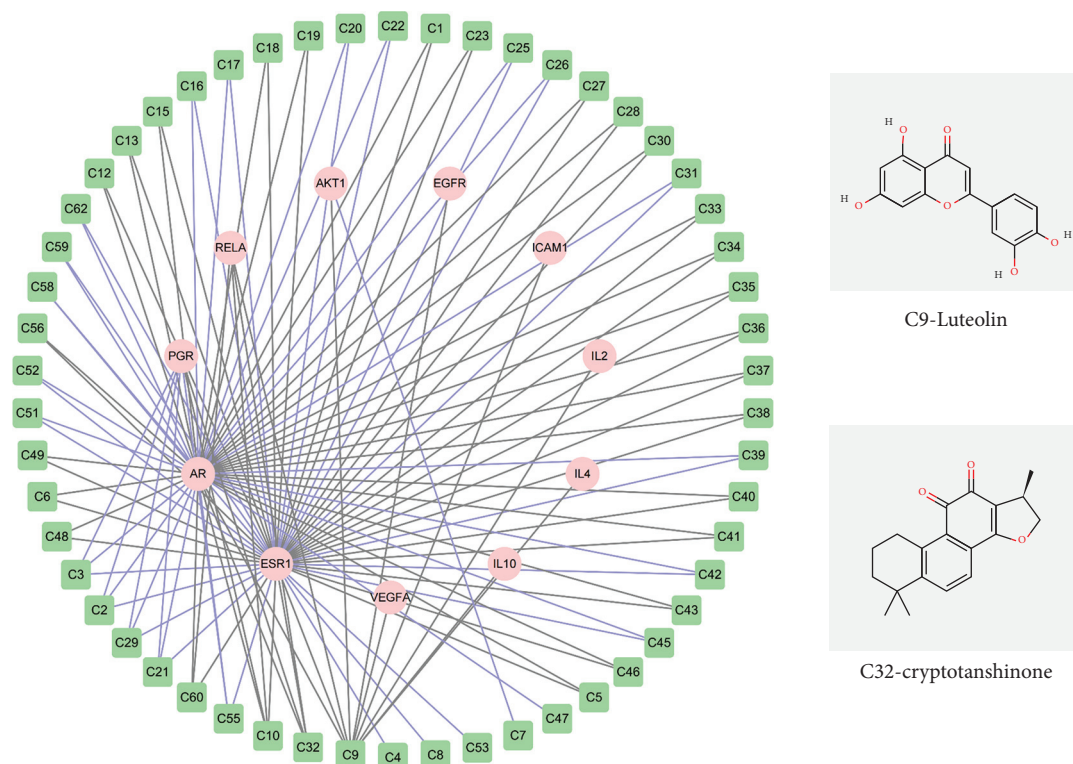Figure 6: Survival analysis of the core target genes.

FIGURE 7: Key active compounds in *Codonopsis pilosula*.

prognostic value, and the components acting on them may affect the whole treatment network through these prognostic targets. In addition, among the 14 prognosis-related targets, 11 have poor prognosis, and the components interacting with these targets may play the role of small molecule inhibitors and thus play a therapeutic role.

3.6. Construction of Core Target-Component Network and Molecular Docking Analysis.

To determine the key components, we further constructed the component network of targets with poor prognosis (Figure 7). The green squares on the periphery of the network represent the components interacting with 11 targets with poor prognosis. By sorting them clockwise according to the magnitude of degree, we can see that the top ranked components are C9, C32, C10, C55, C60, C21, etc., and among the 11 targets, AR and ESR1 have significantly more related components. Therefore, next, we further verify the matching score of the core components. We selected the first two components C9-luteolin and C32-cryptotanshinone with a higher degree to match AR and ESR1, respectively. It is generally believed that the binding energy is less than 0, and the compound and protein can bind spontaneously. The lower the binding energy is, the greater the possibility of interaction is. It is generally believed that the docking score $\leq -5.0\,\text{kJ}\,\text{mol}^{-1}$ indicates a good binding activity. As shown in Figure 8, the core components predicted in this study have strong binding ability with key targets, which confirms the reliability of the prediction results of network pharmacology.
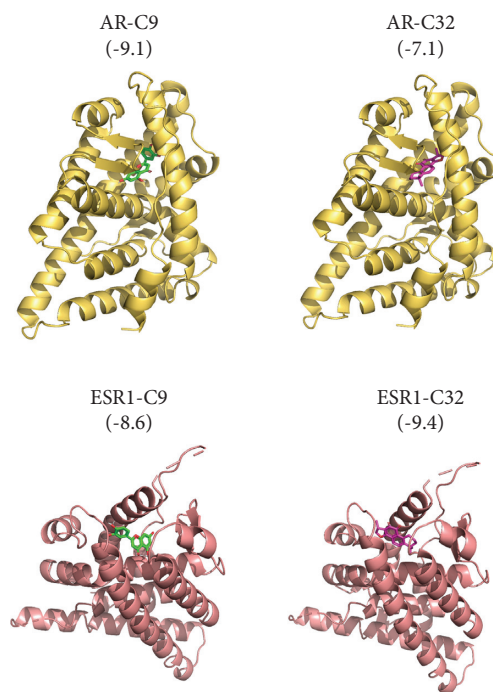

FIGURE 8: Results of molecular docking.

4. Discussion

In recent years, the systematic and complete construction of network pharmacology platform has provided us with an opportunity to explore the mechanism of Radix Codonopsis

in the treatment of gastric cancer. Network pharmacology is applicable to the multicomponent, multitarget, and multichannel characteristics of Chinese medicine to analyze the interaction network of drugs, genes, and diseases. In this study, the main components, action targets, and signaling pathways of Radix Codonopsis in the treatment of gastric cancer were explored by using the network pharmacology platform, which laid a scientific foundation for the clinical application and further research of Radix Codonopsis in the treatment of gastric cancer. We screened and obtained 62 compounds from Radix Codonopsis, and these compounds acted on 155 targets. We obtained a total of 10,479 targets related to gastric cancer. Finally, the obtained common targets of the Radix Codonopsis action target and the gastric cancer-related targets were a potential action target of Radix Codonopsis for treating gastric cancer, and the compound corresponding to the targets may be a component that plays an important role in the treatment of gastric cancer by Radix Codonopsis. We selected an important module from the protein-protein interaction network for in-depth analysis, and the potential action targets mainly included NCOA1, VEGFA, IL10, CDK4, AR, CDK2, PGR, ESR1, NR3C1, EGFR, RXRA, NFKB1, MAPK1, IL4, MYC, PTPN1, RELA, ICAM1, BAX, IL2, AKT1, HSP90AA1, CDK2, AKT1, and JUN. We analyzed the prognosis information of these targets, and the results showed that VEGFA, IL10, AR, PGR, ESR1, EGFR, MAPK1, IL4, MYC, RELA, ICAM1, BAX, IL2, and AKT1 correlated with the overall survival time of gastric cancer. Among these targets related to the total survival time of gastric cancer, MYC, MAPK1, and BAX have better prognosis, while other targets have poor prognosis.

Frycz et al. studied the relationship between mRNA expression of NCOA1, AR, ESR 2, and other genes and clinical pathological characteristics of patients with gastric cancer. The results showed that the levels of AR and NCOA 1 in gastric cancer tissues were significantly reduced. The abnormal expression of AR and NCOA 1 might be related to the occurrence and development of gastric cancer [19]. Studies have shown that tumor angiogenesis plays an important role in the growth and metastasis of gastric cancer. There are many factors that promote tumor angiogenesis, and vascular endothelial growth factor (VEGF) is one of the important factors that promote tumor angiogenesis. The results of the study by Ding S et al. showed significant decreases in serum and plasma VEGFA levels in patients with gastric cancer after surgical resection of the tumor, suggesting that VEGFA may be produced by tumor secretion [20]. IL-10 is a multidirectional cytokine that can regulate tumor suppressor gene. The methylation rate of a CGI fragment of the IL-10 gene in tumor patients was obviously lower than that in normal cells, and the methylation of IL-10 was related to gastric cancer [21]. Through screening, we have obtained that the key active components of Radix Codonopsis in the treatment of gastric cancer are C9-luteolin and C32-cryptotanshinone. Luteolin is one of the common flavonoid compounds with anticarcinogenic effects. The study by Wu et al. has revealed that luteolin has antiproliferation and chemotherapy sensitization effects on human gastric cancer cells [22]. Liu et al. found that

cryptotanshinone can induce extracellular apoptosis and cell cycle arrest through ROS-mediated MAPK and AKT signaling pathways to achieve the effect of treating gastric cancer [23]. Our results are consistent with those in the previous studies and further verified by the molecular docking findings.

Data Availability

All data supporting this work are included within the paper.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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