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Study on Anti-tumor Mechanism of Poria cocos Based on Network Pharmacology

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Abstract

Background: This paper investigates the anti-tumor mechanism of action of Poria cocos on the basis of network pharmacology. **Method:** In this paper, we screen the potential active ingredients of Poria cocos by TCMSP and obtain their corresponding targets with SwissTargetPrediction. The GeneCards and OMIM databases are used to screen the relevant pathogenic candidate targets in various tumor disease processes. Furthermore, we obtain Poria cocos-tumor common targets by taking the intersection of Poria cocos potential targets and candidate target groups. Subsequently, the protein-protein interaction network (PPI) of common target genes is mapped based on the STRING database, and the "drug-active component-target gene-disease" network is constructed with the help of Cytoscape3.7.2. Therefore, the core target genes are obtained. Finally, GO and pathway enrichment analysis of the core target genes are performed by Metascape and DAVID. **Results**: 38 common targets and 7 core genes (i.e. ESR1, MAPK3, MAPK8, MTOR, PIK3CA, JAK2, and IL6) in Poria cocos–tumors are found. They play an anti-tumor role by regulating various classical pathways such as PI3K-Akt signaling pathway, mTOR signaling pathway, Prolactin signaling pathway, ErbB signaling pathway, Choline metabolism in cancer. **Conclusion**: The research reveals the effective anti-tumor function of Poria as a multi-component, multi-target and multi-pathway herbal medicine.

Keywords: Network pharmacology, Poria cocos, Homology of medicine and food, Anti-tumor, Chinese medicine.

Competing interests

The authors declare that there are no competing interests

Acknowledgment

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Background

According to the data of the National Center for Disease, the incidence and mortality of malignant tumors in recent years have gradually increased and have become a major global health problem and an important influencing factor of the worldwide disease burden [1]. Given that early prevention and regular medical examination and diagnosis are important ways to reduce the high morbidity and mortality of malignant tumors, more and more attention has been paid to the prevention of tumors.

The existing treatments for tumors are surgical treatment, radiation therapy, chemotherapy, and gene therapy. Among them, surgical treatment has more significant treatment effect only for patients with early detection of tumor. At the same time, it has great limitations to the tumor growth site, followed by surgical complications such as decreased immune function and wound infection. The radiation therapy (radiotherapy) may induce cancer while treating cancer. In addition, some toxic and side effects in the late radiation stage will affect a series of physiological functions and the quality of life of patients, and even lead to death (such as pulmonary fibrosis) in serious cases. At the same time, due to the non-targeting and weak specificity of its drugs, chemotherapy also has some different degrees of damage to normal tissue cells, especially to the heart, liver and other organs as well as the nervous system. For gene therapy, there are still many theoretical and technical problems, and the harm to the human body has not been figured out. However, TCM treatment can be continuously used in the early, middle, and late stages of tumors. In the treatment process, TCM therapy according to the physical condition of patients at different stages and syndrome differentiation can play a escort role for patients. Moreover, in the advanced stage, Chinese medicine can be used to regulate the spleen and stomach, strengthen the stomach energy, and relieve the patient's pain in order to achieve the treatment effect.

Chinese medicine is becoming increasingly popular in the daily prevention and clinical treatment of malignant tumors. Specifically, herbal medicines of homology of medicine and food have clear efficacy, low side effects and high patient compliance. Moreover, modern pharmacological experiments have shown that the important components such as Poria cocos alcohol, Poria cocos polysaccharide [2] and triterpene including Poria cocos acid [3] extracted from Poria cocos have excellent anti-tumor effect. They function mainly through enhancing immune system activity and inducing apoptosis of tumor cells. Related studies have shown that carboxymethyl Poria polysaccharide can significantly improve the immune response, reduce the toxicity of chemotherapeutic drugs, and improve the tumor microenvironment [4]. Cheng Shuiming et al. suggested that Poria polysaccharides have strong antioxidant capacity and cell activation function, which can reduce the toxicity of intracellular free radicals and thus prevent tumorigenesis [5]. Kang et al [6] found that woolly sterols can achieve selective inhibition of proto-oncogene cells through the blockage of caspase-3 pathway. Bhattarai et al [7] found that new woolly sterols can induce apoptosis in human oral cells, thus acting as an anticancer agent. In conclusion, the antitumor effect of Poria cocos has been clearly established [8,9], but the antitumor research on Poria cocos at home and abroad is still in the initial stage. Whether in vitro cellular experiments or animal experiments, the research on the active ingredients of Poria and their antitumor mechanism mainly focuses on individual monomers, thus neglecting whether some other chemical components in Poria have synergistic antitumor effects and molecular mechanism of action. Therefore, it is still necessary to further study its anti-tumor mechanism through new biotechnology and methods.

Therefore, in this study, the network pharmacology of Poria monocotyledon was investigated by ADME component screening, target prediction, biological function enrichment analysis, network topology parameter analysis and other biotechnologies to further confirm the specific mechanism of its anti-tumor effect and provide a definite basis for the anti-tumor effect of TCM. The research conception is shown as follows.

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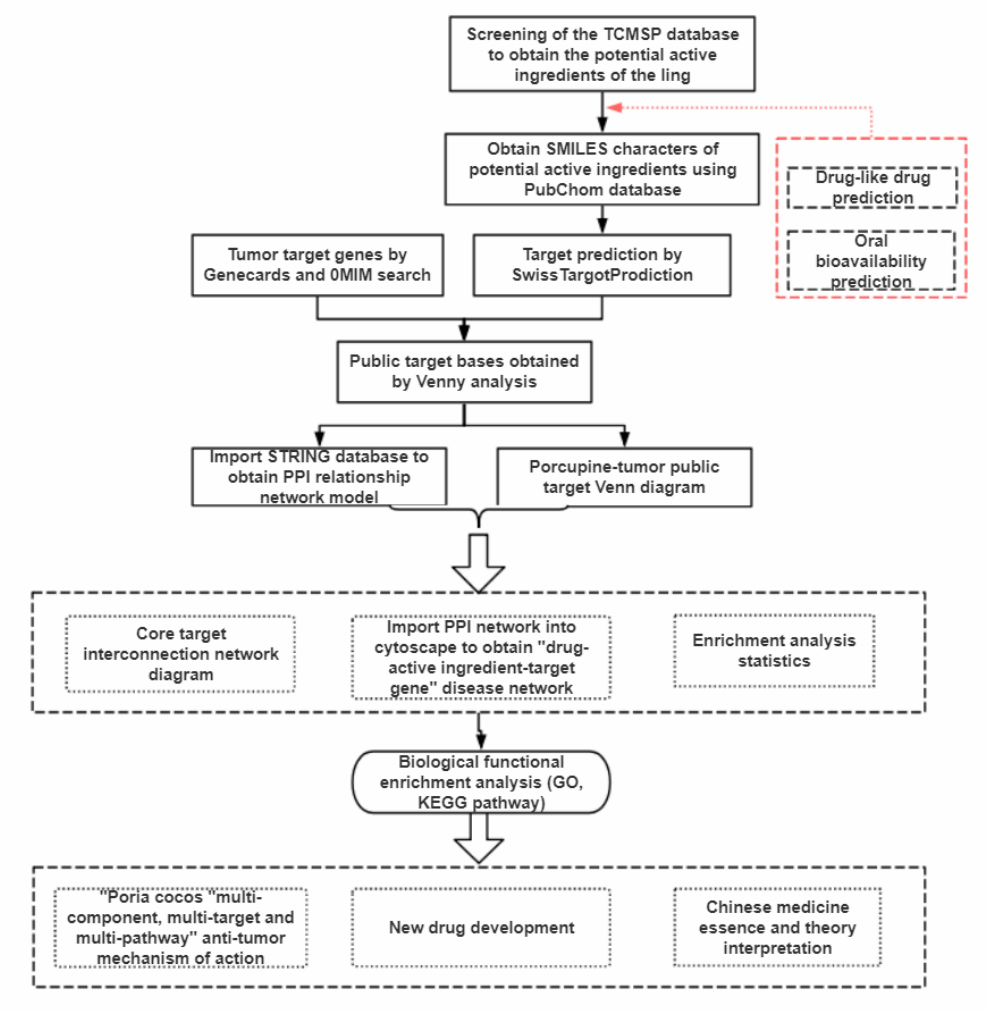

Figure 1. Technology roadmap of this study

Materials and Methods

Screening of Active Ingredients and Target Genes of Poria cocos in Chinese Medicine

The TCMSP is a comprehensive database and visualization platform based on the pharmacological framework of TCM systems, which contains chemical substances, targets and drug target networks of various TCMs and includes the pharmacokinetic properties of several natural compounds. Potential active ingredients are identified by searching for "Poria cocos" or "Poria cocos (Schw.) Wolfd" and setting oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 as screening conditions. Meanwhile, some reported or clinically validated compounds are also retained as candidate active ingredients. Then, SMILES string of potential active components of Poria cocos is obtained by using PubChem database. Finally, component - target prediction is performed by using Swiss Target Prediction to obtain the corresponding target protein.

Identification of Tumor Pathogenicity Candidate Genes

GeneCards (https ://www.genecards.Org/) is a database of the human genome, transcribed proteome. OMIM (https ://OMIM. Org/) is a recent database on Mendelian genetic disorders in humans. It focuses on the relationship between humans and phenotypic traits. By using the databases of GeneCards and OMIM, tumor candidate target genes are searched by setting the keywords "Tumor" or "Cancer". 22335 targets are retrieved from GeneCards, and tumor targets with

Score≥20 are retained. The candidate tumor targets are obtained by combining tumor genes duplicated from OMIM database.

Construction of "Drug-Active Ingredient-Target Gene-Disease" Network

Cytoscape3.7.2 is a professional information data analysis and editing software whose main function is to help users analyze various data and display the analysis results for users through various forms of network graphics. It permits users to better understand the association and trend between data. Venny analysis is used to intersect the potential active component targets of Poria cocos with tumor targets, and Venn diagrams are drawn. Public targets are considered as potential targets for the anti-tumor of Poria cocos, and the "drug-active component-target gene-disease" network of Poria cocos is established by Cytoscape3.7.2 software. Among them, node is a drug and its potential active components, target genes, and diseases, and the interrelationship between components and target genes is expressed by edge and ranked according to the size of network degree. The degree shows that the more the active ingredient is involved in biological function, the stronger the effect.

Constructing Protein-protein Interaction (PPI) Networks

The STRING database (https string-db.org/) is an online search database of known protein interactions. We upload the obtained drug-disease public target genes to the STRING database, set the search condition "Homo sapiens", and obtain PPI network after screening with confidence level ≥0.4. Then the PPI network is imported into Cytoscape 3.7.2 for optimization while its NetworkAnalyzer tool is used for network topology parameter analysis. The nodes with high degree values of each node are screened to determine the genes of the core target, and the core target gene network map is constructed.

Biological Functional Enrichment Analysis

The obtained core target genes are entered into the DAVID database, by GO analysis and KEGG pathway enrichment analysis. We set "OFFICE GENE SYMBOL" and "genelist", select "Homosapiens" for species, use "GO TERM BP DIRECT" under "geneontology" for GO enrichment analysis, and then click "KEGG PATHWAY" under "pathways" for KEGG enrichment pathway analysis. Through GO analysis, the common target genes of drugs and diseases are explored which biological processes are specifically involved and which biological signaling pathways are mediated. According to the number of genes enriched on different pathways, the main functions of genes are understood to explore the anti-tumor mechanism of Poria cocos components.

Results

Screening of Active Ingredients and Target Genes of Poria cocos

The active components of Poria cocos are searched and screened in the TCMSP database, and the results show that there are 34 chemical components in Poria cocos. The compounds that meet the OB ⩾ 30% and DL ⩾ 0.18 and those that have been reported or clinically verified to be effective are identified as the potential active ingredients of Poria cocos. A total of 18 potential active ingredients are obtained, with the results and their parameter values shown in Table 1. Then 259 targets of the above potential active ingredients are obtained by Swiss Target Prediction.

Table 1. Potential active ingredients of Poria cocos and their ADME parameter values

Mol ID	Molecule Name	OB (%)	DL
MOL000273	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid	30.93	0.81

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MOL000275	trametenolic acid	38.71	0.8
MOL000276	7,9(11)-dehydropachymic acid	35.11	0.81
MOL000279	Cerevisterol	37.96	0.77
MOL000280	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	31.07	0.82
MOL000282	ergosta-7,22E-dien-3beta-ol	43.51	0.72
MOL000283	Ergosterol peroxide	40.36	0.81
MOL000285	(2R)-2-[(5R,10S,13R,14R,16R,17R)-16-hydroxy-3-keto-4,4,10,13,14-pentamethyl-1,2,5,6,12,15,16,17-octahydrocyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	38.26	0.82
MOL000287	3beta-Hydroxy-24-methylene-8-lanostene-21-oic acid	38.7	0.81
MOL000288	Pachyman	0.45	0.68
MOL000289	pachymic acid	33.63	0.81
MOL000290	Poricoic acid A	30.61	0.76
MOL000291	Poricoic acid B	30.52	0.75
MOL000292	poricoic acid C	38.15	0.75
MOL000296	hederagenin	36.91	0.75
MOL000297	Tumulosic acid	29.88	0.81
MOL000298	ergosterol	14.29	0.72
MOL000300	dehydroeburicoic acid	44.17	0.83

Identification of Candidate Genes for Tumor Pathogenesis

By searching GeneCards and OMIM database, tumor disease targets can be obtained. A total of 22,335 tumor targets are obtained in GeneCards and 469 tumor targets with Score value $\geqslant$ 20 are selected. With 342 targets obtained from OMIM database combined, a total of 749 tumor targets are obtained after screening to remove duplication.

Construction and Analysis of "Drug-Active Ingredient-Target Gene-Disease" Network

Venny analysis is used to intersect the potential active ingredient targets of Poria cocos with the tumor pathogenic targets to obtain 38 common targets, and Venn diagram is drawn, as shown in Figure 2.

The public targets are considered as the potential targets of Poria cocos anti-tumor, and the "drug-active ingredient-target-disease" network of Poria cocos is established by Cytoscape 3.7.2 software, as shown in Figure 3.

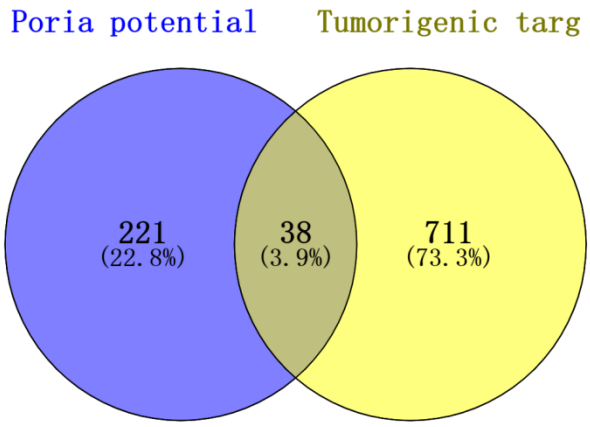

Figure 2. Venn diagram of Porphyra-tumor common target

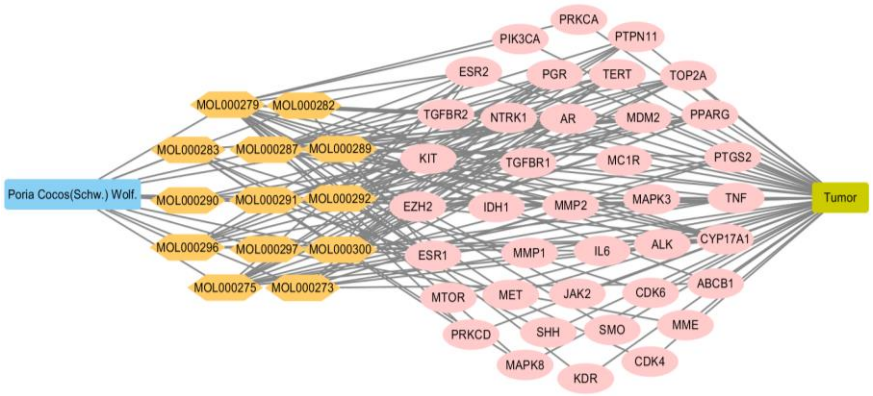

Figure 3. Drug-active ingredient-target gene-disease network diagram

The network consists of 53 nodes and 166 pairs of relationship pairs, with 13 nodes as potential active components and 38 as predicted target genes. Among them, yellow hexagonal nodes indicate the potential active components of Poria cocos, pink oval nodes indicate tumor pathogenic target proteins, and edges represent the interaction relationship between the potential active components of Poria cocos and tumor pathogenic target proteins. The analysis by NetworkAalyzer tool shows that the average value of all node degrees in the network is 6.264, which reflects the characteristics of multi-target of medicinal and food homologous components of Traditional Chinese medicine, and also indicates that these multi-target active molecules can achieve the effect of synergistic therapy at the overall level. After further analysis and statistics, the potential active ingredients with high value can be obtained as cerevisterol, trametenolic acid and 3beta-Hydroxy-24-methylene-8-lanostene-21-oic acid, etc., as shown in Table 2.

Table 2. Core potential active ingredients

No.	chemical composition	degree
1	Cerevisterol	22
2	trametenolic acid	13
3	3beta-Hydroxy-24-methylene-8-lanostene-21-oic acid	13
4	poricoic acid C	13
5	dehydroburicoic acid	12

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Construction and Analysis of PPI Network

The 38 potential target genes obtained by Venny analysis are uploaded to STRING database, and high confidence = 0.7 is set as the minimum interaction score to obtain the protein interaction relationship [10]. The PPI network is constructed as shown in Figure 4.

The PPI network is then imported into Cytoscape 3.7.2 to obtain a network with 38 nodes and 214 edges, and the network topology parameters are analyzed for each node by using Network Analyzer tool, and the bars are arranged according to the degree values, as shown in Figure 5.

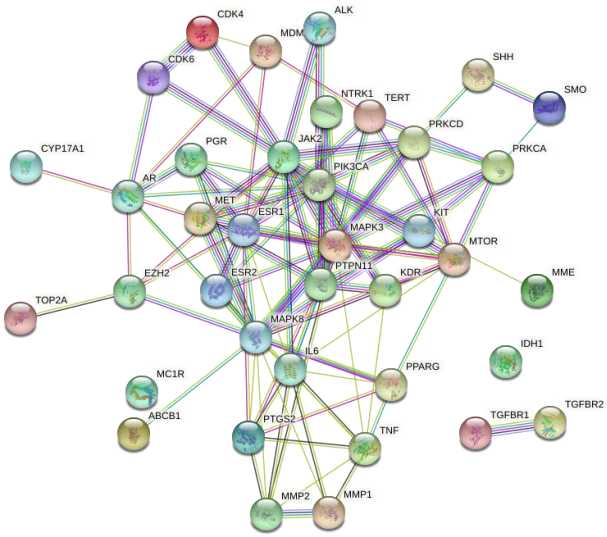

Figure 4. Poria-Tumor Public Target PPI Network

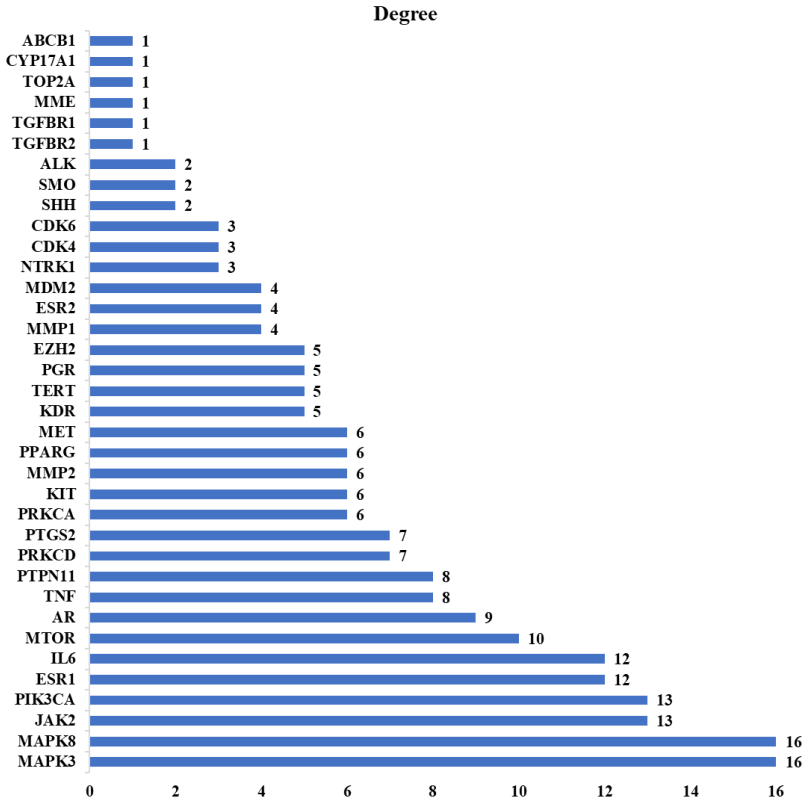

Figure 5. Ranking table of potential target degree values

According to the analysis, the median degree value of all nodes is 5; the median betweenness Centrality value is 10.7. The core target genes ESR1, MAPK3, MAPK8, MTOR, PIK3CA, JAK2 and IL6 are obtained by taking the degree value greater than 2 times the median of all nodes 6.264 and the Betweenness Centrality index greater than the median of all nodes 46.584 as the screening criteria, and the core target interactions network is constructed as shown in Figure 6.

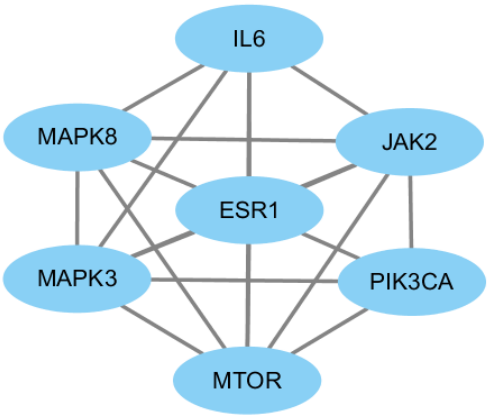

Figure 6. Core target interaction network diagram

Enrichment Analysis of Biological Functions

A total of 290 enrichment results are obtained from the above Poria cocos – tumor common target genes after GO enrichment analysis, of which 222 are involved in biological processes (BP). The top 10 items of -LGP mainly include positive regulation of nitric oxide biosynthesis, protein phosphorylation, translation, positive regulation of peptide tyrosine phosphorylation, sequence-specific DNA binding, platelet activation, positive regulation of transcription factor activity, etc. In addition, a total of 23 cellular components (CC) involved in these diseased genes mainly contain phosphatidylinositol 3-kinase complexes, nucleoplasm, cell surface, and cytosol region; these gene products have 45 possible molecular functions (MF), that is, kinase activity, serine/threonine kinase activity, ATP binding, protein binding, insulin receptor substrate binding, and MAP kinase activity. A bar graph is established by taking −lgP as the ordinate, as shown in Figure 7.

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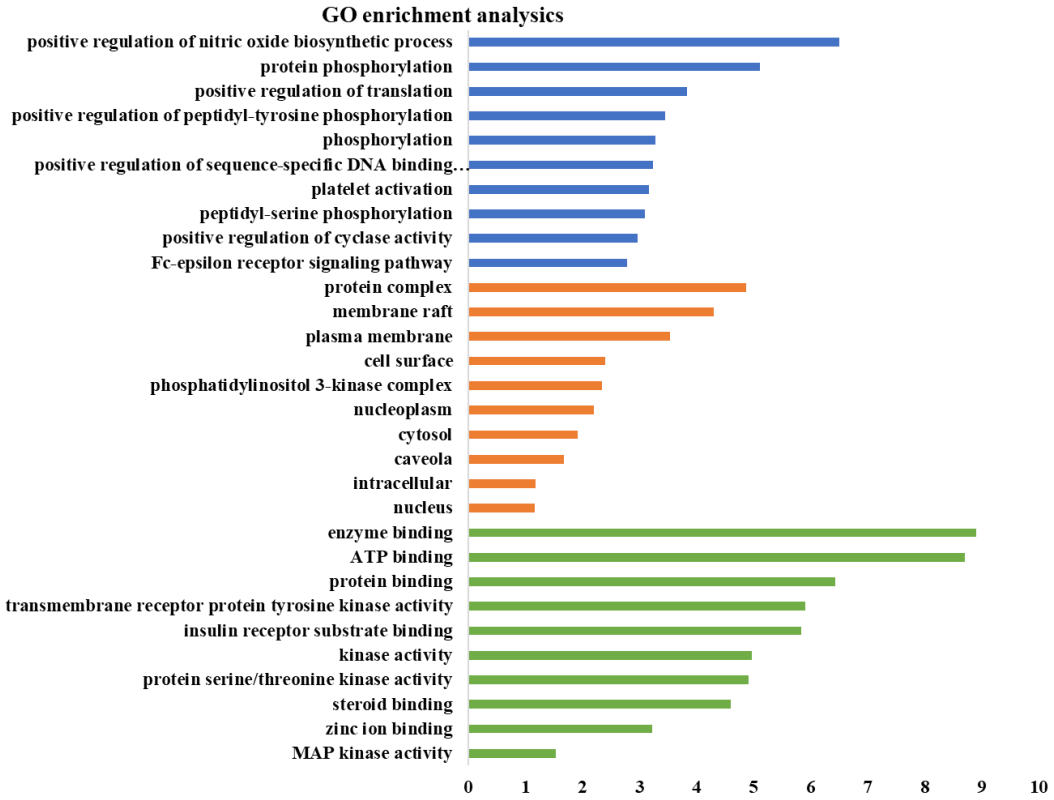

Figure 7. Statistical graph of GO enrichment analysis

Finally, 64 signaling pathways are obtained by KEGG analysis of seven core target genes in DAVID. In addition, 20 pathways closely related to tumor diseases are obtained according to P-value and Count value analysis, of which the pathways involving tumors included ErbB signaling pathway, HIF-1 signaling pathway, Toll-like receptor signaling pathway, TNF signaling pathway and other classical pathways. The enriched pathway results are listed in Table 3.

Table 3. Public target gene enrichment pathways

ID	Description	Count	P-Value
hsa04917	Prolactin signaling pathway	5	0.000000154
hsa04012	ErbB signaling pathway	4	0.000038
hsa04066	HIF-1 signaling pathway	4	0.0000511
hsa05231	Choline metabolism in cancer	4	0.0000595
hsa04620	Toll-like receptor signaling pathway	4	0.0000688
hsa04668	TNF signaling pathway	4	0.0000707
hsa04931	Insulin resistance	4	0.0000727
hsa04151	PI3K-Akt signaling pathway	5	0.0000861
hsa04919	Thyroid hormone signaling pathway	4	0.0000878
hsa04068	FoxO signaling pathway	4	0.000138
hsa05200	Pathways in cancer	5	0.000144
hsa04910	Insulin signaling pathway	4	0.000151

hsa05205	Proteoglycans in cancer	4	0.000454
hsa04150	mTOR signaling pathway	3	0.001025554
hsa05210	Colorectal cancer	3	0.001171389
hsa05230	Central carbon metabolism in cancer	3	0.001247849
hsa05214	Glioma	3	0.001286962
hsa05212	Pancreatic cancer	3	0.001286962
hsa04920	Adipocytokine signaling pathway	3	0.001491331
hsa05215	Prostate cancer	3	0.002347377

Discussion

With the continuous progress of society, the pace of people's life is gradually accelerated. Due to long-term unreasonable diet and rest pattern, mental stress, environmental pollution and many other reasons, the incidence of tumors is increasing year by year, which seriously damages people's health. People pay more and more attention to health care and disease prevention, in which medicinal and food-based drugs gradually appear in daily life, and many medicinal and dietary treatments are also increasingly accepted by people. Modern pharmacological studies have found that many active ingredients extracted from Poria have various antitumor effects, mainly through enhancing immune system activity and inducing apoptosis of tumor cells [11,12]. Although the antitumor effects of Poria are well established, the current research on the antitumor effects of Poria is still at a preliminary stage, with experimental studies focusing on individual monomers. It neglects whether other components of Poria have synergistic antitumor effects and molecular mechanism of action studies.

In this study, the anti-tumor mechanism of poria cocos, a traditional Chinese medicine homologous to food and medicine, is discussed by using the method of network pharmacology and multiple sets of data obtained by multiple software. Firstly, the active components of Poria cocos are preliminarily screened, and a total of 18 potential active components are obtained, resulting in 259 corresponding targets. Among them, there are many corresponding targets of active components such as Cerevisterol, trametenolic acid, 3B-hydroxy-24-methylene-8-lanostene-21-oicacid, poricoic acid C, and dehydroeburicoic acid. They are regarded as the main antitumor components of Poria cocos. After intersection with tumor candidate pathogenic targets, 7 core genes ESR1, MAPK3, MAPK8, MTOR, PIK3CA, JAK2 and IL6 are obtained by network topological parameter analysis. Although the number of core target genes is small, the therapeutic effect is targeted.

For example, ESR1 is an isoform encoded by the ER gene, that is, ERα (13).It is widespread in breast, endometrial, and lung cancer tissue cells, and its receptor protein can regulate the cell cycle, control cell signal transduction, and then affect cell survival time [14].Moreover, studies have shown that ESR gene single nucleotide polymorphism may be associated with tumor metastasis, including central nervous system metastasis [13] [15]. In recent years, mTOR pathway has become a research hotspot in the treatment of gastric cancer, and many scholars treat gastric cancer by inhibiting its expression and blocking transduction signals [16]. Furthermore, studies [17] have shown that the expression of PIK3CA protein is increased in patients with co-infection such as colon cancer, gastric cancer and ovarian cancer. mir-363-3p targeting PIK3CA can regulate the proliferation, invasion and migration of non-small cell lung cancer cells [18], which has a great influence on the proliferation of colon cancer and the expression of glioma [19] . JAK2 is an important subtype of JAK, and macrophages, stimulated by lipopolysaccharide, can significantly activate the JAK2 pathway and produce inflammatory cytokines and different macrophage phenotypes [20]. JAK2 is able to induce a systemic inflammatory response and is associated with the development of tumor cachexia [21, 22].In glioma cells, Dp44mT

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inhibits the IL-6 signaling pathway by stimulating the transcription of NDRG2, thereby inhibiting the proliferation of glioma cells to promote their apoptosis [23].Oleanolic acid affects the proliferation and apoptosis of colon cancer cells by regulating the IL-6 signaling pathway [24]. At the same time, continuous stimulation of IL-6 cytokine signal can lead to the phosphorylation of downstream JAK2, promoting tumor growth, drug resistance and metastasis.

The GO enrichment analysis of the core potential targets mainly includes the positive regulation of nitric oxide biosynthesis process, protein phosphorylation, positive regulation of sequence-specific DNA-binding transcription factor activity, platelet activation and other processes. The KEGG pathway enrichment analysis mainly involves PI3K-Akt signaling pathway, mTOR signaling pathway, ErbB signaling pathway, Toll-like receptor signaling pathway, TNF signaling pathway and so on. Among them, PI3K-Akt signaling pathway is the most significant pathway. Studies have shown that miR-182 can target and regulate PI3K signaling pathway to affect the biological behavior of glioma stem cells [25]. In addition, ErbB signaling pathway is also extremely important another pathway. Via ErbB signaling pathway, it can play an inducing role in the proliferation inhibition and apoptosis of ovarian cancer Skov3 cells [26]. Moreover, green fruit polysaccharide fraction CFW regulates the effects of proliferation, migration, invasion and apoptosis of gastric cancer cells through ErbB signaling pathway [27]. In summary, the anti-tumor mechanism of action of Poria cocos is shown in Figure 8.

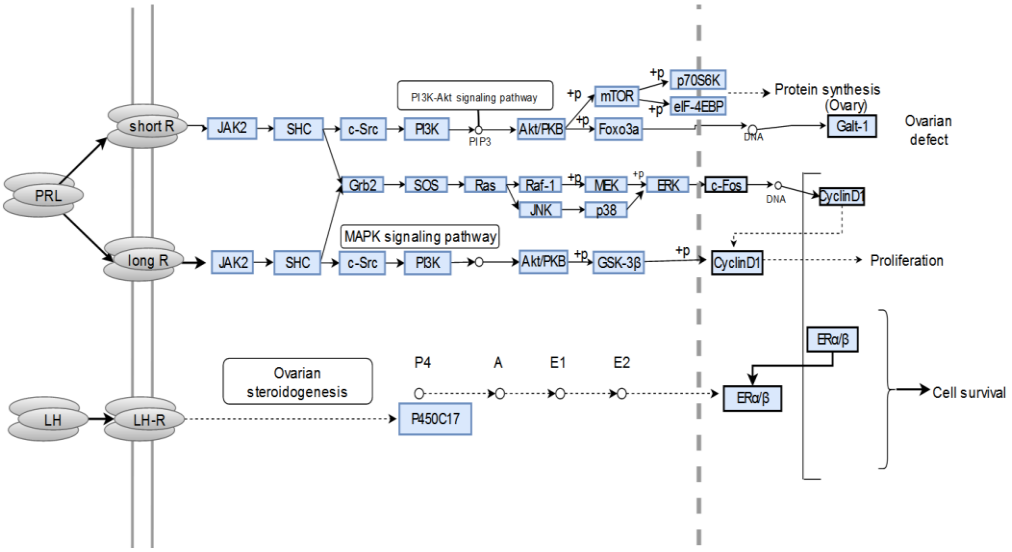

Figure 8. Mechanism of anti-tumor effect of Poria cocos

Conclusion

To sum up, based on the network pharmacology method, this study systematically predicts the potential anti-tumor targets and mechanisms of action of the traditional Chinese medicine Poria cocos, which is homologous to medicine and food. It fully reflects the "multi-component, multi-target and multi-pathway" anti-tumor effects of Poria cocos, and plays a unique advantage in the optimization of dosage form and long-term intervention for the prevention of malignant tumors. Although this study provides a good basis for further basic antitumor research and clinical trial validation, there are still some shortcomings such as inexact data analysis. Therefore, we expect further validation through experimental studies in the future.

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