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Discussion on the mechanism of action of Salvia miltiorrhiza in the treatment of prostate cancer based on network pharmacology

Jiajun Chen[1,a], Xuelin Tan[2,b], Yuting Bai[3,c], Xin Chen[4,d,*]

[1]Department of Clinical Laboratory, Gaoping District People's Hospital of Nanchong, Nanchong, China
[2]Department of Clinical Laboratory, Nanchong Central Hospital Affiliated to North Sichuan Medical College, Nanchong, China
[3]Department of Clinical Laboratory, Affiliated Hospital of North Sichuan Medical College, Nanchong, China
[4]Department of Rehabilitation Medicine, Affiliated Hospital of North Sichuan Medical College, Nanchong, China
[a]419486413@qq.com, [b]2295642729@qq.com, [c]byt67899@163.com, [d]488874309@qq.com
**Corresponding author*

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Abstract: The purpose of this study was to explore the mechanism of action of *Salvia miltiorrhiza* in the treatment of prostate cancer (PCa) based on the network pharmacology approach, and to provide a basis for rational clinical use and cellular experiments. The method used in this study was to obtain the main active components and corresponding targets of *Salvia miltiorrhiza* through the Chinese Medicine System Pharmacology Database and Analysis Platform (TCMSP), Perl, UniProt and other databases. Disease targets for PCa were obtained from GeneCards, OMIM, TTD and DrugBank databases. Using bioinformatics online database mapping tool, Venn diagram was drawn to screen the cross targets of *Salvia miltiorrhiza* and PCa active components. active components of *Salvia miltiorrhiza*-PCa related target network and cross target protein interaction (PPI) network were constructed using STRING platform, and Cytoscape 3.8.2 software was used to screen key targets, and R 4.3.0 software was used to perform gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. A total of 58 active components of *Salvia miltiorrhiza* and their corresponding target genes and 2142 target genes related to PCa were obtained. The results of Venn diagram showed that there were 74 cross targets between the active components of *Salvia miltiorrhiza* and PCa. Luteolin, tanshinone, quercetin and dihydrosalvia miltiorrhiza lactone may be the important nodes of the active components of *Salvia miltiorrhiza*-PCa related target network, while MAPK14, MYC, TP53, ESR1 and JUN may be the key targets of PPI network. The results of GO analysis showed that the cellular components of 74 targets of *Salvia miltiorrhiza* in the treatment of PCa were mainly nuclear, chromatin and cytoplasm, and the biological processes were mainly negative regulation of apoptosis, the response to xenobiotic stimulus, and the positive regulation of cell proliferation, and so on. Molecular functions mainly include enzyme binding process, protein binding process, regulation of protein homodimer activity, binding protein kinase and so on. KEGG pathway enrichment analysis showed that the cross targets were mainly concentrated in cancer signaling pathway, prostate cancer

signaling pathway, PI3K-Akt signaling pathway, IL-17 signaling pathway, HIF-1 signaling pathway and so on. This study preliminarily reveals the molecular and cellular pathway mechanism of *Salvia miltiorrhiza* in the treatment of PCa, which provides a scientific basis for clinical use and a reference direction for follow-up cell experiments.

1. Introduction

According to the data released by the International Cancer Research Group of the World Health Organization (WHO), there were about 1.4 million new cases of prostate cancer (PCa) worldwide in 2020, and about 370000 died of PCa[1]. In 2020, there were about 110000 new cases of PCa and 50 000 deaths in China[1]. It can be seen that PCa has brought a huge economic burden to the global health system, seriously endangering the life safety of men and reducing the quality of life of patients[2, 3]. However, whether it is surgical resection, radiotherapy and chemotherapy or endocrine therapy, there are varying degrees of adverse reactions. Traditional Chinese medicine has obvious advantages in improving immunity and drug tolerance of cancer patients, improving preoperative state, speeding up postoperative recovery, reducing adverse reactions of chemical drugs, relieving clinical symptoms, preventing tumorigenesis and improving quality of life[4].

There is no exclusive disease name of “prostate cancer” in ancient books. combined with the clinical symptoms of PCa and modern oncology research, traditional Chinese medicine believes that it belongs to the category of “cancer”, “dyspnea”, “gonorrhea syndrome”, “hematuria” and “occlusion” and so on. The treatment should be based on tonifying deficiency, clearing heat and detoxification, promoting blood circulation and removing blood stasis, relieving dampness or resolving phlegm and dispersing knot, etc. *Salvia miltiorrhiza* is first seen in the Classic of Shennong Materia Medica, which is bitter and slightly cold, returning to the heart and liver meridian, and has the effects of promoting blood circulation and removing blood stasis, relieving pain, cooling blood and eliminating carbuncle. It is one of the common Chinese herbal medicines in clinic[5]. Studies have shown that *Salvia miltiorrhiza* has the effects of anti-inflammation and improving the ability of hypoxia. So, whether we can give full play to the characteristics of multi-components, multi-pathways and multi-targets of traditional Chinese medicine, give full play to the effects of *Salvia miltiorrhiza* on anti-inflammation, improving hypoxia, improving cell microenvironment or promoting cancer cell apoptosis in the treatment of PCa, the mechanism is not clear and needs to be further studied [6, 7].

On the basis of making full use of bioinformatics analysis software in network pharmacology, this study used gene ontology (GO) enrichment analysis and Kyoto Encyclopedia of Gene and Genome(KEGG)pathway to analyze the active components related to anti-PCa of *Salvia miltiorrhiza*, to explore the possible mechanism of *Salvia miltiorrhiza* in the treatment of PCa, and to provide a theoretical basis for the clinical use of *Salvia miltiorrhiza* in the treatment of PCa. To provide a reference direction for follow-up cell experiments.

2. Materials and methods

2.1. Prediction of active components and Gene targets of *Salvia miltiorrhiza*

The effective components and gene targets of drugs were analyzed by using traditional Chinese medicine system pharmacology database and analysis platform database (https://tcmspw.

com/tcmsp.php)[8]. The database contains the data of oral bioavailability and drug-like properties of traditional Chinese medicine. Enter "*Salvia miltiorrhiza*" as the keyword in the search box of the platform, set oral bioavailability (OB)≥30%, drug-like properties (DL)≥0.18, screen the active components of *Salvia miltiorrhiza* and collect the gene targets of drug active components. Using UniProt database (https://www.uniprot.org) [9], the biological species were selected as homo sapiens (human), and the gene names and abbreviations of all the corresponding targets were queried.

2.2. Screening of disease targets for PCa and construction of disease-efficacy target Venn diagram

Four databases, GeneCards (https://www.genecards.org/)[10], OMIM (https://omim.org/)[11], TTD (http://db.idrblab.net/ttd/)[12] and DrugBank (https://go.drugbank.com/)[13], were used to search and download all prostate cancer related genes with the keyword "Prostate cancer". Using UniProt database (https://www.uniprot.org) [9], select biological species as "Homo sapiens", query all gene abbreviations. By calling the Venn package in R 4.3.0 software, matching the intersection of *Salvia miltiorrhiza* active components gene and PCa gene, the drug-disease relationship diagram was drawn, and the effective target of *Salvia miltiorrhiza* was obtained.

2.3. Construction of protein-protein interaction (PPI) network to screen core targets

The effective targets obtained from the Venn diagram were imported into the String database (http://string-db.org)[14], the biological species were selected as "Homo sapiens", and the minimum interaction score was set to "highest confidence" (0.900) to construct the PPI network. The core target of *Salvia miltiorrhiza* in the treatment of PCa was selected by topological analysis of the network diagram by CytoNCA plug-in in Cytoscape 3.8.2 software.

2.4. GO and KEGG analysis

Bioconductor is developed from computational biology and bioinformatics to facilitate and accurately use data tools to process massive amounts of biological information. The Bioconductor data package is linked in R software (https: //bioconductor.org/)[15], conduct GO and KEGG functional enrichment analysis for intersection genes and analyze the influence of active components of *Salvia miltiorrhiza* on PCa pathway after integrating information. The visual output of the results was shown as a histogram with "P<0.05, gene number≥5" (P values were arranged from small to large, top-down, and distinguished by different colors).

3. Result

3.1. Prediction of effective components and gene targets of *Salvia miltiorrhiza*

We entered *Salvia miltiorrhiza* into the TCMSP database for search and found a total of 202 active components. The OB of *Salvia miltiorrhiza* was set to be≥30%, DL≥0.18, 58 active components were screened, and 2566 drug-related targets were obtained, which were input into the UniProt database, and 933 target gene names and abbreviation were obtained. 118 effective targets were obtained. The 23 active components with high connectivity were selected to carry out protein network visualization processing via Cytoscape software, and the network diagram of "*Salvia miltiorrhiza* - Effective target" was constructed, in which the sky-blue rectangle represented the active ingredient, and the pink rectangle represented the effective target (Figure 1). The active

components with high connectivity are luteolin, tanshinone and quercetin.

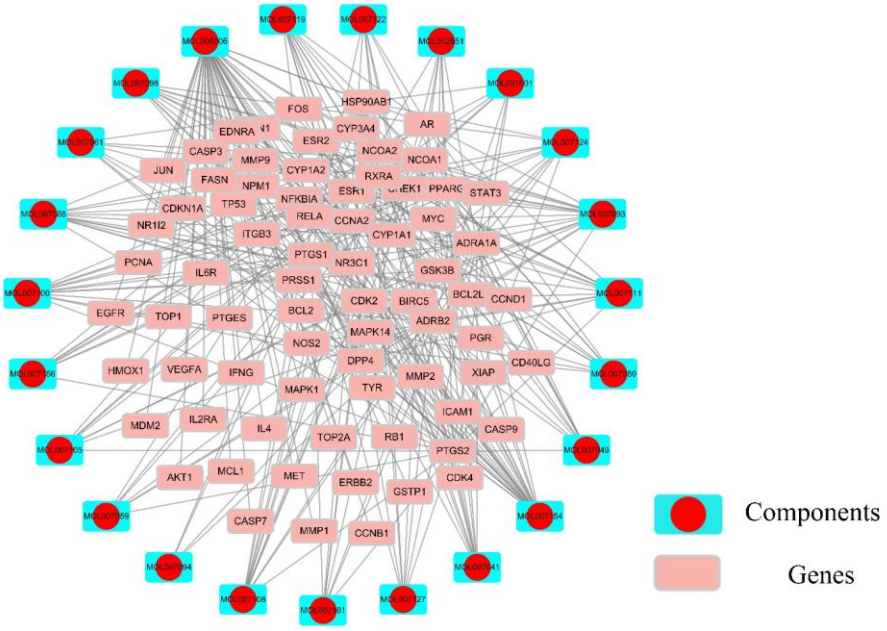

Figure 1: Active Component-target genes network diagram.

3.2. Screening of disease targets for prostate cancer

Search the keyword “prostate cancer”, and find 2142 disease-related genes in GeneCards, OMIM, TTD and DrugBank. Run Venn software package with R 4.3.0 software and take 2142 disease targets and 118 effective drug targets. And draw Venn diagram (Figure 2). The map shows that there are 74 genes in the drug-disease intersection.

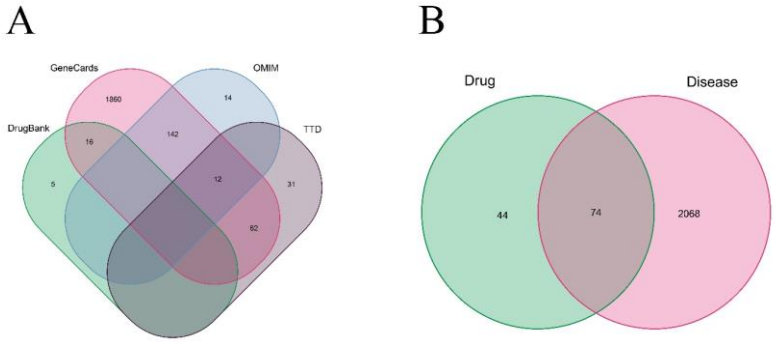

Figure 2: Salvia miltiorrhiza-PCa target map.

3.3. Construction of PPI network and screening of core targets

In order to analyze the interaction between proteins, drug-disease intersection genes were input into String, Homo sapiens was selected to run the web version of String, and the PPI network diagram was drawn (Figure 3). Hide the unlinked node, set the lowest interaction score to “highest confidence”, and output the PPI diagram and information relationship file. Cytoscape 3.8.2 software was used to visualize the file, and CytoNCA plug-in was used to perform topological analysis of the PPI network. The higher the degree of connection with the target, the more likely drugs are to play a major role in the treatment of PCa. Genes with BC value＞124.62, CC value＞0.50, DC value＞16,

EC value＞0.18, LAC value＞6.43, and NC value＞9.47 were intersected to screen out five core targets, namely MAPK14, MYC, TP53, ESR1, and JUN (Figure 4). These genes may be the core targets of *Salvia miltiorrhiza* therapy for PCa.

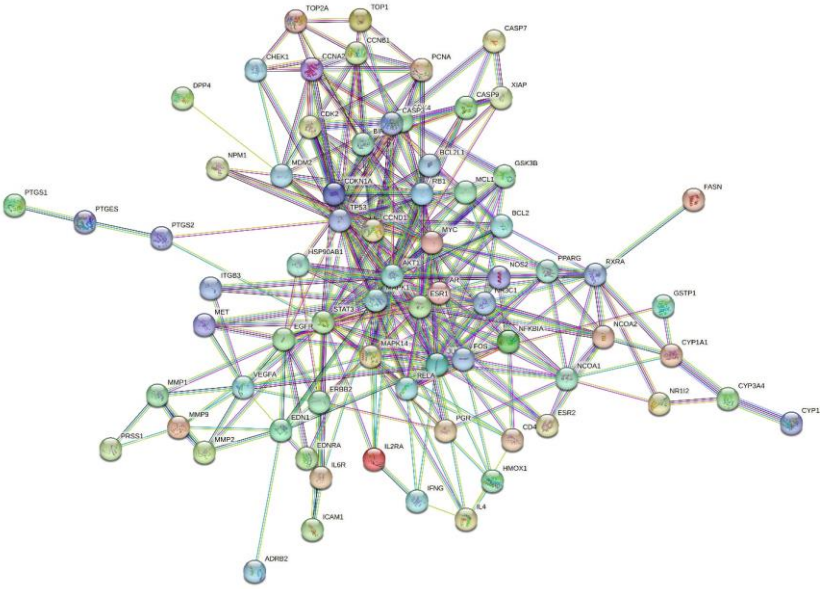

Figure 3: PPI network of Salvia miltiorrhiza target for PCa.

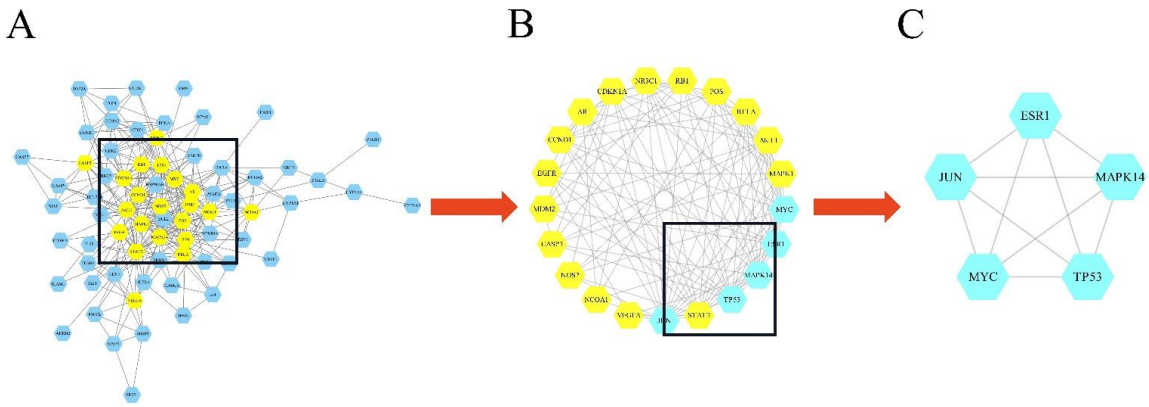

Figure 4: The PPI network construction.

3.4. GO analysis

The *Salvia miltiorrhiza* drug-disease gene target was input into R software, and the GO enrichment analysis was carried out by Cluster Profiler package. Set P＜0.001 as the confidence interval filter, and a total of 171 relevant GO entries were obtained. Among them, there are 115 items of biological processes, mainly related to the negative regulation of apoptosis, the response to xenobiotic stimulus, and the positive regulation of cell proliferation. Including 15 items of cell components, mainly related to nucleoplasm, chromatin, nucleus, etc. It includes 41 items of molecular functions, mainly involving the enzyme binding process, protein binding process, regulation of protein homologous dimer activity, binding protein kinase, etc. In this study, the top 10 items with the highest P-value were selected for mapping through R. The Y-axis represents the names of BP, CC and MF items, the X-axis represents the number of genes enriched in each item, and the color of the box represents the size of the P-value (Figure 5).

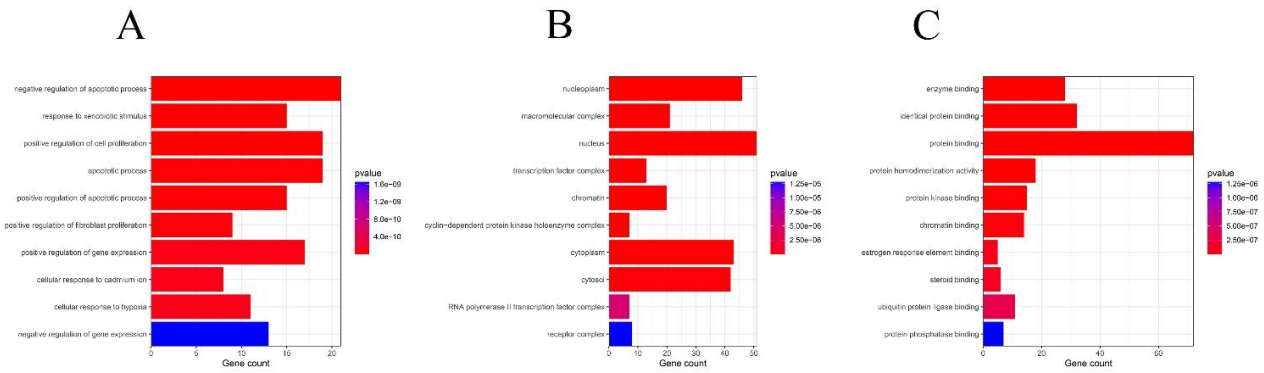

Figure 5: GO analysis of therapeutic targets of Salvia miltiorrhiza in the treatment of PCa.

3.5. KEGG enrichment analysis

The *Salvia miltiorrhiza* drug-disease gene targets were input into R software and KEGG enrichment analysis was performed using Cluster Profiler package. Setting P＜0.001 as confidence interval filtering, 87 relevant KEGG articles were obtained. It mainly involves cancer signaling pathway, prostate cancer signaling pathway, PI3K-Akt signaling pathway, IL-17 signaling pathway, HIF-1 signaling pathway, etc. The interference of some irrelevant diseases was removed, and only the model pathways of related diseases were selected for comparison. In this study, the 10 signaling pathways with the highest P value were selected and mapped by R. As shown in Figure 6, the Y-axis represents the pathway name, the X-axis represents the number of genes enriched by the pathway, and the color of the box represents the size of the P-value.

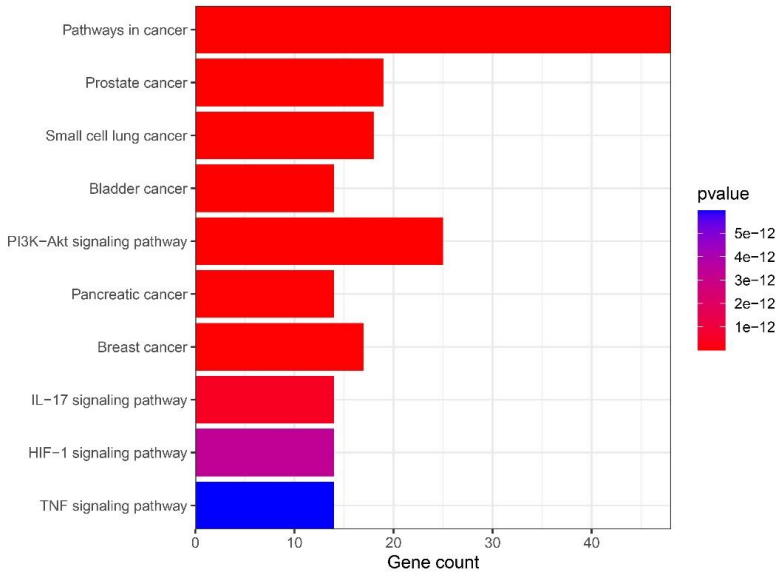

Figure 6: KEGG pathway enrichment analysis of the therapeutic targets of *Salvia miltiorrhiza* in the treatment of PCa (The top 10 signaling pathways).

4. Discussion

Nowadays, traditional Chinese medicine is playing an increasingly important role in the treatment of modern medicine. Due to the lack of clear molecular mechanism, the development and application of traditional Chinese medicine has always been troubled, and the arrival of the era of big data has brought new opportunities for the development of traditional Chinese medicine.

Network pharmacology emphasizes the combination of bioinformatics, systems biology and pharmacology, which not only explains the complex interaction between Chinese medicine and disease at the system level, but also conforms to the systematic and holistic view of TCM theory, becoming a new research method and technical means for the modernization of TCM[16, 17]. In this paper, the active components, targets, related diseases, the interaction between targets and diseases and the signal pathways related to the treatment of PCa of *Salvia miltiorrhiza* were studied. A total of 58 active components of *Salvia miltiorrhiza* were obtained. 74 targets related to PCa. Thus, *Salvia miltiorrhiza* has the characteristics of multi-components, multi-targets and multi-pathways in the treatment of diseases, which reflects the diversity and universality of its pharmacological effects. By studying the relationship between the active components and their corresponding targets in *Salvia miltiorrhiza* and PCa, it was determined that the active components closely related to PCa were luteolin, tanshinone, quercetin and so on. Related pharmacological studies have shown that luteolin has extensive anti-tumor effects by inhibiting proliferation, promoting apoptosis, increasing sensitivity to drug resistance and reducing metastasis [18, 19]. Fang[20] found that luteolin can inhibit insulin-like growth factor-1 (IGF-1) induced IGF-1R and AKT expression in PCa cells. It has been found that tanshinone IIA alone can induce the activation of mitochondrial apoptosis pathway and promote tumor cell apoptosis in PCa cells, and the expression of Beclin1 and LC3II is increased, indicating that tanshinone IIA promotes autophagy of PCa cells. Furthermore, N-acetyl-L-cysteine, a reactive oxygen scavenger, can effectively inhibit the expression of Beclin1, LC3-II and lytic caspase-3, which indicates that apoptosis and autophagy depend on the production of intracellular reactive oxygen species, and further indicates that tanshinone IIA promotes apoptosis and autophagy by up-regulating the expression of reactive oxygen species in PCa cells[21]. Another study found that the direct target of quercetin in PC-3 cells is SIRT1 protein, and quercetin can significantly reduce the expression level of SIRT1 in tumor cells. When the expression level of quercetin was forcefully increased by transfection of SIRT1 plasmid into cells, the synergistic anti-PCa activity of quercetin on TRAIL was significantly inhibited [22-24]. The above results show that the active components in *Salvia miltiorrhiza* are closely related to the treatment of PCa.

This study found that *Salvia miltiorrhiza* may play a role in the treatment of PCa by acting on multiple targets such as MAPK14, MYC, TP53, ESR1, JUN and so on. Mitogen-activated protein kinase 14 (MAPK14) is one of the four kinds of p38MAPK, which can be activated by ultraviolet radiation and inflammatory cytokines. It plays an important role in cell cascade reaction and regulates many important pathophysiological processes such as cell growth, differentiation, environmental stress adaptation and inflammatory response[25].

Chen[26] proved that the activation of MAPK14-related pathway mediated by ROS can promote the G2/M phase arrest of human colon cancer cell line HCT116. Kim [27] observed that the activation of Caspase-3/p38MAPK pathway can promote the production of ROS, and then affect cell apoptosis. MYC is a nuclear oncogene, which is activated mainly by gene amplification in tumorigenesis, resulting in high expression of mRNA, producing many MYC proteins, which can bind to special DNA sequences, and then affect the genes related to tumor growth, metastasis, apoptosis and angiogenesis, such as Bcl2, CCND1, PCNA and so on[28-30]. TP53 gene is located on human chromosome 17. Studies have shown that more than 50% of tumor patients have TP53 gene mutation. Tumor-related mutant p53 protein not only loses the function of tumor inhibition, but also plays an important role in tumor cell proliferation, invasion, metastasis, drug resistance and so on[31].

GO analysis of the efficacy of *Salvia miltiorrhiza* in the treatment of PCa showed that the biological process of *Salvia miltiorrhiza* in the treatment of PCa was mainly the negative regulation of apoptosis, the response to xenobiotic stimulus, and the positive regulation of cell proliferation,

which mainly played a role in nucleus, chromatin and cytoplasm. KEGG signal pathway enrichment analysis shows that *Salvia miltiorrhiza* may act on cancer signaling pathway, prostate cancer signaling pathway, PI3K-Akt signaling pathway, IL-17 signaling pathway, HIF-1 signaling pathway and so on to inhibit inflammation, immune regulation, apoptosis and so on, and then play the role of anti-PCa.

5. Discussion

To sum up, this study analyzed the pharmacological relationship of *Salvia miltiorrhiza* in the treatment of PCa at the molecular level by means of network pharmacology. It was found that the effective molecular targets such as MAPK14, MYC, TP53, ESR1 and JUN were the key targets in the treatment process. These targets influence each other in series and cooperate with each other at multiple molecular levels. It plays a role in the treatment of PCa through tumor signal pathway, prostate cancer signaling pathway, PI3K-Akt signaling pathway, IL-17 signaling pathway, HIF-1 signaling pathway and so on. This result not only reflects the multi-level and multi-way intervention of traditional Chinese medicine, but also reflects the therapeutic advantages of multi-components, multi-targets and multi-pathways. This study provides a scientific basis for clinical use and a reference direction for follow-up cell tests. However, due to the limitations of the network pharmacology platform, its effective ingredients and targets are still being updated, so in-depth animal and cell level experiments should be carried out to verify.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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