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Mechanism of Gibberellic Acid against Prostate Cancer Based on Network Pharmacology and Molecular Docking

Bai Ge[1,a], Tian Bo[2,b,*], Pan Kenian[1,c]

[1]*Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*
[2]*Northwest Polytechnic University Hospital, Xi'an, Shaanxi, 710072, China*
[a]*325149472@qq.com,* [b]*tianbodr@foxmail.com,* [c]*810045892@qq.com*
[*]*Corresponding author*

Abstract: *In order to study the anti-prostate cancer mechanism of gibberellic acid based on network pharmacology and molecular docking method, with a view to providing reference for the elucidation of its clinical anti-prostate cancer mechanism. We used the TCMSP and Swiss TargetPrediction databases to screen the active ingredients and targets of Gynostemma, and used the GeneCards and Disgenet databases to collect the target genes of prostate cancer. Then we used Cytoscape 3.9.1 to construct a drug-active ingredient-target-disease network. For target-disease" network, we used Cytoscape 3.9.1 software, imported potential targets into STRING database to construct protein-protein interaction (PPI) network. And we analyzed the core targets through DAVID database for GO function annotation and KEGG pathway enrichment, and carried out molecular docking between the main active ingredients of Gynostemma gibberelliflorum and the potential targets through Pymol software and AutoDock software. Resultly, the results of GO analysis showed that gibberellic acid's antiprostate cancer may be related to the transcription initiation process of the RNA polymerase II promoter, nuclear chromatin, and DNA binding; the results of KEGG analysis showed that gibberellic acid's antiprostate cancer may involve the cancer pathway, and may be involved in the cancer pathway, and in the cancer. The results of KEGG analysis indicated that gibberellins against prostate cancer might be involved in the cancer pathway, proteoglycan signaling pathway in cancer, microRNA pathway in cancer and thyroid hormone signaling pathway, etc. The results of molecular docking showed that gibberellin LXXIX, the predicted key component of gibberellins, had good binding properties with the core targets of AKT1, IL6 and STAT3. In conclusion, gynostemma gibberelliforme is mainly involved in AKT1, IL6 and STAT3 and 173 signaling pathways, and its active ingredients can inhibit the growth of tumor cells through multi-targets, multi-pathways and multi-mechanisms.*

Keywords: *Gibberellin; prostate cancer; network pharmacology; gibberellin LXXIX; molecular docking*

1. Introduction

Prostate cancer is the second most common tumor among men worldwide [1] and significantly contributes to the global increase in male mortality. According to the WHO GLOBOCAN 2020 data, there are an estimated 19.3 million new cancer cases and nearly 10 million cancer deaths globally, with prostate cancer ranking fourth after breast, lung, and colorectal cancers among new cancer cases, and eighth among the 36 types of cancer in terms of deaths [2]. The number of deaths is the eighth among 36 types of cancers. More prostate cancer patients are effective on androgen deprivation therapy in the early stages, but most will eventually progress from hormone sensitivity to denervation-resistant prostate cancer (CRPC) [3]. CRPC is a highly lethal form of prostate cancer, with more than 84% of patients having metastases [4]. The most commonly used risk stratification scheme combines clinical staging, PSA, and Gleason score, and patients are categorized as low-risk (clinical stage T1-2a, PSA ≤10 ng/mL, Gleason score ≤6), intermediate-risk (PSA ≤20 ng/mL at stage T2b or 10 o or Gleason score 7), or high-risk (stage ≥T2c or PSA 420 ng/mL or Gleason score ≥8), which was associated with disease-free survival at 10 years after radical prostatectomy (RP); low risk 83%, intermediate risk 46%, and high risk 29% [5]. Prostate cancer treatments depend on a variety of factors, such as the rate of cancer progression, the extent of spread, the overall health of the patient, and the potential benefits or side effects of treatment options. Currently, treatments for prostate cancer include prostatectomy,

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radiation therapy (outside the body and placed inside the body), freezing or heating of prostate tissue, hormone therapy (medications to stop the body's production of testosterone, medications to stop testosterone from reaching the cancer cells, and testicular resection), chemotherapy, immunotherapy (genetically engineered to make cells able to fight the cancer and to help the cells of the immune system to recognize the cancer cells), and targeted drug therapy, etc [6].

Chinese medicine has been developing rapidly in recent years, and gradually occupies a certain proportion in the treatment of tumors. Some drugs with clear inhibitory effects on tumor cells are gradually moving towards the clinic, and the drug dosage forms are also being enriched. Although most of the researches on TCM focus on postoperative intervention, the prognosis of any disease is also a concern in addition to the therapeutic process. In the process of postoperative intervention, the inhibitory effects of TCM on cancer cells have also been demonstrated, which include relieving upper limb edema, relieving nausea and vomiting, preventing and controlling cardiotoxicity caused by chemotherapy, improving immune function, reducing toxicity and increasing efficacy, and resisting recurrence and metastasis. These include relieving swelling of the upper limbs, relieving nausea and vomiting, preventing cardiotoxicity caused by chemotherapy, improving immune function, reducing toxicity and synergizing effect, anti-recurrence and metastasis. It can be seen that the application of traditional Chinese medicine in the treatment of prostate cancer is worth recognizing and continuing in-depth research. Gynostemma pentaphyllum (Thunb.) Makino is a perennial herbaceous vine plant of the genus Gynostemma in the family Cucurbitaceae [7]. Gynostemma pentaphyllum is a perennial herbaceous vine of the genus Gynostemma in the family Cucurbitaceae, also known as "seven-leaf gall", "five-leafed ginseng" and "sweet tea creeper", and is also known as "southern ginseng" due to its richness in ginseng glycosides, with a bitter, slightly bitter taste. "It is bitter, slightly sweet, cool, non-toxic, and belongs to the lung, spleen and kidney meridians, with the effects of clearing heat and removing toxins, relieving cough and phlegm, tonifying qi and generating fluids, and invigorating the spleen and tranquilizing the mind [8]. In recent years, it has been reported in the literature that gynostemma and its chemical components can promote apoptosis of liver, lung and stomach cancer cells, which has a good effect on cancer.

In this study, in order to further understand the mechanism of gibberellic acid in treating prostate cancer, bioinformatics technology was utilized to select functional genes related to biological processes such as prostate cancer transformation. In this study, in order to further understand the mechanism of gibberellic acid in the treatment of prostate cancer, bioinformatics technology was used to select functional genes related to prostate cancer transformation and other biological processes. This will provide theoretical basis and new opportunities for the development and application of gynostemma in the treatment of prostate cancer.

2. Methodology

2.1. Screening of gibberellic acid for major active ingredients and targets

We searched the keyword "gynostemma" through TCMSP (https: // tcmspw.com/tcmsp.php) to obtain the active ingredients and their corresponding targets, and the screening conditions were set as oral bioavailability (OB) ≥30%, druglikeness (DL) ≥0.18, and oral bioavailability (OB) ≥30%. The screening conditions were oral bioavailability (OB) ≥30% and druglikeness (DL) ≥0.18, and the active ingredients of Honeysuckle were collected and supplemented through the review of related literature. After obtaining the target ingredient, the target protein name of the active ingredient was obtained at "Related Targets", and the CAS number of the chemical ingredient without target information was obtained from the pubchem database (https://pubchem.ncbi.nlm.nih.gov/). Canonical SMILES, using Swiss Target Prediction database (http://www.swisstargetprediction.ch/) to predict the target information, by setting Probability* >0 as our selection object. The collected target names were standardized and corrected through the Uniprot platform (https: // www.uniprot.org/) with the filter condition: "organism: homo sapiens".

2.2. Prostate Cancer Disease Target Screening

The Genecard database (https://www.genecards.org/) and Disgenet database (https://www.disgenet.org/home/) were searched for targets of "prostate cancer" genes in Genecard database and Disgenet database. And we merged and de-weighted to obtain the relevant disease targets of prostate cancer.

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2.3. Active ingredient-disease shared target screening

The collected prostate cancer-related disease targets and gibberellic acid active ingredient-related targets were imported into the software Venny2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) for analysis, and screened to obtain the intersection to obtain the potential action targets of gibberellic acid in treating prostate cancer and to draw the Venn Venn diagram.

2.4. Construction of Protein Interaction Networks (PPIs)

The potential targets of Gynostemma gibbosum for the treatment of prostate cancer obtained in 1.3 were imported into the String database, and the species was selected as "Homosapiens", the protein interaction network was constructed, the results were saved, and the raw data were processed to create the network file and the type file, respectively. The network file and type file were imported into Cytoscape 3.9.1 software to draw the protein interaction network and set and adjust the parameters, and then CentiScaPe2.2 was used to calculate the Degree value, Betweenness value and Closeness value, which were calculated by the following formula in Excel: "Degree > 26", "Betweenness value" and "Closeness value", and "Degree > 26". "Degree > 26.9929078014184, BetweennessunDir > 338.773049645386, ClosenessunDir > 0.00164233953711703" as the condition to screen the key targets, and finally protein-protein interaction network and core target network were obtained.

2.5. GO and KEGG pathway enrichment analysis

The key targets obtained in 1.4 were imported into the DAVID database (https://david.ncifcrf.gov/), and then clicked "Official-Gene-Symbol" and "GeneList". Click "Official-Gene-Symbol" and "GeneList", and select "Homosapicns" for the species. After uploading the data, KEGG pathway enrichment analysis was performed, and GO analysis was performed in three aspects: biological process (BP), cellular component (CC) and molecular function (MF). The difference was statistically significant. The data were exported to Excel and then imported into the Microbiology website (http: //www.bioin-formatics.com.cn/) for graphing to obtain GO analysis bubble diagrams and KEGG pathway analysis bubble diagrams.

2.6. "Drug-Active Ingredient-Target-Disease" Network Construction

The drug-active ingredient-target network in gibberellic acid was integrated with the results of KEGG-enriched metabolic pathways, and a "drug-active ingredient-target-disease" network diagram was constructed in Cytoscape 3.9.1. Each node in the network represents the active ingredient and the key target gene; edges are used to connect the active ingredient and the key target gene; nodes connected to the network are expressed in degrees. The greater the degree of the node in the network, the stronger the effect of the active ingredient.

2.7. Molecular docking validation

The top three targets in the PPI network were used as receptors, and the top gibberellic acid active ingredients in the "active ingredient-target" network were used as ligands to predict the binding ability of the two, and the lower the value of binding energy, the better the binding ability. The protein numbers corresponding to the top four core genes were queried by Uniprot, and the protein crystal complexes were imported into pymol software for dewatering and ligand removal by PDB database (https://www.rcsb.org/), hydrogenated by AntoDock software and exported to pdbqt file; the 2D structure of the active ingredient of Gynostemma gibberelliforme was downloaded from PubChem and saved as a pdbqt file. 2D structure of the active ingredient was downloaded through PubChem and saved in sdf format, converted to pdb format file through OpenBabel, and pre-processed by AutoDock software such as detection of torsion bonds and centers, and exported to pdbqt file; Autodockvina software was used to dock the small-molecule ligands and protein crystal complexes, and record the free energy of binding to analyze the degree of binding of the active ingredient to the target protein, and to analyze the results of the binding degree of the active ingredient to the target protein. The free energy of binding was recorded to analyze the degree of binding between the active ingredient and the target protein, and the analysis results were visualized by Pymol.

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3. Results

3.1. Gynostemma active ingredients and target screening

A total of 202 chemical components of gibberellic acid were obtained from the TCMSP database, and 24 active components in gibberellic acid that can be absorbed by the human body were screened by taking the bioavailability OB≥30% and the drug-like property DL≥0.18% as the qualifying conditions.Among the 24 components, gibberelloside LXXIX has a higher content in gibberellic acid, and many of the Chinese medicines in which it is found have anticancer effects; therefore, we chose gibberelloside LXXIX to explore its mechanism of action against prostate cancer. At the same time, the target proteins corresponding to the active ingredients of gynostemma were extracted from TCMSP database, and the names of target proteins were converted to gene names in Uniprot database, and a total of 318 target genes were obtained.

3.2. Disease target screening

13,471 genes related to prostate cancer were searched in Genecards database, and 2,135 genes related to prostate cancer were searched in Disgenet. 13,509 target genes for prostate cancer were summarized by taking the concatenated set of prostate cancer-related target genes in the database using the online software Venny 2.1 and removing duplicate entries (see Figure 1).

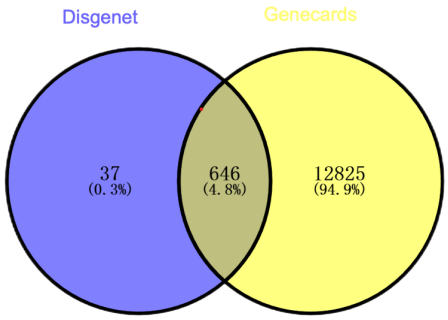

Figure 1: Wayne diagram of targets associated with prostate cancer

3.3. Screening of active ingredient-disease shared targets

The Venny2.1 tool was utilized to obtain 285 targets for the intersection of gibberellic acid active ingredient targets and prostate cancer disease targets (see Figure 2), i.e., gibberellic acid may synergize to treat prostate cancer through multiple potential targets of action.

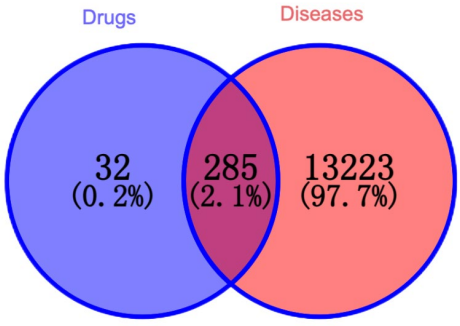

Figure 2: Wayne's diagram of gibberellic acid active ingredient-related targets and prostate cancer-related targets

3.4. Protein Interaction Network (PPI) Construction

The obtained 285 intersecting target genes were imported into the String database to draw the protein interaction network (see Figure 3), and the PPI network contained 282 nodes and 3806 edges, where nodes denote the target genes, and edges denote the interaction relationship between target genes.

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Through the obtained data, after filtering according to the conditions Degree>426.9929078014184, Betweenness>338.773049645386, Closeness>0.00164233953711703, the Cytoscape 3.9.1 software was used to visualize and analyze the obtained The data are visualized and analyzed to draw the core target network (see Figure 4-7), which contains 57 nodes and 785 edges, and the color from dark to light indicates that the degree value of the nodes is from large to small, and the nodes from large to small indicates that the degree value of the nodes is from large to small. The three most core targets were screened according to the node values, which were AKT1 (AKT/protein kinase B signaling channel regulation of cell proliferation and growth, and is involved in cellular processes including apoptosis and glucose metabolism), IL6 (interleukin-6 is the chemokine family of cytokines, genetically encodes a cytokine that plays a role in inflammation and B-cell maturation), STAT3 (Signal transducer and activator of transcription protein, or STAT, is a protein that binds to the DNA binding proteins that bind to DNA), STAT3 (a unique family, containing SH2 and SH3 structural domains that bind to specific phosphorylated tyrosine-containing peptides), and concluded that these targets play a key role in the treatment of prostate cancer by gibberellins.

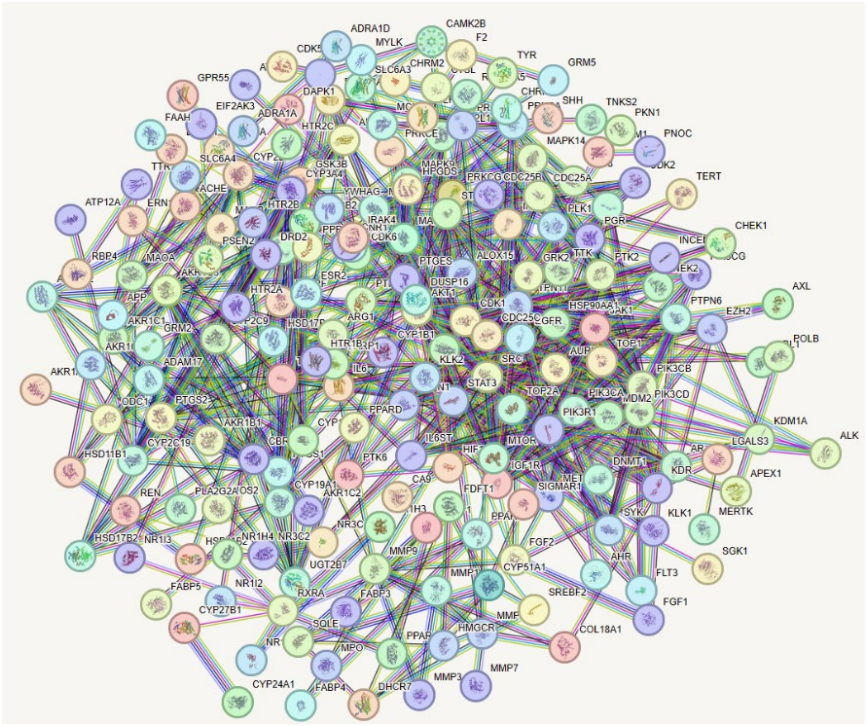

Figure 3: Target protein interaction network diagram

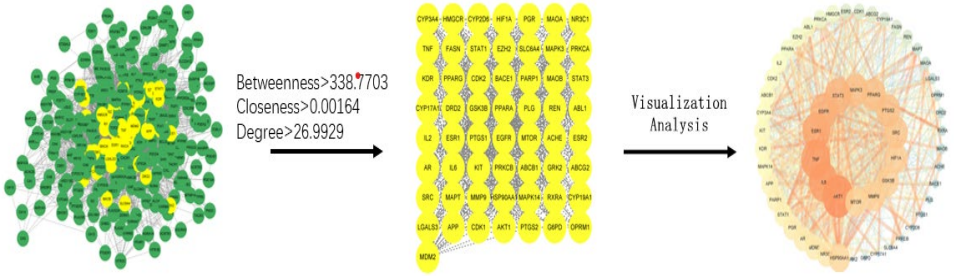

Figure 4: Visualization of PPI core target network

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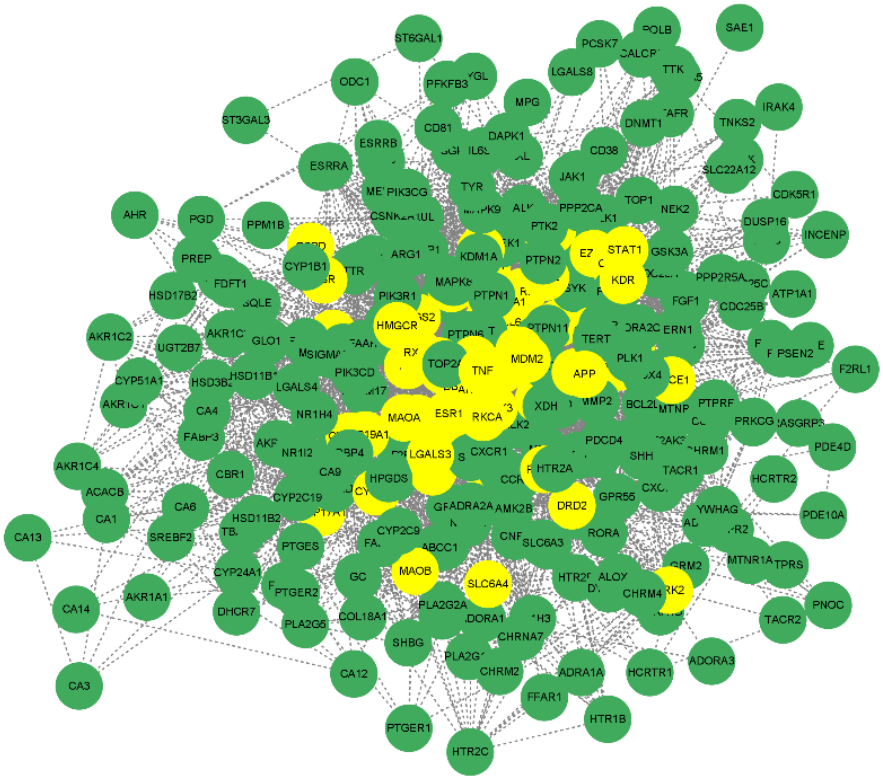

Figure 5: Potential target screening

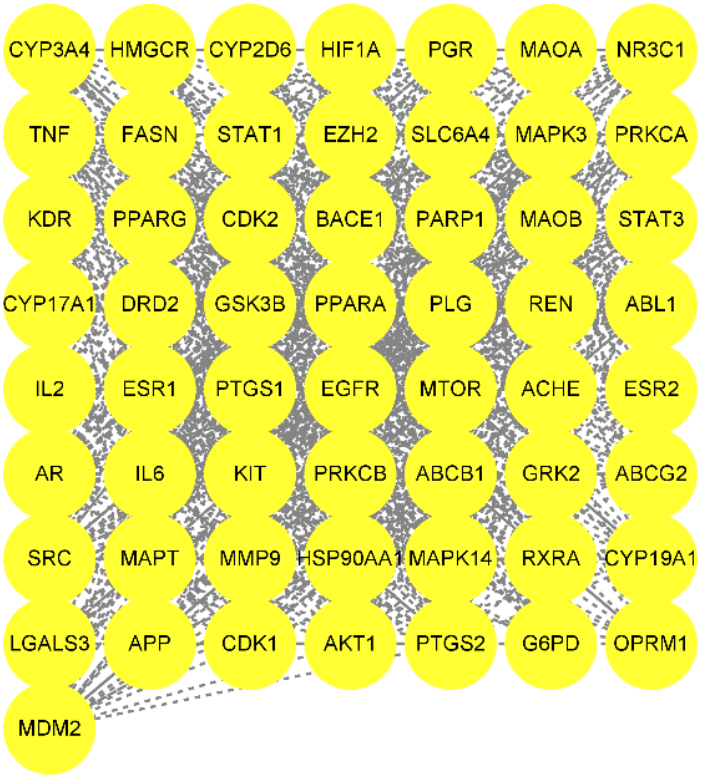

Figure 6: Potential targets

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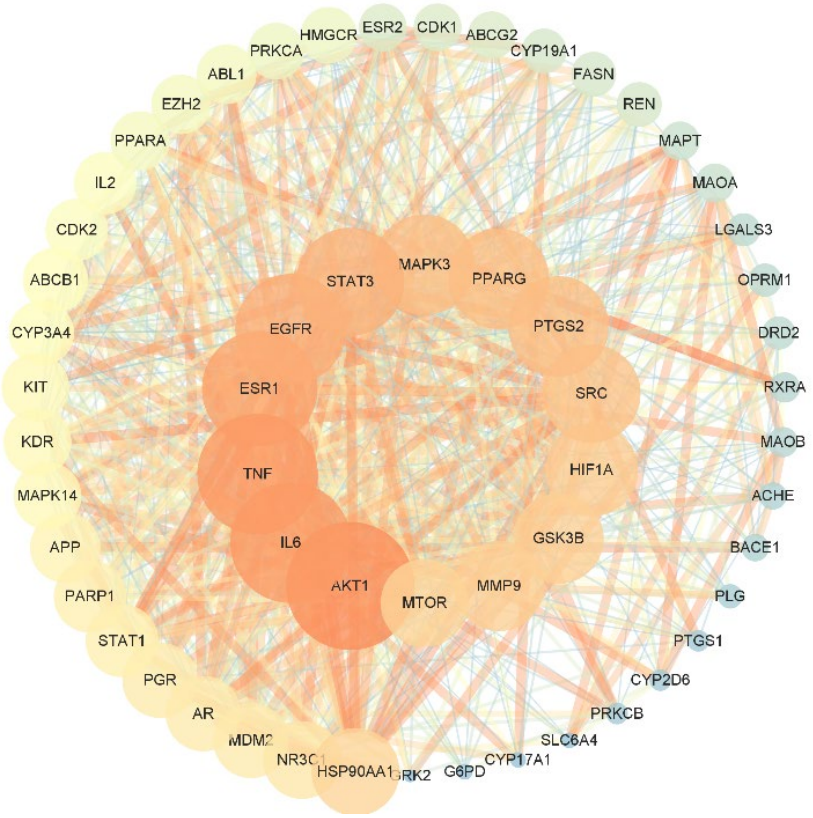
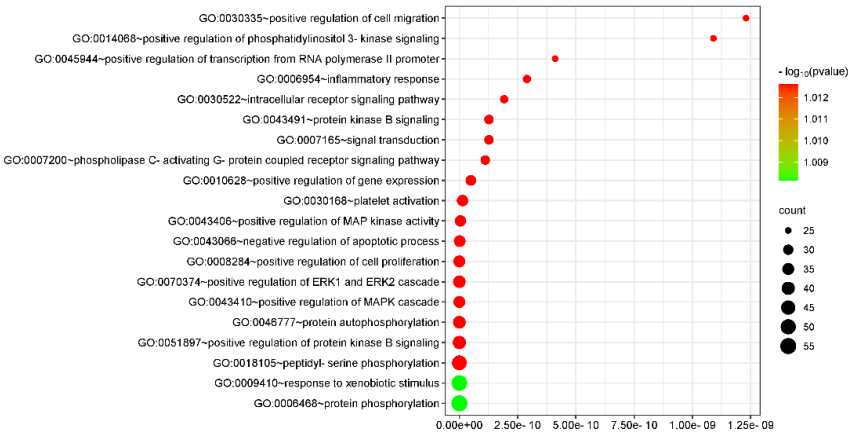


Figure 7: Core targets

3.5. Results of GO Functional Analysis

GO function analysis was performed using the DAVID database, resulting in 1125 biological processes, of which 805 were biologicalprocess (BP), mainly involving protein autophosphorylation, positive regulation of kinase activity, negative regulation of apoptotic process, peptidyl tyrosine phosphorylation, protein phosphorylation, etc.; 98 were molecularfunction (MF), mainly involving receptor complexes, nucleoplasm, nucleus, polymer complexes, plasma membrane, etc.; 98 were molecularfunction (MF), mainly involving receptor complexes, nucleoplasm, nucleus, polymer complexes, plasma membrane, etc. cellcomponent (CC) 98 articles, mainly related to receptor complexes, nucleoplasm, nucleus, polymer complexes, plasma membrane, etc.; molecularfunction (MF) 222 articles, mainly related to transmembrane receptor protein tyrosine kinase activity, adenosine triphosphate (ATP) binding, protein phosphorylation, and protein phosphorylation. ATP) binding, protein tyrosine kinase activity, protein kinase activity, and identical protein binding. The top 20 entries of BP, CC, and MF were selected for bubble plot presentation, respectively (see Figure 8), suggesting that gibberellic acid exerts effects on prostate cancer by modulating multiple biological processes.



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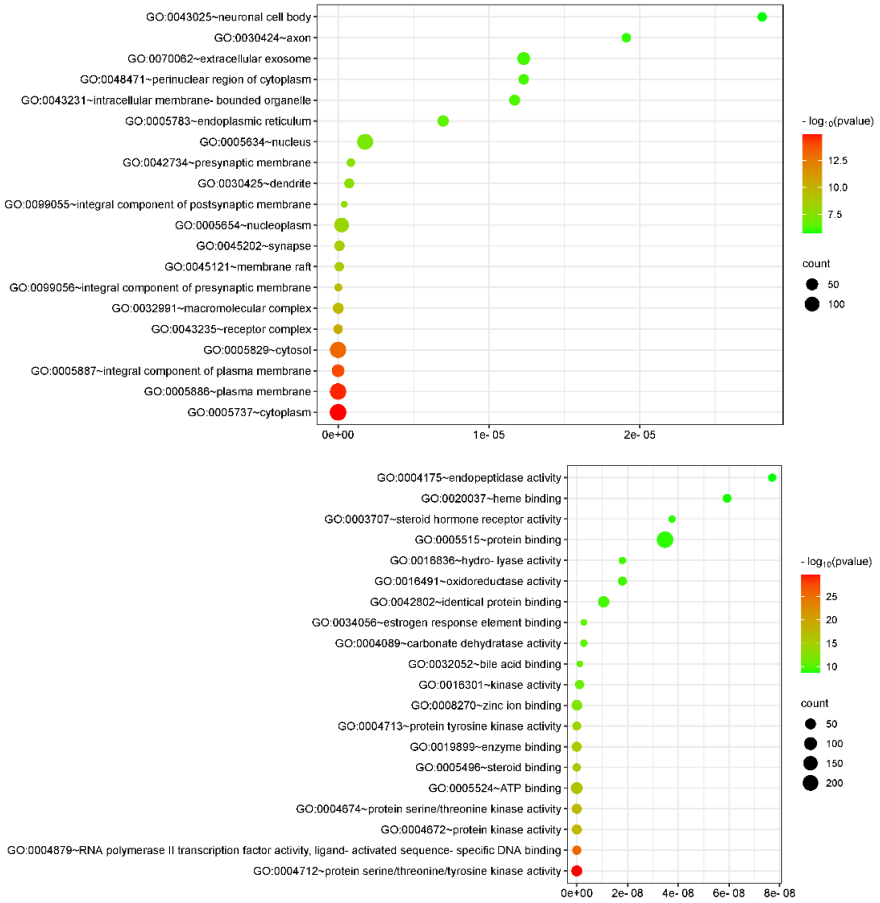

Figure 8: Bubble plot of the results of GO functional analysis of gibberellic acid treatment of prostate cancer (where the horizontal axis is the enrichment factor and the vertical axis is the GO functional name)

3.6. KEGG pathway enrichment analysis

173 signaling pathways were screened in the KEGG pathway enrichment analysis, and the top 20 pathways were taken for KEGG visualization to draw a bubble map (see Figure 9). The main pathways related to prostate cancer are cancer pathway, proteoglycan signaling pathway in cancer, microRNA pathway in cancer and thyroid hormone signaling pathway. The results suggest that gibberellic acid exerts its therapeutic effect on prostate cancer by acting on multiple signaling pathways.

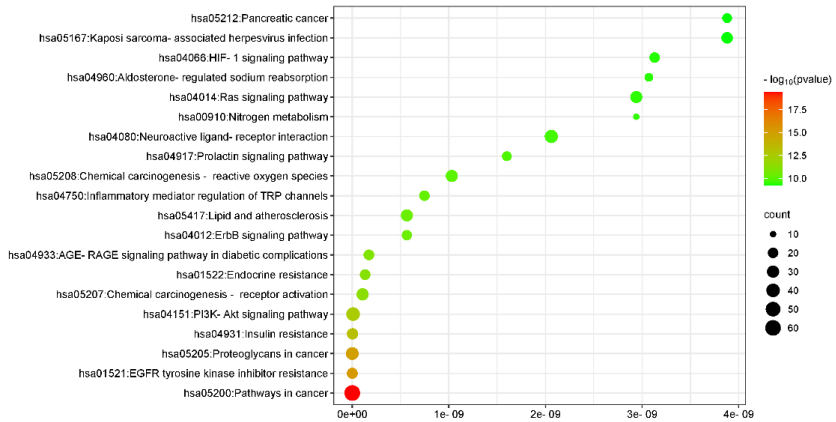

Figure 9: Bubble plot of KEGG pathway enrichment analysis results of gibberellic acid treatment of prostate cancer (where the horizontal axis is the enrichment factor and the vertical axis is the pathway name)

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3.7. "Drug-Component-Target-Disease" Network Construction

Cytoscape 3.9.1 software was used to construct a "drug-component-target-disease" network diagram (see Figure 10), in which the number of associations between nodes was predicted by the degree value (degree), and the larger the degree value indicated that the component or target was more important, and the component with the highest degree value was the component with the degree value of 49. Quercetin LXXIX (quercetin)

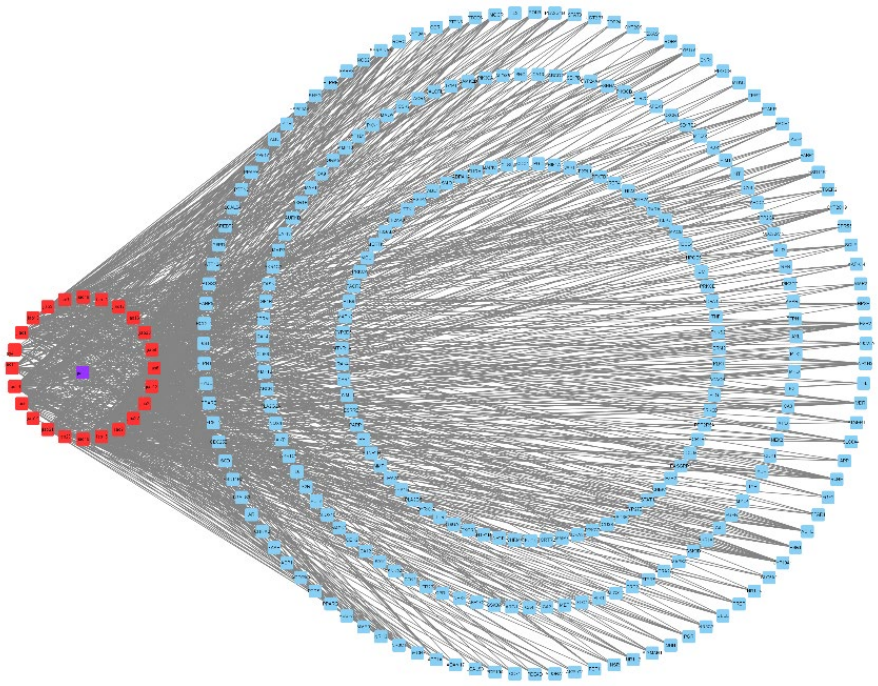
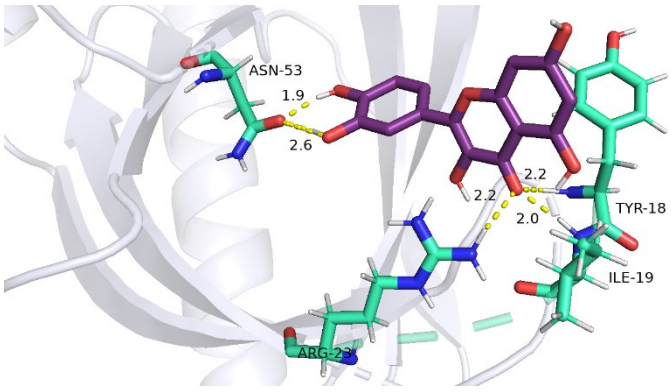


Figure 10: Drug-component-target-disease (DCTD) diagram of gibberellic acid against prostate cancer

3.8. Molecular docking validation

In this study, we compared the top-ranked targets AKT1, IL6 and STAT3 with the top-ranked targets AKT1, IL6 and STAT3 in the PPI network with the top-ranked targets LXXIX in the "active ingredient targets" network diagram. Gynostemma glycoside LXXIX. The target proteins were used as receptors and the active ingredients as ligands, and the lowest binding energy was used as the result of docking between the target proteins and ligands, which was analyzed and visualized using Pymol software (see Figure 11). If the binding energy is <-5.0 kcal/mol, it indicates that the target protein binds well to the active ingredient, and the smaller the binding energy, the better the docking between the two. According to the docking results, the binding energies of both components and targets were less than zero, indicating that most of the components and targets had good binding activities. The study confirmed that the core targets of Gynostemma gibberelliforme and the corresponding active ingredients were well docked.



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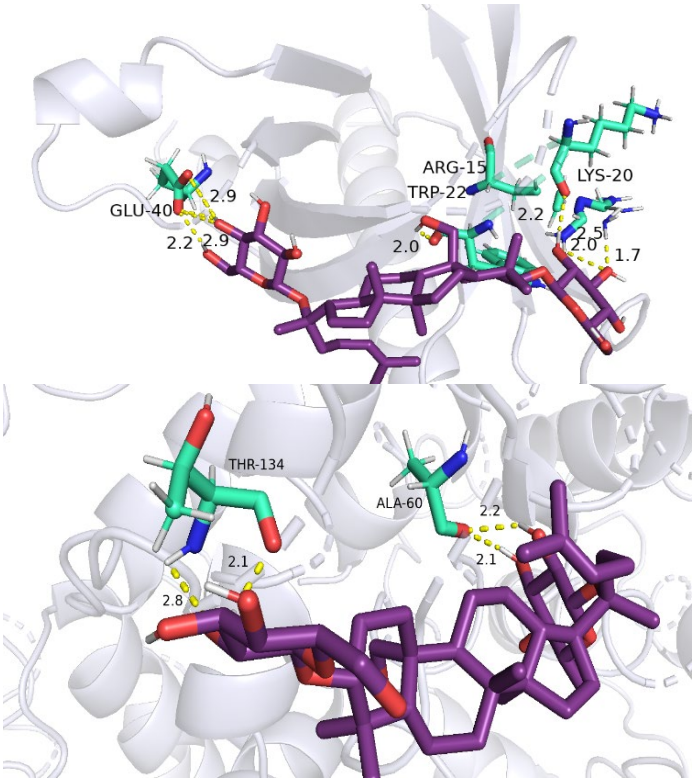

Figure 11: Visualization and analysis of molecular docking results

4. Discussion

Prostate cancer is a highly heterogeneous disease whose morbidity and mortality are increasing year by year, posing a serious threat to patients' life, health and quality of life. Emotional and emotional disorders, positive deficiency, dampness, phlegm, silt and toxicity are the core etiology and pathogenesis of prostate cancer [9]. Contemporary Chinese medicine practitioners also follow this theory, and take supporting the positive and dispelling the evil, dispersing the dampness and removing the phlegm and toxin as the basic treatment of prostate cancer [10]. Contemporary Chinese medicine also follows this theory. In China, Chinese medicine therapy has become one of the important means of prostate cancer treatment. Gynostemma has pharmacological activities such as anti-inflammatory, antibacterial, and immunomodulatory activities, and some studies have shown that the active ingredient of gynostemma, gynostemma glycoside LXXIX, can play an anti-tumor role by regulating various cell signaling pathways, and is closely related to many important molecular targets, such as cell growth, differentiation, and apoptosis. However, during the study of TCM pharmacology, we were unable to identify the mechanism of action due to the complexity of TCM components. The emergence of network pharmacology provides a new method for the study of single and formulated Chinese medicines. Compared with traditional screening experiments, network pharmacology is characterized by high efficiency and purposefulness, which greatly reduces the ineffective and blind pre-experiments [11]. The results of network pharmacology are summarized in the following table.

In this study, based on the network pharmacology method, a total of 24 effective active ingredients such as gibberellin LXXIX were screened by TCMSP database analysis, and the intersections were obtained by mapping the mined gibberellin active ingredient-related targets with the prostate cancer disease target import software VENNY 2.1.0, while the PPI network analysis showed a close connection between these intersected targets. It has been shown that gibberellin LXXIX has pharmacological effects such as inhibiting tumor cell proliferation and inducing apoptosis of tumor cells [12,13]. Gynostemma glycoside LXXIX is the main representative of the flavonol flavonoid subclass with high potential for chemopreventive effects, which have been demonstrated in in vitro and in vivo models.The anticancer effects of gynostemma glycoside LXXIX are dependent on its ability to reduce proliferation, induce apoptosis, lead to cell cycle through the regulation of the molecular pathways of cell cycle proteins, pro-apoptotic, PI3K/Akt, and mitogen-activated protein kinase (MAPK) blockade, and inhibit mitotic processes [14]. The Thus, gibberellins may exert antitumor effects like their active

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ingredient gibberellin LXXIX.

The network diagram of "drug-component-target-disease" showed that 285 targets were obtained after the intersection of gibberellic acid and prostate cancer targets, and the target proteins of gibberellic acid such as AKT1, IL6, and STAT3 were found to be the target of gibberellic acid, which revealed the material basis and molecular mechanism of gibberellic acid's antiprostate cancer. The GO enrichment analysis showed that the target genes of gibberellic acid against prostate cancer involved the positive regulation of kinase activity, the activity of binding protein serine/threonine kinase, the positive regulation of MAPK cascade, the positive regulation of PI3K signaling, and the binding of ATP, which play important roles in gibberellic acid's treatment of prostate cancer. Through KEGG pathway enrichment analysis, it was found that gibberellic acid has a total of 173 pathways against prostate cancer, mainly cancer pathway, proteoglycan signaling pathway in cancer, micro RNA pathway in cancer, and thyroid hormone signaling pathway, etc. EGFR-TKI directly affects the intracellular protein tyrosine kinase of EGFR, and competitively binds to the tyrosine kinase with ATP to inhibit the tyrosine kinase phosphorylation, which in turn affects the tumor cell proliferation and the growth of the tumor cells. And thus affects the processes of tumor cell proliferation, differentiation, invasion and neovascularization, thus achieving the effect of targeted treatment of EGFR mutations [15]. MicroRNAs in cancer can be abnormally expressed in various types of tumors and tumor tissues, and participate in tumor cell proliferation, migration, invasion, apoptosis, etc [16]. Thyroid hormone can promote angiogenesis, anti-apoptosis, and inhibit the growth and metastasis of tumor cells [17]. Thyroid hormone can promote angiogenesis, anti-apoptosis, inhibit tumor cell growth and metastasis.

The molecular docking technique was used to investigate the binding force between the key active ingredients of gibberellins and target proteins, and the results showed that gibberellin LXXIX and other active ingredients had good binding activity with the targets AKT1, IL6 and STAT3, reflecting that the main mechanism of gibberellin in the treatment of prostate cancer may be closely related to the above components and targets, and that gibberellins may exert certain therapeutic effects on prostate cancer through multi-targets and multi-signal pathways. Gynostemma may have certain therapeutic effects on prostate cancer through multi-targets and multi-signal pathways.

In summary, this study applied the network pharmacology data platform to analyze and screen the main active ingredients of gibberellic acid and the disease targets of prostate cancer, and at the same time analyzed the mechanism of action of gibberellic acid in the treatment of prostate cancer in multi-components, multi-targets, and multi-pathways, and the results showed that gibberellic acid may act on the core targets such as AKT1, IL6, and STAT3 through a variety of active ingredients, such as gibberellic acid LXXIX, and regulate prostate cancer through the pathways of cancer The results indicate that gynostemma may act on the core targets such as AKT1, IL6 and STAT3 through the cancer pathway, proteoglycan signaling pathway, microRNA pathway and thyroid hormone signaling pathway, and play the roles of inhibition of proliferation and metastasis of tumor, anti-inflammation and regulation of the microenvironment of the tumor cells in the treatment of prostate cancer, which provides theoretical bases for the follow-up research and clinical treatment of prostate cancer.

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