

ORIGINAL RESEARCH

The use of network pharmacology to investigate the mechanism of action of *Scutellaria barbata* in the treatment of prostate cancer

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(Guanxiong Ding)[†] These authors contributed equally.**Abstract**

We aimed to identify the mechanism of action of the *Scutellaria barbata* in the treatment of prostate cancer. First, the main active components of *Scutellaria barbata* for the treatment of prostate cancer were predicted by network pharmacology. Disease-related targets were then retrieved from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP); GeneCards: The Human Gene Database; and the Online Catalog of Human Genes and Genetic Disorders (OMIM). Then, we identified intersecting genes between the components and targets. Cytoscape software was then used to construct a “Drug-Ingredient-Disease-Target” network. We also used the STRING platform to perform protein interaction analysis. R software was used to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Our analysis identified 212 potential targets for *Scutellaria barbata* in the treatment of prostate cancer; these were closely related to a number of specific pathways, including prostate cancer, the advanced glycation end products and their receptors (AGE-RAGE) signaling pathway in diabetic complications, lipids and atherosclerosis, hepatitis B, fluid shear stress and atherosclerosis, chemical carcinogenesis, receptor activation, Kaposi's sarcoma-associated herpesvirus infection, and human cytomegalovirus infection. Furthermore, the treatment of prostate cancer with *Scutellaria barbata* may act via a range of biological processes, including responses to xenobiotic stimuli, lipopolysaccharides and metal ions. Several molecular functions may be involved, including DNA-binding transcription factor binding, RNA polymerase II-specific DNA-binding transcription factor binding, and nuclear receptor activity. Our research demonstrates the multi-component, multi-target, multi-pathway, and synergistic characteristics of *Scutellaria barbata* for the treatment of prostate cancer, and provides theoretical guidelines for further elucidating its mechanism of action.

KeywordsProstate carcinomatosis; *Scutellaria barbata*; Network pharmacology; Antitumor

1. Introduction

Prostate cancer is a deadly disease of the genitourinary system that is most commonly detected in middle-aged and elderly males; this disease has become the fourth most deadly disease in the world [1, 2]. As the aging population in China increases, and dietary habits change, the prevalence of prostate cancer is increasing annually, thus representing a severe threat to the health of middle-aged and elderly males [3, 4].

The medicinal use of *Scutellaria barbata* was first recorded in the “Authentic Surgery” publication in the Ming Dynasty. This plant is also known as Hanshin narrow leaf herb, tooth-brush herb, *Hedysarum uniflorum* herb, and golden trefoil [5]. This is an exsuccous complete herb of *Scutellaria barbata* a plant of the *Scutellaria* genus in the family of Lamiaceae family

[6]. *Scutellaria barbata* is pungent, bitter and cold, and can eliminate heart, detoxify, enhance the blood cycle, and remove blood stagnation, swelling and pain [7, 8]. Recent research has shown that *Scutellaria barbata* and its active ingredients exert obvious therapeutic effects on prostate cancer; furthermore, the extract of this herb has been used for the treatment of prostate cancer, particularly from a mechanistic point of view.

Scutellaria barbata, is a plant-based medicine, that has been shown to inhibit the proliferation, migration and invasion of cancer cells. It has also been shown to suppress tumor growth, metastasis, angiogenesis and induce autophagy and apoptosis in colorectal and prostate cancer via the miR-195-5p/Lysyl Oxidase Like 2 (LOXL2) axis and the Phosphatidylinositol-3 kinase/AKT Serine/Threonine Kinase 1 (PI3K/AKT) pathways [9, 10]. In addition, *Scutellaria barbata* can exhibit a range

of pharmacological activities and can be applied clinically in different scenarios.

Based on this background, we aimed to use network pharmacology to perform “multi component, multi target and multi pathway” analysis to comprehensively and systematically investigate the potential actions of the main active ingredients of *Scutellaria barbata* from the perspective of prostate cancer treatment [11]. We hope that our findings can facilitate future research to elucidate the precise mechanisms involved in the effect of *Scutellaria barbata* on prostate cancer [12, 13].

2. Materials and methods

2.1 Identification of the active ingredients of *Scutellaria barbata*

Using *Scutellaria barbata* as the key word, the active ingredients were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP). Using an oral bioavailability of $\geq 30\%$ and a dry-like value ≥ 0.18 as thresholds for filtering, we were able to identify a range of potential active ingredients in *Scutellaria barbata*. Gene information was standardized adopting the UniProt database, and genes without “*Homo sapiens*” and “reviewed” UniProt IDs were excluded.

2.2 The identification of target genes associated with prostate cancer

Next, we used the GeneCards database (<https://www.genecards.org/>) and the Online Catalog of Human Genes and Genetic Disorders (OMIM, <https://www.omim.org/>) to identify target genes associated with prostate cancer. We set the search term to “prostate cancer” to identify known target gene information related to prostate cancer; then, we summarized and deleted duplicate genes.

2.3 Collection of underlying therapeutic targets for *Scutellaria barbata* for the treatment of prostate cancer

Next, we used R (version 4.1.2, R Foundation, Bell Laboratories, Murray Hill, NJ, USA) to intersect the active ingredients and disease targets. Then, we used the “venn” package in R to generate Venn diagrams for active ingredients and targets and identify intersecting targets between the two datasets.

2.4 Construction of a “drug-component-disease-target” network

Next, we imported the active ingredients and disease targets identified earlier into Cytoscape (version 3.9.0, National Institute of General Medical Sciences (NIGMS), Bethesda, MD, USA) software to construct a “drug-component-disease-target” network.

2.5 Construction of a protein interaction network

Next, we imported the active ingredients and disease targets into the STRING database. The credibility of the albumose–

albumose interaction in the STRING database is divided into three grades. An interaction score >0.7 represents high credibility, while a score of $0.4–0.7$ represents medium credibility, and a score of $0.15–0.4$ represents low credibility. In this study, we selected targets with an interaction reliability >0.9 and hidden free nodes to build an albumose reaction network for the use of *Scutellaria barbata* in the treatment of prostate cancer targets. This network was downloaded in both Portable Network Graphics (PNG) and Tab-separated values (TSV) format files.

2.6 Filtration of key objects for the treatment of prostate cancer with *Scutellaria barbata*

The TSV file was then imported in Cytoscape version 3.9.0 software. Then, we used the CytoNCA plug-in to analyze the network, identify the topological attributes of the protein–protein interaction (PPI) network, and filter out the nodes in the network whose degree centrality, network centrality, between centrality, closeness centrality, Eigen vector centrality and local average connectivity were greater than the median of the above indicators for all nodes. This analysis identified the key objects for the use of *Scutellaria barbata* in the treatment of prostate cancer.

2.7 Gene ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

Next, we used R version 4.1.2 software to perform for target gene GO function and KEGG pathway enrichment analysis using the “colorspace”, “stringi” and “ggplot2” packages in R. GO functional analysis featured biological processes (BPs), cellular components (CCs), and molecular functions (MFs); results were output in the form of bubble charts. Then, we used R software, the Pathview software package, and the KEGG pathway database to identify and download a map of the top-ranked pathways.

3. Results

3.1 Identification of the active ingredients of *Scutellaria barbata*

A total of 29 active ingredients in *Scutellaria barbata* were identified by the TCMSP database. The target proteins of these 29 active ingredients were then analyzed. The Gene Symbols consistent with these target proteins were retrieved using the UniProt database, resulting in a total of 229 potential targets for *Scutellaria barbata*, as shown in Table 1.

3.2 The identification of potential therapeutic targets for *Scutellaria barbata* in the treatment of prostate cancer

A total of 14,123 target genes related to prostate cancer were acquired from the GeneCards and OMIM databases. The potential targets of *Scutellaria barbata* and targets related to prostate cancer were intersected using R software and a Venn

TABLE 1. The active ingredients of *Scutellaria Barbara*.

Mol ID	Molecule Name	oral bioavailability (OB) (%)	drug-like properties (DL)
MOL001040	(2R)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one	42.36	0.21
MOL012245	5,7,4'-trihydroxy-6-methoxyflavanone	36.63	0.27
MOL012246	5,7,4'-trihydroxy-8-methoxyflavanone	74.24	0.26
MOL012248	5-hydroxy-7,8-dimethoxy-2-(4-methoxyphenyl)chromone	65.82	0.33
MOL012250	7-hydroxy-5,8-dimethoxy-2-phenyl-chromone	43.72	0.25
MOL012251	Chrysin-5-methylether	37.27	0.20
MOL012252	9,19-cyclolanost-24-en-3-ol	38.69	0.78
MOL002776	Baicalin	40.12	0.75
MOL012254	Campesterol	37.58	0.71
MOL000953	cholesterol (CLR)	37.87	0.68
MOL000358	beta-sitosterol	36.91	0.75
MOL012266	Rivularin	37.94	0.37
MOL001973	Sitosteryl acetate	40.39	0.85
MOL012269	Stigmasta-5,22-dien-3-ol-acetate	46.44	0.86
MOL012270	Stigmastan-3,5,22-triene	45.03	0.71
MOL000449	Stigmasterol	43.83	0.76
MOL000173	Wogonin	30.68	0.23
MOL001735	Dinatin	30.97	0.27
MOL001755	24-Ethylcholest-4-en-3-one	36.08	0.76
MOL002714	Baicalein	33.52	0.21
MOL002719	6-Hydroxynaringenin	33.23	0.24
MOL002915	Salvigenin	49.07	0.33
MOL000351	Rhamnazin	47.14	0.34
MOL000359	sitosterol	36.91	0.75
MOL005190	eriodictyol	71.79	0.24
MOL005869	daucostero_qt	36.91	0.75
MOL000006	luteolin	36.16	0.25
MOL008206	Moslosooflavone	44.09	0.25
MOL000098	quercetin	46.43	0.28

diagram was drawn to identify 212 common targets for drugs and diseases, as shown in Fig. 1.

3.3 Construction of a "drug-component-disease-target" network

Fig. 2 shows a "drug-component-disease-target" network of the 29 main active ingredients of *Scutellaria barbata* and the treatment of prostate cancer. The purple diamond represents the effective ingredients of *Scutellaria barbata*, and the green circle stands represents the intersections between *Scutellaria barbata* and prostate cancer. Analysis highlighted a variety of ingredients and a range of synergistic effects.

3.4 Construction of a protein interaction networks

The protein interaction network obtained from the STRING database is shown in Fig. 3. Nodes represent targets, edges represent associations between targets, different colors of edges

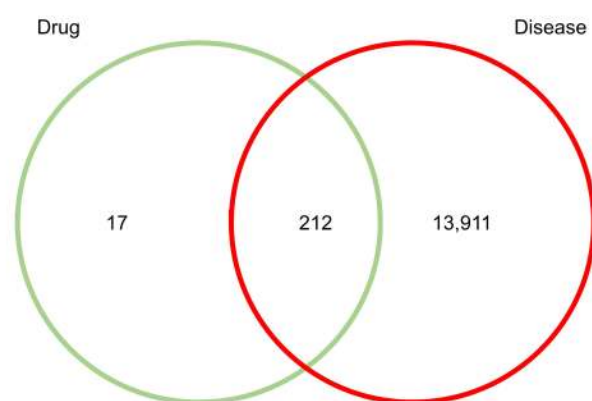


FIGURE 1. Venn diagram showing the common targets for the treatment of prostate cancer with *Scutellaria barbata*.

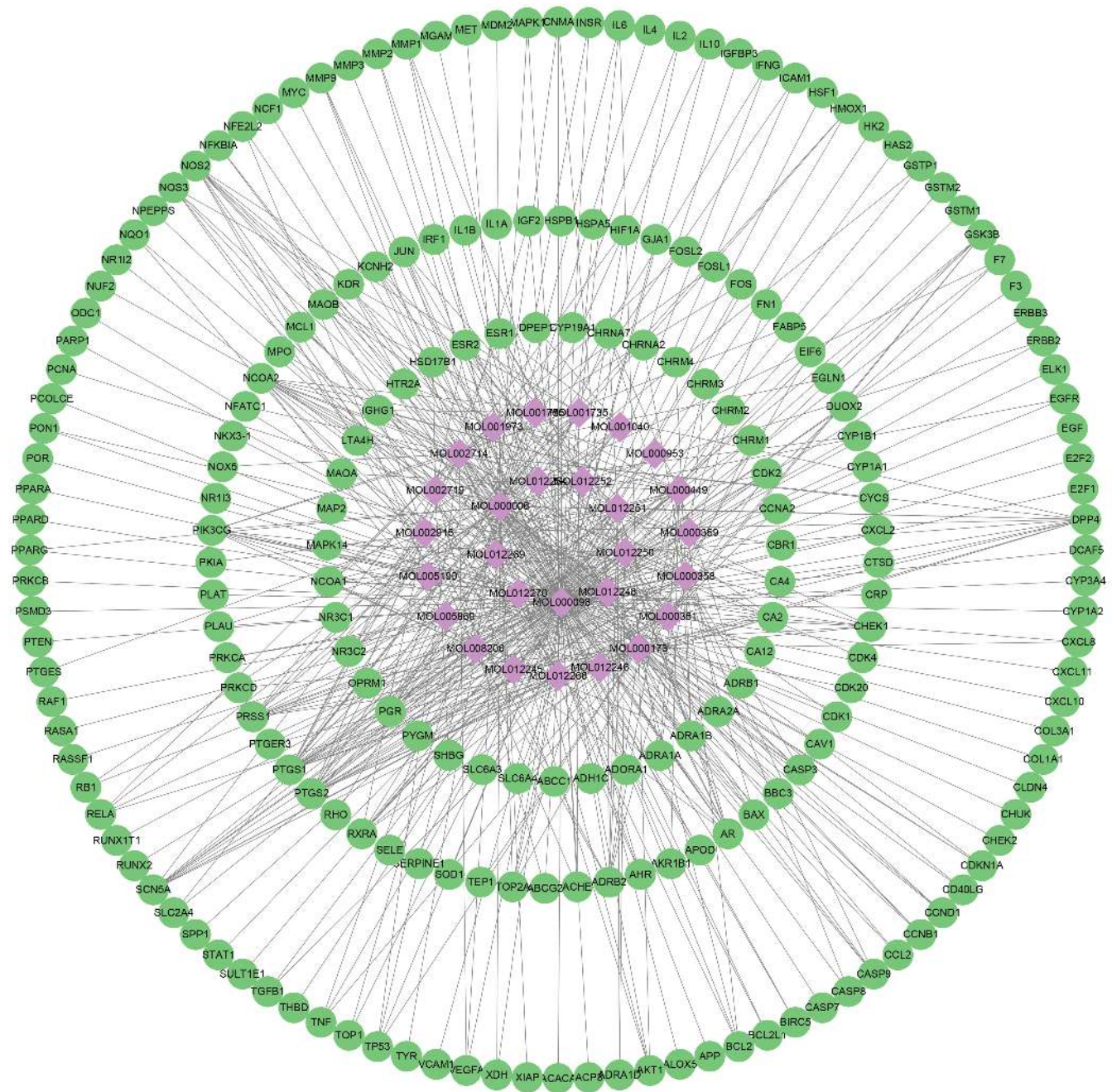


FIGURE 2. Network showing active ingredients and common disease targets associated with the treatment of prostate cancer with *Scutellaria barbata*.

represent different types of evidence, and the thickness of the edges represent different combined scores. The thicker the edges, the higher the association score.

3.5 Filtration of key objects for the therapy of prostate cancer with *Scutellaria barbata*

Next, we selected target genes by Cytoscape version 3.9.0 software and the CytoNCA plugin and identified 16 key nodes based on degree centrality, network centrality, betweenness centrality, closeness centrality, Eigen vector centrality, and local average connectivity (LAC) after two rounds of screening. Fig. 4 shows the key target genes for the treatment of prostate

cancer with *Scutellaria barbata*: Mitogen-Activated Protein Kinase 1 (*MAPK1*), AKT Serine/Threonine Kinase 1 (*AKT1*), Estrogen Receptor 1 (*ESR1*), MYC Proto-Oncogene (*MYC*), Hypoxia Inducible Factor 1 Subunit Alpha (*HIF1A*), Tumor Protein P53 (*TP53*), Nuclear Receptor Subfamily 3 Group C Member 1 (*NR3C1*), RB Transcriptional Corepressor 1 (*RBI*), RELA Proto-Oncogene (*RELA*), Cyclin D1 (*CCND1*), Cyclin Dependent Kinase Inhibitor 1A (*CDKN1A*), Interleukin 6 (*IL6*), Fos Proto-Oncogene (*FOS*), Tumor Necrosis Factor (*TNF*), *MAPK14* and Jun Proto-Oncogene (*JUN*).

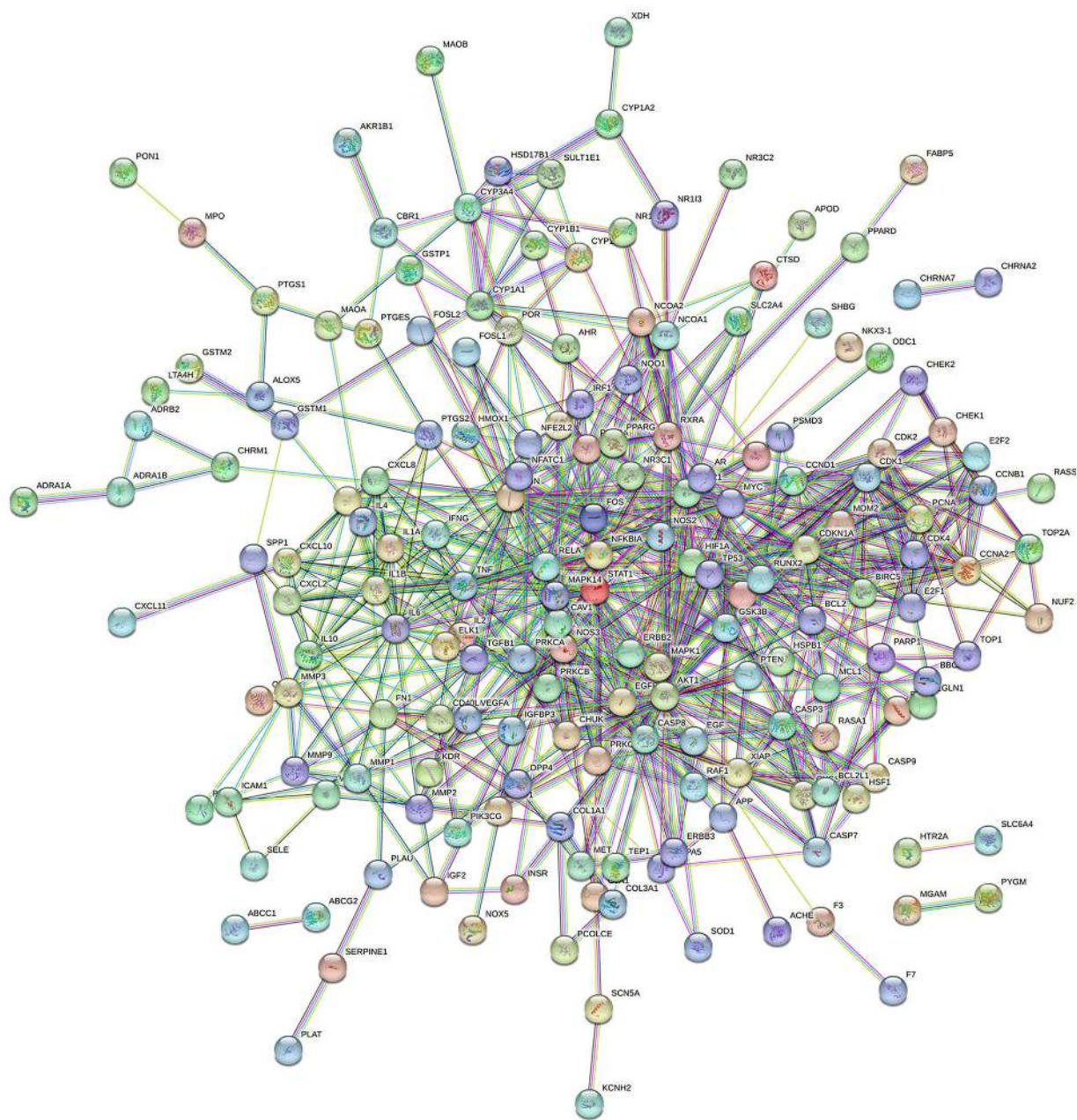


FIGURE 3. PPI network of *Scutellaria barbata* in the treatment of prostate cancer.

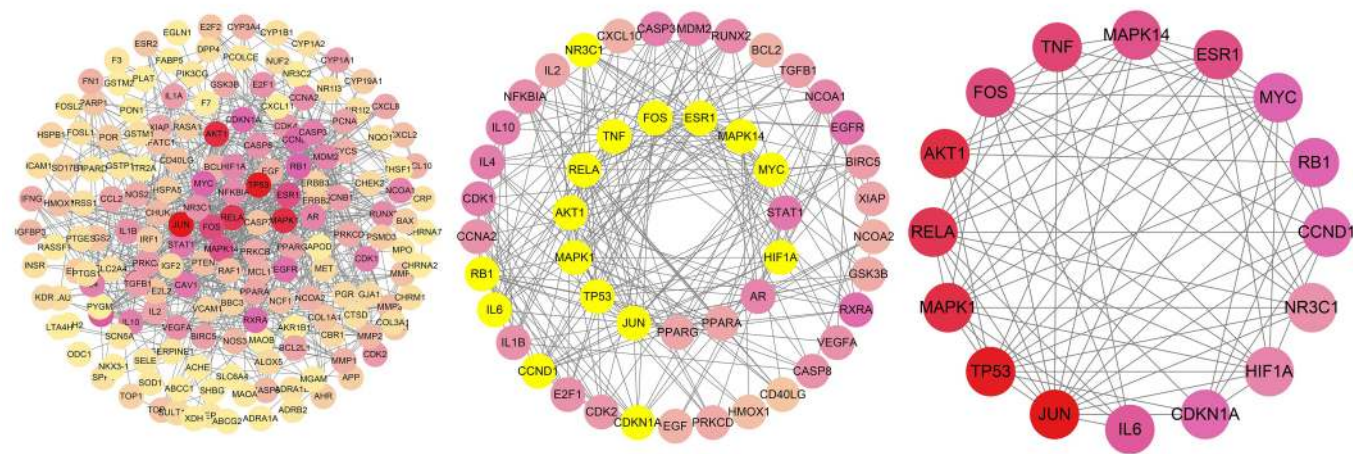


FIGURE 4. The core targets of *Scutellaria barbata* in the treatment of prostate cancer.

3.6 GO functional enrichment analysis

Next, we conducted GO functional enrichment analysis on the potential targets of prostate cancer using R software. Based on corrected p -values, the top 10 BP-related GO entries were sorted from small to large. The top 10 GO entries related to transcription functions, including DNA-bundled translation element binding, RNA polymerase II precise DNA-bundled translation element binding, nuclear receiver activity, ligand-stimulated translation element activity, G albumose connected amine receiver activity, and other functions. The top 10 CC-related GO items were membrane microdomain, adtevak panniculus raft, Caveola, cyclin servient albumose kinase holoenzyme complex, and other components. These data indicate that *Scutellaria barbata* might control a variety of complicated biotic procedures to impose a variety of pharmacological influences. The enrichment outcomes are presented in order of importance, as shown in Fig. 5. The horizontal axis in the figure represents the number of genes enriched on the item, while the vertical axis represents the name of the item. The redder the color, the greater the significance.

3.7 KEGG pathway enrichment analysis

Using R software, we conducted KEGG pathway enrichment analysis for the active targets of *Scutellaria barbata* in the treatment of prostate cancer; this resulted in a total of 174 pathways ($p.adjust < 0.05$, $Q < 0.05$), predominantly involving prostate carcinomatosis, the AGE-RAGE signaling pathway in diabetic applications, lipid and atherosclerosis, hepatitis B, bladder carcinomatosis, fluid shear stress and atherosclerosis, and chemical malignant tumors. Fig. 6 shows the enrichment results in order of importance. The horizontal axis in the figure represents the number of genes enriched on the pathway, while the vertical axis represents the pathway name. The redder the color, the greater the significance. The more target genes on the pathway, the greater the significance. Our data indicates that *Scutellaria barbata* is more likely to exert pharmacological effects during the treatment of prostate cancer by regulating the pathways shown.

4. Discussion

Prostate cancer is one of the most deadly diseases of the genitourinary system in men [2, 14, 15]. With the progression of China's economy, the improvements in medical care, changes in lifestyle, and the extension of life expectancy, the incidence of prostate cancer has continued to rise [4, 16, 17].

Scutellaria barbata can eliminate heat, detoxify, disperse blood stasis, prevent bleeding, diuresis and can reduce swelling [18]. This herb is mainly used to cure hot toxic carbuncles, sore throats, snake bites, bruises, edema and ascites. In the Traditional Chinese Medicine (TCM) clinic, *Scutellaria barbata* is often used in combination with other drugs such as *Scleromitrion diffusum* to treat tumors [19]. By analyzing the experience and prescriptions of TCM in treating tumors, it was found that *Scutellaria barbata* is the most frequently used drug and one of the most important TCM for treating prostate cancer [20, 21]. The main components of *Scutellaria barbata* include flavonoids, alkaloids, organic acids,

sterols, terpenoids, polysaccharides and other compounds. The flavonoids of *Scutellaria barbata* mainly include scutellarein, luteolin, scutellarin (SCU), apigenin, wogonin, baicalin and naringenin [22].

At present, the formulations related to *Scutellaria barbata* in the domestic pharmaceutical market include *Scutellaria barbata* tablets, Shenlian capsules, Reyaning tablets (capsules) and other varieties. Furthermore, hospital formulations also include compound injections, drop pills, capsules, eye drops and oral liquids. Over recent years, new formulations such as *Scutellaria barbata* TCM formula granules have been developed. *Scutellaria barbata*, as the preferred TCM for cancer treatment, has become popular in the international market and has significant potential for development. Therefore, further clarification of its pharmacological basis is needed to ensure the efficacy of clinical application [5, 23].

Over recent years, studies have shown that *Scutellaria barbata* and its active ingredients have obvious therapeutic effects on prostate cancer, and its extract has been used in mechanistic research relating to the treatment of prostate cancer [24, 25]. Scutellaria barbata B is a diterpene alkaloid compound extracted from *Scutellaria barbata*, that can inhibit the progression of human prostate carcinogenesis cells in a dose-dependent manner, thus treating the aggression and metastasis of prostate cancer [26]. SCU inhibits the growth of human brain prostate carcinogenesis cells in a dose-dependent manner [27]; the pharmacological mechanism involved is that SCU reduces the presence of therapeutic anti-dead albumose Bcl2 in human prostate cancer cells, thereby increasing the Associated X Protein (bax)/B cell lymphoma2 (Bcl2) ratio in human brain prostate cancer cells, thus promoting apoptosis and exerting an inhibitory effect on invasion and metastasis in the prostate [9, 28]. In addition, Luteolin can constrain the angiogenesis of endothelial cells by reducing the expression of vascular endothelial growth factor, thus reducing the aggression of prostate cancer [29, 30].

Our study presents an interesting theoretical framework and draws conclusions based on enrichment analyses and predictions so that we can understand the potential effects of *Scutellaria barbata* in the treatment of prostate cancer. However, our findings should be treated with caution. Extensive experimental validation and further bioinformatic analysis is required.

5. Conclusions

In this study, we used network pharmacology to identify the core components and mechanisms of action of *Scutellaria barbata* in the treatment of prostate cancer [31]. *Scutellaria barbata* synergistically exerts its therapeutic effect on prostate cancer at multiple levels through multiple components, genes and pathways; this is consistent with the features of several diseases with TCM [32]. Our findings provide a theoretical basis and direction for the investigation of specific molecular mechanisms, the development of new experimental designs, and provides new ideas and methods for the screening and development of new TCM drugs.

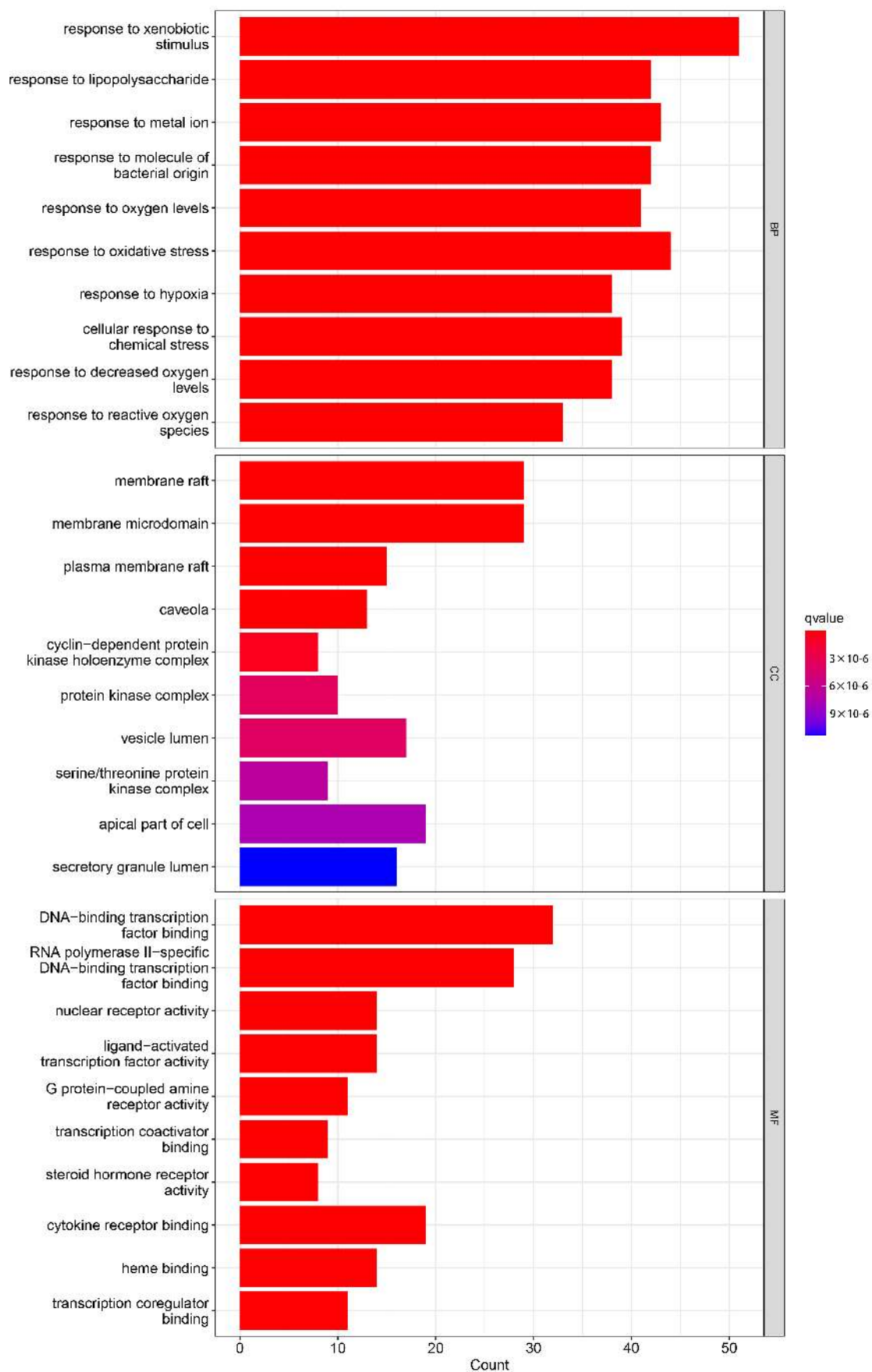


FIGURE 5. GO enrichment analysis of *Scutellaria Barbara* in the treatment of prostate cancer.

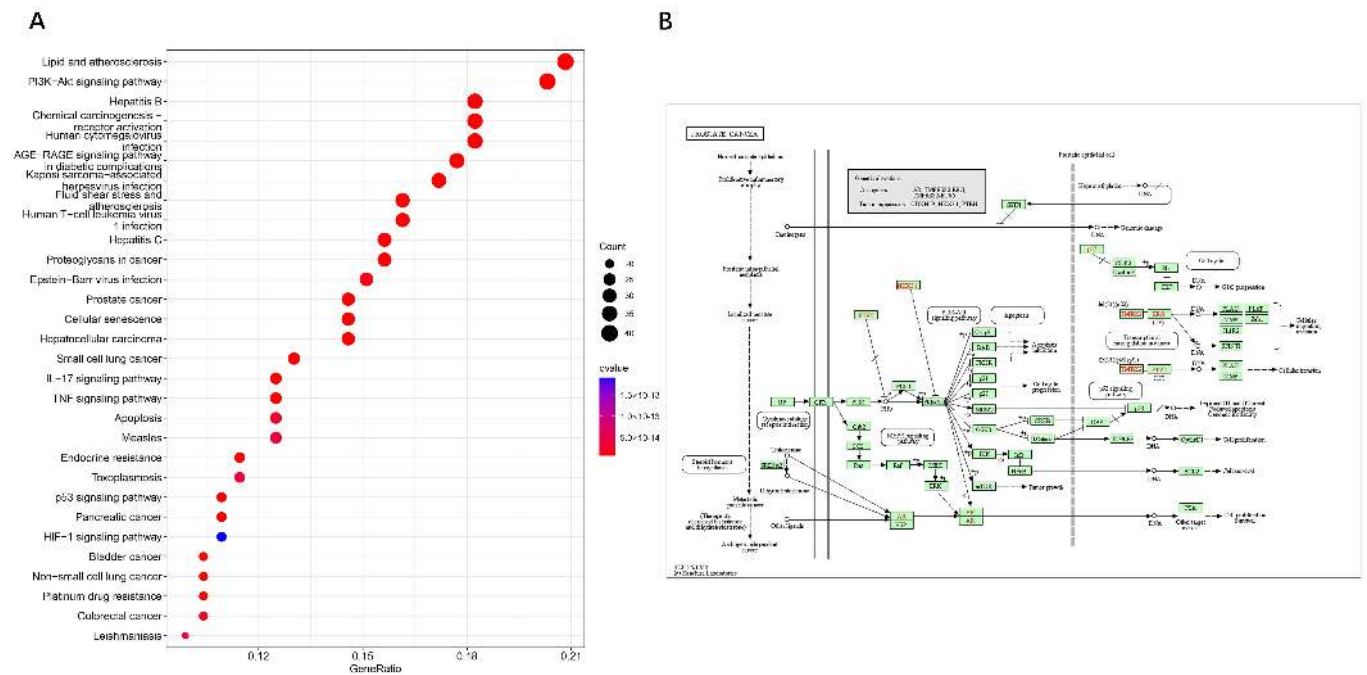


FIGURE 6. KEGG pathway enrichment analysis of *Scutellaria barbata* in the treatment of prostate cancer (A), the prostate cancer signaling pathway (B).

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

GXD and WHZ—designed the research study; wrote the manuscript. RJY, WHZ and LLM—performed the research. SJT and JZ—analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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