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Study on the Mechanism of Salvia Miltiorrhiza in the Treatment of Prostatic Hyperplasia Based on Online Pharmacology

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Abstract: Objective: This study aims to investigate the potential molecular mechanism of Salvia miltiorrhiza in treating benign prostatic hyperplasia (BPH) based on network pharmacology. **Methods:** Active components of Salvia miltiorrhiza were screened via the TCMSP database, and their potential targets were predicted using Swiss Target Prediction. BPH-related targets were obtained from Gene Cards and OMIM databases. Common targets between the herb and BPH were used to construct a protein–protein interaction (PPI) network via STRING and visualized using Cytoscape. Core targets were identified, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted ($P \leq 0.01$). **Results:** A total of 57 active components and 818 targets of Salvia miltiorrhiza were identified. Intersection analysis yielded 458 potential targets associated with BPH. PPI network analysis revealed core targets including SRC, PIK3R1, and PIK3CA. GO enrichment analysis indicated that the targets were primarily associated with biological processes (BP) such as calcium ion homeostasis, cellular components (CC) including focal adhesions, and molecular functions (MF) such as tyrosine kinase activity. KEGG pathway analysis indicated that Salvia miltiorrhiza may exert therapeutic effects through pathways including MAPK, PI3K-Akt, and calcium signaling ($P \leq 0.01$).**Conclusion:** Salvia miltiorrhiza may regulate BPH through a multi-component, multi-target, and multi-pathway network, providing a theoretical basis for its clinical application.

Keywords: Salvia Miltiorrhiza; Benign Prostatic Hyperplasia; Network Pharmacology; Active Components; Signaling Pathway; Molecular Mechanism
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Preface

Benign prostatic hyperplasia (BPH) is a common urological disease in middle-aged and elderly men, characterized by abnormal proliferation of prostate stromal and glandular cells, leading to urethral obstruction. Clinically, it is manifested as frequent urination, urgency, and difficulty in urination, seriously affecting the quality of life of patients[1, 2]. According to statistics, the incidence of BPH in men over 60 years old exceeds 50% globally, and it reaches 83% in those over 80 years old [3]. Although modern medical treatment mainly relies on α-receptor blockers (such as tamsulosin),

5α-reductase inhibitors (such as finasteride), and surgery, these methods have side effects such as drug tolerance and sexual dysfunction [4, 5]. Therefore, exploring safer and more effective treatment strategies has become a current research hotspot.

Traditional Chinese medicine (TCM) shows unique advantages in the treatment of BPH. Its multi-target and low-toxicity characteristics make it a potential treatment option. Among them, Salvia miltiorrhiza Bge., as a representative of blood-activating and stasis-resolving herbs, has been widely used in clinical practice and has significant effects in improving the urination function and microcirculation of the prostate in BPH patients[6, 7]. The active components of Salvia miltiorrhiza include tanshinones (such as tanshinone IIA and cryptotanshinone), salvianolic acids (such as salvianolic acid B), and volatile oils, etc.[8]. Modern pharmacological studies have shown that Salvia miltiorrhiza has significant therapeutic effects on BPH model animals through mechanisms such as anti-inflammation, antioxidation, inhibition of cell proliferation, and regulation of apoptosis[8, 9]. However, its mechanism of action is not yet fully understood, especially the synergistic mechanism of the "component - target - pathway" network, which still requires in-depth research.

Network pharmacology, as an emerging method integrating systems biology and pharmacology, can systematically analyze the multi-target action mechanism of traditional Chinese medicine formulas through the construction of "drug - component - target - disease" networks [10]. This study takes Salvia miltiorrhiza as the object and, relying on databases such as TCMSP and Swiss Target Prediction, constructs a "component - target - pathway" network to reveal the potential molecular mechanism of Salvia miltiorrhiza in the treatment of BPH, providing a theoretical basis for its clinical precise medication and new drug development.

1.Materials and Methods

1.1 Screening of Salvia miltiorrhiza components entering the blood

The active components of Salvia miltiorrhiza were retrieved from the Traditional Chinese System Pharmacology Database and Analysis Platform (TCMSP, https://tcmspw.com/tcmsp.php). According to the TCMSP target screening guidelines and compound ADME (absorption, distribution, metabolism, excretion) parameters, the conditions of oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥0.18 were set to screen and establish a database of core components of Salvia miltiorrhiza[11].

1.2 Prediction of Salvia miltiorrhiza active component targets

The collected chemical components were imported into the Swiss Target Prediction database (http://swisstargetprediction.ch/), and the targets with a result Probability greater than 0 were selected to establish a compound target database and imported into Cytoscape 3.7.2 for visualization.

1.3 Collection of potential targets for the treatment of BPH by Salvia miltiorrhiza 1.3 Gene search and target identification

The human gene database GeneCards (https://www.genecards.org/) and OMIM database (Online Mendelian Inheritance in Man, http://www.omim.org) were used to search for genes related to benign prostatic hyperplasia (BPH) with the keyword "benign prostatic hyperplasia". Duplicates were removed, and the intersection with the targets of the core components of Salvia miltiorrhiza was taken to obtain the potential targets of Salvia miltiorrhiza in the treatment of BPH.

1.4 Construction of protein-protein interaction network

The targets collected in 1.3 were imported into the STRING platform (https://string-db.org/) for protein-protein interaction (PPI) analysis. The species was set as human, and the minimum interaction threshold was set to 0.9 for screening. Disconnected nodes were hidden to construct the PPI network relationship. The results were downloaded in*.tsv format and imported into Cytoscape 3.7.2 for visualization. The Network analyzer plugin was used to analyze the network characteristics of the targets.

1.5 Gene ontology and signaling pathway analysis

The potential targets of Salvia miltiorrhiza in the treatment of BPH were analyzed for gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment using Xiantao Academic Platform. The data obtained from the enrichment analysis tool were sorted according to -10gP value. The top 10 entries of GO biological processes (BP), cellular components (Cc), and molecular functions (MF) were selected, and the top 10 entries of KEGG pathway enrichment analysis results were selected. Enrichment plots were drawn for each.

2.Results

2.1 Prediction results of core components and targets of Salvia miltiorrhiza

A total of 57 active components of traditional Chinese medicine were retrieved and screened from TCMSP to establish a database, as shown in Table 1. A total of 4,354 predicted targets were obtained through Swiss Target Prediction, and 3,536 duplicates were removed, resulting in a final prediction of 818 targets. The network of traditional Chinese medicine components and targets was constructed using Cytoscape 3.7.2, as shown in Figure 1. The network contained 873 nodes and 3,051 edges. In the figure, edges represent interaction relationships, blue square nodes represent component targets, and pink circular nodes represent active components. Using the keyword “benign prostatic hyperplasia”, disease targets were searched through the GeneCards database and OMIM database, resulting in 4,281 and 217 targets related to BPH, respectively. After removing duplicates, a total of 4,354 related targets were obtained. The intersection with the targets of the core components of Salvia miltiorrhiza was taken to obtain 458 potential targets of Salvia miltiorrhiza in the treatment of BPH (Figure 2).

Table 1 Summary of Active Components of Salvia miltiorrhiza

No.	MOL ID	Active ingredient	OB(%)	DL
01	MOL001659	Poriferasterol	43.83	0.76
02	MOL001601	1,2,5,6-tetrahydrotanshinone	38.75	0.36
03	MOL001771	poriferast-5-en-3beta-ol	36.91	0.75
04	MOL001972	isoimperatorin	45.46	0.23
05	MOL002222	sugiol	36.11	0.28
06	MOL002651	Dehydrotanshinone II A	43.76	0.40
07	MOL002776	Baicalin	40.12	0.75
08	MOL000569	digallate	61.85	0.26
09	MOL000006	luteolin	36.16	0.25
10	MOL006824	α-amyrin	39.51	0.76
11	MOL007036	5,6-dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one	33.77	0.29
12	MOL007041	2-isopropyl-8-methylphenanthrene-3,4-dione	40.86	0.23
13	MOL007048	(E)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-benzofuran-4-yl]acrylic acid	48.24	0.31
14	MOL007049	4-methylenemiltirone	34.35	0.23
15	MOL007050	2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde	62.78	0.40
16	MOL007051	6-o-syringyl-8-o-acetyl shanzhiside methyl ester	46.96	0.71
17	MOL007058	formyltanshinone	73.44	0.42
18	MOL007061	Methylenetanshinquinone	37.07	0.36
19	MOL007063	przewalskin a	37.11	0.65
20	MOL007064	przewalskin b	110.32	0.44
21	MOL007069	Przewaquinone c	55.74	0.40
22	MOL007077	sclareol	43.67	0.21
23	MOL007079	tanshinaldehyde	52.47	0.45
24	MOL007081	Danshenol B	57.95	0.56
25	MOL007082	Danshenol A	56.97	0.52

No.	MOL ID	Active ingredient	OB(%)	DL
26	MOL007085	Salvilenone	30.38	0.38
27	MOL007088	cryptotanshinone	52.34	0.40
28	MOL007093	dan-shexinkum d	38.88	0.55
29	MOL007094	danshenspiroketallactone	50.43	0.31
30	MOL007098	deoxyneocryptotanshinone	49.4	0.29
31	MOL007100	dihydrotanshinlactone	38.68	0.32
32	MOL007101	dihydrotanshinoneI	45.04	0.36
33	MOL007105	epidanshenspiroketallactone	68.27	0.31
34	MOL007107	C09092	36.07	0.25
35	MOL007108	isocryptotanshi-none	54.98	0.39
36	MOL007111	Isotanshinone II	49.92	0.40
37	MOL007115	manool	45.04	0.20
38	MOL007119	miltionone I	49.68	0.32
39	MOL007120	miltionone II	71.03	0.44
40	MOL007121	miltipolone	36.56	0.37
41	MOL007122	Miltirone	38.76	0.25
42	MOL007123	miltirone II	44.95	0.24
43	MOL007124	neocryptotanshinone ii	39.46	0.23
44	MOL007125	neocryptotanshinone	52.49	0.32
45	MOL007127	1-methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione	34.72	0.37
46	MOL007130	prolithospermic acid	64.37	0.31
47	MOL007132	(2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid	109.38	0.35
48	MOL007140	(Z)-3-[2-[(E)-2-(3,4-dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid	88.54	0.26
49	MOL007141	salvianolic acid g	45.56	0.61
50	MOL007142	salvianolic acid j	43.38	0.72
51	MOL007143	salvilenone I	32.43	0.23
52	MOL007145	salviolone	31.72	0.24
53	MOL007149	NSC 122421	34.49	0.28
54	MOL007154	tanshinone iia	49.89	0.40
55	MOL007155	(6S)-6-(hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofu-ran-10,11-dione	65.26	0.45
56	MOL007156	tanshinone VI	45.64	0.30

Fig.1 Relationship between the components and targets of drug

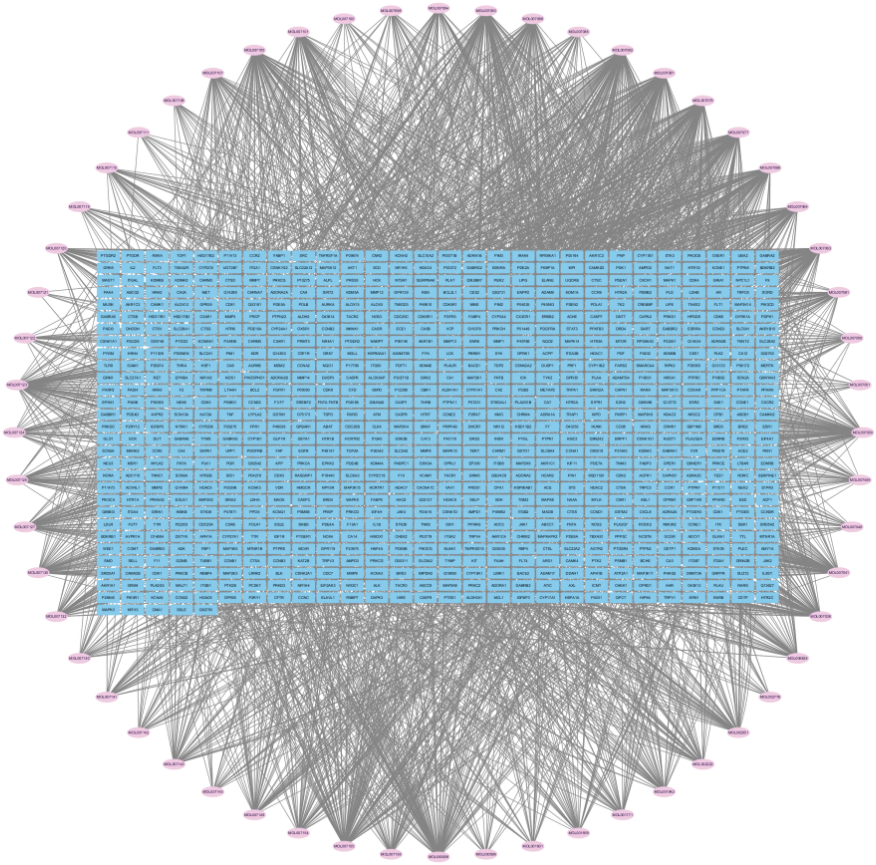
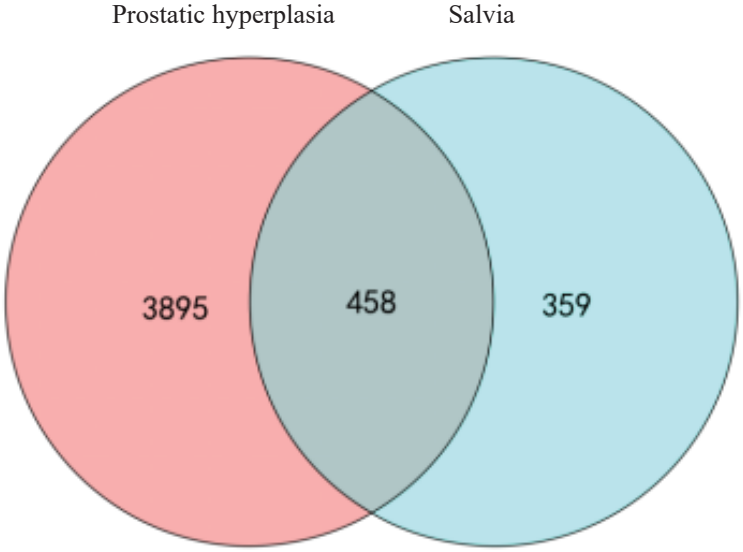


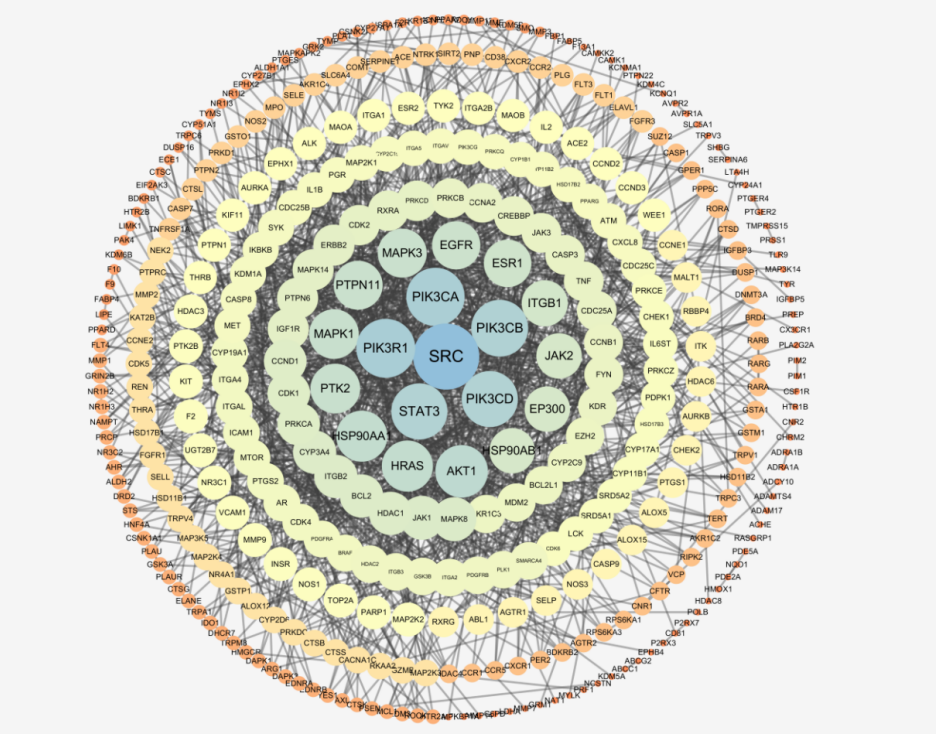
Fig.2 VENN chart of drug-disease targets



2.2 PPI Network Results

The PPI relationships obtained from the STRING 11.0 platform were imported into Cytoscape 3.7.2 software for visualization analysis, generating the PPI network as shown in Figure 3. This network consists of 372 nodes and 1,415 edges, where edges represent PPI relationships, circular nodes represent target proteins, and node colors indicate the degree values. It can be seen that targets such as SRC, PIK3R1, and PIK3CA play a core role in the network, with degree values of 55,44,and 43 respectively,and they are worthy of further study.

Fig.3 Target protein-protein interaction network



Note: Color range , the degree value decreases from left to right

2.3 GO and KEGG Enrichment Results

GO analysis includes three branches, namely molecular function (MF), cellular component (CC), and biological process (BP). The processes with $P \leq 0.01$ were screened, and the top ten enriched processes were listed (Figure 4). Among them, at the BP level, the predicted targets were mainly related to cellular calcium ion homeostasis, calcium ion homeostasis, and regulation of cytosolic calcium ion concentration; at the CC level, tyrosine kinase activity, threonine kinase activity, and focal adhesion had a relatively large proportion; at the MF level, they were closely related to protein binding, identical protein binding, and protein tyrosine kinase activity. Through KEGG enrichment analysis, 183 signaling pathways with $P \leq 0.01$ were obtained for the potential pathways involved in the treatment of benign prostatic hyperplasia by the core components of Salvia miltiorrhiza. Figure 5 lists the top 10 enriched pathways. Among them, MAPK signaling pathway, PI3K-Akt signaling pathway, and Calcium signaling pathway are closely related to benign prostatic hyperplasia. KEGG enrichment analysis indicates that the core components of Salvia miltiorrhiza may act on these pathways, thereby playing a role in the treatment of benign prostatic hyperplasia.

Fig.4 Results of GO enrichment analysis

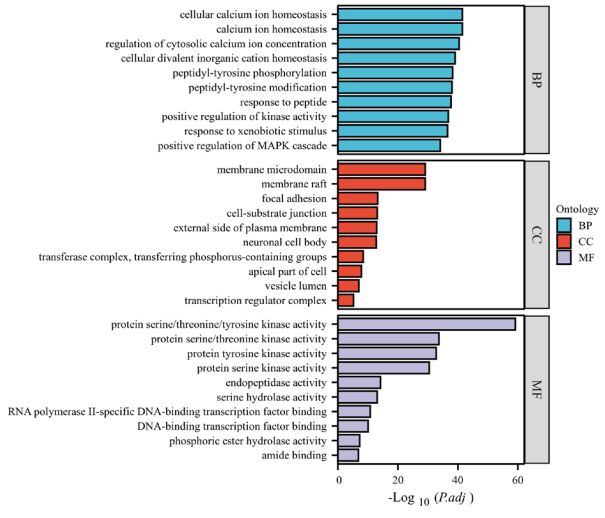
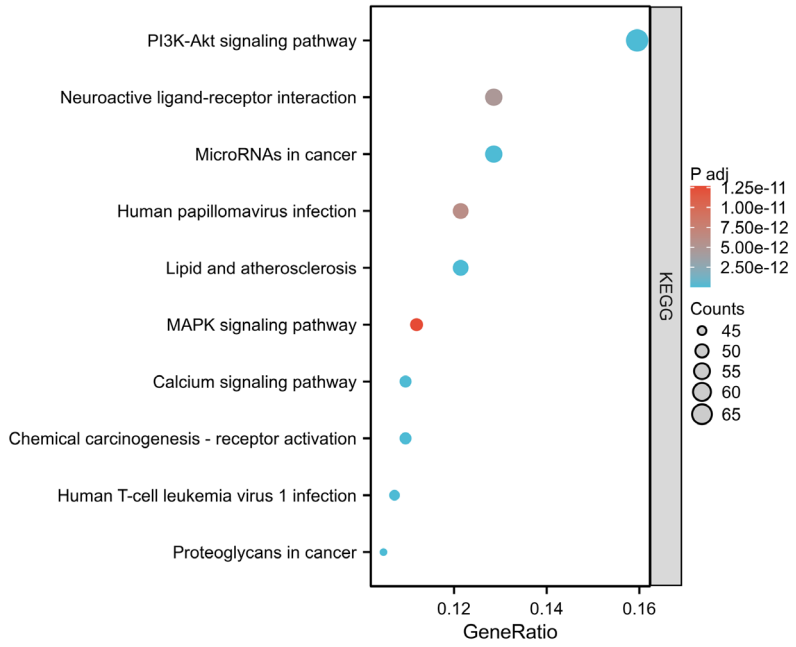


Fig.5 Results of KEGG enrichment analysis



3.Discussion

In this study, 57 active ingredients of Salvia miltiorrhiza were screened by network pharmacology method, and their target sites were predicted. It was found that Salvia miltiorrhiza exerted therapeutic effects on BPH through the synergistic mechanism of multiple components, multiple targets and multiple pathways. The specific results are as follows:

3.1 Core target analysis

PPI network analysis shows that SRC (degree 55), PIK3R1 (44), and PIK3CA (43) are the core targets of Danshen in treating BPH. Among these, SRC, as a non-receptor tyrosine kinase, is highly expressed in prostate stromal cells. Its phosphorylation can activate the MAPK pathway, promoting [12] deposition in the extracellular matrix. PIK3CA (PI3K catalytic subunit) forms an heterodimer with PIK3R1 (regulatory subunit), which regulates the survival and proliferation of prostate cells through the PI3K/Akt pathway[13]. Clinical samples show that p-Akt (Ser473) expression in BPH tissue is significantly higher than in normal tissue ($P<0.01$) [14], consistent with the enrichment results of this study's targets.

3.2 Signal pathway analysis

KEGG enrichment analysis shows that Salvia miltiorrhiza primarily exerts its effects through the MAPK, PI3K-Akt, and calcium signaling pathways. The MAPK pathway plays a crucial role in regulating cell proliferation and apoptosis; its inhibitor U0126 can significantly reduce prostate volume ($p<0.05$)[14].Key nodes in the calcium signaling pathway (hsa04020), such as CACNA1C and CALM1, are involved in the contraction of prostatic smooth muscle, and Salvia miltiorrhiza alleviates urethral obstruction by modulating calcium homeostasis[15].Notably, GO enrichment analysis indicates that the "focal adhesion" (CC layer) pathway is closely associated with interstitial fibrosis in the prostate. Salvia miltiorrhiza IIA can inhibit the expression of fibrosis markers (α-SMA, Collagen I) induced by TGF-β1, which aligns well with the CC enrichment results from this study [16].

3.3 Synergistic action of multiple targets

The synergistic effects of multiple components in Salvia miltiorrhiza are key mechanisms for its treatment of BPH. For example, shenqu can act on multiple targets simultaneously (such as SRC and EGFR), reflecting the characteristic of "synergistic action" in traditional Chinese medicine. Additionally, the anti-inflammatory effects of Salvia miltiorrhiza enhance its therapeutic efficacy by modulating the inflammatory-proliferative axis (such as PTGS2 and ESR1).

In summary, this study systematically analyzed the potential molecular mechanisms of Salvia miltiorrhiza in treating BPH using network pharmacology methods, revealing its multi-pathway, multi-target, and multi-channel synergistic action pattern. This research provides a theoretical framework for the combined traditional Chinese and Western medicine treatment of BPH

and offers candidate targets for the development of new drugs targeting BPH. Future studies can further explore the specific mechanisms of action of the core components of Salvia miltiorrhiza through molecular docking and experimental validation, providing a more comprehensive evidence chain for the development of novel BPH treatment strategies derived from Salvia miltiorrhiza.

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no

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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