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Targeting PI3K/Akt/NF-κB and PI3K/Akt/FOXO signaling pathways by Wenshen Qianlie Capsules mitigates testosterone-induced benign prostate hyperplasia in rats

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Abstract

Introduction and Objective. Benign prostatic hyperplasia (BPH) is a prevalent chronic disease in men. In China, Wenshen Qianlie Capsules are usually used for treatment of BPH. The aim of the study is to comprehensively map the targets and pathways of the capsule using network pharmacology, and to validate its efficacy and possible cellular and molecular mechanisms using animal and cellular experiments.

Materials and Method. Targets and meridian tropism for the herbs in Capsules were collected from the ETCM 2.0 database. Disease genes were collected from the ETCM 2.0 and Genecards databases. Common genes were subjected to enrichment analysis. Male Wistar rats and human prostatic epithelial/stromal cell lines were induced by testosterone propionate (TP). The prostate weight, body weight, serum dihydrotestosterone (DHT), 5α-reductase, and prostate-specific antigen (PSA) in rats were determined. PCNA and caspase-3 in prostate tissue were assayed. Viability, apoptosis, inflammation cytokines, and pathway factors were detected in cells.

Results. A total of 516 targets were predicted for the 14 herbs in Capsules. Among them, 90 targets have the potential against BPH. The therapeutic targets were enriched in multiple biological progress and pathways, including PI3K/AKT signaling pathway. Capsules treatment reduced the prostate weight, serum PSA/DHT/5α-reductase levels, and prostatic PCNA level, but increased prostatic caspase-3 level. Furthermore, Capsules treatment inhibited the cell viability and inflammatory factors but induced apoptosis of BPH-1 and WPMY-1 cells. Additionally, Capsules treatment decreased the ratios of p-Akt/Akt, p-I-κB/I-κB, p-FoxO3a/ FoxO3a, p-NF-κB/NF-κB, and p-FoxO1/FoxO1.

Conclusions. Wenshen Qianlie Capsules may avoid BPH by blocking the activation of PI3K/Akt/NF-κB and PI3K/Akt/FOXO signaling pathways.

Key words

PI3K/Akt pathway, network pharmacology, benign prostatic hyperplasia, Wenshen Qianlie Capsules

INTRODUCTION

Benign prostatic hyperplasia (BPH) is commonly known as the most common benign neoplasm in aging men [1]. The benign enlargement of the prostate gland in this disease result from uncontrolled hyperplastic growth of the epithelial and fibromuscular tissues of the transitional zone and the periurethral area [2]. The common symptoms associated with BPH include frequent micturition, poor urinary flow, incomplete bladder emptying, and nocturia, all referred to as lower urinary tract symptoms (LUTS) [3]. Symptomatic manifestations in men with BPH range from the absence of symptoms to mild symptoms managed by lifestyle changes, up to requiring medication or surgery [4]. In most parts of the world, the absolute burden of benign prostatic hyperplasia is increasing at an alarming rate [5]. In 2021, BPH was the leading cause of urologic disease burden, with an incidence rate of 5531.88 per 100,000 persons [6]. A study of the difference in the burden of BPH between China and the United States from 1990–2019 shows that the burden is much higher in China than in the United States [7]. The absolute burden of BPH is expected to continue to rise in the coming years as China's population ages, underscoring the importance of developing effective therapies for the disease.

Men with bothersome LUTS from BPH may be offered pharmacologic or even surgical treatment. However, the treatment of BPH remains unsatisfactory with pharmacological interventions or surgery [8]. Given the side-effects of inhibitor medications, the use of alternative therapies to treat LUTS is of interest to many men. Many herbal supplements have been tried

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for the treatment of BPH [9]. Clinical Chinese patent drugs, such as Shuangshi Tonglin Capsule [10], Qianliexin Capsule [11], and Qianlie Tongqiao Capsule [12], showed efficacy and safety for the treatment of BPH. Wenshen Qianlie Capsules are a traditional Chinese patent medicine commonly used in clinics for BPH [13]. This capsule contained fourteen Chinese herbs (Tab. 1) [13]. However, the underlying mechanism of Wenshen Qianlie Capsules in BPH has not been fully elucidated.

Table 1. Chinese herb formula for Wenshen Qianlie Capsules

Herb name in pinyin	Herb name in Latin	Weight (g per 1000 capsule)
CheQianZi	Plantago asiatica L.	100
FuLing	Poria cocos (Schw.) Wolf.	130
BianXu	Polygonum aviculare L.	130
HuZhang	Polygonum cuspidatum Sieb. et Zucc	130
FuZi	Aconitum carmichaelii Debx	30
MuDanPi	Paeonia suffruticosa Andr.	100
ShanZhuYu	Cornus officinalis Sieb. et Zucc.	80
QuMai	Dianthus chinensis L.	130
ShanYao	Dioscorea opposita Thunb.	100
NiuXi	Achyranthes bidentata Blume.	100
YinYangHuo	Epimedium brevicornu Maxim.	150
ShuDiHuang	Rehmannia glutinosa Libosch.	150
ZeXie	Alisma orientale(Sam.) Juzep.	130
RouGui	Cinnamomum cassia Presl	30

Therefore, this study performed network pharmacology analysis, rat modelling experiments, and cell function experiments to investigate the potential effects and underlying mechanisms of Wenshen Qianlie Capsules in BPH.

MATERIALS AND METHOD

Network pharmacology analysis. *Collection of potential targets for Wenshen Qianlie Capsules.* The targets of Wenshen Qianlie Capsules, along with meridian tropism for each herb, were retrieved in the *Encyclopedia of Traditional Chinese Medicine 2.0* (http://www.tcmip.cn/ETCM2/front/#/) using key words 'Wen Shen Qian Lie Jiao Nang'.

Collection of BPH genes. The BPH-associated genes were collected from Genecards database (https://www.genecards.org/) and the *Encyclopedia of Traditional Chinese Medicine 2.0,* respectively. The search results from the two databases were compared to identify overlapping genes, and common genes were considered potential therapeutic genes.

Enrichment analysis of potential therapeutic genes. The potential therapeutic genes were input into STRING platform (https://version-12–0.string-db.org/cgi/) to obtain a protein-protein interaction network, and visualized using Cytoscape 3.7.1 software based on the node degree. Biological process and pathway enrichment analyses were conducted using clusterProfiler and pathview R packages.

Network construction. After the collection of meridian tropism for each herb in Wenshen Qianlie Capsules, a network of herb-meridian tropism network was constructed. After the collection of targets for each herb, an herb-target network was constructed. After BPH-associated genes were obtained, a capsule-herb-target-disease network was constructed. Based on the genes involved in PI3K/AKT pathway, a capsule-herb-target-pathway network was constructed. All the networks were constructed using Cytoscape 3.7.1 software.

Rat experiments – *ethical statement and animals.* Adult male Wistar rats (200 ± 20 g) were obtained from the Cyagen (Suzhou) animal facility in China (Approved No. SYXK(Su)2022–3998). Animals had access to water and food *ad libitum* under a controlled environment (a temperature of 25 ± 2°C, a humidity of 60 ± 10%, and an alternating 12/12-h light/ dark cycle). All rat experiment procedures were completed by the Animal Ethics Committee of Qinba Biomedical Research Institute of Xiuzheng Pharmaceutical Group. All animal experiments were carried out in strict compliance with the NIH Guide for the Care and Use of Laboratory Animals.

BPH modelling. After a recovery period, the rats received a daily subcutaneous injection of testosterone propionate (TP) at 1 mL/kg (5 mg/kg) in olive oil from day 0 to day 13 (a total of 14 days).

Sham modelling. After a recovery period, the rats received a daily subcutaneous injection of olive oil at 1 mL/kg from day 0 to day 13 (a total of 14 days).

Grouping of rats. On day 13, 30 BPH modelling rats were allocated into the following three groups: BPH group (n = 8); (2) BPH+L-WQ group (n = 10, 41.2 mg/kg/time, twice every day); (3) BPH+H-WQ group (n = 10, 62.5 mg/kg/time, three times a day). The low (L) and high (H) dosages for rats were calculated based on the upper (0.5g/capsule, three capsules per time, three times a day) and lower (0.5g/capsule, two capsules per time, twice a day) limits of the human dosage stated in the instruction of Wenshen Qianlie Capsules. The treatments were given through intragastric administration for a continued five weeks. Rats in the sham modelling group were given the equivalent of an isotonic sodium chloride solution, termed the control group.

Preparation of drug-containing serum. In the drug direction, the maximum dose of Wenshen Qianlie Capsules for humans is 3 g. When this human dose was converted into a rat dose (a person of 60 kg, and a conversion factor of 6.25 between human and rat), it was equivalent to a dose of 0.3125 g/kg for the rat. Rats (n=10) received intragastric administration of Wenshen Qianlie Capsules (three times a day) for a continuous five weeks. The rats were then euthanized with CO_2. Blood was taken from the carotid artery and centrifuged at 4°C (3,000 r/min for 10 min) to obtain the serum. The serum was inactivated at 56°C for 20 min, filter sterilized, then dispensed and stored at 4°C.

Parameter measurements in rats. At the end of the experimental period, rats were subjected to euthanasia in a cage with progressive CO_2 delivery. Blood samples were extracted and centrifuged. Serum prostatic specific antigen (PSA), dihydrotestosterone (DHT), and 5α-reductase activity were assessed using a rat PSA ELISA kit (Biomatik, Canada),

a rat 5α-reductase ELISA kit (KEMOBIO, China), and a rat DHT ELISA kit (YLKBIO, China), respectively, following the manufacturer's guidelines. The weight of each prostate tissue was obtained for the ratio to body weight. Then, part of the prostate tissues was homogenized, and the protein levels of PCNA and caspase-3 were measured using Western blot assays. The remaining part of each prostate tissue was embedded in paraffin, dewaxed, dehydrated, sectioned, and stained with haematoxylin and eosin to determine the prostate epithelial thickness.

Cell experiments – *Cell culture.* BPH-1 (a human prostatic hyperplasia epithelial cell line) and WPMY-1 (a human normal prostatic stromal cell line) were obtained from Sangon Biotech (Shanghai, China) and American Type Culture Collection (USA). BPH-1 cells were cultured in RPMI 1640 medium (Gibco, USA). WPMY-1 cells were maintained in Dulbecco's Modified Eagle's Medium. Both media contained 10% foetal bovine serum.

Drug-containing serum intervention. The cell BPH model was induced using 100 nM TP. The cells were then treated with drug-containing serum for 24 hours.

Cell viability. Cell viability was determined using Cell Counting Kit-8 (Absin, China) according to the manufacturer's instructions. The percentage of cell viability was calculated against the control as follows:

$$\text{Cell viability}(\%) = (A450_{\text{sample}} - A450_{\text{blank}})/(A450_{\text{control}} - A450_{\text{blank}}) \times 100.$$

Cell apoptosis. The apoptotic cells were signalled using the Annexin V/PI kit (Vazyme Biotech, China) as per the manufacturer's instructions. The percentage of apoptotic cells was detected by flow cytometry.

Determination of IL-8/IL-1β levels in culture supernatants. The cell supernatants were harvested. Determination of IL-8 levels was performed using Rat IL-8 ELISA KIT (Solarbio, China). Supernatant IL-1β levels were quantified using Rat IL-1β ELISA Kit (MultiSciences, China). All experimental procedures followed the kit instructions from each manufacturer.

Western blot for protein detection. Western blot was used to analyze the protein levels involved in PI3K/Akt/NF-κB and PI3K/Akt/FOXO signalling pathways. Briefly, protein extracted from cells was separated using sodium dodecyl sulphatepolyacrylamide gel electrophoresis (Bio-Rad) and transferred to polyvinylidene fluoride (PVDF) membranes (Millipore, USA). Membrane-bound blots were incubated with the indicated primary antibodies and then with secondary antibodies. Finally, the protein bands were revealed using ECL Prime (GE Healthcare, USA) and visualized by the iBright1500 system (Thermo Fisher, USA).

Statistical analysis. All parameters were subjected to analysis of variance, followed by the Bonferroni or Tukey-Kramer as *post-hoc* tests for multiple comparisons. Data are displayed as the mean ± SD. Significance signs were as follows: $p<0.05$*, $p<0.01$**, and $p<0.001$***.

RESULTS

Whole targets for Wenshen Qianlie Capsules. Based on the information from the ETCM 2.0 database, Polygonum aviculare L. and Alisma orientale (Sam.) Juzep in Wenshen Qianlie Capsules return to the bladder; Plantago asiatica L., Poria cocos (Schw.) Wolf, Aconitum carmichaelii Debx, Paeonia suffruticosa Andr., Cornus officinalis Sieb. et Zucc, Dioscorea opposita Thunb., Achyranthes bidentata Blume, Epimedium brevicornu Maxim, Rehmannia glutinosa Libosch, Alisma orientale (Sam.) Juzep, and Cinnamomum cassia Presl return to the kidney meridian (Fig. 1A). A total of 516 targets were predicted for the 14 herbs in Wenshen Qianlie Capsules (Fig. 1B). The herb-targets contained 2,311 edges (Fig. 1B).

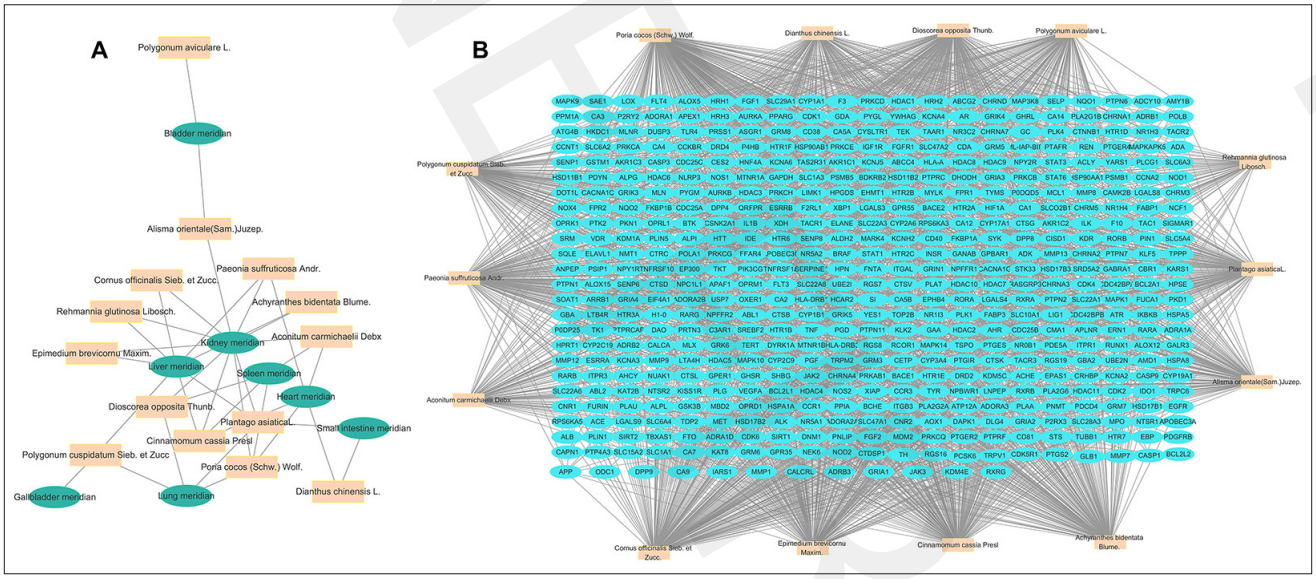


Figure. 1. Potential targets of Wenshen Qianlie Capsules. (A) Herb-meridian tropism network. Orange rectangles – herbs; green ellipses – meridian tropism. (B) Herb-target network. Orange rectangles – herbs; blue ellipses – potential targets

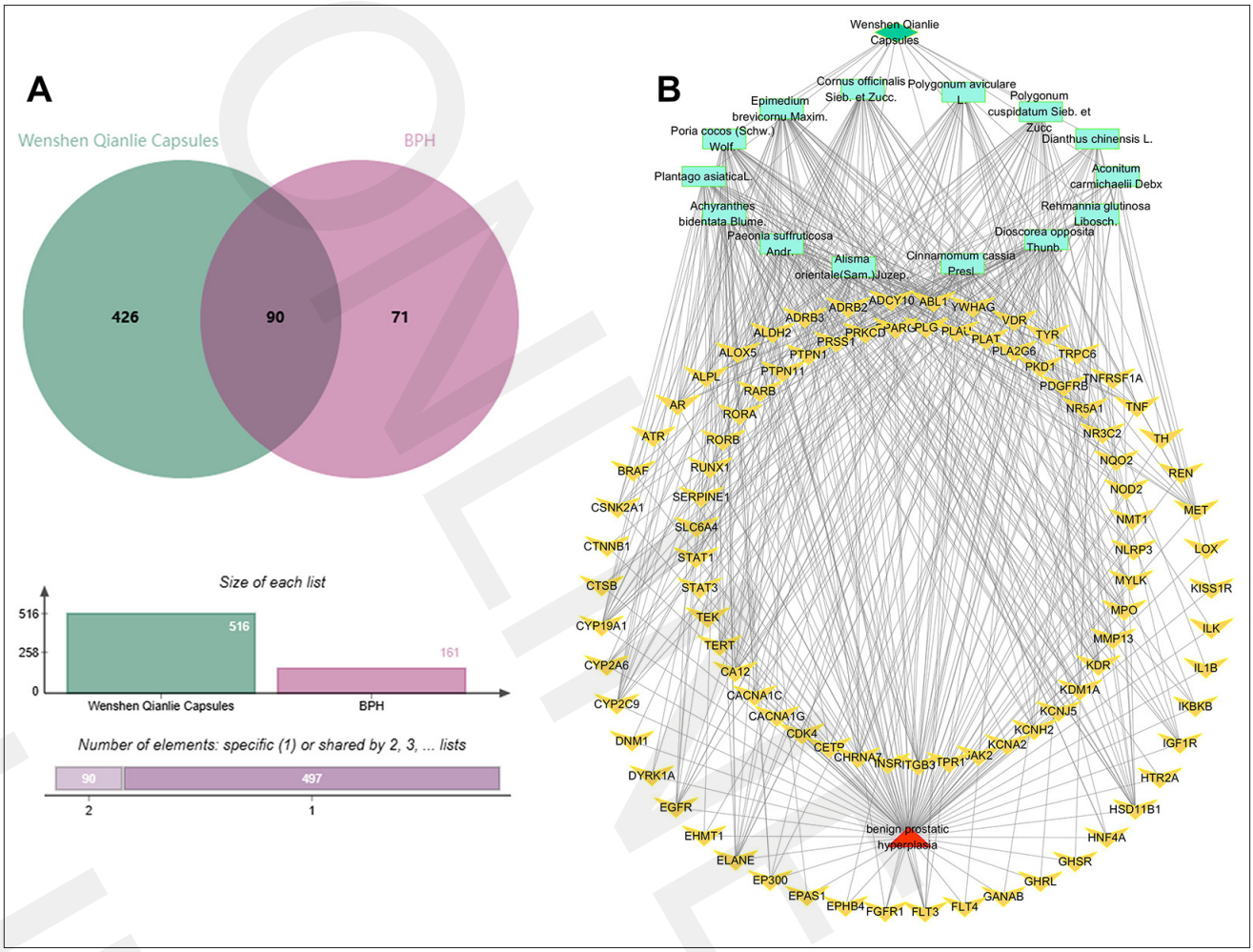


Figure 2. Potential targets of Wenshen Qianlie Capsules against benign prostate hyperplasia. (A) Venn diagram of targets for Wenshen Qianlie Capsules and disease genes. (B) Capsule-herb-target-disease network. Green diamond – Wenshen Qianlie Capsules; green rectangles – herbs; Orange arrows – targets; red triangle – benign prostate hyperplasia

Targets of Wenshen Qianlie Capsules against BPH. After the collection of BPH-related genes from two databases, ninety common genes were obtained with targets of Wenshen Qianlie Capsules (Fig. 2A). These targets of Wenshen Qianlie Capsules against BPH were imported into Cytoscape 3.7.1, and a capsule-herb-target-disease network was constructed. The capsule-herb-target-disease network contained 109 nodes and 526 edges, among which all 14 herbs were included (Fig. 2B).

Enrichment analysis of targets of Wenshen Qianlie Capsules against BPH. The targets of Wenshen Qianlie Capsules against BPH were input into STRING, and a protein-protein interaction network was obtained (Fig. 3A). This interaction network comprised 265 edges, with an average node degree of 13.9 (PPI enrichment p-value < 1.0e-16). The biological processes enriched by these 90 targets included peptidyl-tyrosine phosphorylation, peptidyl-tyrosine modification, positive regulation of protein serine/threonine kinase activity, regulation of inflammatory response, regulation of hormone secretion, regulation of epithelial cell proliferation, and protein autophosphorylation (Fig. 3B). After KEGG pathway enrichment analysis, PI3K/AKT signalling pathway was significantly enriched by 90 targets (Fig. 3C). By specifically analyzing the PI3K/AKT signalling pathway, 12 herbs targeted it through 16 genes (CDK4, EGFR, FGFR1, FLT3, FLT4, IGF1R, IKBKB, INSR, ITGB3, ITPR1, JAK2, KDR, MET, PDGFRB, TEK, and YWHAG) (Fig. 3D). In addition, the downstream FoxO signalling pathway and NF-κB signalling pathway were involved in the enriched PI3K/AKT signaling pathway.

Effect of Wenshen Qianlie Capsules on BPH in rats. Figure 4A-4C shows that TP treatment in rats resulted in a considerable rise in prostate weight and epithelial thickness ($p<0.01$). Moreover, treatment with Wenshen Qianlie Capsules significantly reduced the prostate weight ($p<0.01$; Fig. 4A), prostate weight/body weight ratio ($p<0.05$; Fig. 4B), and epithelial thickness ($p<0.001$; Fig. 4C), compared to the BPH rats. Moreover, increased PCNA and caspase-3 protein levels caused by TP were significantly suppressed in the prostatic tissues treated with Wenshen Qianlie Capsules ($p<0.01$; Fig. 4D-E). Treatment with Wenshen Qianlie Capsules significantly decreased TP-induced serum levels of PSA, 5α-reductase, and DHT, compared to diseased rats ($p<0.01$; Fig. 4F-H).

Effect of Wenshen Qianlie Capsules on cell proliferation/apoptosis and inflammatory markers. Based on the results of cell experiments, TP increased the cell viability of BPH-1 and

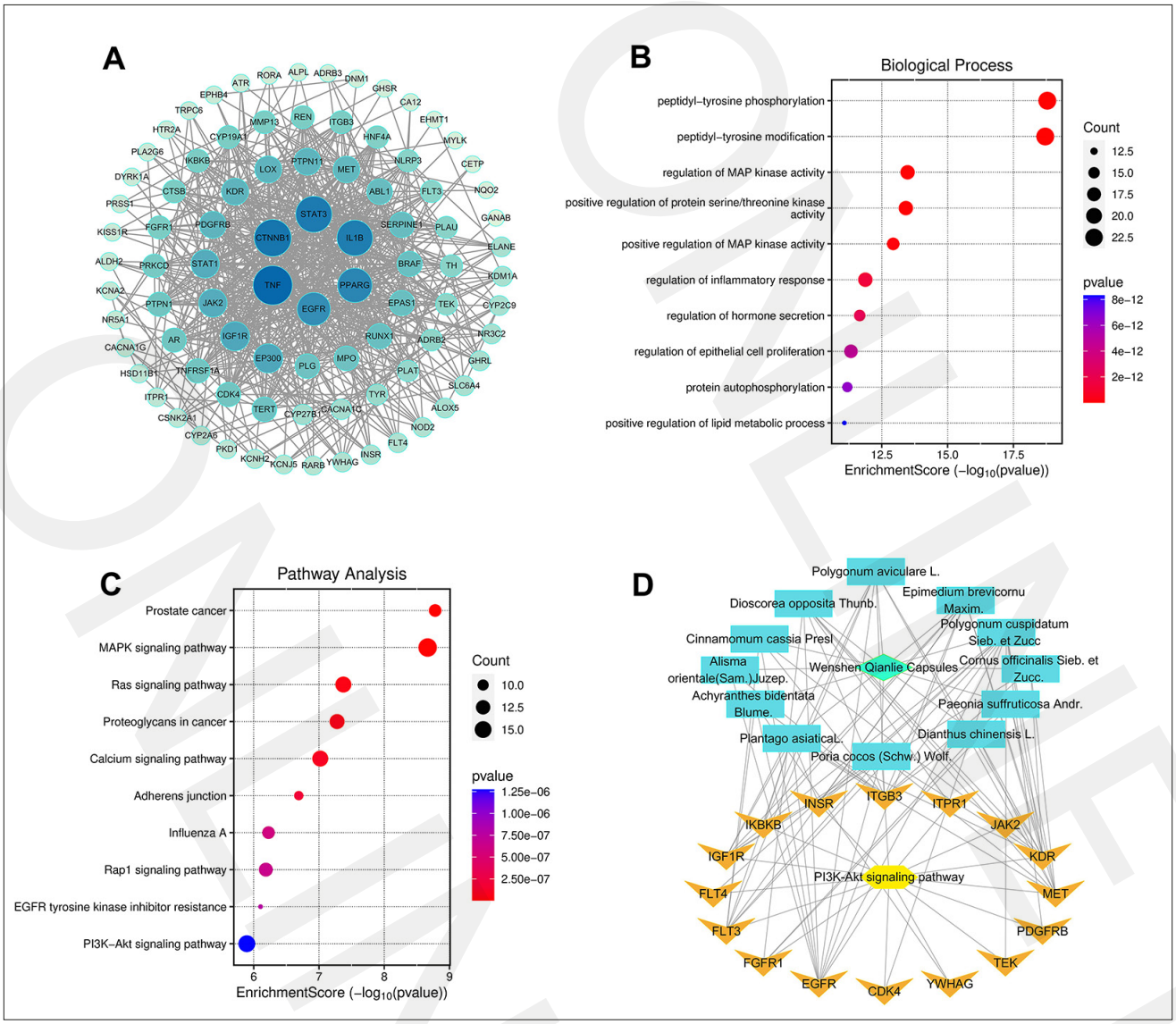


Figure 3. Results of enrichment analysis for targets. (A) Protein-protein interactions among the 90 targets. (B) Top 10 enriched biological processes. (C) Top 10 enriched KEGG pathways. (D) Components involved in PI3K/AKT signaling pathway

WPMY-1 cells, while drug-containing serum intervention inhibited cell viability (p<0.001; Fig. 5A-B). The cell apoptosis exhibited a significant decrease after TP induction, which was increased by the drug-containing serum intervention (p<0.001; Fig. 5C-D). This was accompanied by increases in the IL-1β and IL-8 following TP induction, which was reduced by the drug-containing serum intervention (p<0.001; Fig. 5E-H).

Effect of Wenshen Qianlie Capsules on PI3K/Akt pathway markers. PI3K/Akt cascade has been described as one of the highlighted pathways in BPH development [14]. As depicted in TP treatment revealed a significant elevation in signals involved in PI3K/AKT pathway (Fig. 6). However, the drug-containing serum intervention resulted in a marked reduction in ratios of phospho-Akt/Akt (p<0.001; Fig. 6A and 6D), p-IκB kinase β (IKKβ)/IKKβ (p<0.001; Fig. 6B), p-FoxO3a/FoxO3a (p<0.01; Fig. 6C), p-NF-κB/NF-κB (p<0.001; Fig. 6E), and p-FoxO1/FoxO1 (p<0.01; Fig. 6F).

DISCUSSION

In China and a number of other countries, Chinese herbal medicines are widely utilized in the treatment of BPH [15]. Chinese medicine has demonstrated its traditional strengths of multi-component, multi-target, and multi-pathway therapy in the treatment of BPH [16, 17]. Chinese medicines have been shown to reduce the severity of BPH disease and improve LUTS, and are expected to provide reliable therapeutic options in the future [15]. Wenshen Qianlie Capsules are a proprietary Chinese medicine formulated on the basis of accumulated clinical experience for the symptomatic treatment of BPH [13]. The current study, we employed network pharmacology, animal experiments, and cell experiments to elucidate the comprehensive molecular mechanisms underlying BPH. The current research demonstrates that Wenshen Qianlie Capsules can target hundreds of targets, among which 90 targets were against BPH.

In rats afflicted with BPH, Wenshen Qianlie Capsules displayed a defensive role against the condition induced by TP.

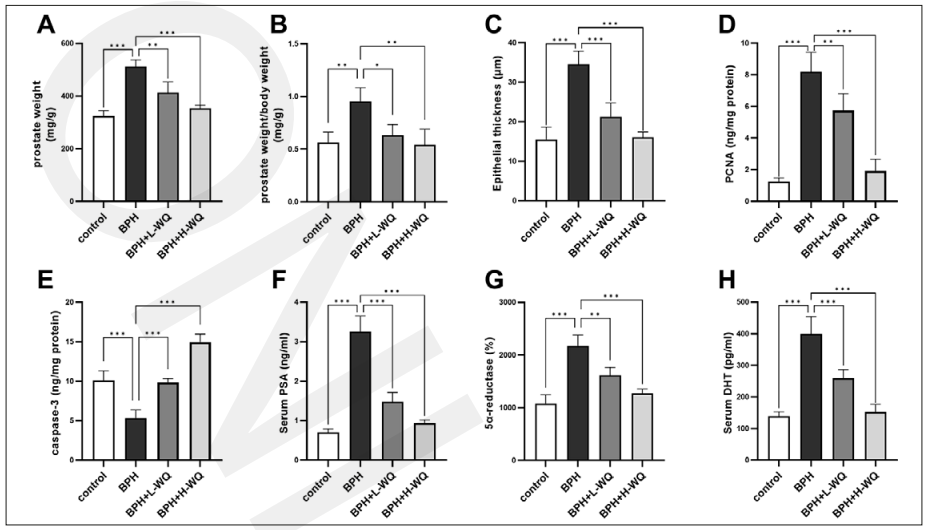


Figure 4. Effect of Wenshen Qianlie Capsules treatment on rat parameters. (A) Prostate weight of rats. (B) Prostate index was indicated by ratio of prostate weight/body weight in rats. (C) Epithelial thickness in the prostate tissues. (D) Protein expression of PCNA in prostate tissues. (E) Protein expression of caspase-3 in prostate tissues. (F) Serum prostate-specific antigen (PSA) levels. (G) Serum 5α-reductase activity. (H) Serum dihydrotestosterone (DHT) levels.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

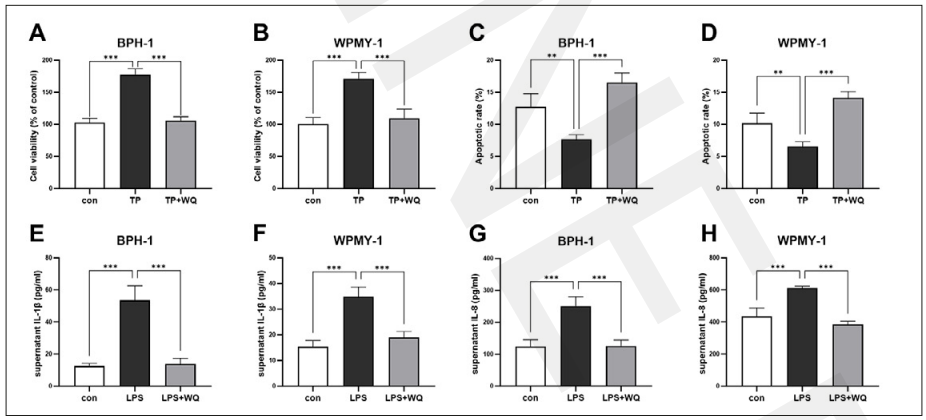


Figure 5. Effect of Wenshen Qianlie Capsules treatment on cell function. CCK-8 assay to determine cell viability of BPH-1 (A) and WPMY-1 (B) cells. Flow cytometry with Annexin V/PI staining to detect apoptotic BPH-1 (C) and WPMY-1 (D) cells. The supernatant concentration of inflammation cytokine IL-1β in BPH-1 (E) and WPMY-1 (F) cells. The supernatant concentration of inflammation cytokine IL-8 in BPH-1 (G) and WPMY-1 (H) cells.
** $p<0.01$; *** $p<0.001$

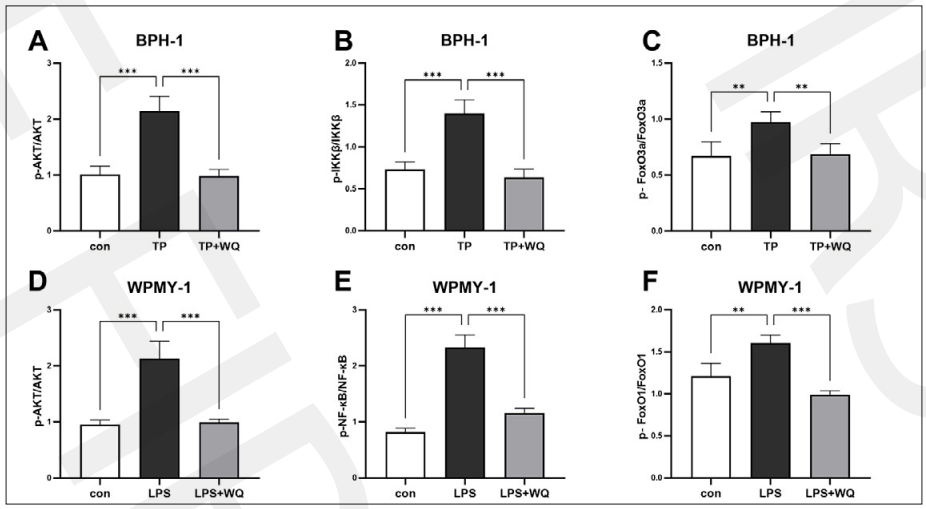
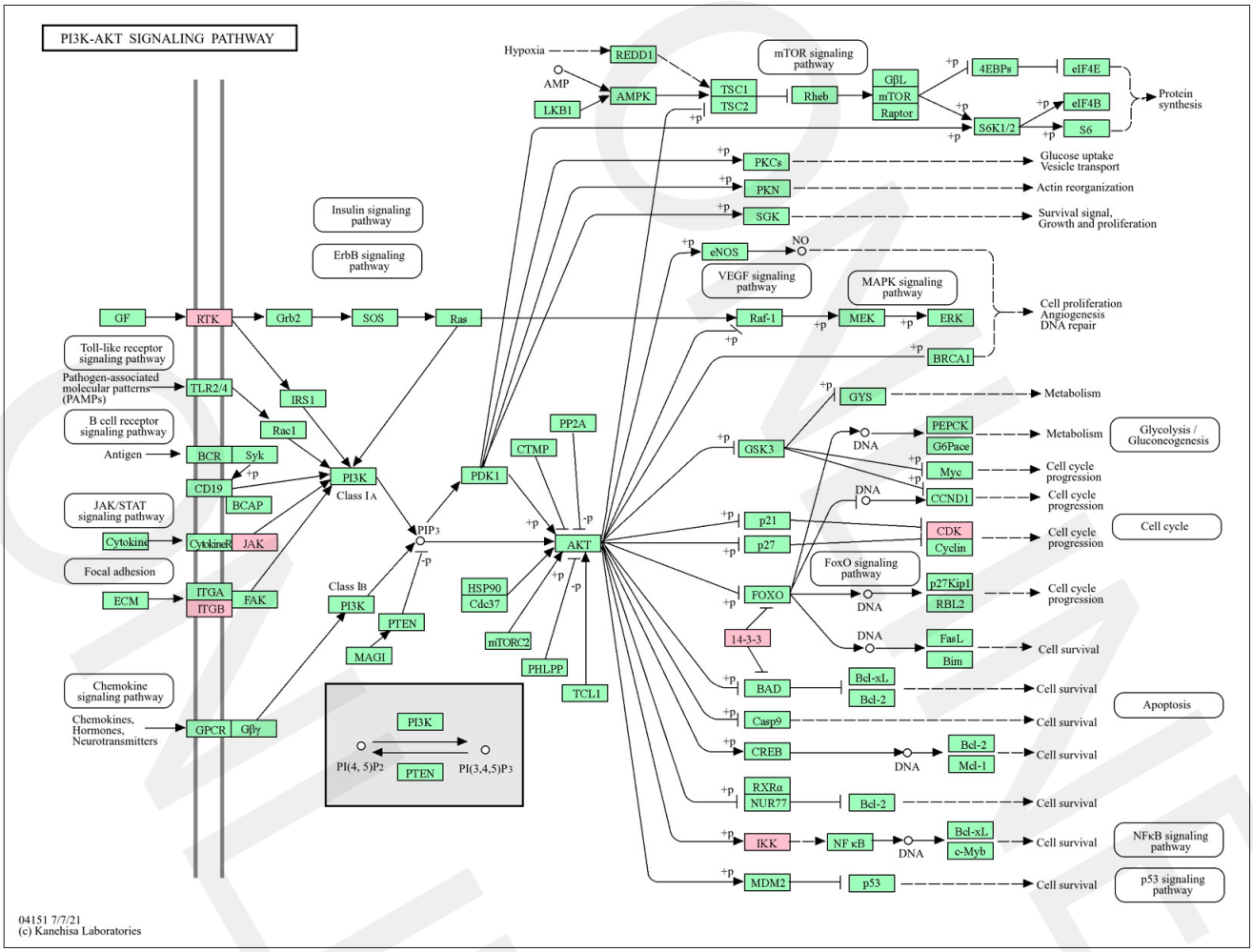


Figure 6. Effect of Wenshen Qianlie Capsules treatment on PI3K/AKT cascades. Ratio of p-Akt/Akt (A), p-IKKβ/IKKβ (B), and p-FoxO3a/ FoxO3a (C) in BPH-1 cells. Ratio of p-Akt/Akt (D) p-NF-κB/NF-κB (E), p-FoxO1/FoxO1 (F) in WPMY-1 (F) cells. p-, phospho-; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; NF-κB, nuclear factor kappa-B; FoxO, forkhead box O; IKKβ, IκB kinase β.
** $p<0.01$; *** $p<0.001$



Supplementary Figure 1. Visualization of enriched PI3K/Akt Signalling Pathway with KEGG Mapper

Network pharmacology and cell experiments revealed that the threptic influence of Wenshen Qianlie Capsules was mainly due to the cell viability inhibition and apoptosis induction, at least through modulation of the phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt)/ nuclear factor kappa-B (NF-κB) and PI3K/Akt/forkhead box O (FOXO) signaling pathways.

In the present study, therapy using Wenshen Qianlie Capsules in BPH rats reduced the prostatic weight and serum PSA increments driven by TP. This finding is consistent with the results of a previous study which demonstrated that Wenshen Qianlie Capsules were effective in reducing prostate weight, prostate index, and PSA values in a model of BPH [13]. As is well established in the literature, the development of BPH is associated with testosterone [18]. Within the prostate, testosterone can be converted by the 5α-reductase isoenzyme to the more active metabolite DHT [19]. To address this single issue, an evaluation of 5α-reductase activity and DHT production was conducted in the Wenshen Qianlie Capsules treatment group. The results demonstrated that Wenshen Qianlie Capsules effectively reduced 5α-reductase activity and DHT production in rats with BPH. The findings of this study suggest that Wenshen Qianlie Capsules have a potent ability to treat BPH and its underlying mediators.

BPH is characterized by the proliferation of prostate epithelial and mesenchymal cells, resulting in bladder outlet obstruction and elevated lower urinary tract symptoms [20]. It was observed to enhance cell activity and reduce apoptosis in BPH-1 and WPMY-1 after TP induction. Treatment with Wenshen Qianlie Capsules was found to attenuate BPH-1 and WPMY-1 cell activity and increased apoptosis. There is growing evidence to suggest that chronic prostate inflammation is associated with the pathogenesis and progression of BPH [21]. Inflammatory cytokines, particularly IL-1β and IL-8, may play a key role in tissue remodelling and smooth muscle contraction within the prostate, thereby influencing the progression of BPH [22]. The present study demonstrated that the administration of Wenshen Qianlie Capsules resulted in a reduction in the release of inflammatory factors from BPH-1 and WPMY-1 cells. This finding is consistent with the observations reported by Liu et al. in murine models [13].

It has been reported that the PI3K/Akt cascade can influence the development of testosterone-induced BPH in rats [14]. As indicated by the preceding study, PI3K/Akt activity has been shown to be elevated during periods of prostate hypertrophy and is thought to be associated with cell proliferation [14, 23]. Moreover, a direct decrease in PI3K/Akt activity may reduce the hypertrophic response to androgen stimulation [29]. The current study found that testosterone induction significantly increased the ratio of p-Akt/Akt in BPH-1 and WPMY-1 cells. Furthermore, the study also revealed that Wenshen Qianlie Capsules effectively inhibited Akt phosphorylation. It was found that Wenshen Qianlie

Capsules significantly reduced the testosterone-induced elevation of p-Akt expression. FoxO signalling pathway is identified to be crucial for the progression of BPH [24]. The present study posits that Wenshen Qianlie Capsules have the capacity to curtail the phosphorylation of FoxO3a and FoxO1 in response to TP. Moreover, the findings of this study indicate that the administration of Wenshen Qianlie Capsules resulted in the inhibition of NF-κB and IKKβ phosphorylation. As demonstrated in [25], NF-κB activation has been shown to promote prostate cancer cell survival through a Bcl-xL-dependent mechanism. This finding is consistent with the effect of Wenshen Qianlie Capsules in mice, which has been shown to ameliorate NF-κB and its downstream inflammatory factors [13].

CONCLUSIONS

In conclusion, the present study illustrates that Wenshen Qianlie Capsules can alleviate TP-induced BPH both *in vivo* and *in vitro*. These potential properties are mainly likely to be achieved by blocking the activation of PI3K/Akt/NF-κB and PI3K/Akt/FOXO signalling pathways. Combined with the previous data, it can be concluded that Wenshen Qianlie Capsules have anti-proliferative, pro-apoptotic, and anti-inflammatory properties in the prevention of BPH. These results may provide a foundation for further investigation into the mechanism of Wenshen Qianlie Capsules in the treatment of BPH.

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