Material Basis of Ningmitai Capsule for the Treatment of Urinary Tract Infections Based on Network Pharmacology

Lei HE, Yan LIN, Xu ZHANG, Minghui HE, Bo TU, Qingde LONG*

School of Pharmaceutical Sciences, Guizhou Medical University/Engineering Research Center of Chronic Disease Prevention and Treatment of Authentic Medicinal Materials for Colleges and Universities of Guizhou Province, Guiyang 550025, China

Abstract [**Objectives**] To study the main active components, targets and related pathways of Ningmitai capsule for the treatment of urinary tract infections (UTIs) based on network pharmacology. [**Methods**] The chemical components of Ningmitai capsule were collected through literature search, and the relevant target information of the components was sorted out. The UTIs-associated targets were also screened out using DisGeNET database and GeneCards database. Cytoscape 3.6.1 software and STRING platform were used to construct the protein-protein interaction (PPI) network, and MCODE plug-in in this software was used to analyze the action pathway and key targets of Ningmitai capsule for the treatment of UTIs. GO and KEGG pathway enrichment analysis of key targets was conducted using David database, and the component-target-pathway network diagram of Ningmitai capsule for the treatment of UTIs was established. [**Results**] A total of 37 active compounds, including salicylate, ferulic acid, baicalin, quercetin, apigenin and ellagic acid were screened from seven TCM components of Ningmitai capsule. There were 26 possible targets related to the treatment of UTIs, such as NFKB1, JUN, CTNNB1 and STAT3, which play an important role for the treatment of UTIs through prostate cancer, bladder cancer, pancreatic cancer and other signaling pathways. [**Conclusions**] The study provides a theoretical basis for the study of the mechanism of Ningmitai capsule in the treatment of UTIs.

Key words Ningmitai capsule, Urinary tract infections, Network pharmacology, Mechanism of action

1 Introduction

Urinary tract infections (UTIs) has become a common clinical disease, and it is estimated that about 150 million people worldwide are affected by such bacterial infections every year[1 – 4]. There are many causes of UTIs, and the most common pathogenic bacterium is uropathogenic *Escherichia coli*[5], which is considered to be the leading cause of UTIs. At present, traditional Chinese medicine preparations such as Sanjin tablet[6] and Relinqing granule[7] are commonly used for the treatment of UTIs in China.

Ningmitai capsule is derived from traditional Miao medicine in China, and it is mainly composed of *Imperata cylindrica*, *Forsythia suspense*, *Cocculus orbiculatus*, *Berberis soulieeana*, *Agrimonia pilosa*, *Polygonum capitatum* and *Hibiscus mutabilis*, with the effects of clearing heat and detoxifying, removing dampness and treating stranguria. Clinical application has shown that Ningmitai capsule has significant therapeutic effect on UTIs, chronic prostatitis and other diseases[8]. However, the pharmacodynamic substances, related molecular mechanisms and targets of Ningmitai capsule for the treatment of UTIs are still unclear. Therefore, this study explored the component-target-pathway relationship by screening the pharmacodynamic substances, targets and related pathways of Ningmitai capsule via network pharmacology[9 – 12], and initially clarified the molecular mechanism of Ningmitai capsule for the treatment of UTIs, in order to provide a certain theoretical basis for the study of the mechanism of Ningmitai capsule in the treatment of UTIs.

2 Materials and methods

2.1 Collection of effective compounds and targets of Ningmitai capsule Through previous studies and related literature, the chemical components of *I. cylindrica*, *F. suspense*, *C. orbiculatus*, *B. soulieeana*, *A. pilosa*, *P. capitatum* and *H. mutabilis* were collected, and screened by PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The targets of active components of *I. cylindrica*, *F. suspense*, *C. orbiculatus*, *B. soulieeana*, *A. pilosa*, *P. capitatum* and *H. mutabilis* were obtained from PubChem, TCMSP (http://lsp.nwu.edu.cn/tcmsp.php)[13] and BATMAN-TCM databases (http://bionet.ncpsb.org.cn/batman-tcm/)[14]. The target proteins collected from the three databases were combined, and the repeated target proteins were removed.

2.2 Collection of the targets for UTIs-associated diseases The targets of diseases associated with UTIs were collected from GeneCards database (https://www.genecards.org/)[15] and DisGeNET database (http://www.disgenet.org/)[16] with "urinary tract infections" as the keyword, and repeated targets were deleted and combined.

2.3 Prediction of the targets of Ningmitai capsule on UTIs The compound targets of Ningmitai capsule on UTIs were obtained by inputting the compound targets of Ningmitai capsule and the protein targets of UTIs-associated diseases into VENNY 2.1 platform. Finally, the "compound-target" diagram was built by Cytoscape 3.6.1 view software. Topological analysis was used to sort the data according to the degree value, and compounds and protein tar-

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* Corresponding author. E-mail: longqingde@gmc.edu.cn

gets with higher correlation were selected for subsequent experimental analysis.

2.4 Constructing protein-protein interaction (PPI) network between Ningmitai capsule and UTIs targets The targets of chemical components and common proteins of disease-related protein were screened, that is, the common targets of chemical components of Ningmitai capsule for the treatment of UTIs. The protein-protein interaction (PPI) was analyzed using STRING database (https://string-db.org/)[17]. In addition, module analysis of PPI networks was performed using the MCODE function of Cytoscape 3.6.1 software.

2.5 GO and KEGG pathway enrichment analysis of Ningmitai capsule on UTIs targets Common targets were imported into DAVID database (https://david.ncifcrf.gov/summary.jsp)[18-19]. The biological process (BP), cell component (CC) and molecular function (MF) were performed GO and KEGG pathway enrichment analysis. The result of $P<0.05$ in the analysis was made into a visual bubble map with R language.

2.6 Construction of component-target-pathway network of Ningmitai capsule The component-target-pathway network of Ningmitai capsule was established by using Cytoscape 3.6.1, and the core target of Ningmitai capsule core components acting on UTIs was obtained.

3 Results and analysis

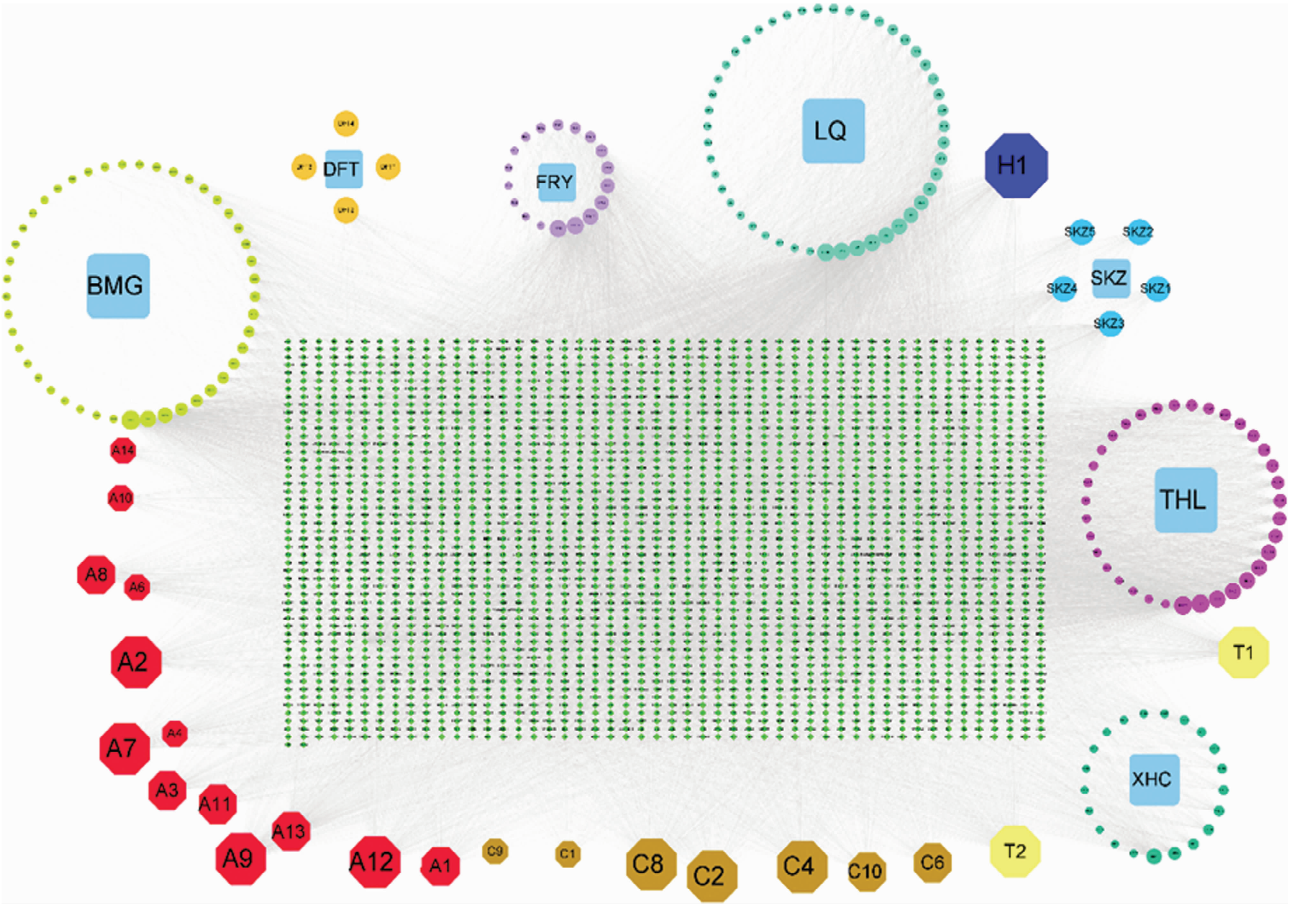
3.1 Collection of chemical components of Ningmitai capsule A total of 398 compounds were screened from Ningmitai capsule through relevant literature reports, and 73 active compounds were obtained according to ADME ($OB \geqslant 30\%$, $DL \geqslant 0.18$), including 20 effective components of *I. cylindrica*, 4 effective compounds of *C. orbiculatus*, 14 effective compounds of *H. mutabilis*, 31 effective compounds of *F. suspensa*, 7 effective compounds of *B. soulieana*, 29 effective compounds of *P. capitatum*, and 17 effective compounds of *A. pilosa* (Table 1).

Table 1 Summary of effective compounds in Ningmitai capsule

No.	Component No.	PubChem CID	Compound name	Medicinal material
1	A1	439503	Salicin	TMG, LQ
2	A2	445858	Ferulic acid	TMG, LQ
3	A4	19009	Palmatine	DFT, SKZ
4	A7	5281703	Wogonin	LQ, XHC
5	A8	5280459	Quercitrin	LQ, THL
6	A9	5280443	Apigenin	FRY, XHC
7	A12	5281855	Ellagic acid	THL, XHC
8	A13	10494	Oleanolic acid	THL, LQ
9	A14	237332	5-Hydroxymethylfurfural	THL, TMG
10	BMG10	5281702	Tricin	TMG
11	BMG13	10680	Flavone	TMG
12	BMG15	11536299	5-Hydroxy-2-(2-phenylethyl) chromone	TMG
13	BMG22	126	4-Hydroxybenzaldehyde	TMG
14	BMG23	1983	N-acetyl-p-aminophenol	TMG
15	BMG26	10772	Coixol	TMG
16	BMG28	5280435	Phytol	TMG
17	BMG29	5862	L-cysteine	TMG
18	BMG30	4004	Malathion	TMG
19	BMG32	8434	Sobrol A	TMG
20	C1	5742590	Daucosterol	THL, TMG
21	C2	985	Palmitic acid	TMG, DFT, XHC
22	C3	8468	Vanillic acid	TMG, LQ, THL
23	C4	72	Protocatechuic acid	TMG, XHC, THL
24	C5	689043	Caffeic acid	TMG, LQ, FRY
25	C8	222284	Beta-sitosterol	TMG, DFT, LQ
26	C10	5280445	Luteolin	THL, FRY, LQ
27	DFT2	73337	Magnoflorine	DFT
28	FRY2	114776	Isoorientin	FRY
29	FRY13	5281416	Esculetin	FRY
30	FRY15	10494	Oleanic acid	FRY
31	FRY16	73659	Maslinic acid	FRY
32	FRY17	2266	Azelaic acid	FRY
33	H1	5280343	Quercetin	XHC, FRY, LQ, THL, SKZ
34	LQ1	5281773	Forsythiaside	LQ
35	LQ2	34751	Forsythin	LQ
36	LQ3	64981	Arctigenin	LQ
37	LQ5	1110	Succinic acid	LQ
38	LQ8	8768	Protocatechualdehyde	LQ
39	LQ11	135	P-hydroxybenzoic acid	LQ
40	LQ12	125	P-hydroxybenzyl alcohol	LQ
41	LQ16	11230	4-Terpineol	LQ
42	LQ17	64685	Borneol	LQ
43	LQ18	64971	Betulinic acid	LQ
44	LQ19	638072	Squalene	LQ
45	LQ21	11005	Myristic acid	LQ
46	LQ22	7460	Phellandrene	LQ
47	LQ23	6549	Linalool	LQ
48	LQ25	11168203	Boswellia C	LQ
49	SKZ1	275182	Berbamine	SKZ
50	SKZ2	5988	Sucrose	SKZ
51	SKZ3	72323	Jatrorrhizine	SKZ
52	SKZ4	10143	Isocorydine	SKZ
53	T1	64945	Ursolic acid	XHC, FRY, LQ, THL
54	T2	5280863	Kaempferol	THL, FRY, LQ, XHC
55	THL1	439533	Taxifolin	THL
56	THL3	31553	Silybin	THL
57	THL5	5281673	Myricetrin	THL
58	THL7	107971	Daidzin	THL
59	THL11	107905	Epicatechin-3-O-gallate	THL
60	THL14	13250	Ethyl gallate	THL
61	THL16	5280681	Quercetin 3-methyl ether	THL
62	THL18	240	Benzaldehyde	THL
63	THL19	289	Catechol	THL
64	THL22	3469	2,5-Dihydroxybenzoic acid	THL
65	THL23	3220	Emodin	THL
66	THL24	6305	L-tryptophan	THL
67	THL25	1174	Uracil	THL
68	THL26	6140	L-phenylalanine	THL
69	THL29	5280450	Linoleic acid	THL
70	THL35	1110	Succinic acid/Butanedioic acid	THL
71	XHC3	6918774	Eicosanoic acid	XHC
72	XHC11	9798666	Corosolic acid	XHC
73	XHC15	10467	Cryptochlorogenic acid	XHC

Note: TMG. *Imperata cylindrica*; LQ. *Forsythia suspensa*; DFT. *Cocculus orbiculatus*; SKZ. *Berberis soulieana*; XHC. *Agrimonia pilosa*; THL. *Polygonum capitatum*; FRY. *Hibiscus mutabilis*.

3.2 Effective targets of Ningmitai capsule on UTIs A total of 8 797 UTIs-associated targets were obtained through GeneCards database. The targets with relevance score ≥20 were selected as potential targets of UTIs, and a total of 304 relevant targets were obtained. Related targets were supplemented through DisGeNet database, and repeated targets were deleted. Finally, the two databases were combined to obtain 522 targets associated with UTIs. Relevant target data were imported into Cytoscape 3.6.1 software to build the "active component-target" network diagram (Fig. 1).



Note: TMG. *Imperata cylindrica*; LQ. *Forsythia suspensa*; DFT. *Cocculus orbiculatus*; SKZ. *Berberis soulieana*; XHC. *Agrimonia pilosa*; THL. *Polygonum capitatum*; FRY. *Hibiscus mutabilis*. The component information of A1-A14, C1-C10 and T1-T2 are shown in Table 1. The square represents 7 medicinal materials; the circle represents the active components of medicinal materials; the regular octagon represents the total active components of medicinal materials; the green diamond represents the target of UTIs. The darker the color and the larger the figure, the stronger the interaction between the component and the target protein.

Fig. 1 Component-target network diagram of Ningmitai capsule

3.3 PPI network of the targets of Ningmitai capsule for the treatment of UTIs The 2 552 targets retrieved from Ningmitai capsule and 522 targets collected from UTIs were combined to screen out the common targets, and PPI network analysis was performed through STRING database. The interaction network diagram between targets was established through Cytoscape 3.6.1 software. PPI network diagram was drawn for common targets with medium reliability (>0.400) (Fig. 2), and the difference in PPI enrichment $P<1.0^{e-16}$ was statistically significant. The network diagram of data was made through Cytoscape 3.6.1 software (Fig. 3), and topological analysis was performed to obtain the connectivity of each target. The key target of Ningmitai capsule on UTIs with the connectivity greater than 20 was selected (Table 2). In addition, the MCODE function results of Cytoscape 3.6.1 software showed that there were two modules with a score greater than 10 (Fig. 4). These two modules might be its core function modules.

3.4 GO and KEGG functional enrichment analysis of Ningmitai capsule on UTIs GO and KEGG functional enrichment analysis was performed on the total PPI network diagram and each module. Through the analysis of DAVID database, 523 GO enrichment items were obtained, of which 305, 51 and 167 were related to BP, CC and MF, respectively (Fig. 5). Through data and image view, the intervention of Ningmitai capsule in the process of UTIs mainly involves protein phosphorylation, MAPK cascade, drug metabolic process, phosphatidylinositol-mediated signaling and intracellular receptor signaling pathway. The enrichment results

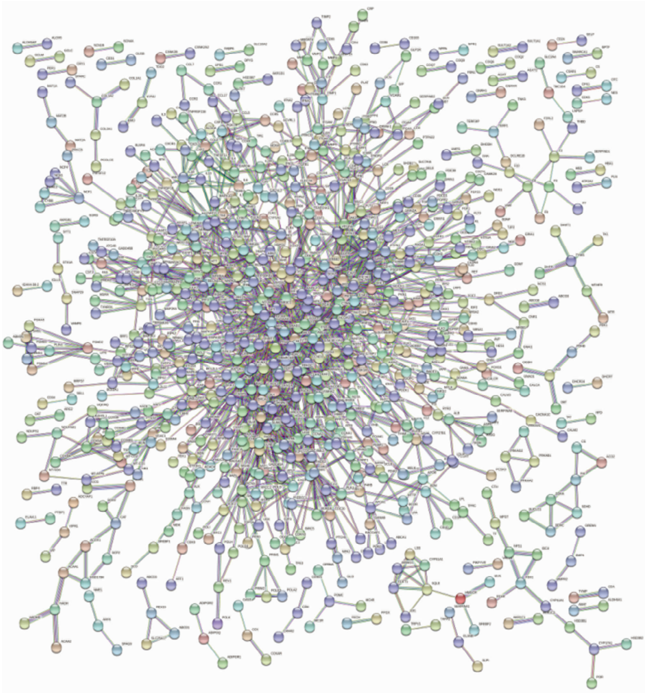
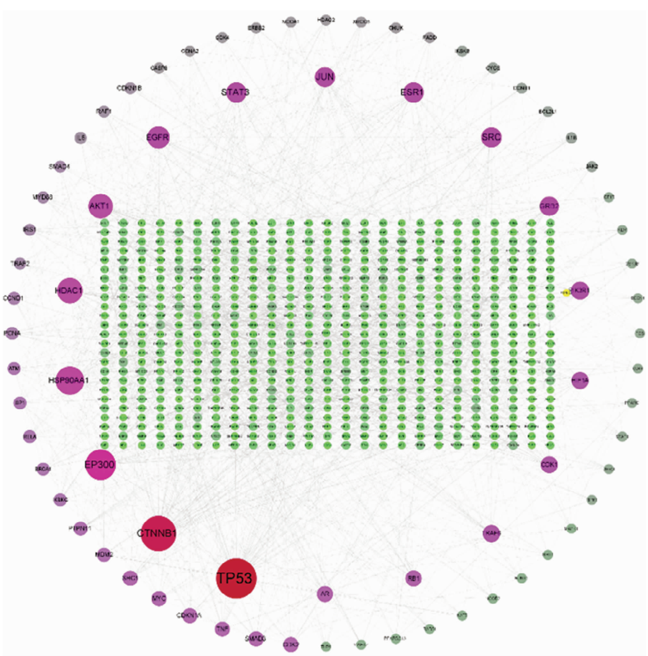


Fig. 2 PPI network diagram of common targets



Note: The red, pink, grey and purple circles represent the pathways associated with UTIs; the redder the color and the larger the shape, the greater the correlation of the pathway; the green circle inside the rectangle represents the target of the path; the size of each node represents its degree value.

Fig. 3 PPI network diagram of common targets

of KEGG pathway showed that the treatment of UTIs by Ningmitai capsule is associated with prostate cancer, pancreatic cancer, chagas disease, bladder cancer, toxoplasmosis and other signaling pathways. Particularly, the target in Mould 2 is the part of Ningmitai capsule that has the closest effect on UTIs.

3.5 Component-target-pathway network diagram of Ningmitai capsule The core targets of Ningmitai capsule acting on UTIs were mapped in Cytoscape 3.6.1 software to obtain the network diagram of core component-target-pathway. The results showed that 38 core components were screened from 7 TCM components of Ningmitai capsule, including salicin, ferulic acid, wogonin, ellagic acid, vanillic acid, and ursolic acid. There were 20 major pathways associated with UTIs, including prostate cancer, pancreatic cancer, chagas disease, bladder cancer and toxoplasmosis, which mainly acted on 26 core targets such as NFKB1, JUN, CTNNB1, TP53, MYC, CDK1 and STAT3 to treat UTIs (Fig. 6).

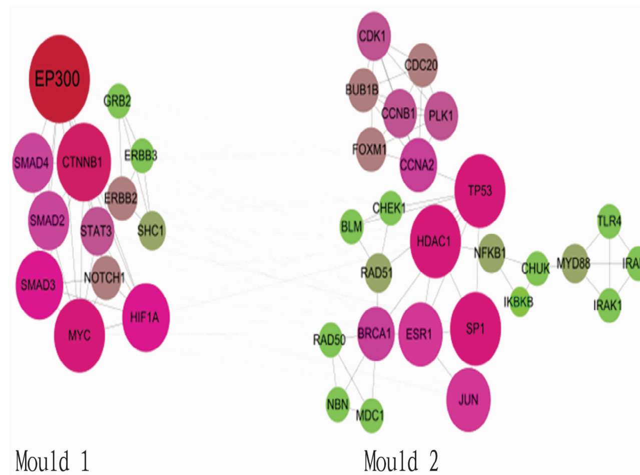


Fig. 4 Action of Ningmitai capsule on PPI network module of UTIs

Table 2 Correlated significant targets of Ningmitai capsule acting on UTIs

No.	Name	Degree
1	TP53	63
2	CTNNB1	58
3	EP300	44
4	HDAC1	34
5	STAT3	28
6	JUN	28
7	GRB2	27
8	CDK1	22
9	SMAD3	19
10	MYC	19
11	SMAD4	15
12	MYD88	15
13	CHUK	13
14	CCNA2	13
15	ERBB2	13
16	CCNB1	12
17	IKBKB	12
18	TLR4	10
19	PLK1	9
20	SMAD2	8

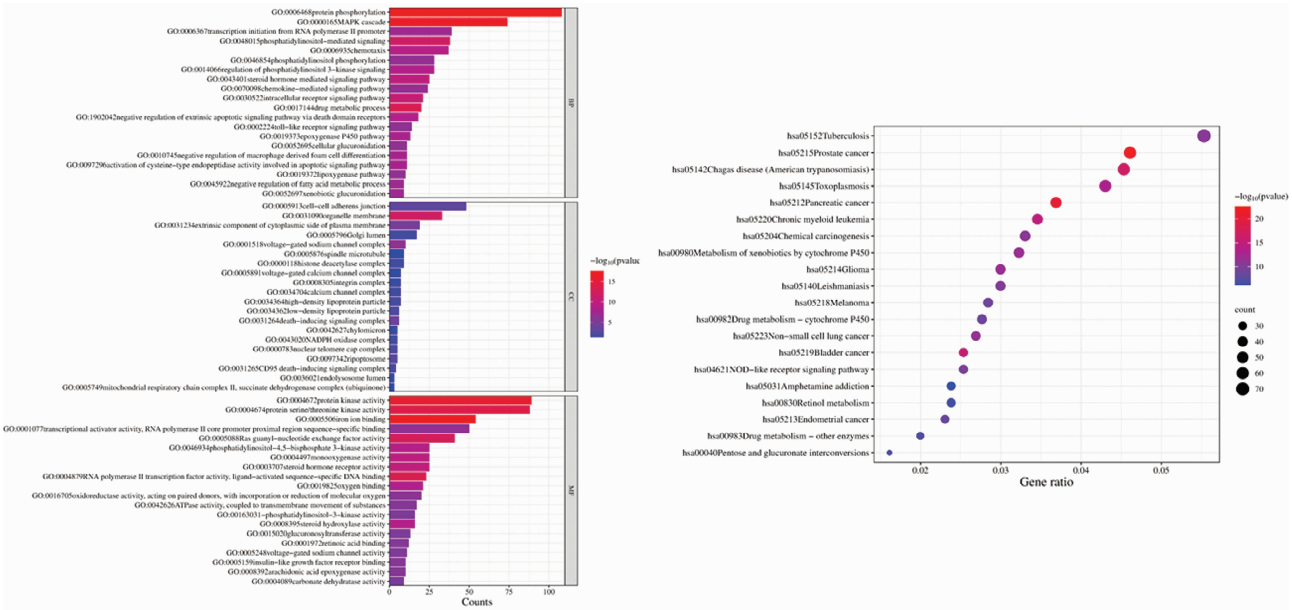
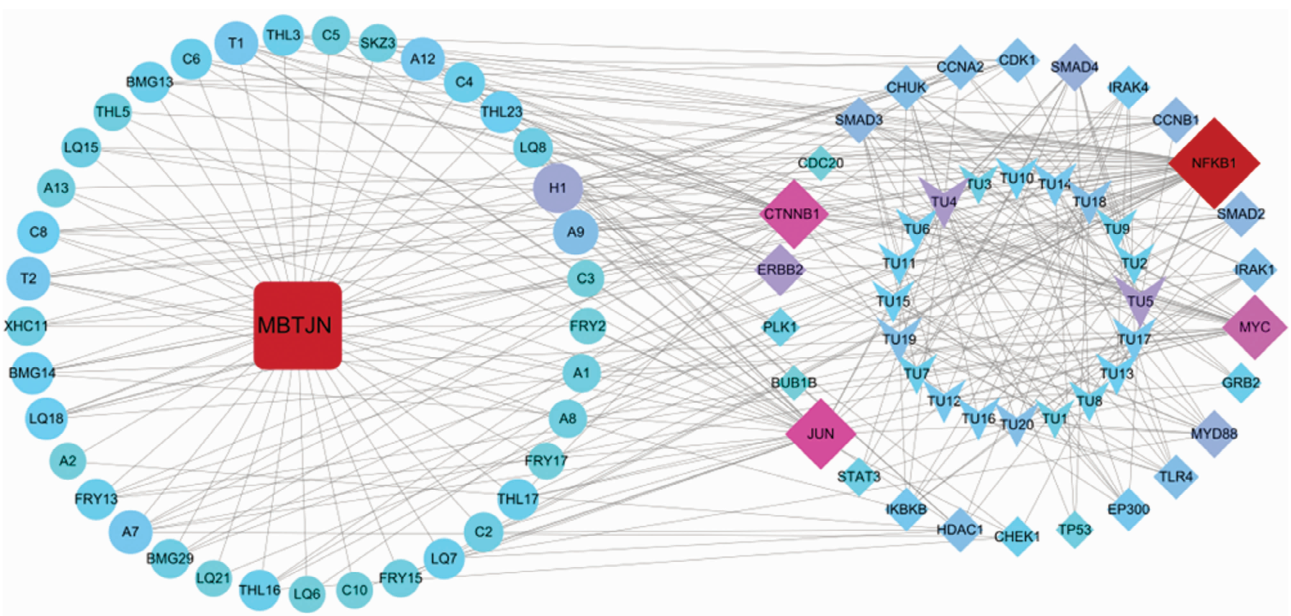


Fig. 5 GO and KEGG function enrichment analysis of Ningmitai capsule on PPI network of UTIs



Note: The red square represents Ningmitai capsule; the blue circle represents the core component; the diamond represents targets associated with UTIs; the lower triangle represents UTIs-associated pathways; the size of each shape represents its degree value.

Fig. 6 Component-target-pathway network diagram of Ningmitai capsule

4 Conclusions

The main active components, pathways and targets of Ningmitai capsule for the treatment of UTIs were predicted and screened through literature search, target prediction, PPI network, and GO and KEGG functional enrichment analysis based on network pharmacology. The results showed that there were 37 main active components of Ningmitai capsule for the treatment of UTIs, including salicin, ferulic acid and wogonin. Ningmitai capsule may treat UTIs by acting on prostate cancer, pancreatic cancer, chagas disease, bladder cancer, toxoplasmosis and other 20 pathways through 26 targets such as NFKB1, JUN, CTNNB1, STAT3, *etc*.

It has been reported in the literature that the target TLR4 in the Toll-like pathway can be triggered to promote IL-6 secretion, urinary STAT3 phosphorylation and antimicrobial peptide transcriptional activation after the pathogen reaches the bladder, indicating that the target of STAT3 is related to UTIs[20]. Nitroxoline (NTX) is a kind of antibiotic for the treatment of UTIs. Studies have found that it can be used as a new STAT3 target inhibitor, and has certain effect on the treatment of drug-resistant urothelial bladder cancer (UBC)[21]. It preliminarily indicates that bladder cancer and UTIs have common targets, providing a certain theoretical basis for the treatment of UTIs.

In summary, the main active components, pathways and targets of Ningmitai capsule for the treatment of UTIs were predicted and screened. The results showed that there were 37 main active components, including salicin, ferulic acid, wogonin, ellagic acid, vanillic acid, ursolic acid, kaempferol, jatrorrhizine, isoorientin, quercetin, *etc*. In addition, Ningmitai capsule for the treatment of UTIs may mainly act on NFKB1, JUN, CTNNB1, TP53, MYC, CDK1, STAT3, HDAC1, EP300, CTNNB1 and other targets, and play a role in the treatment of UTIs through prostate cancer, pancreatic cancer, chagas disease, bladder cancer, toxoplasmosis and other pathways. These preliminary results provide a basis for further study of pharmacological mechanism and clinical application of Ningmitai capsule.

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