European Review for Medical and Pharmacological Sciences 2022; 26: 4709-4720

Analysis of ginseng in the treatment of Interstitial Cystitis/Bladder Pain Syndrome based on network pharmacology

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Abstract. – OBJECTIVE: The network pharmacology is adopted in the paper to elaborate the active components, targets, and pathways of ginseng in the treatment of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS).

MATERIALS AND METHODS: The active components and potential targets of ginseng were obtained through the Traditional Chinese Medicine System Pharmacology Database and Analysis Platform (TCMSP). The OMIM, Disgenet, and Genecards databases for IC/BPS targets, and the STRING11.0 database were used for the protein-protein interaction (PPI) network. Meanwhile, the latter covers R language was used for the target of ginseng for IC/BPS, Bioconductor bioinformatics software for GO and KEGG functional enrichment analysis of key target genes, and the Cytoscape 3.8.2 software for constructing the "component-target" network and the "component-target-pathway" network map.

RESULTS: The results are categorized into three camps: components, targets, and pathways. As for components, 22 active components of ginseng that perform biological activities in the cell membrane, cytoplasm, and nucleus were observed, among which kaempferol, girinimbin, suchilacton, arachidonate, and gomisin B are the main active ones. 650 targets were found, mainly represented by PTGS2, PTGS1, AR, SLC6A4, and CHRM2, 134 of which (especially AKT1, TNF, VEGFA, TP53, EGFR, STAT3, IL-1β, ESR1, and JUN) contribute to the treatment of IC/BPS. Moreover, the pathways that serve as major contributors are the PI3K-Akt signaling pathway, the HIF-1 signaling pathway, the STAT3 signaling pathway, the MAPK signaling pathway, the NF-κB signaling pathway, and the apoptosis-related pathway.

CONCLUSIONS: Ginseng can exert anti-inflammatory, anti-oxidative stress and anti-apoptotic effects on IC/BPS thanks to its multi-component, multi-target and multi-way functions.

Key Words:
Interstitial cystitis/bladder pain syndrome, Ginseng, Network pharmacology, Active components, PI3K-Akt signaling pathway.

Introduction

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) refers to a chronic inflammatory disease of unknown etiology characterized by frequent urination, urgency, and suprapubic or pelvic pain after bladder filling, whose main victims are women aged 30-50 with an incidence of about 450-60/100,000, which is growing annually[1,2]. The available treatment strategies for IC/BPS at present are oral drugs, intravesical instillation, botulinum toxin bladder injection, and sacral neuromodulation, whose individual or collective application still fails to avoid symptoms covering urgency, frequent urination, and pelvic pain after treatment, which troubles 41-54% of patients[1-3]. Some patients develop remission, repeated attacks even without obvious incentives, and resistance to treatment[1-3]. The bladder contracture, hydronephrosis, and renal function damage is inevitable without taking the IC/BPS under control, leading to cystectomy, which highlights the urgency to elucidate the pathogenesis of IC/BPS and find effective therapeutic drugs[1-3].

Ginseng is one of the precious Chinese herbal medicines with extensive and time-honored applications[4,5]. Pharmacological studies[5-7] have proved that ginseng abounds with various proteins, polysaccharides and saponins, which have anti-inflammatory, anti-oxidant, anti-tumor, anti-cardiovascular, and anti-aging functions. Despite ginseng's favorable anti-inflammatory, antioxidant, immune regulation, and other functions supported by clinical studies that reveal the beneficial role of ginseng on diabetes, coronary heart disease, hypertension, Alzheimer's disease, rheumatic diseases, and other inflammatory diseases, reports on the ginseng's effects

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on IC/BPS are scarce[7-9]. Network pharmacology, an emerging technology combining network biology with polypharmacology with wide application in research concerning drug-disease interactions, directly identifies drug and disease targets from a sea of data, and understands their underlying mechanisms and pathways[10,11]. Therefore, together with network pharmacology, this paper explores the active components, core targets, and mechanisms of action of ginseng in the treatment of IC/BPS, providing a theoretical insight for the future treatment with ginseng.

Materials and Methods

Online Database and Analysis Software

Numerous databases and software were adopted in the paper. The former include Pubchem (https://pubchem.ncbi.nlm.nih.gov/), PharmMapper (http://www.lilab-ecust.cn/pharmmapper/), Swiss Target Prediction (http://www.swisstargetprediction.ch/), OMIM (https://omim.org/), Genecards (https://www.genecards.org/), Disgenet (https://www.disgenet.org/), STRING (https://string-db.org/), DAVID (https://david.ncifcrf.gov/), and Uniprot (https://www.uniprot.org/). The latter cover Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/), Cytoscape 3.8.2, and R 4.0.5.

Identification of Active Components and Targets of Ginseng

As mentioned above, the TCMSP database was used to retrieve the effective chemical components of ginseng with taking the oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 as the screening criteria[12-14]. The corresponding targets obtained based on such components were corrected by Uniprot (https://www.uniprot.org/), and selected as "Homo sapiens". The components and 650 targets in ginseng were input into Cytoscape to draw a "component-target" network, and the top 10 components and targets by degree value are listed thanks to the Network Analyzer plug-in.

Construction of IC/BPS Target Database

The disease targets were searched on OMIM, Disgenet, and Genecards databases with "Bladder Pain Syndrome" and "Interstitial Cystitis" as keywords.

Screening of Common Drug-Disease Targets and Network Diagram Construction of Disease-Target-Component Interactions

In this paper, the Venny 2.1 online software mapping tool was employed to analyze the interaction targets of ginseng and IC/BPS, and obtain common drug-disease targets. The PPI network of protein interaction was constructed by String database, and the protein interaction network map was created using Cytoscape 3.8.2. Later, the NetworkAnalyzer was taken to perform topological analysis, and genes whose degree value was greater than the average were picked as the core target. In addition, a bar graph of the target was drawn using R 4.0.5.

GO and KEGG Pathway Enrichment Analysis

Bioconductor bioinformatics based on R software was used to perform GO and KEGG functional enrichment analysis of key target genes with p-value < 0.05 and q-value < 0.05, and the results were displayed as a bubble chart. In the KEGG pathway, the first 20 pathways were collected by p-value. The components, targets, and signaling pathways were integrated using Cytoscape 3.8.2 to construct a "component-target-pathway" network map.

Results

Ginseng Active Ingredient Screening and Target Prediction

A total of 22 potential active ingredients of ginseng (Table I) and 650 drug targets were screened and input into Cytoscape to draw a "component-target" network (Figure 1). The top 10 components and targets by degree were listed through the Network Analyzer plugin as shown in Table II, in which the active components (kaempferol, Girinimbin, and suchilactone) and main targets (PTGS2, PTGS1, and AR) were depicted.

Screening of the Target of Ginseng for IC/BPS

A total of 1,462 disease targets were obtained after deduplication on OMIM, Disgenet, and Genecards databases using "Bladder Pain Syndrome" and "Interstitial Cystitis" as keywords. The 134 common drug-disease targets were later revealed through the analysis of the 650 drug targets of ginseng and 1,462 disease targets of

Table I. Active ingredients in ginseng.

Mol ID	Molecule Name	OB (%)	DL
MOL002879	Diop	43.59	0.39
MOL000449	Stigmasterol	43.83	0.76
MOL000358	beta-sitosterol	36.91	0.75
MOL003648	Inermin	65.83	0.54
MOL000422	kaempferol	41.88	0.24
MOL004492	Chrysanthemaxanthin	38.72	0.58
MOL005308	Aposiopolamine	66.65	0.22
MOL005314	Celabenzine	101.88	0.49
MOL005317	Deoxyharringtonine	39.27	0.81
MOL005318	Dianthramine	40.45	0.2
MOL005320	arachidonate	45.57	0.2
MOL005321	Frutinone A	65.9	0.34
MOL005344	ginsenoside rh2	36.32	0.56
MOL005348	Ginsenoside-Rh4_qt	31.11	0.78
MOL005356	Girinimbin	61.22	0.31
MOL005357	Gomisin B	31.99	0.83
MOL005360	malkangunin	57.71	0.63
MOL005376	Panaxadiol	33.09	0.79
MOL005384	suchilactone	57.52	0.56
MOL005399	alexandrin_qt	36.91	0.75
MOL005401	ginsenoside Rg5_qt	39.56	0.79
MOL000787	Fumarine	59.26	0.83

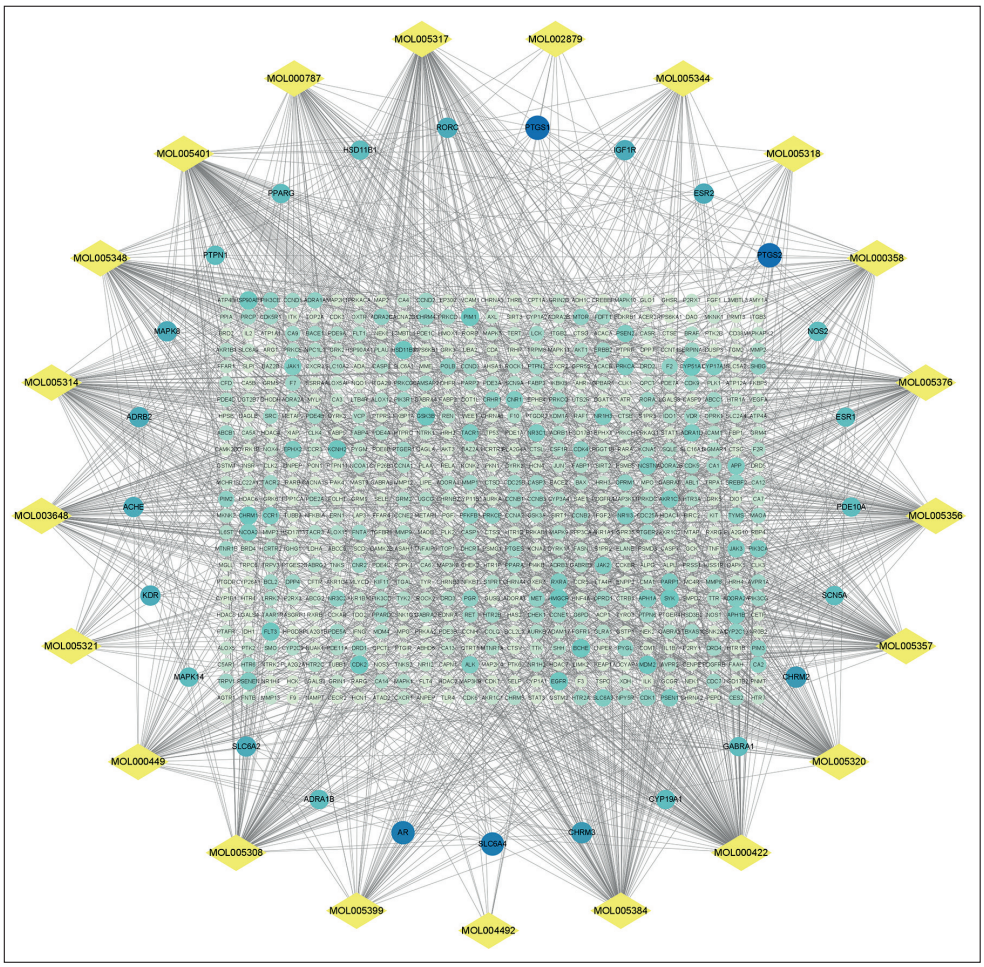

Figure 1. Network diagram of component targets of ginseng. The yellow rhombus represents the active ingredient of ginseng and the circles the drug targets. The larger the yellow rhombus and the circle, the darker the color, the higher the degree value of the active ingredient and target.

Table II. Major compositions and targets in ginseng (Top 10).

Composition	Degree value	Target	Degree value
MOL000422	150	PTGS2	13
MOL005356	119	PTGS1	13
MOL005384	114	AR	12
MOL005320	112	SLC6A4	12
MOL005357	109	CHRM2	10
MOL005317	108	CHRM3	10
MOL005401	107	ESR2	9
MOL005308	105	RORC	9
MOL005348	105	ACHE	9
MOL005314	103	SLC6A2	9

IC/BPS (Figure 2A), which were input into Cytoscape software to draw the "disease-target-component" interaction network diagram (Figure 2B), protein interaction network (Figure 3A, the node, color, and the value of the degree parameter were proportional), and PPI network (Figure 3B). Figure 4A and 4B, based on PPI topological analysis and cluster analysis, list the main targets of ginseng for IC/BPS treatment: AKT1, TNF, VEGFA, TP53, EGFR, STAT3, IL-1β, ESR1, and JUN.

GO Enrichment Analysis of Ginseng for IC/BPS Treatment

The results show the rich existence of 134 intersecting genes in 2,201 biological process pathways, 49 in the expression process of cellular components, and 173 in molecular function. Figure 5 shows the top 20 results based on the combined score, displayed in a bar graph. The main enrichment biological processes include positive regulation of protein serine/threonine

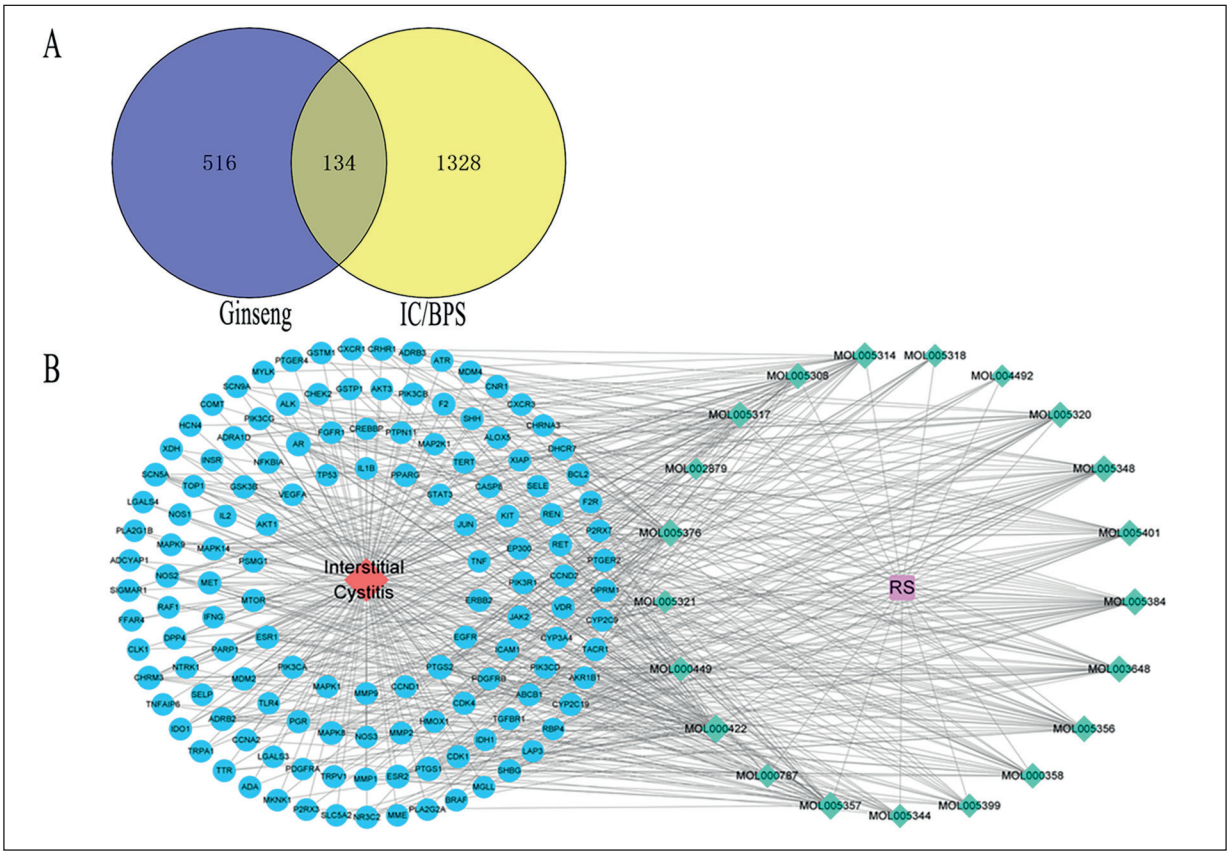

Figure 2. Network analysis of common targets in ginseng and IC/BPS. **A**, Venn diagram analysis of common targets of ginseng and IC/BPS. **B,** Network graph analysis of the interaction between active components of ginseng and a common target in IC/BPS.

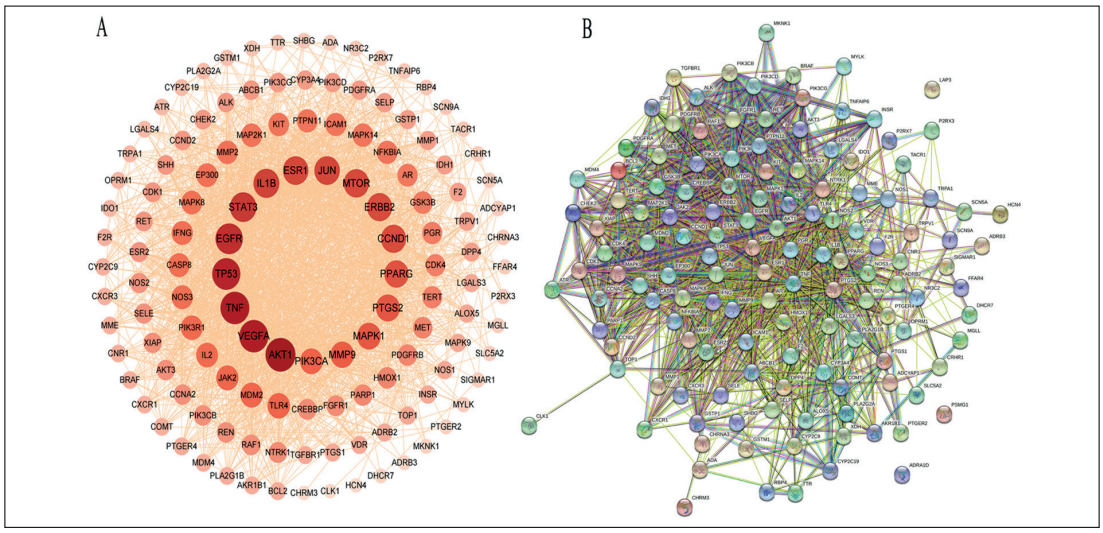

Figure 3. Ginseng and IC/BPS common target protein interaction analysis. **A,** Core target protein PPI network diagram. **B,** Core target protein interaction network diagram.

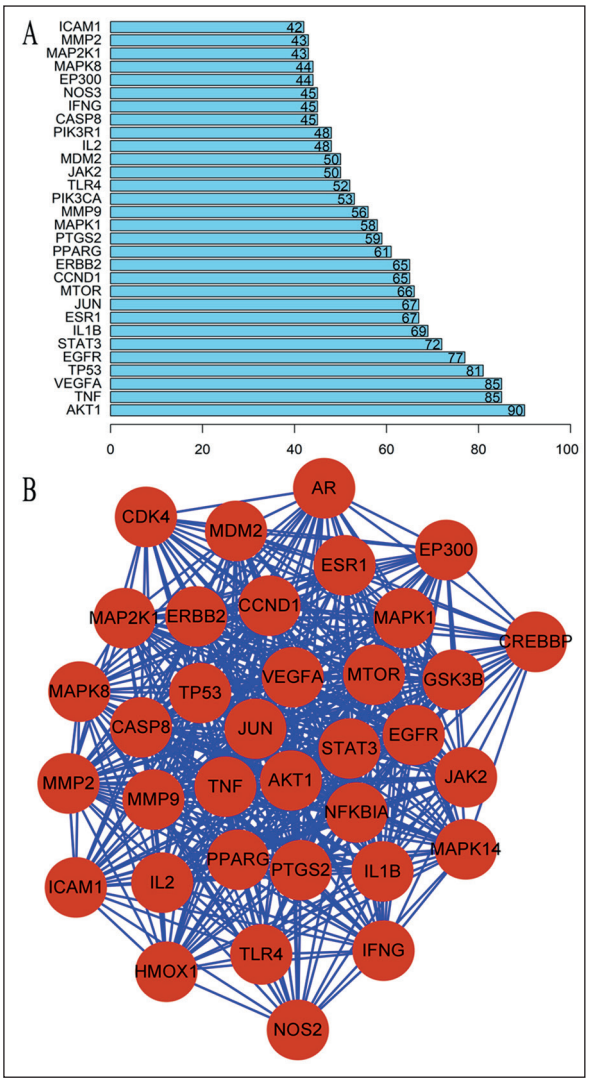

Figure 4. Topological and cluster analysis of human-involved IC/BPS common targets (Top 20). **A,** top 20 core target molecular bar graph; **B,** top 20 core target protein interaction network diagram.

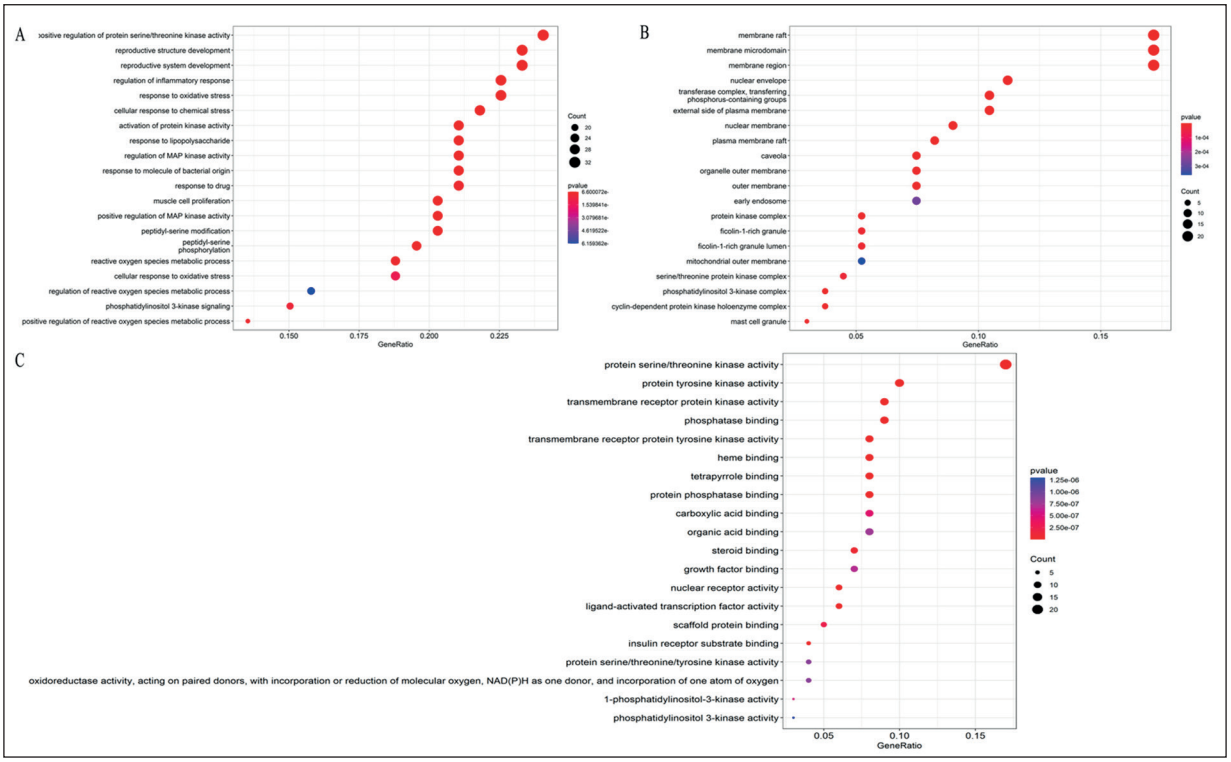

Figure 5. GO enrichment analysis of core targets of ginseng and IC/BPS (Top 20). **A,** Biological process. **B,** Cellular component. **C,** Molecular function.

kinase activity, reproductive structure development, reproductive system development, inflammatory response regulation, oxidative stress response, etc. The main enrichment cellular components consist of membrane raft, membrane microdomain, membrane region, nuclear envelope, transferase complex, transferring phosphorus-containing groups, etc. The main molecular functions are: protein serine/threonine kinase activity, protein tyrosine kinase activity, transmembrane receptor protein kinase activity, phosphatase binding, DNA-binding transcription factor binding, etc.

KEGG Enrichment Analysis of Ginseng for IC/BPS Treatment

KEGG analysis verifies the rich application of 134 intersecting genes in 167 signaling pathways. The top 20 results are presented in Table III and Figure 6A, according to *p*-values. Meanwhile, the first 20 active ginseng drugs and core targets are integrated to construct a "component-target-pathway" network diagram (Figure 6B – node size varies by degree value). Figure 6A displays the main pathways with abundant KEGG pathway: PI3K-Akt signaling pathway, lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway, tumor, and infection-Related Pathways, etc. Figure 6B describes ginseng's main active components, including kaempferol, gomisin B, panaxadiol, ginsenoside-rh4, deoxyharringtonine, girinimbin, and suchilactone, as well as the main molecular targets, covering PIK3, AKT1, MAPK1, EGFR, MAPK8, MAPK14, PTGS2, STAT3, and PTGS1.

Discussion

The involvement of inflammation and immune regulation disorders in the complex pathogenesis of IC/BPS is supported by existing evidence[15-17]. Current studies suggest that anti-inflammatory and immunomodulatory agents can improve the disease and its progression in IC/BPS patients, which makes natural active ingredients with such properties a new option for the treatment of IC/BPS[18,19]. Ginseng, known as the dried root and rhizome of Panax ginseng C.A.Mey. (a plant of the *Araliaceae* family), enjoys long and mature application. However, its complex material components limit the exploration of its action mechanism[20]. Studies[16-24] have identified ginsenosides, polysaccharides, and flavonoids the active

Table III. KEGG enrichment analysis of ginseng for IC/BPS treatment (Top 20).

ID	Description	*p*-value	*q*-value	geneID	Count
hsa04151	PI3K-Akt signaling pathway	1.23E-17	4.85E-17	BCL2/AKT1/INSR/MAP2K1/GSK3B/ NOS3/EGFR/ERBB2/JAK2/TP53/MDM2/ MET/NTRK1/TLR4/ MTOR/PIK3CA/ CCND1/CDK4/CCND2/PIK3CB/PIK3CG/ FGFR1/PIK3CD/F2R/KIT/IL2/VEGFA/ MAPK1/PDGFRB/PIK3R1/AKT3/ RAF1/PDGFRA	33
hsa05417	Lipid and atherosclerosis	6.06E-20	4.79E-19	BCL2/JUN/CASP8/PPARG/AKT1/MAPK8/ MMP1/ICAM1/SELE/NFKBIA/IL1B/ GSK3B/MAPK14/NOS3/JAK2/TP53/TLR4/ PIK3CA/PIK3CB/SELP/MMP9/PIK3CD/ CYP2C9/MAPK9/STAT3/MAPK1/ PIK3R1/TNF/AKT3	29
hsa05167	Kaposi sarcoma-associated herpesvirus infection	4.46E-20	3.91E-19	PTGS2/JUN/CASP8/AKT1/MAPK8/ICAM1/ NFKBIA/MAP2K1/GSK3B/MAPK14/JAK2/ TP53/EP300/CREBBP/MTOR/PIK3CA/CCND1/ CDK4/PIK3CB/PIK3CG/PIK3CD/ MAPK9/ STAT3/VEGFA/MAPK1/PIK3R1/AKT3/RAF1	28
hsa05205	Proteoglycans in cancer	2.06E-19	1.48E-18	AKT1/ESR1/SHH/MAP2K1/MAPK14/EGFR/ ERBB2/PTPN11/TP53/MDM2/MET/TLR4/ MTOR/PIK3CA/CCND1/PIK3CB/FGFR1/ MMP9/MMP2/PIK3CD/STAT3/VEGFA/ MAPK1/BRAF/PIK3R1/TNF/AKT3/RAF1	28
hsa05207	Chemical carcinogenesis - receptor activation	5.19E-19	2.56E-18	ADRB2/PGR/BCL2/JUN/AR/AKT1/ CYP3A4/GSTM1/ESR1/ESR2/VDR/ADRB3/ MAP2K1/EGFR/JAK2/CHRNA3/MTOR/ PIK3CA/CCND1/XIAP/PIK3CB/PIK3CD/ STAT3/VEGFA/MAPK1/PIK3R1/AKT3/RAF1	28
hsa05215	Prostate cancer	1.73E-27	1.36E-25	BCL2/AR/AKT1/GSTP1/NFKBIA/MAP2K1/ GSK3B/EGFR/ERBB2/TP53/MDM2/EP300/ CREBBP/MTOR/PIK3CA/CCND1/PIK3CB/ FGFR1/MMP9/PIK3CD/MAPK1/BRAF/ PDGFRB/PIK3R1/AKT3/RAF1/PDGFRA	27
hsa05161	Hepatitis B	4.55E-21	5.75E-20	BCL2/JUN/CASP8/AKT1/MAPK8/NFKBIA/ MAP2K1/MAPK14/JAK2/TP53/EP300/ CREBBP/TLR4/PIK3CA/PIK3CB/CCNA2/ MMP9/PIK3CD/MAPK9/STAT3/MAPK1/ BRAF/PIK3R1/TNF/AKT3/RAF1/TGFBR1	27
hsa01522	Endocrine resistance	7.10E-26	2.80E-24	BCL2/JUN/AKT1/MAPK8/ESR1/ESR2/ MAP2K1/MAPK14/EGFR/ERBB2/TP53/ MDM2/MTOR/PIK3CA/CCND1/CDK4/ PIK3CB/MMP9/MMP2/PIK3CD/MAPK9/ MAPK1/BRAF/PIK3R1/AKT3/RAF1	26
hsa04933	AGE-RAGE signaling pathway in diabetic complications	9.10E-23	2.39E-21	BCL2/JUN/AKT1/ MAPK8/ICAM1/SELE/IL1B/ MAPK14/NOS3/JAK2/PIK3CA/CCND1/CDK4/ PIK3CB/MMP2/PIK3CD/MAPK9/STAT3/ VEGFA/MAPK1/PIK3R1/TNF/AKT3/TGFBR1	24
hsa05418	Fluid shear stress and atherosclerosis	3.77E-19	2.29E-18	BCL2/JUN/AKT1/MAPK8/HMOX1/ICAM1/ SELE/GSTP1/GSTM1/IL1B/IFNG/MAPK14/ NOS3/TP53/PIK3CA/PIK3CB/MMP9/MMP2/ PIK3CD/MAPK9/VEGFA/PIK3R1/TNF/AKT3	24

Continued

Table III *(Continued)*. KEGG enrichment analysis of ginseng for IC/BPS treatment (Top 20).

ID	Description	*p*-value	*q*-value	geneID	Count
hsa04066	HIF-1 signaling pathway	1.84E-20	1.82E-19	BCL2/NOS2/AKT1/HMOX1/INSR/IFNG/ MAP2K1/MKNK1/NOS3/EGFR/ERBB2/ EP300/CREBBP/TLR4/MTOR/PIK3CA/ PIK3CB/PIK3CD/STAT3/VEGFA/MAPK1/ PIK3R1/AKT3	23
hsa04926	Relaxin signaling pathway	1.05E-18	4.60E-18	JUN/NOS2/AKT1/MAPK8/MMP1/NFKBIA/ MAP2K1/MAPK14/NOS3/EGFR/PIK3CA/ PIK3CB/NOS1/MMP9/MMP2/PIK3CD/ MAPK9/VEGFA/MAPK1/PIK3R1/AKT3 /RAF1/TGFBR1	23
hsa05230	Central carbon metabolism in cancer	2.95E-22	5.82E-21	AKT1/MAP2K1/EGFR/ERBB2/TP53/MET/ NTRK1/MTOR/PIK3CA/PIK3CB/FGFR1/ PIK3CD/KIT/MAPK1/IDH1/PDGFRB/RET/ PIK3R1/AKT3/RAF1/PDGFRA	21
hsa05212	Pancreatic cancer	2.06E-21	3.26E-20	AKT1/MAPK8/MAP2K1/EGFR/ERBB2/ TP53/MTOR/PIK3CA/CCND1/CDK4/ PIK3CB/PIK3CD/MAPK9/STAT3/VEGFA/ MAPK1/BRAF/PIK3R1/AKT3/RAF1/TGFBR1	21
hsa01521	EGFR tyrosine kinase inhibitor resistance	5.10E-21	5.75E-20	BCL2/AKT1/MAP2K1/GSK3B/EGFR/ERBB2/ JAK2/MET/MTOR/PIK3CA/PIK3CB/ PIK3CD/STAT3/VEGFA/MAPK1/BRAF/ PDGFRB/PIK3R1/AKT3/RAF1/PDGFRA	21
hsa05210	Colorectal cancer	8.72E-19	4.05E-18	BCL2/JUN/AKT1/MAPK8/MAP2K1/GSK3B/ EGFR/TP53/MTOR/PIK3CA/CCND1/ PIK3CB/PIK3CD/MAPK9/MAPK1/BRAF/ PIK3R1/AKT3/RAF1/TGFBR1	20
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	1.82E-18	7.56E-18	JUN/AKT1/NFKBIA/IFNG/MAP2K1/ MAPK14/EGFR/JAK2/PTPN11/ALK/TLR4/ MTOR/PIK3CA/PIK3CB/PIK3CD/STAT3/ MAPK1/PIK3R1/AKT3/RAF1/	
hsa04917	Prolactin signaling pathway	2.78E-19	1.83E-18	AKT1/MAPK8/ESR1/ESR2/MAP2K1/GSK3B/ MAPK14/JAK2/PIK3CA/CCND1/CCND2/ PIK3CB/PIK3CD/MAPK9/STAT3/MAPK1/ PIK3R1/AKT3/RAF1	19
hsa05218	Melanoma	5.03E-19	2.56E-18	AKT1/MAP2K1/EGFR/TP53/MDM2/MET/ PIK3CA/CCND1/CDK4/PIK3CB/FGFR1/ PIK3CD/MAPK1/BRAF/PDGFRB/PIK3R1/ AKT3/RAF1/PDGFRA	19
hsa05223	Non-small cell lung cancer	5.03E-19	2.56E-18	AKT1/MAP2K1/EGFR/ERBB2/TP53/ALK/ MET/PIK3CA/CCND1/CDK4/PIK3CB/ PIK3CD/STAT3/MAPK1/BRAF/RET/PIK3R1/ AKT3/RAF1	19

ingredients of ginseng with pharmacological activities, including anti-inflammatory, anti-tumor, anti-viral, anti-aging, anti-senile dementia, and immune regulation, which help combatting inflammatory diseases such as hepatitis, enteritis, asthma, and diabetes by crippling the production of inflammatory cytokines and regulating the activity of inflammatory signaling pathways. However, the relationship between ginseng and IC/BPS remains untouched, which explains our efforts to explore the active components, targets and molecular mechanisms of ginseng in the treatment of IC/BPS in the hope of starting more related discussions.

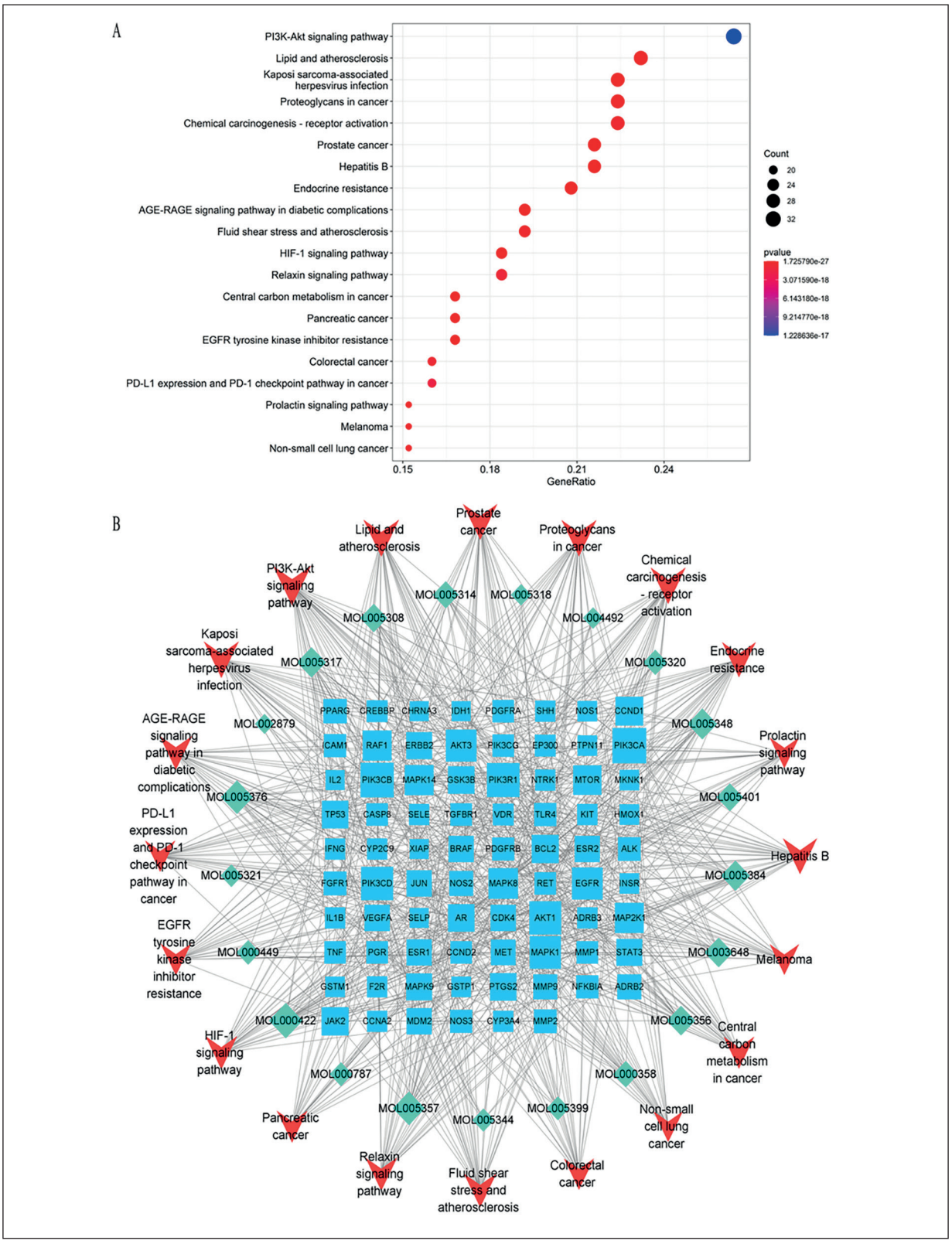

Figure 6. KEGG pathway enrichment and Composition-Target-Pathway analysis of core targets of ginseng and IC/BPS (top 20). **A,** KEGG pathway enrichment analysis of core targets of ginseng and IC/BPS. **B,** Ginseng and IC/BPS interaction network diagram of Composition-Target-Pathway (green the active component; blue the target; red the KEGG pathway; the size of the shape in the figure represents the size of the degree value).

Network pharmacology, which explores and analyzes the active components, targets, and action mechanisms of Chinese herbal medicines with extensive application, first elaborates the pharmacological properties of ginseng with a complex network model, and clarifies the complex interaction between components-targets-disease[25,26]. 22 active components of ginseng with 650 targets are screened, among which kaempferol, girinimbin, suchilacton, arachidonate, and gomisin B are the main active components in ginseng, while PTGS2, PTGS1, AR, SLC6A4, and CHRM2 the main targets. Further analysis finds that the main active components are mostly flavonoids, polysaccharides, ginsenosides and other compounds, and the main targets are highly related to oxidative stress, inflammatory response, lipid metabolism, and apoptosis[20-24].

The core targets of ginseng in the treatment of IC/BPS are observed to be AKT1, TNF, VEGFA, TP53, EGFR, STAT3, IL-1β, ESR1, and JUN through drug-disease common targets. Among them, AKT, TNF, TP53, STAT3, IL-1β, ESR1, and JUN participate in biological processes such as inflammation, oxidative stress, and apoptosis, the blocking of whose biological activity drops inflammation and tissue damage[26-28]. The GO enrichment analysis of ginseng for IC/BPS supports the ability of active components to exert biological activities in the cell membrane, cytoplasm, and nucleus, which cannot be realized by participating in protein kinase activity regulation, inflammatory response regulation, oxidative stress response, DNA binding, and transcription factor binding. In addition, KEGG analysis finds that the enriched genes abound in signaling pathways, mainly PI3K-Akt signaling pathway, lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway, infection-related pathways, etc. Among them, the PI3K-Akt, HIF-1, STAT3, MAPK, NF-κB signaling pathways, and apoptosis-related pathway targets are especially enriched.

Given the involvement of the PI3K-Akt, HIF-1, and STAT3 signaling pathways in the occurrence and development of various inflammatory diseases, targeted regulating of their activation makes significantly better the inflammatory response and tissue damage in many inflammatory diseases[29-31]. They are found to be up-regulated in IC/BPS patients and animal models, and their activation can be blocked by the active components in ginseng (ginsenosides and flavonoids), thus exerting anti-inflammatory, anti-apoptotic, and anti-oxidative stress activities[9,31-35]. MAPK and NF-κB signaling pathways are essential in regulating inflammation and immunity, whose activation facilitates the gene transcription of various inflammatory factors, resulting in inflammatory response and tissue damage[36-38]. Besides, they are activated in IC/BPS patients and IC/BPS model animals[32,37]. Blockade of MAPK signaling pathway and activation of NF-κB signaling pathway can significantly improve the inflammatory response and tissue damage in IC/BPS model animals[32,37]. The kaempferol is proved to be an active ingredient with the peak degree value in the treatment of IC/BPS in ginseng, which shares existing studies[38,39] about the fact that kaempferol can block MAPK signaling pathway and NF-κB signaling pathway, exert anti-inflammatory and anti-oxidative stress, and improve tissue damage and function.

Conclusions

The components of ginseng contributing to the treatment of IC/BPS in a multi-component, multi-target, and multi-path synergistic manner include aempferol, gomisin B, panaxadiol, ginsenoside-rh4, deoxyharringtonine, girinimbine, and suchilactone, which act on PIK3, AKT1, MAPK1, EGFR, MAPK8, VEGFA, TP53, EGFR, STAT3, IL-1β, ESR1, and JUN targets *via* the PI3K-Akt, HIF-1, STAT3, MAPK and NF-κB signaling pathways. However, this paper, limited by incomplete database and potential targets, fails to take the low-abundance active components into consideration, calling for further verification.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Ueda T, Hanno PM, Saito R, Meijlink JM, Yoshimura N. Current Understanding and Future Perspectives of Interstitial Cystitis/Bladder Pain Syndrome. Int Neurourol J 2021; 25: 99-110.
2) Patnaik SS, Laganà AS, Vitale SG. Etiology, pathophysiology and biomarkers of interstitial cystitis/painful bladder syndrome. Arch Gynecol Obstet 2017; 295: 1341-1359.
3) Hanno PM, Erickson D, Moldwin R. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol 2015; 193: 1545-1553.

4) Tyagi P, Moon CH, Janicki J. Recent advances in imaging and understanding interstitial cystitis. 2018; 7: 1696-1771.
5) Mancuso C, Santangelo R. Panax ginseng and Panax quinquefolius: From pharmacology to toxicology. Food Chem Toxicol 2017; 107: 362-372.
6) Wu W, Jiao C, Li H, Ma Y, Jiao L, Liu S. LC-MS based metabolic and metabonomic studies of Panax ginseng. Phytochem Anal 2018; 29: 331-340.
7) Kiefer D, Pantuso T. Panax ginseng. Am Fam Physician 2003; 68: 1539-1542.
8) Razgonova MP, Veselov VV, Zakharenko AM, Golokhvast KS, Nosyrev AE, Cravotto G, Tsatsakis A, Spandidos DA. Panax ginseng components and the pathogenesis of Alzheimer's disease (Review). Mol Med Rep 2019; 19: 2975-2998.
9) Fan W, Huang Y, Zheng H, Li S, Li Z, Yuan L, Cheng X, He C, Sun J. Ginsenosides for the treatment of metabolic syndrome and cardiovascular diseases: Pharmacology and mechanisms. Biomed Pharmacother 2020; 132: 1109-1115.
10) Zhang R, Zhu X, Bai H, Ning K. Network Pharmacology Databases for Traditional Chinese Medicine: Review and Assessment. Front Pharmacol 2019; 10: 123-130.
11) Saikia S, Bordoloi M. Molecular Docking: Challenges, Advances and its Use in Drug Discovery Perspective. Curr Drug Targets 2019; 20: 501-521.
12) Guo W, Huang J, Wang N, Tan HY, Cheung F, Chen F, Feng Y. Integrating Network Pharmacology and Pharmacological Evaluation for Deciphering the Action Mechanism of Herbal Formula Zuojin Pill in Suppressing Hepatocellular Carcinoma. Front Pharmacol 2019; 10: 1185-1190.
13) Jin J, Chen B, Zhan X, Zhou Z, Liu H, Dong Y. Network pharmacology and molecular docking study on the mechanism of colorectal cancer treatment using Xiao-Chai-Hu-Tang. PLoS One 202; 16: 252-258.
14) Mu C, Sheng Y, Wang Q, Amin A, Li X, Xie Y. Potential compound from herbal food of Rhizoma Polygonati for treatment of COVID-19 analyzed by network pharmacology: Viral and cancer signaling mechanisms. J Funct Foods 2021; 77: 144-149.
15) Birder LA. Pathophysiology of interstitial cystitis. Int J Urol 2019; 26: 12-15.
16) Akiyama Y, Luo Y, Hanno PM, Maeda D, Homma Y. Interstitial cystitis/bladder pain syndrome: The evolving landscape, animal models and future perspectives. Int J Urol 2020; 27: 491-503.
17) Grundy L, Caldwell A, Brierley SM. Mechanisms Underlying Overactive Bladder and Interstitial Cystitis/Painful Bladder Syndrome. Front Neurosci 2018; 12: 922-931.
18) Ogawa T, Ishizuka O, Ueda T, Tyagi P, Chancellor MB, Yoshimura N. Current and emerging drugs for interstitial cystitis/bladder pain syndrome (IC/BPS). Expert Opin Emerg Drugs 2015; 20: 555-570.
19) anno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, Forrest JB, Gordon B, Gray M, Mayer RD, Newman D, Nyberg L Jr, Payne CK, Wesselmann U, Faraday MM; Interstitial Cystitis. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 2011; 185: 2162-2170.
20) Liu Y, Zhang H, Dai X, Zhu R, Chen B, Xia B, Ye Z, Zhao D, Gao S, Orekhov AN, Zhang D, Wang L, Guo S. A comprehensive review on the phytochemistry, pharmacokinetics, and antidiabetic effect of Ginseng. Phytomedicine 2021; 92: 1537-1547.
21) Mostafa RE, Shaffie NM, Allam RM. Panax Ginseng alleviates thioacetamide-induced liver injury in ovariectomized rats: Crosstalk between inflammation and oxidative stress. PLoS One 2021; 16: e0260507.
22) Wang CZ, Hou L, Wan JY, Yao H, Yuan J, Zeng J, Park CW. Ginseng berry polysaccharides on inflammation-associated colon cancer: inhibiting T-cell differentiation, promoting apoptosis, and enhancing the effects of 5-fluorouracil. J Ginseng Res 2020; 44: 282-290.
23) Xue K, Ruan L, Hu J, Fu Z, Tian D, Zou W. Panax notoginseng saponin R1 modulates TNF-α/NF-κB signaling and attenuates allergic airway inflammation in asthma. Int Immunopharmacol 2020; 88: 106860.
24) Kim JH, Yi YS, Kim MY, Cho JY. Role of ginsenosides, the main active components of Panax ginseng, in inflammatory responses and diseases. J Ginseng Res 2017; 41: 435-443.
25) Luo TT, Lu Y, Yan SK, Xiao X, Rong XL, Guo J. Network Pharmacology in Research of Chinese Medicine Formula: Methodology, Application and Prospective. Chin J Integr Med 2020; 26: 72-80.
26) Zhang L, Han L, Wang X, Wei Y, Zheng J, Zhao L, Tong X. Exploring the mechanisms underlying the therapeutic effect of Salvia miltiorrhiza in diabetic nephropathy using network pharmacology and molecular docking. Biosci Rep 2021; 41: BSR20203520.
27) Ryu KY, Lee HJ, Woo H, Kang RJ, Han KM, Park H, Lee SM, Lee JY, Jeong YJ, Nam HW, Nam Y, Hoe HS. Dasatinib regulates LPS-induced microglial and astrocytic neuroinflammatory responses by inhibiting AKT/STAT3 signaling. J Neuroinflammation 2019; 16: 190-198.
28) Zheng WJ, Yan Q, Ni YS, Zhan SF, Yang LL, Zhuang HF, Liu XH, Jiang Y. Examining the effector mechanisms of Xuebijing injection on COVID-19 based on network pharmacology. BioData Min 2020; 16: 13-17.
29) Burgos RA, Alarcón P, Quiroga J, Manosalva C, Hancke J. Andrographolide, an Anti-Inflammatory Multitarget Drug: All Roads Lead to Cellular Metabolism. Molecules 2020; 26: 5-11.
30) Yeung YT, Aziz F, Guerrero-Castilla A, Arguelles S. Signaling Pathways in Inflammation and Anti-inflammatory Therapies. Curr Pharm Des 2018; 24: 1449-1484.

31) Akiyama Y, Miyakawa J, O'Donnell MA, Kreder KJ, Luo Y, Maeda D, Ushiku T, Kume H, Homma Y. Overexpression of HIF1α in Hunner Lesions of Interstitial Cystitis: Pathophysiological Implications. J Urol 2022; 207: 635-646.

32) Liu M, Shen S, Kendig DM, Mahavadi S, Murthy KS, Grider JR, Qiao LY. Inhibition of NMDAR reduces bladder hypertrophy and improves bladder function in cyclophosphamide induced cystitis. J Urol 2015; 193: 1676-1683.

33) Hou Y, Li H, Huo W. MicroRNA-495 alleviates ulcerative interstitial cystitis via inactivating the JAK-STAT signaling pathway by inhibiting JAK3. Int Urogynecol J 2021; 32: 1253-1263.

34) Lü JM, Yao Q, Chen C. Ginseng compounds: an update on their molecular mechanisms and medical applications. Curr Vasc Pharmacol 2009; 7: 293-302.

35) Xie W, Zhou P, Qu M, Dai Z, Zhang X, Zhang C, Dong X, Sun G, Sun X. Ginsenoside Re Attenuates High Glucose-Induced RF/6A Injury via Regulating PI3K/AKT Inhibited HIF-1α/VEGF Signaling Pathway. Front Pharmacol 2020; 21: 687-695.

36) Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2017; 9: 7204-7218.

37) Luo J, Yang C, Luo X, Yang Y, Li J, Song B, Zhao J, Li L. Chlorogenic acid attenuates cyclophosphamide-induced rat interstitial cystitis. Life Sci 2020; 254: 1175-1190.

38) Sun Z, Li Q, Hou R, Sun H, Tang Q, Wang H, Hao Z, Kang S, Xu T, Wu S. Kaempferol-3-O-glucorhamnoside inhibits inflammatory responses via MAPK and NF-κB pathways in vitro and in vivo. Toxicol Appl Pharmacol 2019; 364: 22-28.

39) Feng H, Cao J, Zhang G, Wang Y. Kaempferol Attenuates Cardiac Hypertrophy via Regulation of ASK1/MAPK Signaling Pathway and Oxidative Stress. Planta Med 2017; 83: 837-845.