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Molecular mechanisms of Biyu decoction as treatment for psoriasis: A network pharmacology and molecular docking study

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Abstract

BACKGROUND

The therapeutic effects of a combination of Chinese medicines called Biyu decoction have been clinically verified, although its molecular targets in psoriasis remain unknown.

AIM

To explore the molecular mechanisms of Biyu decoction for psoriasis treatment.

METHODS

In this network pharmacology and molecular docking study, the Traditional Chinese Medicine Systems Pharmacology database was searched for Biyu decoction active ingredients. GeneCards, Online Mendelian Inheritance in Man, PharmGkb, Therapeutic Target Database, and DrugBank databases were searched for psoriasis-related genes. The genes targeted by the decoction's active ingredient and disease genes were intersected to obtain predictive targets of the drug during psoriasis treatment. Cytoscape 3.8.0 was used to construct a drug component/target disease network. The The functional protein association networks database and Cytoscape were used to construct a protein-protein interaction network and streamline the core network. The Gene Ontology and Kyoto Encyclopedia of Genes and Genomes were used for pathway enrichment analysis. Molecular docking technology was used to verify the drug component/target disease network.

RESULTS

We screened 117 major active ingredients, including quercetin, kaempferol, naringenin, and acetyl-shikonin, and identified 213 gene targets, such as *MAPK3*, *JUN*, *FOS*, *MYC*, *MAPK8*, *STAT3*, and *NFKBIA*. Using a molecular docking analysis, the main active ingredients demonstrated good binding to the core targets. The Gene Ontology analysis showed that these ingredients were significantly associated with biological activities, such as transcription factor DNA

binding, RNA polymerase II-specific DNA binding of transcription factors, and cytokine receptor binding; responses to lipopolysaccharides, molecules of bacterial origin, and oxidative stress; and were mainly distributed in membrane rafts, microdomains, and regions. The Kyoto Encyclopedia of Genes and Genomes analysis showed that decoction ingredients act on Th17 cell differentiation, tumor necrosis factor and mitogen-activated protein signaling pathways, the interleukin-17 signaling pathway, and the PI3K-Akt signaling pathway.

CONCLUSION

Biyu decoction may be effective against psoriasis through multi-component, multi-target, and multi-channel synergy.

Key Words: Medicine; Chinese traditional; Molecular docking simulation; Protein interaction maps; Psoriasis; Gene ontology; Network pharmacology

Core Tip: Biyu decoction has significant effects on psoriasis; however, its molecular targets in psoriasis remain unknown. We conducted a network pharmacology and molecular docking study to determine whether Biyu decoction ingredients target molecules and signaling pathways related to psoriasis pathogenesis. The main active ingredients identified include quercetin, kaempferol, beta-sitosterol, naringenin, and acetyl-shikonin. Target genes included *MAPK3*, *JUN*, *FOS*, *MYC*, *MAPK8*, *STAT3*, and *NFKBIA*, which can regulate the inflammatory state mediated by psoriasis immune cells and mediate the expression of factors that adjust local skin inflammation. Our results confirm that Biyu decoction can treat psoriasis through multi-component, multi-target, and multi-channel synergy.

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INTRODUCTION

Psoriasis (PSO) is an immune-mediated chronic and recurrent inflammatory disease that affects the skin or joints. The global incidence of PSO is approximately 2%[1]. It also affects approximately 0.47% of the Chinese population[2]. Although gender does not have a clear effect on the incidence of PSO, genetic susceptibility and increasing age are known to increase its incidence[3].Because of the disfigurement and teratogenicity associated with this disease that seriously affect the quality of life, PSO confers a marked psychological burden[4]. The physiological burden is related to recurrent episodes of itching and several accompanying diseases[5]. Plaque PSO (PSO vulgaris) accounts for more than 90% of cases. The clinical manifestations are well-defined erythema and silvery scaly skin, which can occur anywhere on the body[6].

Conventional treatment for PSO includes topical glucocorticoids, vitamin D derivatives, calcineurin inhibitors, corticosteroids, phototherapy, and systemic therapy[7]. Practicability (the time required to apply treatment), convenience, and adverse reactions (*e.g.*, skin irritation) limit the use of topical drugs, whereas drug interactions and accumulated organ toxicity limit systemic treatment. PSO is mediated by dendritic and T cells in a complex feedback loop involving antigen-presenting cells, neutrophils, keratinocytes, vascular endothelial cells, and the skin's nervous system. Tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1, and other cytokines mediate innate and adaptive immune responses, and resident immune cell interaction disorder in the skin is the main PSO pathogenesis[8]. Therefore, targeted therapy blocking the PSO-related immune pathway is effective; however, the cost of biological agents is high and thus difficult to popularize.

In the current medical environment in China, traditional Chinese medicine (TCM) has a high penetration rate among psoriasis patients due to various advantages, such as less adverse reactions, long-term use, discontinuation at any time, and low long-term recurrence rate[9]. According to Chinese medicine, "blood-heat" runs through psoriasis from beginning to end[10]. "Blood heat" is mainly characterized by bleeding and fiery heat. "Heat" stagnates blood collaterals, and erythema is seen on the skin. "Heat" forces blood to rush out of the veins, and causes spot-like bleeding. These correspond to the bright red patches, bleeding spots of a psoriatic rash. Biyu decoction (BYT) is a combination of Chinese medicines with significant effects on PSO; its selection is based on Xiaoyinjiedu granules[10] by Professor Jin Qifeng (National TCM Doctor of Dongzhimen Hospital, Beijing University of Chinese

Medicine) and our preliminary research results. BYT comprises Zicao[11,12] (Lithospermum Erythrorhizon), Diyu[13] (Radix Sanguisorbae), Cebaiye[14] (Platycladi Cacumen), and Gancao[15] (licorice), which are Chinese herbal medicines with cooling blood effect, and *in vitro* and *in vivo* studies have revealed their therapeutic effects on immunity and inflammation. The therapeutic effects of BYT on PSO have been verified clinically. However, the BYT molecular targets of PSO remain unknown. To improve PSO treatment, we investigated whether BYT ingredients target molecules and signaling pathways related to PSO pathogenesis.

MATERIALS AND METHODS

Drug and gene data

Drug data were obtained from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (http: //tcmspw.com/tcmsp.php). Gene data were obtained from the Human Gene Database (GeneCards; https://www.genecards.org), Online Mendelian Inheritance in Man (OMIM; https://omim.org), Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB; https://www.pharmgkb.org), Therapeutic Target Database (TTD; http://db.idrblab.net/ttd), and Drugbank database (Drugbank; https://www.drugbank.ca). The functional protein association networks database (STRING; https://string-db.org) was used to construct the protein-protein interaction (PPI) network. The molecular structure data of the receptors and ligands required for molecular docking were obtained from PubChem (PubChem; https://pubchem.ncbi.nlm.nih.gov) and Protein Data Bank (PDB; http://www.rcsb.org). The above data were obtained in May 2021. In addition, we conducted a relevant search by Reference Citation Analysis (https://www.referencecitationanalysis.com).

Screening of traditional Chinese medicine ingredients and target prediction

We searched the TCMSP database for active components of BYT, namely, the chemical components of Zicao, Diyu, Cebaiye, and Gancao. After performing screen filtering by oral bioavailability (OB; > 30%) and drug-like properties (DL; > 0.18) and removing duplicate components, we obtained effective drug components. The TCMSP database was searched to obtain the molecular targets of each active ingredient and identify molecular targets corresponding to all the active ingredients of BYT.

PSO-related genes targeted by BYT

Genes related to PSO were identified by searching the following five databases: GeneCards, OMIM, PharmGKB, TTD, and Drugbank. After removing the duplicate and false-positive targets, genes related to PSO were identified. The intersection of the retrieved molecular targets of the BYT active ingredients and these PSO-related genes were identified to retrieve PSO-related target genes of BYT.

Drug target-PSO network construction

We used Cytoscape (version 3.8.0) software to establish the drug-disease network based on the BYT components targeting PSO-related genes obtained from TCMSP and the PSO-related drug targets of BYT obtained from the gene database. The network comprised drug nodes, target nodes, and related events. The larger the number of associated events, the larger the corresponding target node. The attributes of different traditional Chinese medicine sources in the drug nodes were represented by different colors; however, the drug nodes could show multiple colors because they were derived from multiple drugs.

Construction of the PPI network and screening of core proteins

A PPI network was established based on the selected BYT target genes in PSO. The lines between gene nodes defined the interaction between proteins. After filtering out free gene nodes, a large PPI network was obtained. Using the CytoNCA plug-in of the Cytoscape software, a topology analysis was performed to filter out the central network. We analyzed the following six indicators: Betweenness centrality (BC), closeness centrality (CC), degree centrality (DC), eigenvector centrality (EC), local average connectivity (LAC), and network centrality (NC); these provide a standard for the in-depth analysis of the attributes of each node. A higher quantitative value for each index indicated that the node was more important in the network and allowed identification of the core network.

Molecular docking

The PDB database was searched for core genes to perform molecular docking experiments. The structures of the corresponding proteins were downloaded. PyMOL (version 2.4.0) software was used to remove water molecules and small ligand molecules from these receptor macromolecular structures. AutoDockTools (version 1.5.6) software was used to add polar hydrogen ions and set the grid box to determine the search range of the active pockets of the proteins, which were unknown. To include as many receptor structures as possible, the size of the active pocket had to be increased appropriately to

improve the docking results. According to the core genes identified, the drug components that interacted with the core genes were sought in the constructed drug-disease network. The two-dimensional structures of these small ligand molecules were downloaded from the PubChem database, and the MM2 calculation tool in ChemBio3D (version 14.0) software was used to optimize the three-dimensional structure of the small ligand molecule with the smallest free energy. Vina (version 1.1.2) software was used to perform the docking work, and the optimal model of molecular docking was calculated.

Gene ontology and kyoto encyclopedia of genes and genomes

We used R (version 4.0.3) software to perform a Gene Ontology (GO) biological functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) metabolic pathway enrichment analysis of the intersection genes. These were filtered using $P < 0.05$ (with the q-value for correction if they were not in compliance). GO term enrichment was performed for biological processes (BP), CC, and molecular function (MF), and the GO term most likely to be related to the target gene was identified. We explored which functions in PSO were regulated by BYT and determined the connections between functional units and their potential significance in biological system networks. We also selected PSO-related pathways during the KEGG enrichment analysis and drew pathway diagrams.

RESULTS

Screening of BYT active ingredients and target prediction

According to the TCMSP database, BYT contained a total of 458 ingredients (Zicao, 51; Diyu, 41; Cebaiye, 86; and Gancao, 280). After screening, based on OB and DL values, 124 active ingredients were obtained (Zicao, 12; Diyu, 13; Cebaiye, 7; and Gancao, 92). After deleting the compounds with no action targets and duplicated components, 117 active ingredients were obtained (Table 1). Based on these ingredients, 2410 pairs of ingredient-predicted target combinations were identified (Zicao, 83 pairs; Diyu, 269 pairs; Cebaiye, 289 pairs; and Gancao, 1769 pairs). After removing duplicate targets, 213 targets of BYT Chinese medicine were obtained.

PSO disease gene screening

We used "Psoriasis" as a keyword to search GeneCards, OMIM, PharmGkb, TTD, and DrugBank databases. With a relevance score > 1.0, genes from the GeneCards database were filtered. Overall, 1700 PSO-related genes were retrieved (GeneCards, 1497; OMIM, 13; PharmGkb, 12; TTD, 100; and DrugBank, 78). After deduplication of the retrieved genes, a Venn diagram of the identified genes was drawn (Figure 1A), yielding 1585 PSO gene targets.

BYT-PSO intersection genes

The intersection of 1585 PSO-related genes and the 213 predicted BYT targets yielded a total of 110 BYT-PSO genes, and a Venn diagram was drawn (Figure 1B). *MAPK8*, *NFKBIA*, *STAT3*, *TNFAIP6*, *IFNG*, *ICAM1*, *IL1A*, *IL2RA*, *IL10RA*, *VCAM1*, *EGFR*, *VEGFA*, *MMP2*, and other genes associated with PSO were included in this intersection. The target gene mapping rate for BYT in PSO was 51.6%, indicating some specificity (Figure 2).

BYTPSO network construction

Cytoscape software was used to construct a BYT active ingredient/PSO gene target network (Figure 2). The network comprised 110 potential target genes and 104 active ingredients. The larger the metric value of the target, the more the target and drug components constituted the events, implying a greater role in the network. The same ingredient could be derived from multiple drugs simultaneously. Each potential target gene interacted with multiple active ingredients, which indicated that BYT has effects on PSO *via* multiple pathways, multiple components, and multiple targets.

Construction of the PPI network of BYT-PSO intersection genes

We imported the 110 BYT-PSO intersection genes into the STRING database (species: *Homo sapiens*; filter: Highest confidence, 0.900) and removed free nodes to obtain the BYT-PSO PPI network (Figure 3A). The network comprised 101 nodes and 399 edges, with lines of different colors representing different ways of proving the protein interaction relationship between nodes.

Screening of core genes

We imported the obtained PPI network diagram into Cytoscape software (Figure 3B) and used the CytoNCA plug-in to score nodes for BC, CC, DC, EC, LAC, and NC. The nodes for which all values exceeded the median were retained in the PPI network diagram (Figure 3C). The filter conditions were as follows: BC > 55.53, CC > 0.21, DC > 6, EC > 0.05, LAC > 2.55, and NC > 3.5. This secondary PPI network contained 29 nodes and 157 edges. The calculation was repeated with the following filter

Table 1 Effective pharmaceutical active ingredients in Biyu decoction

Drug	Mol ID	Mol name	OB	DL
Cebaiye	MOL002005	Hinokinin	56.5	0.64
Cebaiye	MOL002034	(5aR, 8aS, 9R)-9-(3, 4, 5-trimethoxyphenyl)-5a, 6, 8a, 9-tetrahydro-5H-isobenzofurano[5, 6-f][1, 3]benzodioxol-8-one	52.7	0.83
Cebaiye	MOL000358	Beta-sitosterol (Diyu)	36.91	0.75
Cebaiye	MOL002032	Di-n-octylphthalate	40.59	0.4
Cebaiye	MOL002039	Isopimaric acid	36.2	0.28
Cebaiye	MOL000422	Kaempferol (Diyu, Gancao)	41.88	0.24
Cebaiye	MOL000098	Quercetin (Diyu, Gancao)	46.43	0.28
Diyu	MOL005858	3, 7, 8-tri-O-methylellagic acid	37.54	0.57
Diyu	MOL005860	3-O-galloylprocyanidin B-3	30.06	0.33
Diyu	MOL005399	Alexandrin_qt	36.91	0.75
Diyu	MOL005869	Daucostero_qt	36.91	0.75
Diyu	MOL005883	Gambiriin B-3	34.99	0.75
Diyu	MOL000211	Mairin (Gancao)	55.38	0.78
Diyu	MOL005862	Methyl 4, 6-di-O-galloyl-beta-D-glucopyranoside	48.07	0.68
Diyu	MOL005853	Methyl-2, 3, 6-tri-O-galloyl-β-D-glucopyranoside	44.95	0.67
Diyu	MOL005864	Methyl-6-O-galloyl-β-D-glucopyranoside	44.85	0.29
Diyu	MOL005880	Sauvissimoside R1	37.39	0.31
Gancao	MOL004924	(-)-medicocarpin	40.99	0.95
Gancao	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	71.12	0.18
Gancao	MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8, 8-dimethyl-2, 3-dihydropyrano[2, 3-f]chromen-4-one	31.79	0.72
Gancao	MOL004824	(2S)-6-(2, 4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2, 3-dihydrofuro[3, 2-g]chromen-7-one	60.25	0.63
Gancao	MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one	36.57	0.32
Gancao	MOL004815	(E)-1-(2, 4-dihydroxyphenyl)-3-(2, 2-dimethylchromen-6-yl)prop-2-en-1-one	39.62	0.35
Gancao	MOL004898	(E)-3-[3, 4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2, 4-dihydroxyphenyl)prop-2-en-1-one	46.27	0.31
Gancao	MOL004914	1, 3-dihydroxy-8, 9-dimethoxy-6-benzofurano[3, 2-c]chromenone	62.9	0.53
Gancao	MOL004913	1, 3-dihydroxy-9-methoxy-6-benzofurano[3, 2-c]chromenone	48.14	0.43
Gancao	MOL005013	18α-hydroxyglycyrrhetic acid	41.16	0.71
Gancao	MOL004959	1-methoxyphaseollidin	69.98	0.64
Gancao	MOL004866	2-(3, 4-dihydroxyphenyl)-5, 7-dihydroxy-6-(3-methylbut-2-enyl)chromone	44.15	0.41
Gancao	MOL004978	2-[(3R)-8, 8-dimethyl-3, 4-dihydro-2H-pyrano[6, 5-f]chromen-3-yl]-5-methoxyphenol	36.21	0.52
Gancao	MOL004849	3-(2, 4-dihydroxyphenyl)-8-(1, 1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	59.62	0.43
Gancao	MOL004863	3-(3, 4-dihydroxyphenyl)-5, 7-dihydroxy-8-(3-methylbut-2-enyl)chromone	66.37	0.41
Gancao	MOL004905	3, 22-dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid	34.32	0.55
Gancao	MOL004966	3'-hydroxy-4'-O-methylglabridin	43.71	0.57
Gancao	MOL004974	3'-methoxyglabridin	46.16	0.57
Gancao	MOL004864	5, 7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone	30.49	0.41
Gancao	MOL004989	6-prenylated eriodictyol	39.22	0.41
Gancao	MOL004990	7, 2', 4'-trihydroxy-5-methoxy-3-arylcoumarin	83.71	0.27
Gancao	MOL004991	7-acetoxy-2-methylisoflavone	38.92	0.26
Gancao	MOL003896	7-methoxy-2-methyl isoflavone	42.56	0.2
Gancao	MOL004838	8-(6-hydroxy-2-benzofuranyl)-2, 2-dimethyl-5-chromenol	58.44	0.38

Gancao	MOL004993	8-prenylated eriodictyol	53.79	0.4
Gancao	MOL000417	Calycosin	47.75	0.24
Gancao	MOL005020	Dehydroglyasperins C	53.82	0.37
Gancao	MOL001792	Dihydroxyflavanone	32.76	0.18
Gancao	MOL004806	Euchrenone	30.29	0.57
Gancao	MOL004915	Eurycarpin A	43.28	0.37
Gancao	MOL000392	Formononetin	69.67	0.21
Gancao	MOL004996	Gadelaidic acid	30.7	0.2
Gancao	MOL004856	Gancaonin A	51.08	0.4
Gancao	MOL004857	Gancaonin B	48.79	0.45
Gancao	MOL005000	Gancaonin G	60.44	0.39
Gancao	MOL005001	Gancaonin H	50.1	0.78
Gancao	MOL004910	Glabranin	52.9	0.31
Gancao	MOL004911	Glabrene	46.27	0.44
Gancao	MOL004908	Glabridin	53.25	0.47
Gancao	MOL004912	Glabrone	52.51	0.5
Gancao	MOL004828	Glepidotin A	44.72	0.35
Gancao	MOL004829	Glepidotin B	64.46	0.34
Gancao	MOL004808	Glyasperin B	65.22	0.44
Gancao	MOL004811	Glyasperin C	45.56	0.4
Gancao	MOL004810	Glyasperin F	75.84	0.54
Gancao	MOL005007	Glyasperins M	72.67	0.59
Gancao	MOL004879	Glycyrin	52.61	0.47
Gancao	MOL002311	Glycyrol	90.78	0.67
Gancao	MOL004917	Glycyroside	37.25	0.79
Gancao	MOL005008	Glycyrrhiza flavonol A	41.28	0.6
Gancao	MOL004835	Glypallichalcone	61.6	0.19
Gancao	MOL004907	Glyzaglabrin	61.07	0.35
Gancao	MOL004957	3-(4-hydroxyphenyl)-7-methoxychromen-4-one	38.37	0.21
Gancao	MOL004985	Icos-5-enoic acid	30.7	0.2
Gancao	MOL001484	Inermine	75.18	0.54
Gancao	MOL004980	Inflacoumarin A	39.71	0.33
Gancao	MOL004948	Isoglycyrol	44.7	0.84
Gancao	MOL004949	Isolicoflavonol	45.17	0.42
Gancao	MOL000354	Isorhamnetin	49.6	0.31
Gancao	MOL004814	Isotrifoliol	31.94	0.42
Gancao	MOL000239	Jaranol	50.83	0.29
Gancao	MOL004988	Kanzonol F	32.47	0.89
Gancao	MOL004820	Kanzonols W	50.48	0.52
Gancao	MOL005003	Licoagrocarpin	58.81	0.58
Gancao	MOL005012	Licoagroisoflavone	57.28	0.49
Gancao	MOL000497	Licochalcone a	40.79	0.29
Gancao	MOL004841	Licochalcone B	76.76	0.19

Gancao	MOL004848	Licochalcone G	49.25	0.32
Gancao	MOL004882	Licocoumarone	33.21	0.36
Gancao	MOL004885	Licoisoflavanone	52.47	0.54
Gancao	MOL004883	Licoisoflavone	41.61	0.42
Gancao	MOL004884	Licoisoflavone B	38.93	0.55
Gancao	MOL004904	Licopyranocoumarin	80.36	0.65
Gancao	MOL004860	Licorice glycoside E	32.89	0.27
Gancao	MOL004855	Licoricone	63.58	0.47
Gancao	MOL004903	Liquiritin	65.69	0.74
Gancao	MOL003656	Lupiwighteone	51.64	0.37
Gancao	MOL002565	Medicarpin	49.22	0.34
Gancao	MOL004328	Naringenin	59.29	0.21
Gancao	MOL005016	Odoratin	49.95	0.3
Gancao	MOL005017	Phaseol	78.77	0.58
Gancao	MOL004833	Phaseolinisoflavan	32.01	0.45
Gancao	MOL004961	Quercetin der.	46.45	0.33
Gancao	MOL004827	Semilicoisoflavone B	48.78	0.55
Gancao	MOL004891	Shinpterocarpin	80.3	0.73
Gancao	MOL004935	Sigmoidin-B	34.88	0.41
Gancao	MOL000359	Sitosterol (Zicao)	36.91	0.75
Gancao	MOL000500	Vestitol	74.66	0.21
Gancao	MOL005018	Xambioona	54.85	0.87
Zicao	MOL002372	(6Z, 10E, 14E, 18E)-2, 6, 10, 15, 19, 23-hexamethyltetracosa-2, 6, 10, 14, 18, 22-hexaene	33.55	0.42
Zicao	MOL007715	[(1R)-1-(5, 8-dihydroxy-1, 4-dioxo-2-naphthyl)-4-methyl-pent-3-enyl] propanoate	54.64	0.29
Zicao	MOL007714	1-methoxyacetylshikonin	73.09	0.29
Zicao	MOL007734	5-[(E)-5-(3-furyl)-2-methyl-pent-2-enyl]-2, 3-dimethoxy-p-benzoquinone	61.8	0.24
Zicao	MOL007716	Acetylshikonin	62.39	0.27
Zicao	MOL007735	Des-O-methyllasiodiplodin	30.12	0.2
Zicao	MOL002883	Ethyl oleate (NF)	32.4	0.19
Zicao	MOL007722	Isoarnebin 4	64.79	0.2
Zicao	MOL007728	Lithospermidin A	75.08	0.38
Zicao	MOL007736	Lithospermidin B	60.48	0.39
Zicao	MOL001494	Mandenol	42	0.19

Mol: Molecular; ID: Identification; OB: Oral bioavailability; DL: Drug-like properties.

conditions: BC > 7.18, CC > 0.58, DC > 9, EC > 0.15, LAC > 5.45, and NC > 7.18. The obtained core PPI network comprised 11 nodes and 47 edges (Figure 3D), with an average degree of 8.55. Based on the degree value, the order of the targets that have a major role in BYT treatment of PSO was as follows: *MAPK3*, *JUN*, *MAPK1*, *FOS*, *MAPK14*, *MYC*, *MAPK8*, *TP53*, *RELA*, *STAT3*, and *NFKBIA* (Table 2).

Molecular docking simulation of active ingredients and target genes

We searched the literature for PSO gene research and selected two core targets from the PPI core network: *MAPK8* and *STAT3*. *MAPK8* and *STAT3* proteins (3ELJ and 6NJS, respectively) were retrieved from the PDB database. We pretreated the receptor protein macromolecules by removing water molecules and small ligand molecules and adding polar hydrogen; then, we set the active pocket search range. Based on the BYT active ingredient/PSO gene target network, the active ingredients kaempferol (for *MAPK8*) and licochalcone A (for *STAT3*) were selected.

Table 2 Protein-protein interaction core network gene score

Name	Betweenness	Closeness	Degree	Eigenvector	LAC	Network
MAPK8	0.793650794	0.833333333	8	0.287379682	6.25	7.142857143
TP53	0.472222222	0.833333333	8	0.290343016	6.5	7.428571429
RELA	1.205555556	0.833333333	8	0.280704081	6	7.142857143
NFKBIA	0.222222222	0.714285714	6	0.217291564	4.666666667	5.6
STAT3	0.472222222	0.833333333	8	0.290343136	6.5	7.428571429
MAPK3	2.576984127	1	10	0.341228724	7.4	10
JUN	2.576984127	1	10	0.341228724	7.4	10
MAPK1	2.354761905	0.909090909	9	0.30924511	6.444444444	7.978571429
FOS	1.043650794	0.909090909	9	0.31924358	7.111111111	8.482142857
MAPK14	2.354761905	0.909090909	9	0.30924511	6.444444444	7.978571429
MYC	1.926984127	0.909090909	9	0.311044633	6.666666667	8.196428571

LAC: Local average connectivity.

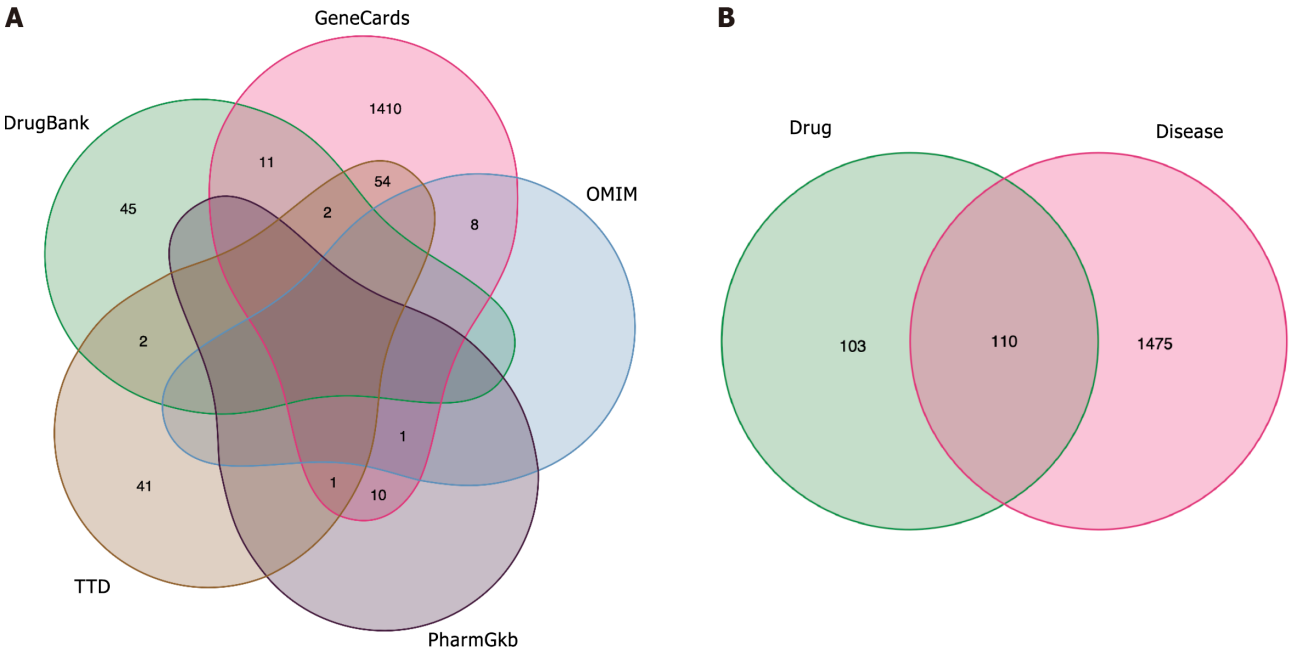


Figure 1 Gene screening. A: Psoriasis (PSO)-related genes. GeneCards, Online Mendelian Inheritance in Man, PharmGkb, Therapeutic Target Database, and DrugBank databases of PSO-related genes were searched for PSO gene targets, and 1585 PSO gene targets were identified; B: Biyu decoction (BYT)-PSO intersection genes. The gene intersection between PSO-related genes and the predicted targets of BYT active ingredients represents the target of BYT in PSO. PSO: Psoriasis; OMIM: Online Mendelian Inheritance in Man; TTD: Therapeutic Target Database; BYT: Biyu decoction.

Vina software was used to verify molecular docking between the receptor macromolecule and Chinese medicine small molecule component. The 20 main interaction methods were identified by calculating binding energies from small to large (Table 3). The model with the smallest binding energy was selected, and PyMOL software was used for visualization (Figure 4). The smaller the binding energy, the stronger the bond between the ligand and receptor. When affinity is less than -4.25 kcal/mol, the ligand shows certain binding to the receptor. Affinity less than -5.0 kcal/mol indicates good binding activity, and affinity less than -7.0 kcal/mol indicates strong binding activity. The energy of the binding of BYT core targets in PSO treatment with active ingredients was between -5.0 kcal/mol and -8.7 kcal/mol, indicating that the main active ingredients of BYT demonstrate good binding activity with the core gene targets of the disease with relatively reliable prediction.

Table 3 Docking results of the main active ingredients and core target molecules

Number	MAPK8/kaempferol Affinity (kcal/mol)	STAT3/licochalcone A Affinity (kcal/mol)
1	-8.7	-6.6
2	-8.7	-6.2
3	-8.6	-6
4	-8.6	-5.8
5	-8.5	-5.7
6	-8.4	-5.7
7	-8.2	-5.5
8	-8	-5.5
9	-8	-5.5
10	-7.9	-5.4
11	-7.8	-5.3
12	-7.7	-5.3
13	-7.7	-5.3
14	-7.6	-5.3
15	-7.5	-5.3
16	-7.4	-5.2
17	-7.4	-5.2
18	-7.3	-5.1
19	-7.2	-5.1
20	-7.1	-5

MAPK: Mitogen-activated protein kinase; STAT: Signal transducer and activator of transcription.

GO enrichment analysis

GO enrichment of the BYT-PSO intersection genes indicated 2083 types of BP, 42 types of CC, and 150 types of MF. We selected the first 30 with significant enrichment to draw images (Figure 5A). In terms of BP, these target genes were mainly involved in biological reactions, such as the response to lipopolysaccharides, response to molecules of bacterial origin, and response to oxidative stress. In terms of CC, target genes were mainly distributed in cell parts, such as membrane rafts, membrane microdomains, and membrane regions. In terms of MF, the target genes were significantly associated with DNA binding of transcription factors, RNA polymerase II-specific DNA binding of transcription factors, and cytokine receptor binding.

KEGG enrichment analysis

Overall, 170 signal pathways were obtained by KEGG pathway enrichment analysis. The first 30 signal pathways were screened out by statistical significance ($P < 0.05$; if not, then the q-value correction was used) for visual analysis (Figure 5B). The target genes had a role in multiple classic PSO-related pathways, such as the IL-17 signaling pathway, Th17 cell differentiation, TNF signaling pathway, T-cell receptor signaling pathway, mitogen-activated protein kinase (MAPK) signaling pathway, and PI3K-Akt signaling pathway. Therefore, BYT acts synergistically on PSO through multiple pathways. The more relevant Th17 cell differentiation and TNF signaling pathways were selected to draw a pathway diagram (Figure 6).

DISCUSSION

In this study, we explored the mechanism of BYT in PSO treatment using a network pharmacology and molecular docking study. We screened 117 major active ingredients, including quercetin, kaempferol, naringenin, and acetyl-shikonin, and identified 213 gene targets, including *MAPK3*, *JUN*, *FOS*, *MYC*, *MAPK8*, *STAT3*, and *NFKBIA*. Molecular docking analysis revealed that the main active ingredients

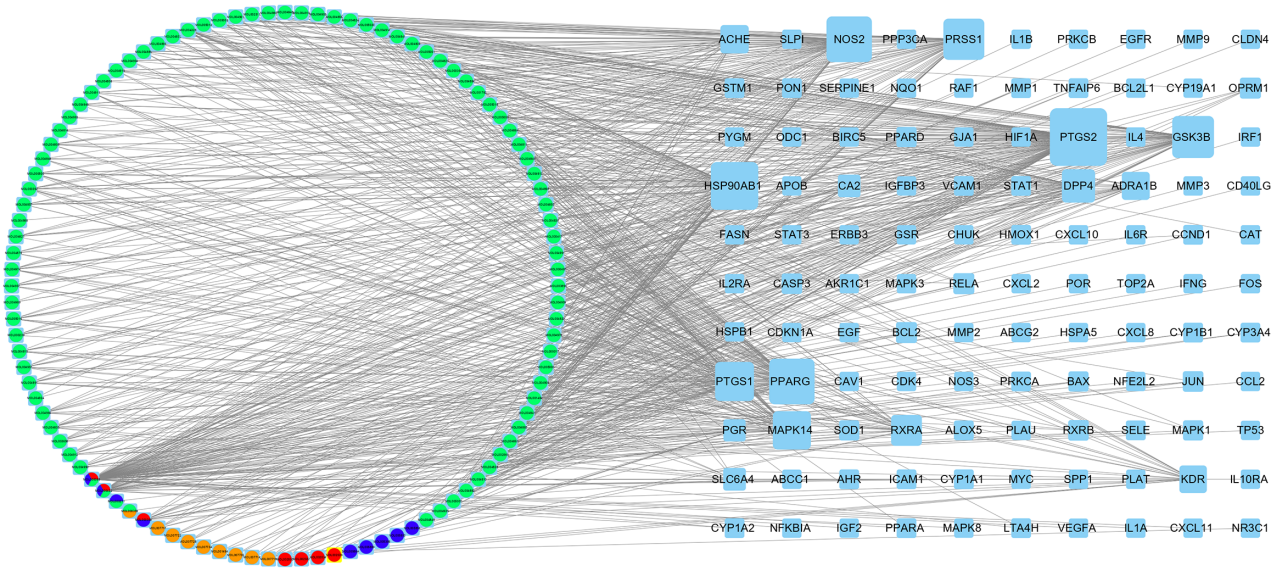


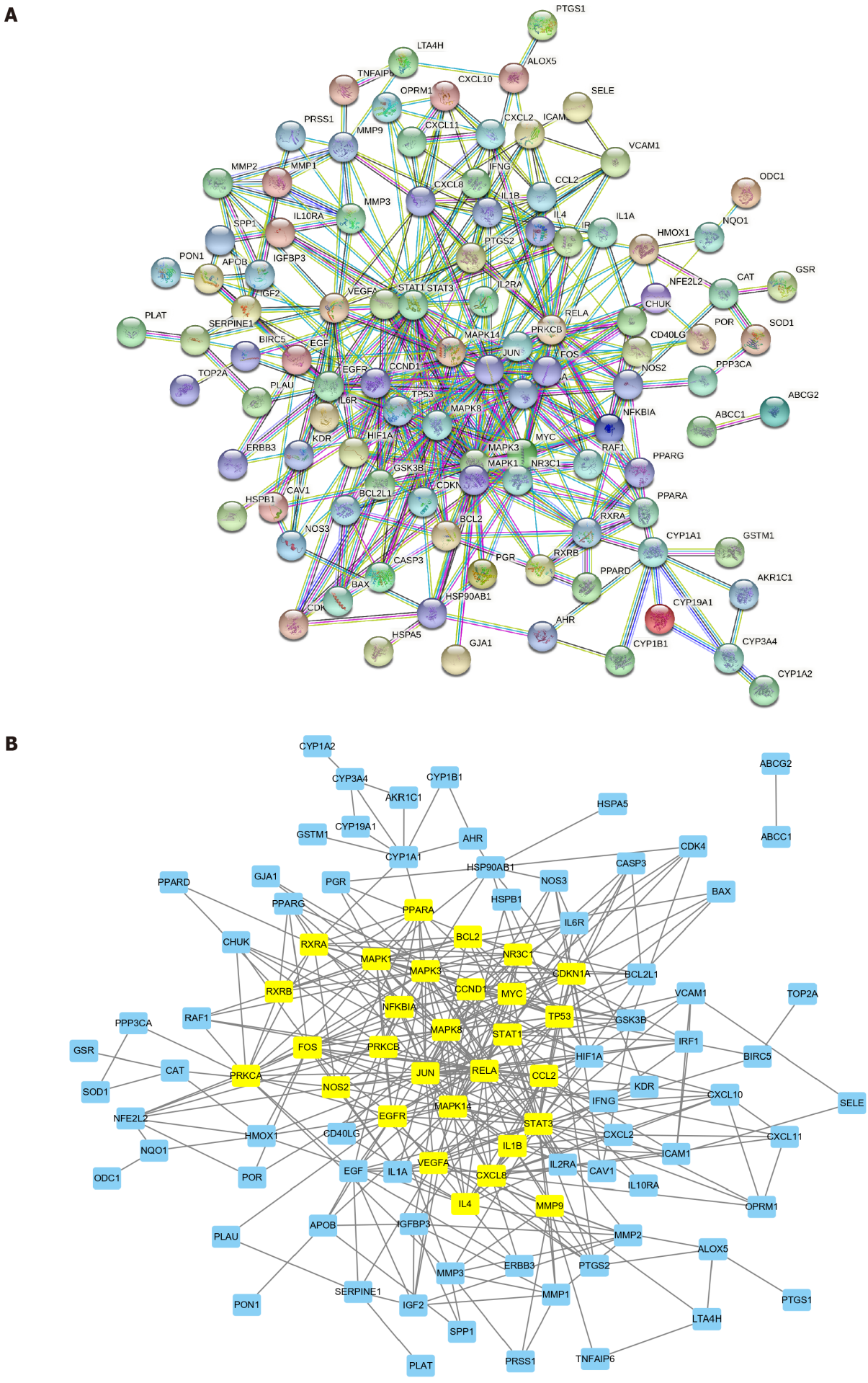
Figure 2 Biyu decoction-psoriasis network. The circle indicates the drug component, orange represents Zicao, blue represents Diyu, red represents Cebaiye, and light green represents Gancao. The square represents the gene target. The larger the target, the more strongly the target is associated with the drug component. PSO: Psoriasis; BYT: Biyu decoction.

demonstrated good binding to the core targets. The GO analysis showed that these ingredients were significantly associated with biological activities, such as DNA binding of transcription factors and cytokine receptor binding, whereas the KEGG analysis showed that the decoction ingredients act on Th17 cell differentiation and the TNF, MAPK, and other important PSO signaling pathways.

PSO pathogenesis has not been fully elucidated[16]. Excessive activation of the adaptive immune system is considered to be at the core of PSO[17]. Early during PSO, various cell types secrete cytokines to activate myeloid dendritic cells. When activated, these cells secrete IL-12 and IL-23[18] . IL-23-mediated activation of the Th17 pathway is considered the main pathway that guides the transcription of key inflammatory mediators *via* the Tyk2-Jak2 and STAT3 pathways[19]. These cytokines cause abnormal proliferation of downstream keratinocytes, increase the expression of vascular endothelial growth factor (VEGF) and vascular cell adhesion molecules, and cause immune cells to continue to infiltrate the affected skin[20].

Because of limited therapeutic effects or unavoidable side effects, the long-term use of modern medical traditional therapies for PSO remains a challenge. Complementary and alternative therapies, such as traditional Chinese medicine (TCM), are widely used in East Asia. TCM formulations are complex drug systems. The complex interactions between their multiple components and multiple targets can lead to the regulation of various pathways and biological processes, thus providing treatment for numerous complex diseases. TCM treatment of PSO has a therapeutic effect that is not inferior to the therapeutic effects of modern conventional medical therapies[21]; furthermore, it could possibly strengthen the therapeutic effects of modern conventional medical therapies[22]. Because of the unique theory regarding their clinical use and successful application as PSO treatment agents, we believe that the development of new small-molecule drugs based on TCM will be a promising strategy to provide safe, effective, and less costly treatment for patients with PSO. Therefore, we used a network pharmacology research method to explore the mechanism by which BYT can treat PSO from the perspective of active ingredients, target genes, and signaling pathways.

Most of the BYT ingredients have good oral bioavailability and drug-like properties. The 124 active ingredients screened out during this study have affinity for 213 cell targets, thus providing a pharmacodynamic basis for the diversity and effectiveness of TCM formulations. In the BYTPSO network, there were 104 active ingredients of BYT. Among them, quercetin, kaempferol, beta-sitosterol, naringenin, acetyl-shikonin, and other compounds have affinity for multiple gene targets. Quercetin is a polyflavonoid compound in the human diet that has biological activity. It regulates many intracellular and extracellular signaling pathways related to disease progression. It is considered a promising natural compound for the prevention and treatment of diseases[23]. The anti-psoriatic mechanism of quercetin may be related to its antioxidant and anti-inflammatory effects, inhibition of nuclear factor (NF)-κB signaling pathway activation, and downregulation of miR-155, which is highly expressed in PSO[24,25]. Kaempferol is a natural flavanol found in many plants that has powerful anti-inflammatory, antioxidant, and anticancer properties. Kaempferol can protect mice from PSO-like skin damage caused by topical imiquimod[26]. It can also improve imiquimod-induced psoriatic lesions, mainly by reducing $CD3^+$T cell infiltration and the expression of proinflammatory cytokine genes (including IL-6, IL-17A, and TNF-α) in psoriatic lesions, downregulating NF-κB signal transduction in the skin, and reducing the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ALOX5
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PRSS1
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CXCL11
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ICAM
VCAM1
MMP2
MMP1
IFNG
CXCL8
CCL2
ODC1
IL1B
MMP3
IL10RA
IL4
IL1A
NQO1
SPP1
IR
HMOX1
PTGS2
PON1
APOB
IGFBP3
GSR
CAT
NFE2L2
IGF2
VEGFA
STAT1
STAT3
IL2RA
CHUK
PLAT
RELA
SERPINE1
POR
SOD1
BIRC5
EGF
MAPK14
PRKCB
CD40LG
JUN
FOS
EGFR
CCND1
NOS2
PPP3CA
TOP2A
PLAU
TP53
ABCG2
IL6R
MAPK8
NFKBIA
ABCC1
KDR
HIF1A
MYC
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RAF1
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NOS3
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GSTM1
CASP3
PGR
RXRB
PPARD
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BAX
CYP19A1
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ABCC1
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CDK4
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IL6R
CHUK
BCL2
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MAPK1
MAPK3
CDKN1A
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RXRB
CCND1
MYC
VCAM1
TOP2A
NFKBIA
TP53
GSK3B
PPP3CA
RAF1
MAPK8
STAT1
IRF1
GSR
FOS
PRKCB
HIF1A
BIRC5
CAT
JUN
RELA
CCL2
PRKCA
SOD1
NOS2
KDR
CXCL10
SELE
IFNG
MAPK14
NFE2L2
EGFR
STAT3
HMOX1
CD40LG
CXCL2
CXCL11
IL1B
NQO1
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VEGFA
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ERBB3
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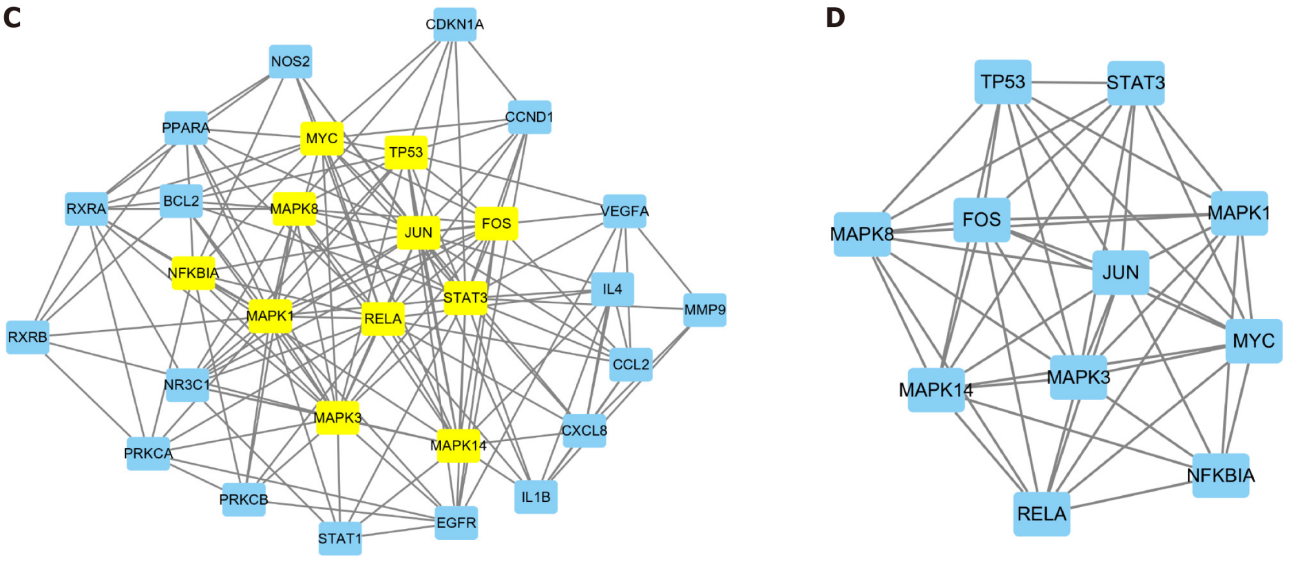

Figure 3 Protein-protein interaction network constructed from Biyu decoction-psoriasis intersection genes. A: Biyu decoction-psoriasis intersection gene protein-protein interaction (PPI) network; B-D: PPI core gene network screening process. PSO: Psoriasis; BYT: Biyu decoction; PPI: Protein-protein interaction.

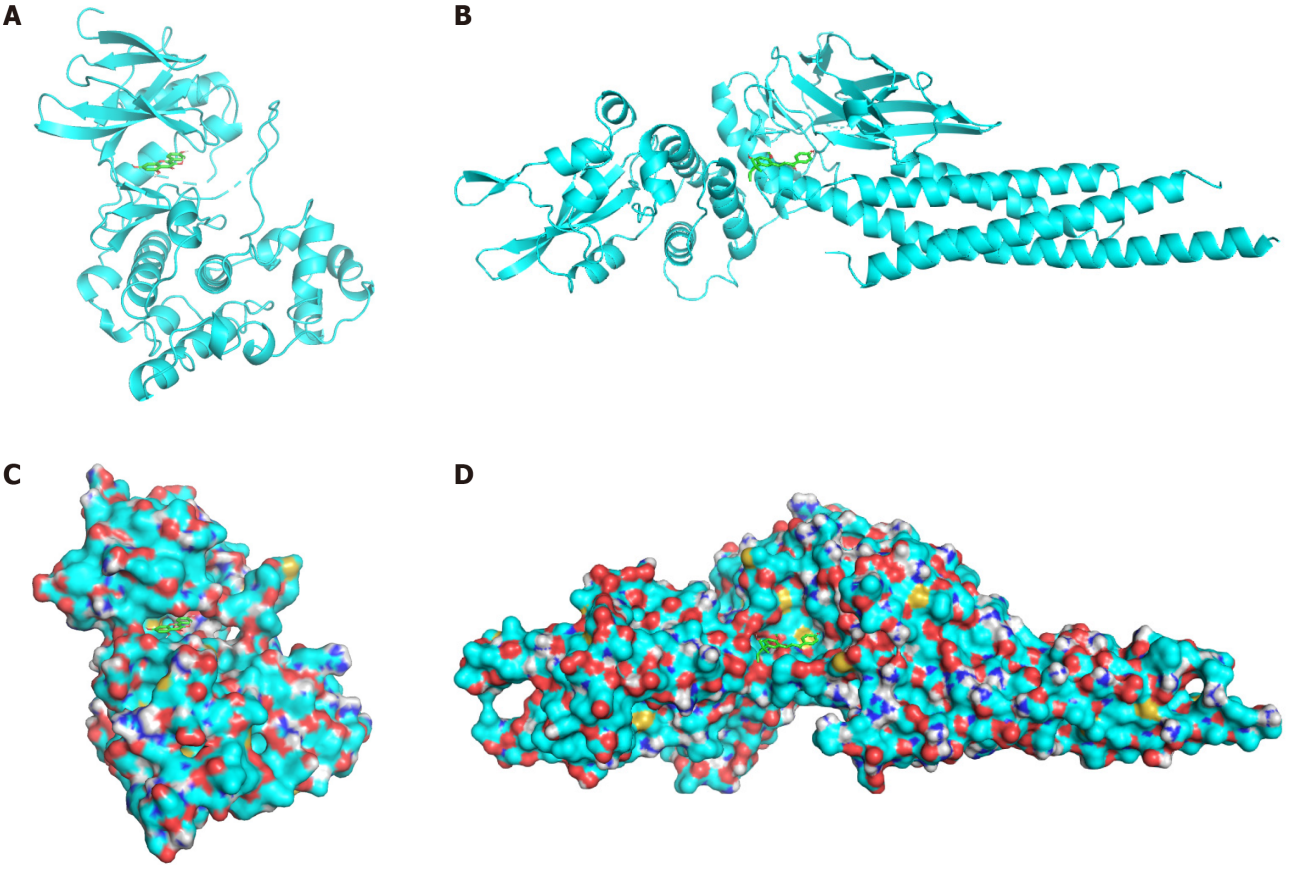

Figure 4 The docking model of the main active ingredients and core targets. A and C: The docking models of kaempferol and MAPK8, respectively, and the compound surface is hidden; B and D: The docking models of licochalcone A and STAT3, respectively, and the compound surface is shown.

percentage of IL-17A$^+$CD4$^+$ T cells in the spleen and lymph nodes of the PSO mice model. Kaempferol can also inhibit T cell proliferation and mTOR signal transduction, which is associated with PSO, in vitro. Naringenin is a citrus flavonoid with various pharmacological properties. It demonstrates anti-inflammatory activity by inhibiting TNF-α and IL-1β[27]. Hepatotoxicity is an adverse side effect of methotrexate, which is used for the treatment of malignant tumors, PSO, and rheumatoid arthritis. Naringenin may inhibit methotrexate-related hepatotoxicity by scavenging active free radicals and

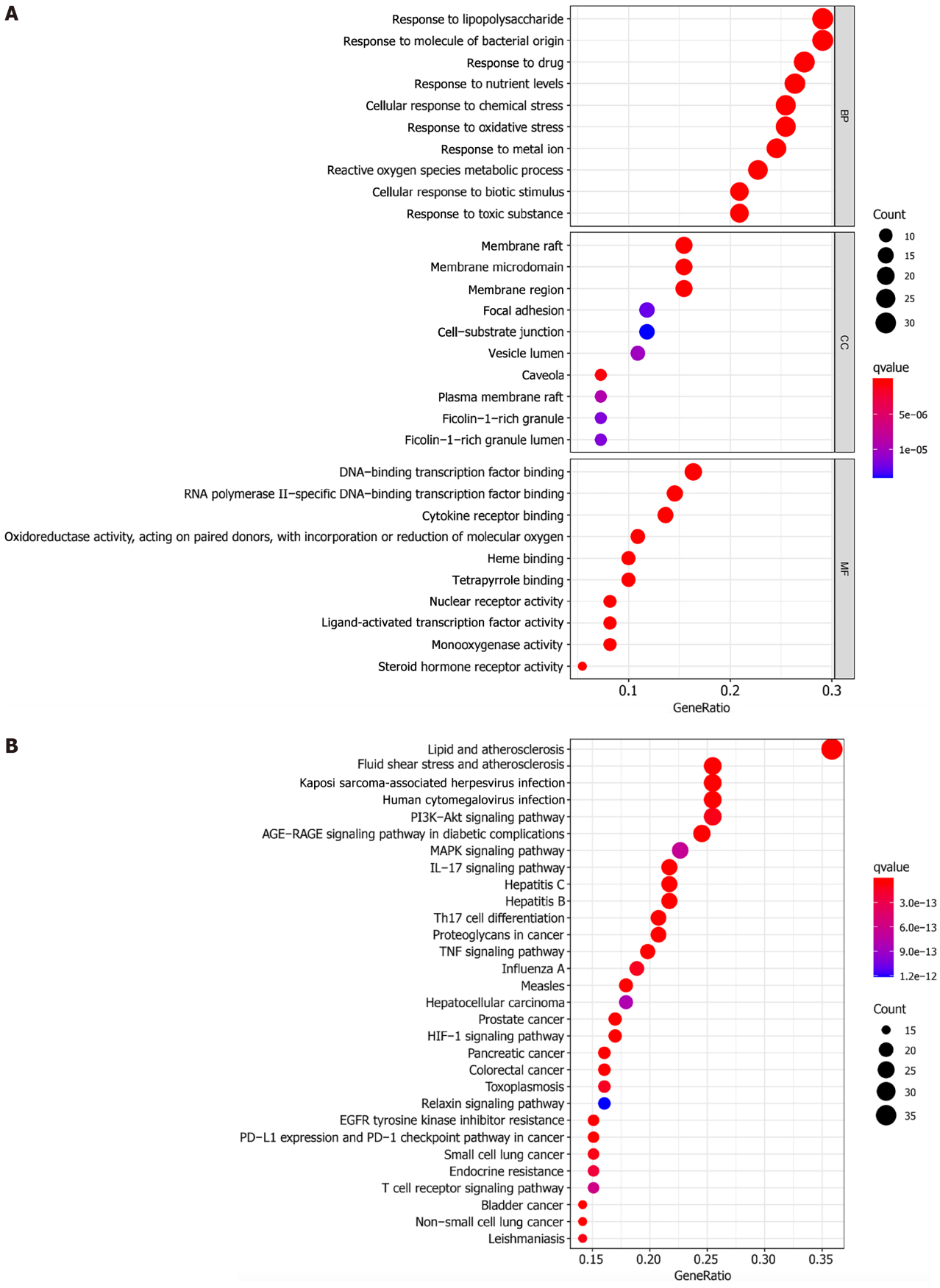

Figure 5 Enrichment analysis. In the bubble chart, the ordinate is the name of the biological process or pathway, the abscissa is the proportion of genes, the size of the bubble represents the number of genes enriched in each gene ontology, and the color represents the significance of the enrichment. A: The Gene Ontology enrichment analysis indicates the biological response, gene distribution, and molecular function in which the target gene is mainly involved; B: The Kyoto Encyclopedia of Genes and Genomes enrichment analysis indicates the main pathway in which the target gene has a role. GO: Gene Ontology; KEGG: Kyoto

Encyclopedia of Genes and Genomes; AGE-RAGE: Advanced glycation end products/receptor of AGE; TNF: Tumor necrosis factor; MAPK: Mitogen-activated protein kinase; HIF-1: Hypoxia-inducible factor 1; EGFR: Endothelial growth factor receptor; PD-L1: Programmed death-ligand 1; PD-1: Programmed cell death protein 1.

exerting anti-inflammatory effects[28]. Naringenin significantly improved the changes in methotrexate-related biochemical markers and liver histopathology. Shikonin is the main active compound of Zicao and has been widely proven to inhibit PSO-like inflammation. Shikonin can reduce the overexpression of IL-17-related VEGF and K17 proteins by blocking the JAK2/STAT3 pathway. Additionally, shikonin can significantly inhibit the proliferation of HaCaT cells and induce apoptosis. However, the relationship of acetyl-shikonin in Zicao with PSO requires further research[29,30].

During this study, 11 target genes that are closely related to PSO, such as *MAPK3*, *JUN*, *FOS*, *MYC*, *MAPK8*, *STAT3*, and *NFKBIA*, were obtained through the PPI core network diagram. With PSO and related inflammatory skin diseases, innate and/or adaptive immune cells are activated and recruited to the site of inflammation, thus promoting further inflammation[31]. Continuous recruitment and activation of immune cells are regulated by a combination of cytokines and chemokines, which is, in turn, regulated by transcription factors, such as AP-1 (FOS/JUN), NF-κB, STATs, and MAPK[32]. MYC—a proto-oncogene involved in a variety of cellular processes, including cell growth, proliferation, and apoptosis—can play an important role in angiogenesis through a VEGF-dependent mechanism[33], is often amplified with skin cancer[34], and can stimulate the abnormal proliferation of normal keratinocytes. These effects of MYC are consistent with the pathological characteristics of abnormal proliferation and incomplete differentiation of psoriatic epithelial cells and abnormal dermal vascular proliferation. These core genes require further study to clarify their mechanisms of action and to provide new insights into the prevention and treatment of PSO.

We obtained low binding energies (-8.7 kcal/mol and -6.6 kcal/mol, respectively) for the molecular docking of MAPK8 with Kaempferol and STAT3 with licochalcone A, which show that the selected drug molecule-gene target combinations have a good binding activity. These results suggest that these drug molecules may directly bind to the corresponding core targets with high and stable affinity and provide evidence for the key role of these drug components in psoriasis treatment. The docking results confirm the accuracy of the PPI network analysis in identifying the core targets.

Based on the KEGG pathway enrichment analysis, BYT has a wide range of effects on the IL-17 signaling pathway, Th17 cell differentiation, TNF signaling pathway, PI3K-Akt signaling pathway, T cell receptor signaling pathway, MAPK signaling pathway, and other signaling pathways directly related to the pathological mechanism of PSO. The TNFα/IL-23/Th17 inflammatory pathway is a characteristic pathway of PSO. To date, clinically relevant signaling pathways in PSO have mainly been shown to be mediated by IL-17, which leads to the activation of a series of intracellular kinases (such as extracellular signal-regulated kinase, p38 MAPK, transforming growth factor-β-activated kinase 1, and others)[31]. These internal kinases enhance signaling pathways, such as the NF-κB pathway, thus promoting the expression of proinflammatory cytokines, chemokines, and antimicrobial peptides. Cytokines produced by Th1 and Th2 have a role through the JAK-STAT signaling pathway, whereas NF-κB can mediate the Th17 response[6]. Fluid shear stress and atherosclerosis affect hemodynamics by regulating the expression of genes and proteins in endothelial cells and changing the differentiation, morphology, and permeability of blood vessel walls of vascular endothelial cells[35]. It is inferred that this pathway may be related to the proliferation and expansion of blood vessels in the dermis, leading to persistent abnormalities in local skin function. Signaling pathways related to PSO comorbidities, such as the advanced glycation end products (AGEs)/receptor of AGE (RAGE) signaling pathway in diabetic complications, have been identified as well. AGEs and their receptors in the AGE-RAGE signal transduction pathway have been a focus of research recently. This pathway activates the NF-κB pathway and induces oxidative and inflammatory reactions by expressing and releasing VEGF, transforming growth factor-β1, nicotinamide adenine dinucleotide phosphate, and other factors, which ultimately cause cell and tissue damage[36,37].

TCM network pharmacology is the network biology basis for understanding complex diseases, TCM syndromes, and TCM treatment, reflecting the new trend of combining computation, experimentation, and clinical practices[38]. In this study, we used network pharmacology to establish drug target pathways and networks and predicted the possible protein targets of BYT in the treatment of psoriasis and the main interactions between these targets and drugs. Nonetheless, this study has some limitations. First, all data were from public databases and public data, and multi-faceted analysis was performed using bioinformatics. The management of public databases is heterogeneous and beyond our control; thus, the possibility of selection bias cannot be ruled out. Second, considering the multiple components, proteins, genes, and pathways involved in TCM, greater algorithm support is needed for a deeper understanding of the correlation between different data to reveal the internal biological network regulation mechanisms of TCM. Finally, this study lacks experimental validation, but it provides a possible direction for further *in vitro* and *in vivo* experimental studies to explore the detailed mechanism between BYT and psoriasis.

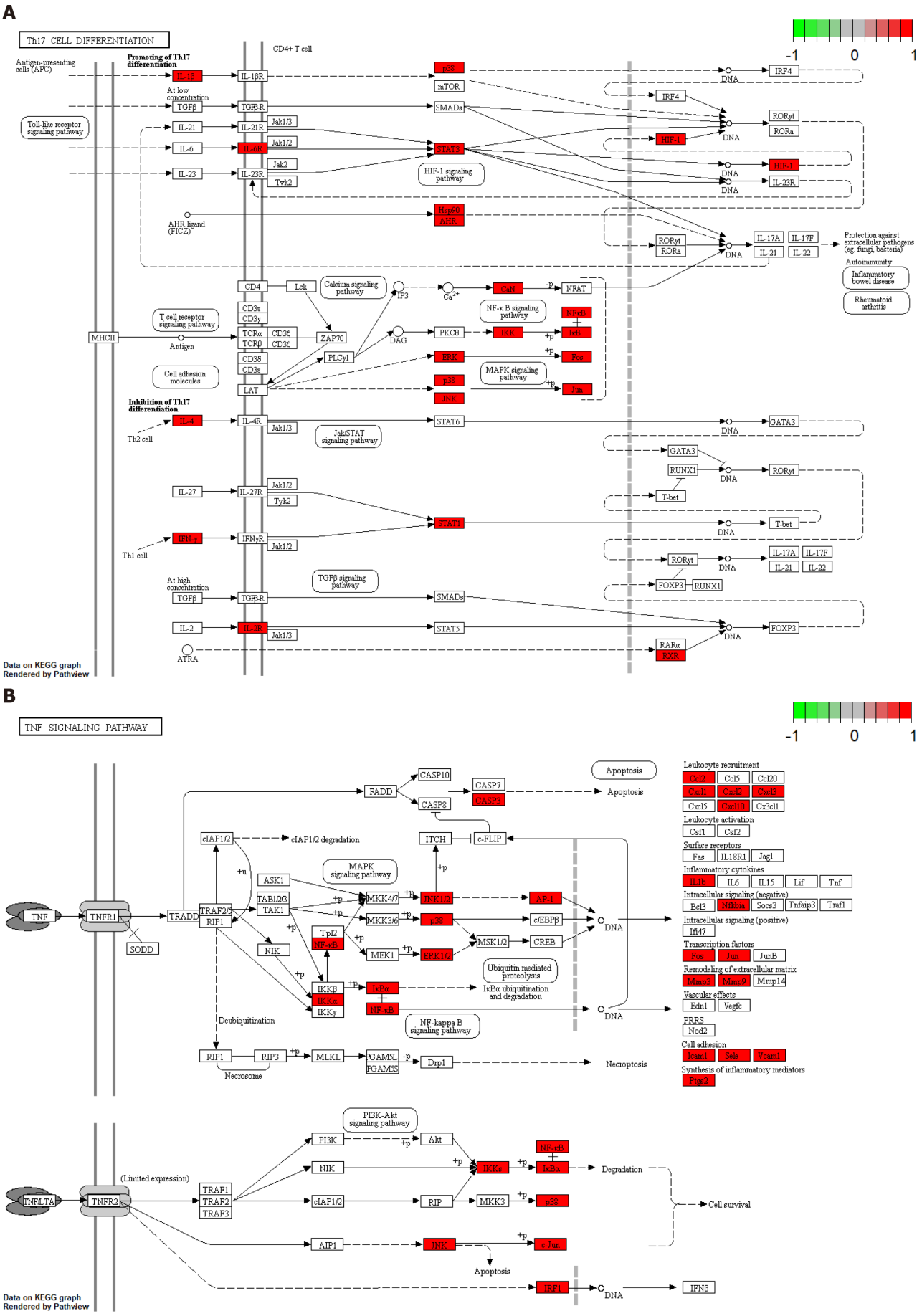

Figure 6 Pathway analysis of Biyu decoction-psoriasis intersection genes. A: Pathway analysis of Th17 cell differentiation; B: Tumor necrosis factor

signaling pathway potential target genes. PSO: Psoriasis; BYT: Biyu decoction; TNF: Tumor necrosis factor.

CONCLUSION

Using a network pharmacology approach, this study combined bioinformatics technology with TCM theory to analyze the chemical components, effective active ingredients, and targets of BYT compounds as TCM and the target genes in PSO. Relevant software was used to analyze and construct the target network and cell pathways targeted by BYT. The main active ingredients identified include quercetin, kaempferol, beta-sitosterol, naringenin, and acetyl-shikonin. Target genes include *MAPK3*, *JUN*, *FOS*, *MYC*, *MAPK8*, *STAT3*, and *NFKBIA*, which can regulate the inflammatory state mediated by PSO immune cells and mediate the expression of factors that adjust local skin inflammation. Our results confirm that BYT can work on PSO through multi-component, multi-target, and multi-channel synergy and provide a basis for further in-depth clinical research of BYT treatment for PSO.

ARTICLE HIGHLIGHTS

Research background

Psoriasis (PSO) is a major public health challenge, causing great physical, psychological and economic burden. Biyu Decoction (BYT) has clear clinical efficiency in treating PSO.

Research motivation

The molecular mechanism of BYT treatment for PSO is still unclear.

Research objectives

To identify the targets and pathways through which BYT interferes with PSO.

Research methods

Therapeutic targets for BYT were predicted by network pharmacology and validated by molecular docking.

Research results

A total of 213 gene targets corresponding to 117 active components of BYT can intervene in PSO through a variety of biological pathways highly related to PSO, such as Th17 cell differentiation and TNF signaling Pathway. The stability of these biological reactions was verified by molecular docking.

Research conclusions

BYT can the pathogenesis of PSO with multiple targets.

Research perspectives

The results of this study could serve as a fundamental basis for the further exploration in the *in vitro* and *in vivo* experiments for clinical promotions.

FOOTNOTES

Author contributions: Li LL designed the research; Wang Z, Zhang HM, and Guo YR performed the research; Zhang HM, and Guo YR analyzed the data; Wang Z wrote the paper.

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Clinical trial registration statement: This registration policy applies to prospective, randomized, controlled trials only.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare that there is no conflict of interest regarding the publication of this

paper.

Data sharing statement: Technical appendix, statistical code, and dataset available from the manuscript.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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