World Journal of Cardiology

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World J Cardiol 2024 July 26; 16(7): 422-435

DOI: 10.4330/wjc.v16.i7.422

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Clinical and Translational Research

Network pharmacology-based exploration of molecular mechanisms underlying therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure with spleen Qi deficiency syndrome

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Chhipa AS

Received: May 23, 2024
Revised: July 2, 2024
Accepted: July 4, 2024
Published online: July 26, 2024
Processing time: 62 Days and 4.7 Hours

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Abstract

BACKGROUND

Chronic heart failure is a complex clinical syndrome. The Chinese herbal compound preparation Jianpi Huatan Quyu recipe has been used to treat chronic heart failure; however, the underlying molecular mechanism is still not clear.

AIM

To identify the effective active ingredients of Jianpi Huatan Quyu recipe and explore its molecular mechanism in the treatment of chronic heart failure.

METHODS

The effective active ingredients of eight herbs composing Jianpi Huatan Quyu recipe were identified using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform. The target genes of chronic heart failure were searched in the Genecards database. The target proteins of active ingredients were mapped to chronic heart failure target genes to obtain the common drug-disease targets, which were then used to construct a key chemical component-target network using Cytoscape 3.7.2 software. The protein-protein interaction network was constructed using the String database. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were performed through the Metascape database. Finally, our previously published relevant articles were searched to verify the results obtained *via* network pharmacology.

RESULTS

A total of 227 effective active ingredients for Jianpi Huatan Quyu recipe were

identified, of which quercetin, kaempferol, 7-methoxy-2-methyl isoflavone, formononetin, and isorhamnetin may be key active ingredients and involved in the therapeutic effects of TCM by acting on STAT3, MAPK3, AKT1, JUN, MAPK1, TP53, TNF, HSP90AA1, p65, MAPK8, MAPK14, IL6, EGFR, EDN1, FOS, and other proteins. The pathways identified by KEGG enrichment analysis include pathways in cancer, IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, calcium signaling pathway, cAMP signaling pathway, NF-kappaB signaling pathway, AMPK signaling pathway, *etc.* Previous studies on Jianpi Huatan Quyu recipe suggested that this Chinese compound preparation can regulate the TNF-α, IL-6, MAPK, cAMP, and AMPK pathways to affect the mitochondrial structure of myocardial cells, oxidative stress, and energy metabolism, thus achieving the therapeutic effects on chronic heart failure.

CONCLUSION

The Chinese medicine compound preparation Jianpi Huatan Quyu recipe exerts therapeutic effects on chronic heart failure possibly by influencing the mitochondrial structure of cardiomyocytes, oxidative stress, energy metabolism, and other processes. Future studies are warranted to investigate the role of the IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, and other pathways in mediating the therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure.

Key Words: Jianpi Huatan Quyu recipe; Traditional Chinese medicine; Chronic heart failure; Data mining; Network pharmacology; Bioinformatics; Spleen Qi deficiency syndrome

Core Tip: Based on the clinical characteristics of patients, the dialectical treatment of chronic heart failure is often performed primarily by strengthening Qi and nourishing Yin, promoting blood circulation and removing blood stasis, resolving phlegm and alleviating water retention, and warming and tonifying heart Yang. In this study, the authors found that the Chinese medicine compound preparation Jianpi Huatan Quyu recipe exerts therapeutic effects on chronic heart failure possibly by influencing the mitochondrial structure of cardiomyocytes, oxidative stress, energy metabolism, and other processes.

Citation: Li SQ, Min DY, Jiang JW, Li XY, Yang XN, Gu WB, Jiang JH, Chen LH, Nan H, Chen ZY. Network pharmacology-based exploration of molecular mechanisms underlying therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure with spleen Qi deficiency syndrome. *World J Cardiol* 2024; 16(7): 422-435
URL: https://www.wjgnet.com/1949-8462/full/v16/i7/422.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i7.422

INTRODUCTION

Chronic heart failure is a complex clinical syndrome due to abnormal changes in cardiac structure and/or function caused by multiple factors, resulting in ventricular systolic and/or diastolic dysfunction[1]. Its main manifestations are dyspnea, fatigue, and fluid retention. As the end-stage manifestation of cardiovascular disease and the main cause of death, chronic heart failure is thought to belong to "chest impediment", "palpitation", "true heart pain", and other categories in traditional Chinese medicine (TCM). Based on the clinical characteristics of patients, the dialectical treatment of chronic heart failure is often performed primarily by strengthening Qi and nourishing Yin, promoting blood circulation and removing blood stasis, resolving phlegm and alleviating water retention, and warming and tonifying heart Yang[2]. We have been studying the curative effect and mechanism of the Chinese herbal compound preparation Jianpi Huatan Quyu recipe, which has the effects of strengthening the spleen, dissolving phlegm, and removing blood stasis, in the treatment of chronic heart failure. In order to further explore the therapeutic mechanism of this compound recipe, network pharmacology was applied in the present study to identify the effective active ingredients of eight herbs composing Jianpi Huatan Quyu recipe, as well as common target proteins shared by Jianpi Huatan Quyu recipe and chronic heart failure. In addition, our previous studies on the mechanism of action of Jianpi Huayu Qutan recipe in different conditions were searched to provide support for the results obtained *via* network pharmacology.

MATERIALS AND METHODS

Analysis of effective active components of Jianpi Huatan Quyu recipe

Jianpi Huatan Quyu recipe is composed of eight Chinese herbs: Dangshen, Fuling, Baizhu, Zhigancao, Danshen, Qingbanxia, and Gualou. The effective active components of these eight herbs were searched using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP)[3]. Oral bioavailability ≥ 30% and

drug-likeness ≥ 0.18 were used as the screening criteria to ensure that the selected active ingredients have good oral absorption and high druggability.

Identification of common targets shared by Jianpi Huatan Quyu recipe and chronic heart failure

The TCMSP database was used to identify the targets of the effective active ingredients as mentioned above. Human gene names and corresponding target proteins were downloaded from the UniProt database (https://www.uniprot.org/)[4]. The target genes of chronic heart failure were searched in the Genecards database (https://www.genecards.org/)[5]. The target proteins of active ingredients were mapped to chronic heart failure target genes to obtain the common drug-disease targets and to find out the key chemical components corresponding to these targets.

Key chemical component-target network construction

Common drug-disease targets and their corresponding key chemical components were sorted into a table, which was then imported into Cytoscape 3.7.2 software to obtain their relationship network.

Protein-protein interaction network construction

Protein-protein interaction (PPI) networks can graphically describe the interactions between common drug-disease targets. The common drug-disease targets identified above were input into the String database (https://string-db.org/ Version 10.5)[6] to obtain the PPI network. The protein interaction score was further set to 0.9 to optimize the network diagram. Data on protein interactions were downloaded to screen out the top 15 core proteins.

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis

The common drug-disease targets identified above were imported into the Metascape database (http: //metascape.org/gp/index.html)[7] for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, with the parameters set as follows: *P* value = 0.01, minimum overlap = 3, and minimum enrichment = 1.5, GO biological process (BP), cellular component (CC), and molecular function (MF) and KEGG pathways were enriched, respectively. Bubble maps were generated online using the ImageGP website tool. The target-pathway network was constructed with Cytoscape software.

Confirmatory study

According to the key targets and proteins belonging to the signal pathways identified above, our previously published relevant articles were analyzed to verify the therapeutic mechanism of Jianpi Huatan Quyu recipe in the treatment of chronic heart failure.

RESULTS

Identification of effective active ingredients of Jianpi Huatan Quyu recipe

There are eight herbs in the Chinese herbal compound preparation Jianpi Huatan Quyu recipe: Huangqi, Dangshen, Fuling, Baizhu, Zhigancao, Danshen, Qingbanxia, and Gualou. As shown in Table 1, a total of 227 active ingredients were identified in the TCMSP database according to the oral bioavailability and drug-likeness.

Identification of common drug-disease targets

A total of 4123 genes were downloaded from the Genecard database and screened for genes with a score of 5 or greater, which might be associated with chronic heart failure. Mapping of the target proteins of active ingredients of Jianpi Huatan Quyu recipe to chronic heart failure target genes led to the identification of 201 common targets. The Venn diagram indicating these common targets is shown in Figure 1.

Construction of key chemical component-target network

Cytoscape software was used to construct the relationship network of key active components in Jianpi Huatan Quyu recipe and chronic heart failure associated genes. As shown in Figure 2, the top 5 key chemical components are as follows: Quercetin (MOL000098, degree = 236), kaempferol (MOL000422, degree = 94), 7-methoxy-2-methyl isoflavone, (MOL003896, degree = 60), formononetin (MOL000392, degree = 53), and isorhamnetin (MOL000354, degree = 47). The top 15 common target proteins are as follows: PTGS2, ESR1, AR, PTGS1, NOS2, SCN5A, PRSS1, GSK3B, PPARG, CCNA2, ESR2, ADRB2, DPP4, F10, and RXRA.

PPI network analysis

The PPI network was obtained by inputting the common drug-disease targets into the String database. As shown in Figure 3, the PPI network contains 200 nodes and 906 edges. Among them, the interacting protein pairs with a PPI score equal to 0.999 are AKT1-NOS3, AKT1-GSK3B, BCL2 L1-TP53, BCL2 L1-CASP8, CASP3-CASP8, CASP7-CASP8, CCNA2-CDK2, CCNA2-CDKN1A, CCND1-CDKN1A, CCND1-CDK2, CDK2-RB1, CDK2-CDKN1A, CDKN1A-TP53, CDKN1A-PCNA, E2F1-RB1, EDN1-EDNRA, EGF-EGFR, F3-F7, FOS-JUN, IKBKB-NFKBIA, IKBKB-TNF, JUN-MAPK8, KDR-VEGFA, MDM2-TP53, PLAT-SERPINE1, and PLAU-SERPINE1. By calculating the number of connection points in the network, the top 15 core proteins were identified: STAT3, MAPK3, AKT1, JUN, MAPK1, TP53, TNF, HSP90AA1, RELA,

Table 1 Active ingredients of herbs composing Jianpi Huatan Quyu recipe

Molecule ID	Molecule name	Drug(s)	Molecule ID	Molecule name	Drug(s)
MOL007059	3-β-hydroxymethyllenetanshiquinone	Danshen, Dangshen	MOL001792	DFV	Gancao
MOL004355	Spinasterol	Dangshen, Gualou	MOL001484	Inermine	Gancao
MOL003896	7-methoxy-2-methyl isoflavone	Dangshen, Gancao	MOL000500	Vestitol	Gancao
MOL002776	Baicalin	Banxia, Danshen	MOL000497	Licochalcone a	Gancao
MOL000449	Stigmasterol	Banxia, Dangshen	MOL000359	Sitosterol	Gancao
MOL000422	Kaempferol	Gancao, Huangqi	MOL000300	Dehydroeburicoic acid	Fuling
MOL000417	Calycosin	Gancao, Huangqi	MOL000292	Poricoic acid C	Fuling
MOL000392	Formononetin	Gancao, Huangqi	MOL000291	Poricoic acid B	Fuling
MOL000354	Isorhamnetin	Gancao, Huangqi	MOL000290	Poricoic acid A	Fuling
MOL000296	Hederagenin	Fuling, Huangqi	MOL000289	Pachymic acid	Fuling
MOL000239	Jaranol	Gancao, Huangqi	MOL000287	3-β-hydroxy-24-methylene-8-lanostene-21-oic acid	Fuling
MOL000211	Mairin	Gancao, Huangqi	MOL000285	(2R)-2-[(5R,10S,13R,14R,16R,17R)-16-hydroxy-3-keto-4,4,10,13,14-pentamethyl-1,2,5,6,12,15,16,17-octahydrocyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	Fuling
MOL000098	Quercetin	Gancao, Huangqi	MOL000283	Ergosterol peroxide	Fuling
MOL000033	(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	Baizhu, Huangqi	MOL000282	Ergosta-7,22E-dien-3beta-ol	Fuling
MOL000006	Luteolin	Danshen, Dangshen	MOL000280	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	Fuling
MOL000442	1,7-dihydroxy-3,9-dimethoxy pterocarpene	Huangqi	MOL000279	Cerevisterol	Fuling
MOL000439	Isomucronulatol-7,2'-di-O-glucosiole	Huangqi	MOL000276	7,9(11)-Dehydropachymic acid	Fuling
MOL000438	(3R)-3-(2-hydroxy-3,4-dimethoxyphenyl)chroman-7-ol	Huangqi	MOL000275	Trametenolic acid	Fuling
MOL000433	FA	Huangqi	MOL000273	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid	Fuling
MOL000398	Isoflavanone	Huangqi	MOL008411	11-Hydroxyrankinidine	Dangshen
MOL000387	Bifendate	Huangqi	MOL008407	(8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-1,2,4,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one	Dangshen
MOL000380	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	Huangqi	MOL008406	Spinoside A	Dangshen
MOL000379	9,10-dimethoxypterocarpan-3-O-β-D-glucoside	Huangqi	MOL008400	Glycitein	Dangshen
MOL000378	7-O-methylisomucronulatol	Huangqi	MOL008397	Daturilin	Dangshen

MOL000374	5'-hydroxyiso-muronulatol-2',5'-di-O-glucoside	Huangqi	MOL008393	7-(β-xylosyl)cephalomannine_qt	Dangshen
MOL000371	3,9-di-O-methylnissolin	Huangqi	MOL008391	5α-Stigmastan-3,6-dione	Dangshen
MOL007180	Vitamin E	Gualou	MOL007514	Methyl icosa-11,14-dienoate	Dangshen
MOL007179	Linolenic acid ethyl ester	Gualou	MOL006774	Stigmast-7-enol	Dangshen
MOL007175	Karounidiol 3-O-benzoate	Gualou	MOL006554	Taraxerol	Dangshen
MOL007172	7-oxo-Dihydrokaro-unidiol	Gualou	MOL005321	Frutinone A	Dangshen
MOL007171	5-Dehydrokarounidiol	Gualou	MOL004492	Chrysanthemaxanthin	Dangshen
MOL007165	10α-cucurbita-5,24-diene-3β-ol	Gualou	MOL003036	ZINC03978781	Dangshen
MOL006756	Schottenol	Gualou	MOL002879	Diop	Dangshen
MOL005530	hydroxygenkwanin	Gualou	MOL002140	Perlolyrine	Dangshen
MOL002881	Diosmetin	Gualou	MOL001006	Poriferasta-7,22E-dien-3β-ol	Dangshen
MOL001494	Mandenol	Gualou	MOL007156	Tanshinone VI	Danshen
MOL005020	Dehydroglyasperins C	Gancao	MOL007155	(6S)-6-(hydroxymethyl)-1,6-Dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	Danshen
MOL005018	Xambioona	Gancao	MOL007154	Tanshinone iia	Danshen
MOL005017	Phaseol	Gancao	MOL007152	Przewaquinone E	Danshen
MOL005016	Odoratin	Gancao	MOL007151	Tanshindiol B	Danshen
MOL005013	18α-hydroxyglycyrrhetic acid	Gancao	MOL007150	(6S)-6-hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone	Danshen
MOL005012	Licoagroisoflavone	Gancao	MOL007149	NSC 122421	Danshen
MOL005008	Glycyrrhiza flavonol A	Gancao	MOL007145	Salviolone	Danshen
MOL005007	Glyasperins M	Gancao	MOL007143	Salvilenone I	Danshen
MOL005003	Licoagrocarpin	Gancao	MOL007142	Salvianolic acid J	Danshen
MOL005001	Gancaonin H	Gancao	MOL007141	Salvianolic acid G	Danshen
MOL005000	Gancaonin G	Gancao	MOL007140	(Z)-3-[2-[(E)-2-(3,4-dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid	Danshen
MOL004996	Gadelaidic acid	Gancao	MOL007132	(2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid	Danshen
MOL004993	8-prenylated eriodictyol	Gancao	MOL007130	Prolithospermic acid	Danshen
MOL004991	7-acetoxy-2-methylisoflavone	Gancao	MOL007127	1-methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione	Danshen
MOL004990	7,2',4'-trihydroxy-5-methoxy-3-arylcoumarin	Gancao	MOL007125	Neocryptotanshinone	Danshen
MOL004989	6-prenylated eriodictyol	Gancao	MOL007124	Neocryptotanshinone II	Danshen
MOL004988	Kanzonol F	Gancao	MOL007123	Miltirone II	Danshen
MOL004985	Icos-5-enoic acid	Gancao	MOL007122	Miltirone	Danshen
MOL004980	Inflacoumarin A	Gancao	MOL007121	Miltipolone	Danshen
MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol	Gancao	MOL007120	Miltionone II	Danshen
MOL004974	3'-methoxyglabridin	Gancao	MOL007119	Miltionone I	Danshen
MOL004966	3'-hydroxy-4'-O-methylglabridin	Gancao	MOL007118	Microstegiol	Danshen
MOL004961	Quercetin der.	Gancao	MOL007115	Manool	Danshen
MOL004959	1-methoxyphaseollidin	Gancao	MOL007111	Isotanshinone II	Danshen
MOL004957	HMO	Gancao	MOL007108	Isocryptotanshi-none	Danshen
MOL004949	Isolicoflavonol	Gancao	MOL007107	C09092	Danshen
MOL004948	Isoglycyrol	Gancao	MOL007105	Epidanshenspiroketallactone	Danshen

MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one	Gancao	MOL007101	Dihydrotanshinone I	Danshen
MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	Gancao	MOL007100	Dihydrotanshinlactone	Danshen
MOL004935	Sigmoidin-B	Gancao	MOL007098	Deoxyneocryptotanshinone	Danshen
MOL004924	(-)-medicocarpin	Gancao	MOL007094	Danshenspiroketallactone	Danshen
MOL004917	Glycyroside	Gancao	MOL007093	Dan-shexinkum d	Danshen
MOL004915	Eurycarpin A	Gancao	MOL007088	Cryptotanshinone	Danshen
MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone	Gancao	MOL007085	Salvilenone	Danshen
MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone	Gancao	MOL007082	Danshenol A	Danshen
MOL004912	Glabrone	Gancao	MOL007081	Danshenol B	Danshen
MOL004911	Glabrene	Gancao	MOL007079	Tanshinaldehyde	Danshen
MOL004910	Glabranin	Gancao	MOL007077	Sclareol	Danshen
MOL004908	Glabridin	Gancao	MOL007071	Przewaquinone f	Danshen
MOL004907	Glyzaglabrin	Gancao	MOL007070	(6S,7R)-6,7-dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	Danshen
MOL004905	3,22-dihydroxy-11-oxo-delta(12)-oleanene-27-α-methoxycarbonyl-29-oic acid	Gancao	MOL007069	Przewaquinone C	Danshen
MOL004904	Licopyranocoumarin	Gancao	MOL007068	Przewaquinone B	Danshen
MOL004903	Liquiritin	Gancao	MOL007064	Przewalskin B	Danshen
MOL004898	(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one	Gancao	MOL007063	przewalskin a	Danshen
MOL004891	Shinpterocarpin	Gancao	MOL007061	Methylenetanshinquinone	Danshen
MOL004885	Licoisoflavanone	Gancao	MOL007058	Formyltanshinone	Danshen
MOL004884	Licoisoflavone B	Gancao	MOL007051	6-O-syringyl-8-o-acetyl shanzhiside methyl ester	Danshen
MOL004883	Licoisoflavone	Gancao	MOL007050	2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde	Danshen
MOL004882	Licocoumarone	Gancao	MOL007049	4-methylenemiltirone	Danshen
MOL004879	Glycyrin	Gancao	MOL007048	(E)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-benzofuran-4-yl]acrylic acid	Danshen
MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone	Gancao	MOL007045	3α-hydroxytanshinone IIa	Danshen
MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone	Gancao	MOL007041	2-isopropyl-8-methylphenanthrene-3,4-dione	Danshen
MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone	Gancao	MOL007036	5,6-dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one	Danshen
MOL004860	Licorice glycoside E	Gancao	MOL006824	α-amyrin	Danshen
MOL004857	Gancaonin B	Gancao	MOL002651	Dehydrotanshinone IIA	Danshen
MOL004856	Gancaonin A	Gancao	MOL002222	Sugiol	Danshen
MOL004855	Licoricone	Gancao	MOL001942	Isoimperatorin	Danshen
MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	Gancao	MOL001771	Poriferast-5-en-3β-ol	Danshen
MOL004848	Licochalcone G	Gancao	MOL001659	Poriferasterol	Danshen
MOL004841	Licochalcone B	Gancao	MOL001601	1,2,5,6-tetrahydrotanshinone	Danshen
MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol	Gancao	MOL000569	Digallate	Danshen

MOL004835	Glypallichalcone	Gancao	MOL006967	β-D-Ribofuranoside, xanthine-9	Banxia
MOL004833	Phaseolinisoflavan	Gancao	MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl)piperazine-2,5-quinone	Banxia
MOL004829	Glepidotin B	Gancao	MOL006937	12,13-epoxy-9-hydroxynonadeca-7,10-dienoic acid	Banxia
MOL004828	Glepidotin A	Gancao	MOL006936	10,13-eicosadienoic	Banxia
MOL004827	Semilicoisoflavone B	Gancao	MOL005030	Gondoic acid	Banxia
MOL004824	(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one	Gancao	MOL003578	Cycloartenol	Banxia
MOL004820	Kanzonols W	Gancao	MOL002714	Baicalein	Banxia
MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethyl-chromen-6-yl)prop-2-en-1-one	Gancao	MOL002670	Cavidine	Banxia
MOL004814	Isotrifoliol	Gancao	MOL001755	24-ethylcholest-4-en-3-one	Banxia
MOL004811	Glyasperin C	Gancao	MOL000519	Coniferin	Banxia
MOL004810	Glyasperin F	Gancao	MOL000358	β-sitosterol	Banxia
MOL004808	Glyasperin B	Gancao	MOL000072	8β-ethoxy atractylenolide III	Baizhu
MOL004806	Euchrenone	Gancao	MOL000049	3β-acetoxyatractylone	Baizhu
MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one	Gancao	MOL000028	α-amyrin	Baizhu
MOL004328	Naringenin	Gancao	MOL000022	14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol	Baizhu
MOL003656	Lupiwighteone	Gancao	MOL000021	14-acetyl-12-senecioyl-2E,8E,10E-atractylentriol	Baizhu
MOL002565	Medicarpin	Gancao	MOL000020	12-senecioyl-2E,8E,10E-atractylentriol	Baizhu
MOL002311	Glycyrol	Gancao			

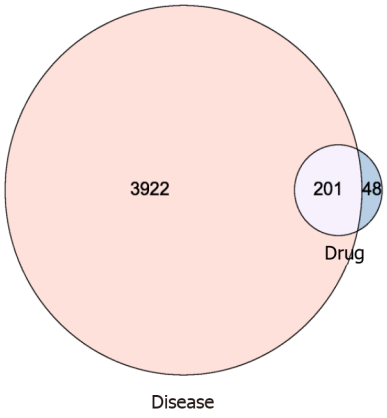


Figure 1 Venn diagram showing common targets of chronic heart failure and Jianpi Huatan Quyu recipe.

MAPK8, MAPK14, IL6, EGFR, EDN1, and FOS, which may be the core proteins mediating the therapeutic effects of Jianpi Huatan Quyu recipe in treating chronic heart failure (Figure 4).

GO enrichment analysis

BP enrichment analysis results are shown in Figure 5A. The BPs enriched include response to lipopolysaccharide, inflammatory response, response to drug, reactive oxygen species metabolic process, response to wounding, cellular response to organic cyclic compound, response to inorganic substance, cellular response to nitrogen compound, circulatory system process, positive regulation of cellular component movement, response to oxygen levels, apoptotic signaling pathway, response to extracellular stimulus, positive regulation of ion transport, regulation of MAPK cascade, regulation of DNA-binding transcription factor activity, regulation of cell adhesion, response to growth factor, response to steroid hormone, fine negative regulation of cell differentiation, *etc.*

Figure 5B shows the results of CC enrichment analysis. The CCs enriched are membrane raft, receptor complex, vesicle lumen, postsynaptic membrane, dendrite, perinuclear region of cytoplasm, side of membrane, extracellular matrix, protein kinase complex, cytoplasmic vesicle membrane, organelle outer membrane, focal adhesion, basal part of cell,

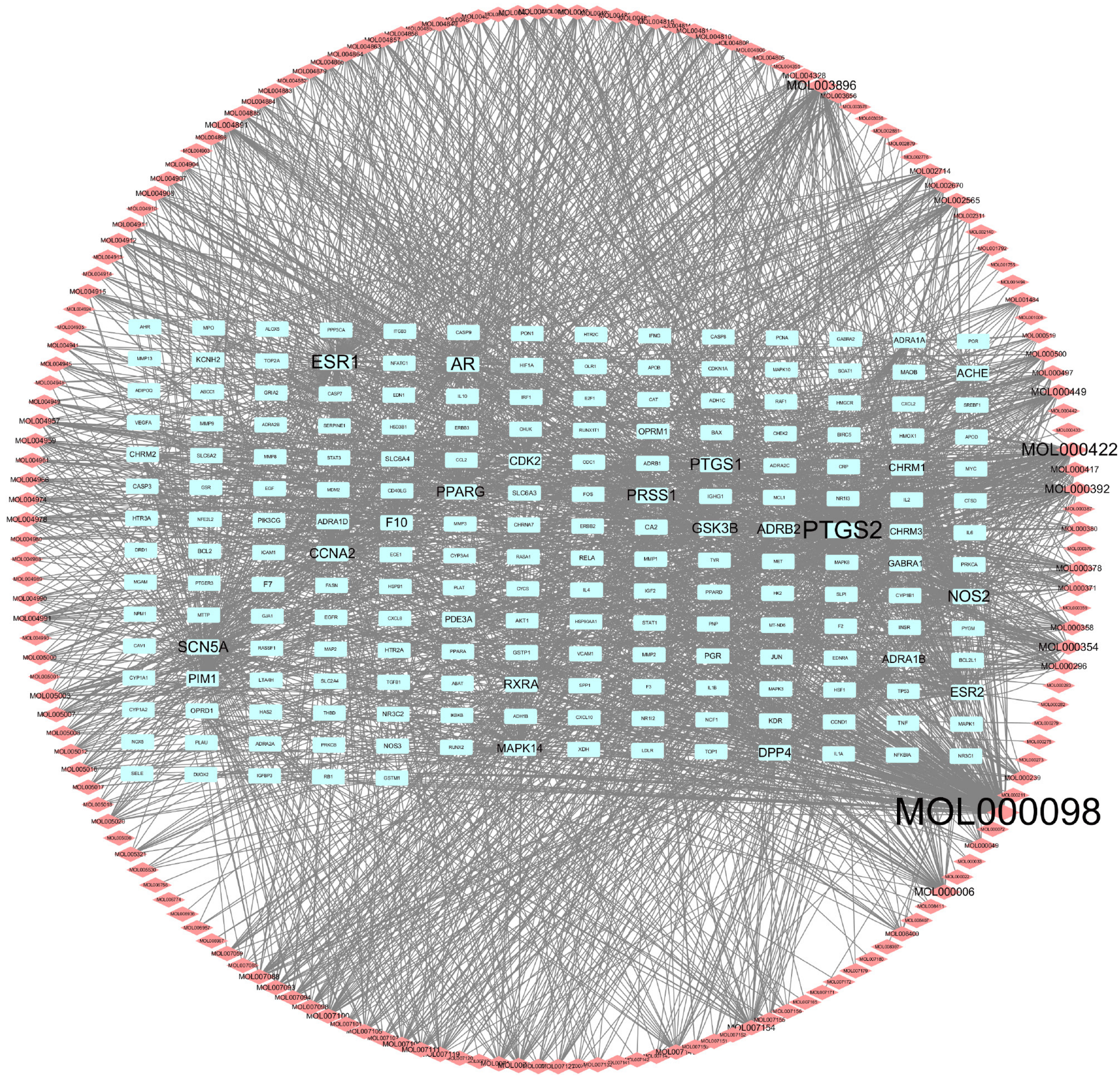


Figure 2 Network of target proteins shared by key active components in Jianpi Huatan Quyu recipe and chronic heart failure. Boxes represent target genes, and diamonds represent active ingredients. The size of the text in boxes and diamonds indicates "degree".

RNA polymerase II transcription regulator complex, dendrite membrane, endocytic vesicle, dopaminergic synapse, *etc*.

Figure 5C shows the results of MF enrichment analysis. The MFs enriched include nuclear receptor activity, protein homodimerization activity, DNA-binding transcription factor binding, G protein-coupled amine receptor activity, protein domain specific binding, protein kinase activity, cytokine receptor binding, protein heterodimerization activity, oxidoreductase activity, transcription coactivator binding, amide binding, neurotransmitter receptor activation activity, endopeptidase activity, drug binding, phosphatase binding, protease binding, core promoter sequence-specific DNA binding, MAP kinase activity, repressing transcription factor binding, kinase regulator activity, *etc.*

KEGG pathway enrichment analysis

KEGG pathway enrichment analysis demonstrated that the pathways enriched include pathways in cancer, IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, calcium signaling pathway, cAMP signaling pathway, NF-kappaB signaling pathway, AMPK signaling pathway, *etc.* (Figure 5D).

Target-pathway network construction

The target-pathway network constructed is shown in Figure 6. The selected core targets are IKBKB, RELA, AKT1, MAPK8, MAPK10, CHUK, JUN, MAPK1, TNF, CASP3, IL6, MAPK3, NFKBIA, MAPK14, TP53, CASP8, *etc.*

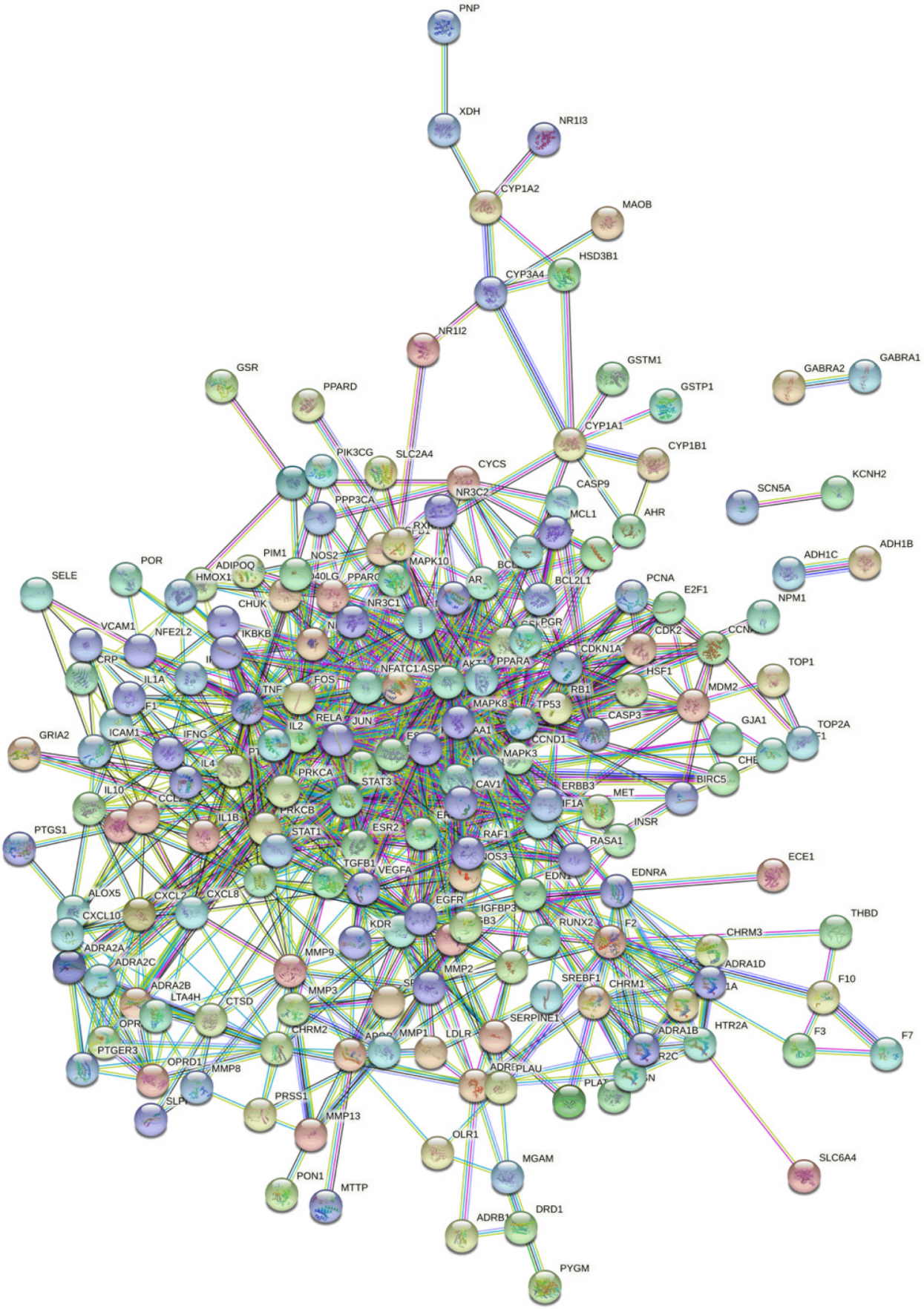


Figure 3 Protein-protein interaction protein interaction network.

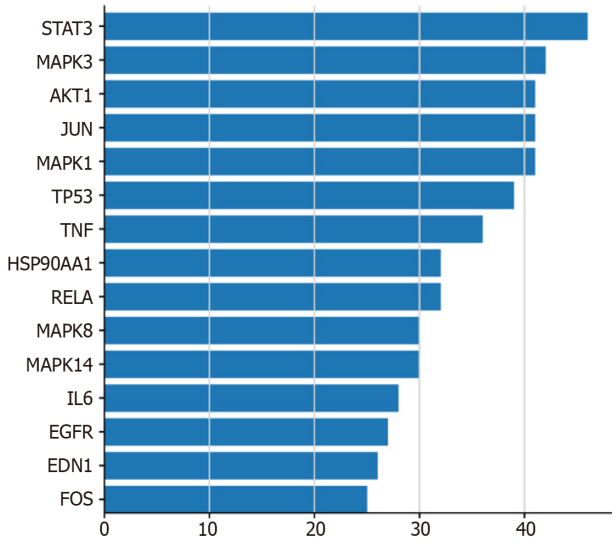


Figure 4 Core proteins identified by protein-protein interaction.

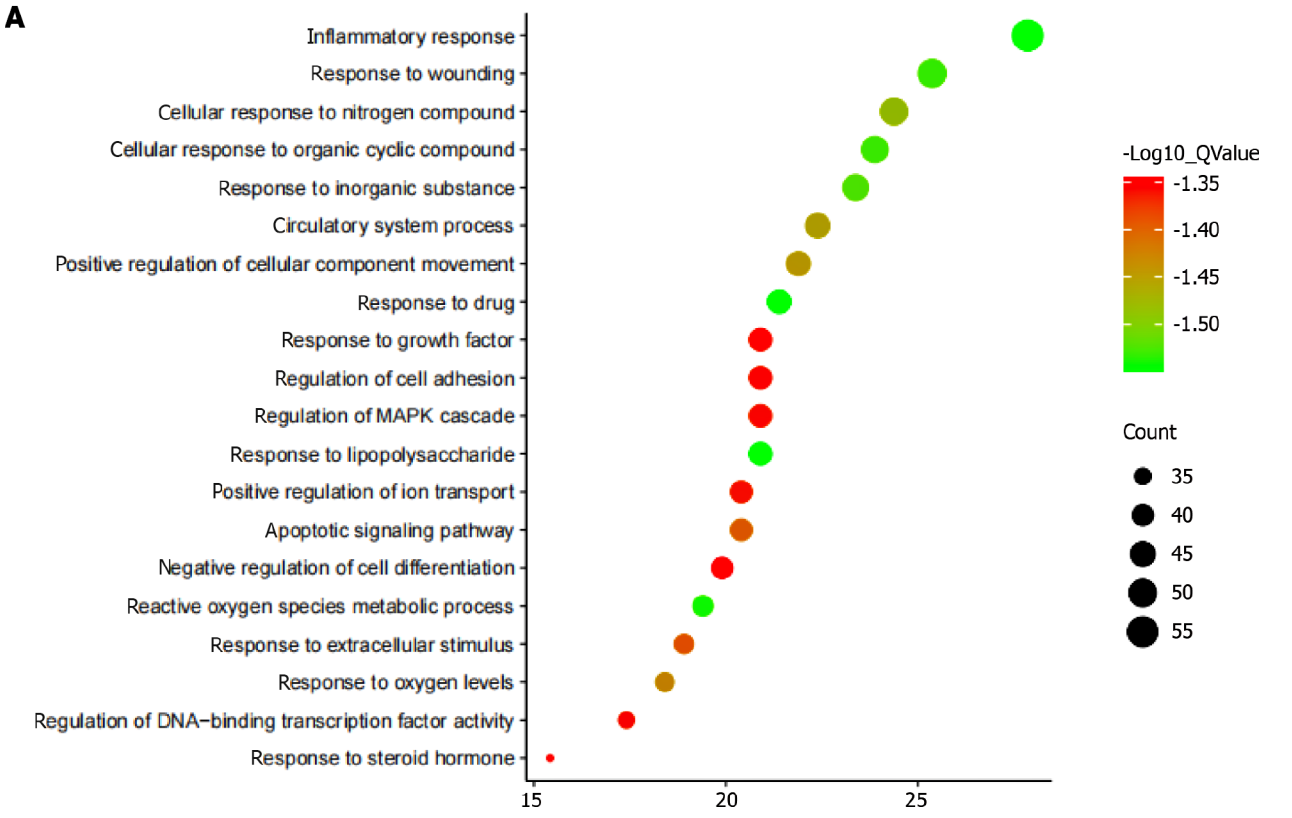
Confirmatory results of our previous studies

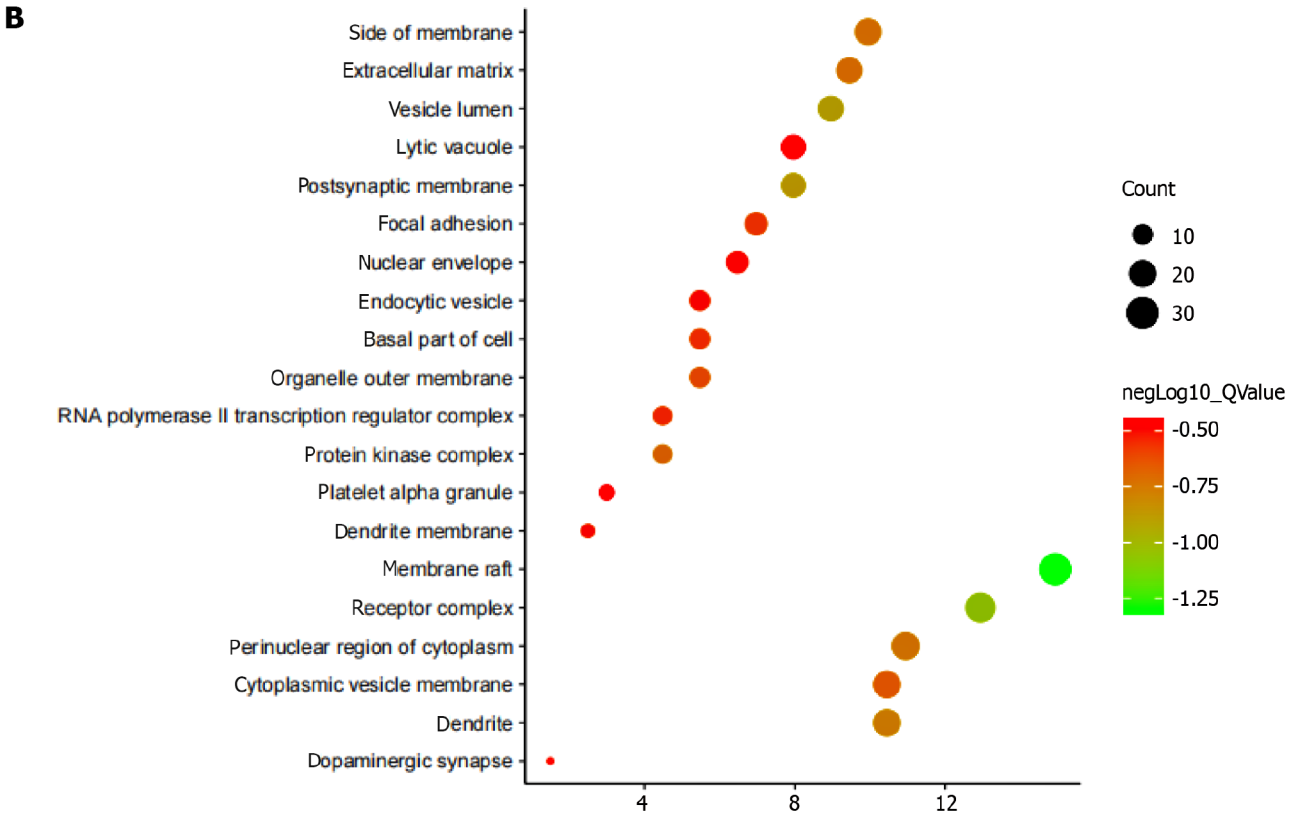
Our previous studies have explored the mechanism of action of Jianpi Huayu Qutan recipe in different conditions, which demonstrated that this recipe functions by regulating the expression of proteins involved in the TNF-α, IL-6, MAPK, cAMP, and AMPK pathways[8-11].

DISCUSSION

From the perspective of TCM, chronic heart failure is a disease characterized by deficiency in origin and excess in superficiality, which initially occurs in the heart, and then involves the lungs, spleen, and kidneys. With deficiency of heart Qi as the root cause, chronic heart failure mainly manifests as phlegm turbidity, fluid retention, and blood stasis[12]. The Chinese herbal compound preparation Jianpi Huatan Quyu recipe, derived from the TCM preparation Sijunzi decoction, was initially used to treat the syndrome of deficiency of spleen Qi[13]. Correcting the deficiency of Qi and blood is essential for the treatment of diseases. The spleen and stomach are the sources of Qi and blood. In Jianpi Huatan Quyu recipe, Huangqi, Dangshen, Baizhu, Fuling, and Zhigancao have strong spleen-strengthening effects and can promote blood circulation by flourishing the spleen Qi. Spleen dysfunction will lead to the accumulation of phlegm, so Qingbanxia is included in the recipe for removing dampness to reduce phlegm, and Gualou is used to relieve depression in the chest and regulate the flow of Qi, both of which can help eliminate the phlegm accumulated in the chest. Qi deficiency results in poor blood circulation and stagnation of blood stasis. Zhang *et al*[14] wrote in the ancient book "Thoroughly Revised Materia Medica" that "Danshen tonifies the heart, removes blood stasis, and promotes fresh blood production.....having multiple therapeutic effects". Therefore, Danshen is included in the Jianpi Huatan Quyu recipe to tonify the heart, promote blood circulation, and remove blood stasis. Combined use of all these herbs can achieve the effects of strengthening the spleen, tonifying the heart, eliminating phlegm, and removing blood stasis. Our previous studies have shown that Jianpi Huatan Quyu recipe can effectively improve patients' blood lipids, improve myocardial function, and affect patients' myocardial mitochondrial energy metabolism[15,16]. This study further explored the molecular mechanism underlying the therapeutic effects of Jianpi Huatan Quyu recipe in chronic heart failure.

In the present study, according to oral bioavailability and drug-likeness, 227 active ingredients of eight herbs composing Jianpi Huatan Quyu recipe were identified, among which quercetin, kaempferol, 7-methoxy-2-methyl isoflavone, formononetin, and isorhamnetin may be the key active ingredients. These chemical components can be highly matched with the following targets of chronic heart failure: PTGS2, ESR1, AR, PTGS1, NOS2, SCN5A, PRSS1, GSK3B, PPARG, CCNA2, ESR2, ADRB2, DPP4, F10, and RXRA. Further analysis of the relationship between these targets and chronic heart failure revealed that STAT3, MAPK3, AKT1, JUN, MAPK1, TP53, TNF, HSP90AA1, p65, MAPK8, MAPK14, IL6, EGFR, EDN1, and FOS may be involved in the development and progression of chronic heart failure. These proteins may also play an important role in the treatment of chronic heart failure. The molecular mechanisms that are involved in the therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure include nuclear receptor activity, protein homodimerization activity, DNA-binding transcription factor activity, G protein-coupled amine receptor activity, protein domain specific binding, protein kinase activity, cytokine receptor binding, protein heterodimerization activity, oxidoreductase activity, transcription coactivator binding, amide binding, and neurotransmitter receptor activity, endopeptidase activity, drug binding, phosphatase binding, protease binding, core promoter sequence-specific DNA binding, MAP kinase activity, repressing transcription factor binding, kinase regulator activity, *etc*. KEGG signaling pathway enrichment analysis indicated that the compound may act on multiple pathways, such as pathways in cancer, IL-17 signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, calcium signaling pathway, cAMP signaling


A
Inflammatory response
Response to wounding
Cellular response to nitrogen compound
Cellular response to organic cyclic compound
Response to inorganic substance
Circulatory system process
Positive regulation of cellular component movement
Response to drug
Response to growth factor
Regulation of cell adhesion
Regulation of MAPK cascade
Response to lipopolysaccharide
Positive regulation of ion transport
Apoptotic signaling pathway
Negative regulation of cell differentiation
Reactive oxygen species metabolic process
Response to extracellular stimulus
Response to oxygen levels
Regulation of DNA−binding transcription factor activity
Response to steroid hormone
15
20
25
-Log10_QValue
-1.35
-1.40
-1.45
-1.50
Count
35
40
45
50
55


B
Side of membrane
Extracellular matrix
Vesicle lumen
Lytic vacuole
Postsynaptic membrane
Focal adhesion
Nuclear envelope
Endocytic vesicle
Basal part of cell
Organelle outer membrane
RNA polymerase II transcription regulator complex
Protein kinase complex
Platelet alpha granule
Dendrite membrane
Membrane raft
Receptor complex
Perinuclear region of cytoplasm
Cytoplasmic vesicle membrane
Dendrite
Dopaminergic synapse
4
8
12
Count
10
20
30
negLog10_QValue
-0.50
-0.75
-1.00
-1.25

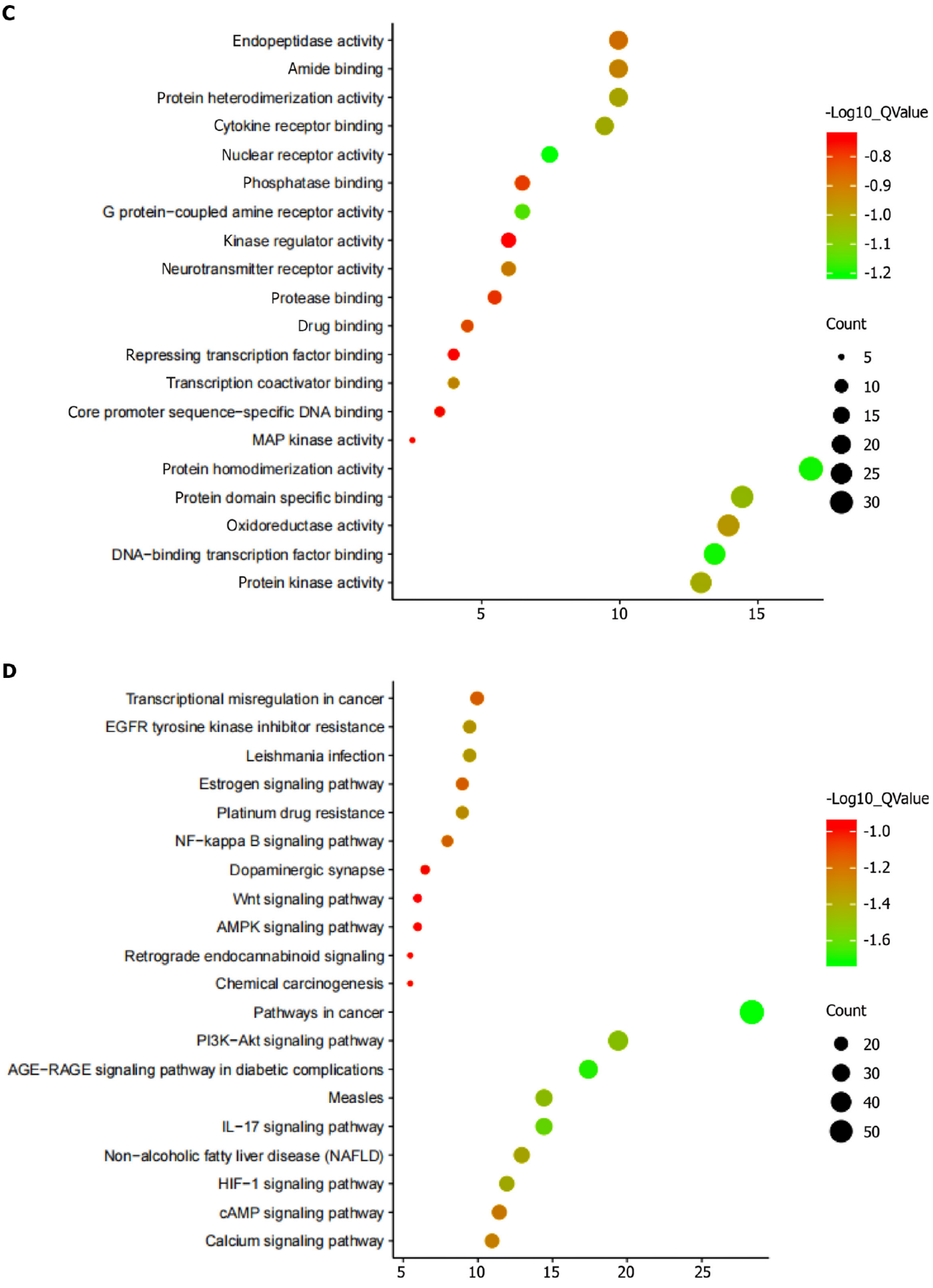


Figure 5 GO and KEGG enrichment analyses. A: GO biological process enrichment analysis; B: GO cellular component enrichment analysis; C: GO molecular function enrichment analysis; D: KEGG enrichment analysis.

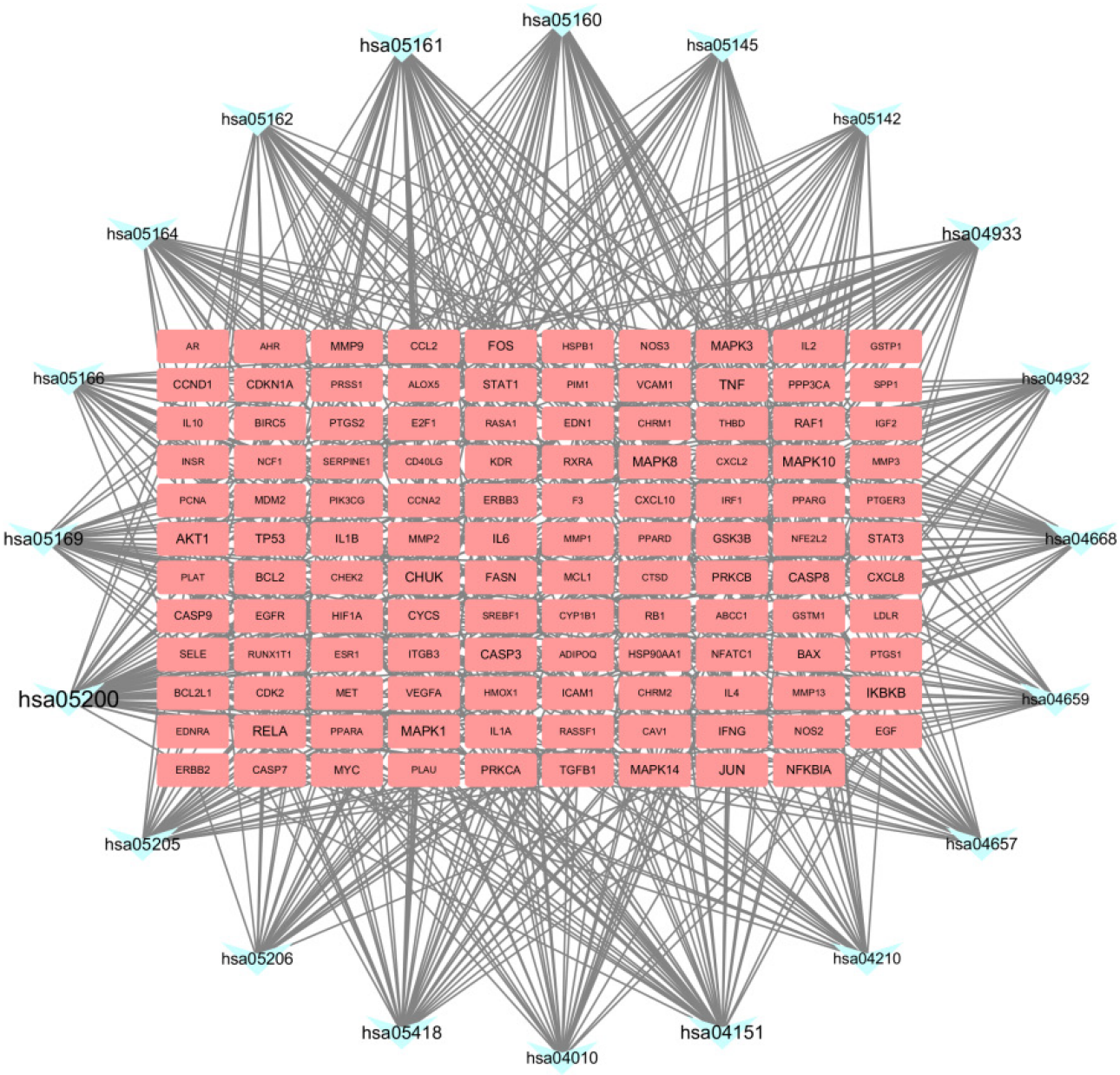


Figure 6 Target-pathway network diagram. The size of the node text is proportional to the number of lines connecting the node, with larger text indicating more targets or pathways associated with the target.

pathway, NF-kappaB signaling pathway, and AMPK signaling pathway. Among these pathways, IKBKB, RELA, AKT1, MAPK8, MAPK10, CHUK, JUN, MAPK1, TNF, CASP3, IL6, MAPK3, NFKBIA, MAPK14, TP53, CASP8, *etc.* may be the key protein targets of Jianpi Huatan Quyu recipe.

CONCLUSION

To sum up, the Chinese herbal compound preparation Jianpi Huatan Quyu recipe acts on multiple targets through a variety of active ingredients, exerting therapeutic effects on chronic heart failure *via* multiple pathways. The TNF-α, IL-6, MAPK, cAMP, and AMPK pathways have been experimentally verified to be involved in the therapeutic effects of Jianpi Huatan Quyu recipe on chronic heart failure in previous studies. The pathways such as the IL-17, PI3K-Akt, and HIF-1 signaling pathways can be used as the targets in the treatment of chronic heart failure. Future research is warranted to further explore the mechanism of Jianpi Huatan Quyu recipe in the treatment of chronic heart failure.

FOOTNOTES

Author contributions: Li SQ designed the study and drafted the manuscript; all authors contributed to revising and proofreading the manuscript.

Supported by 2021 Shenyang Science and Technology Program-Public Health R&D Special Project (Joint Project) of Shenyang Municipal Science and Technology Bureau, No. 21-174-9-04.

Conflict-of-interest statement: There is no conflict of interest to disclose.

Country of origin: China

ORCID number: Si-Qi Li 0009-0009-4222-716X.

S-Editor: Lin C
L-Editor: Wang TQ
P-Editor: Wang WB

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