Network Pharmacology-Based Mechanism Exploration of Buyang Huanwu Decoction in Chronic Heart Failure

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Abstract: Exploring the potential molecular mechanism of Buyang Huanwu Decoction in the treatment of chronic heart failure based on network pharmacology. Methods: The effective active ingredients of Buyang Huanwu Decoction were screened by searching TCMSP database, Chinese medicine Database@Taiwan and literature, and the targets of the effective active ingredients were predicted by SEA database and Binding Database. The targets related to chronic heart failure were obtained by Genecards, TTD, OMIM, Drugbank and PharmGkb Database, and the intersection targets of Buyang Huanwu Decoction and CHF were obtained. Cystoscape3.8.0 was used to construct a compound - disease - intersection target network diagram. The String database was used to construct PPI network, and R4.0.3 software was used to perform GO function enrichment analysis and KEGG signal pathway enrichment analysis for the intersection targets. Results: 1) A total of 104 chemical components and 841 targets were screened out in Buyang Huanwu Decoction. A total of 2908 targets were collected for chronic heart failure. There were 404 intersection targets of Buyang Huanwu Decoction and chronic heart failure. 2) Through PPI network, 28 core targets were screened out. 3) GO biological enrichment results showed 3964 GO entries; KEGG analysis co-enriched PI3K-Akt,MAPK, ect. 191 signaling pathways. Conclusion: Buyanghuanwu decoction can treat chronic heart failure through multi-component, multi-target and multi-channel mechanism.

1. Introduction

Heart failure is a complex set of clinical syndromes caused by abnormal changes in cardiac structure and/or function resulting in ventricular systolic and/or diastolic dysfunction due to a variety of causes, mainly manifested by dyspnea, fatigue, and fluid retention (pulmonary stasis, body circulation stasis, and peripheral edema)[1] . Heart failure has become a serious public health problem globally, with an estimated 6.2 million Americans aged ≥20 years suffering from heart failure according to NHANES data from 2013 to 2016[2]. Epidemiologic data in recent years have reported that the prevalence of heart failure in our population is 0.9% (0.7% in men and 1.0% in women), with an incidence rate of 0.7‰~0.9‰, 4.5 million existing patients with heart failure, and approximately 500,000 new cases of heart failure each year[3].

Chronic heart failure in Chinese medicine is characterized by the syndrome of "basic deficiency", with "basic deficiency" dominated by "qi deficiency", which is often accompanied by "yang deficiency" and "yin deficiency", while "basic deficiency" is dominated by "blood stasis", which is often accompanied by "water-drinking" and "phlegm turbidity". Qi deficiency and blood stasis are the most common elements of the above six syndromes [4]. Suwen - Lifting Pain Theory recorded: "labor is gasping and sweating, both external and internal, so the gas is consumed". Excessive labor depletes qi, heart qi is insufficient, blood can not be transported, stopping for blood stasis, and lead to disease. In recent years, many medical practitioners to benefit qi and blood rule of law, or by prescription tailoring, or by self-proposed formula with additional subtractions, have achieved satisfactory results.

Studies have shown that tonifying Yang and returning five soup can protect the structure and function of mitochondria by inhibiting the conversion of α-MHC to β-MHC and inhibiting the detachment of Drp1 mRNA from mitochondria, activating AMPK and up-regulating the expression of the AMPK/PPARα signaling pathway, thus improving energy metabolism in the failing heart and delaying the progression of heart failure [5-7]. Some studies have also shown that tonifying yang and returning five soup may improve cardiac function and myocardial remodeling in rats with heart failure by inhibiting the TGF-β1/Smads pathway [8]. However, the composition of this formula is complex, and the pathway and target mechanism of its action need to be more comprehensively investigated. Cyberpharmacology, as an emerging discipline in recent years, integrates the techniques of bioinformatics, network analysis and other multidisciplinary disciplines to explore the mechanism of drug-disease interactions [9]. Based on network pharmacology, this study combined with literature mining to construct a network of interaction between tonifying Yang and Wuzhu Tang and chronic heart failure, to explore the action targets of drugs and the pathway relationship between drugs and diseases, so as to reasonably predict and scientifically infer the action targets of the active ingredients and their regulation of biological processes and mechanisms, and strive to more comprehensively and deeply reveal the effective material basis of tonifying Yang and Wuzhu Tang and the therapeutic efficacy of the treatment of chronic heart failure and the mechanism of the treatment of chronic heart failure.

2. Material and Methods

2.1. Screening of the active ingredients of the Buyang Huanwu Decoction

Through searches on the TCMSP platform (http://tcmspw.com/index.php/) and the Chinese Medicine Database@Taiwan (http://tcm.cmu.edu.tw/), as well as literature mining, the chemical constituents of seven herb —Astragalus membranaceus, Ligusticum chuanxiong, Paeonia lactiflora, Danggui, Taoren, Honghua, and Diling. Based on relevant parameters of the compounds' pharmacokinetic properties (AMED), compounds with oral bioavailability (OB%) ≥ 30% and drug-like properties (DL) ≥ 0.18 were selected. These compounds were standardized using the "Canonical SMILES" format in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

2.2. Prediction of the active ingredient targets of Buyang Huanwu Decoction

Predicting Targets for Active Compounds Based on Chemical Structural Similarity by SEA platform (http://sea.bkslab.org/) and Binding Database (http://www.bindingdb.org/).Finally, all targets were normalized using UniProt (http://www.UniProt.org/).

2.3. Screening of CHF-related genes

The GeneCards database (https://www.genecards.org/), TTD database (http://db.idrblab.net/ttd/), OMIM database (https://mirror.omim.org/), Drugbank database (https. //go.drugbank.com/), and PharmGkb database (https://www.pharmgkb.org/) were searched for the keyword "chronic heart failure" to collect CHF-related genes, of which the following were screened. The genes with relevance score >10 were selected from GeneCards database.

2.4. Chemical compound---illnesses---Construction and analysis of intersecting target networks

The intersection of the predicted targets of Buyang Huanwu Decoction and CHF-related proteins was performed in R language, and the intersection targets were taken as the potential targets of Buyang Huanwu Decoction for the treatment of CHF, and the Wayne diagram was drawn. Cytoscape 3.8.0 software was used to construct the compound-disease-intersection target network for the treatment of CHF with Buyang Huanwu Decoction, and topological analysis was performed.

2.5. Construction and analysis of intersecting target protein interaction networks

The potential targets of action for the treatment of CHF by Buyang Huanwu Decoction and restoring five soups were imported into the STRING database (hops://string-db. org/, with the species set to human (homo sapines), and interaction plots of the target proteins were obtained with the highest confidence level of >0.95.Based on the protein interactions obtained from the STRING database, we imported them into Cytoscape 3.8.0 software, constructed the target protein interaction (PPI) network, scored each node using the CytoNCA plug-in, and screened the targets that simultaneously satisfied above the median of the degree, BC, CC, EC, and NC twice as the core targets for the Decoction treatment of CHF.

2.6. Functional and pathway enrichment analysis of core targets

The gene names of the core targets were converted to gene IDs, and filtered by corrected $p<0.05$ through R. The core targets were analyzed for GO (gene ontology) function, KEGG (Kyoto encyclopedia of genes and genomes) pathway enrichment, and the top 10 enriched genes were displayed, and the top 10 genes were selected to be related with CHF The top 10 enriched genes were displayed, and the genes related to CHF were selected and mapped.

3. Result

3.1. Active ingredient screening and target prediction

A total of 104 compounds that met the screening criteria were excavated from TCMSPing, Chinese Medicine Database@Taiwan and literature, and the specific compositions are shown in Table 1.Includes 16 pieces of Astragalus, 1 piece of Angelica sinensis, 25 pieces of Paeonia lactiflora, 9 pieces of Ligusticum chuanxiong, 19 pieces of Prunus persica kernel, 15 pieces of Carthamus tinctorius, 6 pieces of Pheretima aspergillum, and 13 duplicate components, as shown in Table 2.Some of these compounds, such as ferulic acid (Angelica sinensis), amygdalin (peach kernel), oleic acid, linoleic acid, palmitic acid (Paeonia lactiflora), chuanxionglactone I, and geraniolactone (Rhizoma Ligusticum chuanxiong), did not meet the screening criteria,However, based on the literature study, it was confirmed that most of the above ingredients are the main

ingredients of each traditional Chinese medicine, so the above ingredients were also included in the active ingredients of the Decoction.The above 104 active ingredients were imported into the SEA platform and Binding Database for target prediction, and a total of 841 targets were obtained after removing duplicates.

Tab.1 active ingredients of Buyang Huanwu Decoction

ID	Compound	OB%	DL	ID	Compound	OB%	DL	
HQ1	Mairin	55.38	0.78	CX5	wallichilide	42.31	0.71	
HQ2	Jaranol	50.83	0.29	CX6	cis-ligustilide	51.30	0.07	
HQ3	(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	36.23	0.78	CX7	tetramethylpyrazine	20.01	0.03	
HQ4	isorhamnetin	49.60	0.31	CX8	Senkyunolide A	26.56	0.07	
HQ5	3,9-di-O-methylnissolin	53.74	0.48	CX9	senkyunolide I	46.80	0.08	
HQ6	5'-hydroxyiso-muronulatol-2',5'-di-O-glucoside	41.72	0.69	TR1	Sitosterol alpha1	43.28	0.78	
HQ7	7-O-methylisomucronulatol	74.69	0.30	TR2	campesterol	37.58	0.71	
HQ8	9,10-dimethoxypterocarpan-3-O-β-D-glucoside	36.74	0.92	TR3	Amygdalin	4.42	0.61	
HQ9	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	64.26	0.42	TR4	2,3-didehydro GA70	63.29	0.50	
HQ10	Bifendate	31.10	0.67	TR5	2,3-didehydro GA77	88.08	0.53	
HQ11	formononetin	69.67	0.21	TR6	Gibberellin A120	84.85	0.45	
HQ12	isoflavanone	109.99	0.30	TR7	GA121-isolactone	72.70	0.54	
HQ13	Calycosin	47.75	0.24	TR8	GA122-isolactone	88.11	0.54	
HQ14	(3R)-3-(2-hydroxy-3,4-dimethoxyphenyl)chroman-7-ol	67.67	0.26	TR9	Gibberellin A17	94.64	0.49	
HQ15	isomucronulatol-7,2'-di-O-glucosiole	49.28	0.62	TR10	4a-formyl-7alpha-hydroxy-1-methyl-8-methylidene-4aalpha,4bbeta-gibbane-1alpha,10beta-dicarboxylic acid	88.60	0.46	
HQ16	1,7-Dihydroxy-3,9-dimethoxy pterocarpene	39.05	0.48	TR11	Gibberellin A44	101.61	0.54	
DG1	FER	39.56	0.06	TR12	Gibberellin A54	64.21	0.53	
CS1	(+)-catechin	54.83	0.24	TR13	Gibberellin A60	93.17	0.53	
CS2	ellagic acid	43.06	0.43	TR14	Gibberellin A63	65.54	0.54	
CS3	paeoniflorgenone	87.59	0.37	TR15	Gibberellin A7	73.80	0.50	
CS4	Lactiflorin	49.12	0.80	TR16	Gibberellin A77	87.89	0.53	
CS5	paeoniflorin	53.87	0.79	TR17	Gibberellin A87	68.85	0.57	
CS6	paeoniflorin_qt	68.18	0.40	TR18	3-O-p-coumaroylquinic acid	37.63	0.29	
CS7	Ethyl oleate (NF)	32.40	0.19	TR19	Populoside_qt	108.89	0.20	
CS8	Spinasterol	42.98	0.76	HH1	poriferast-5-en-3beta-ol	36.91	0.75	
CS9	campest-5-en-3beta-ol	37.58	0.71	HH2	4-[(E)-4-(3,5-dimethoxy-4-oxo-1-cyclohexa-2,5-dienylidene)but-2-enylidene]-2,6-dimethoxycyclohexa-2,5-dien-1-one	48.47	0.36	
CS10	Schottenol	37.42	0.75	HH3	lignan	43.32	0.65	
CS11	(1S,2S,4R)-trans-2-hydroxy-1,8-cineole-B-D-glucopyranoside	30.25	0.27	HH4	lupeol-palmitate	33.98	0.32	
CS12	(2R,3R)-4-methoxyl-distylin	59.98	0.30	HH5	Phytoene	39.56	0.50	
CS13	1-o-beta-d-glucopyranosyl-8-o-benzoylpaeonisuffrone_qt	36.01	0.30	HH6	phytofluene	43.18	0.50	
CS14	1-o-beta-d-glucopyranosylpaeonisuffrone_qt	65.08	0.35	HH7	Pyrethrin II	48.36	0.35	
CS15	stigmast-7-en-3-ol	37.42	0.75	HH8	kaempferol	62.13	0.27	
CS16	benzoyl paeoniflorin	31.14	0.54	HH9	qt_carthamone	51.03	0.20	
CS17	Albiflorin	30.25	0.77	HH10	6-Hydroxynaringenin	33.23	0.24	
CS18	Albiflorin_qt	48.70	0.33	HH11	quercetagetin	45.01	0.31	
CS19	4-ethyl-paeoniflorin_qt	56.87	0.44	HH12	7,8-dimethyl-1H-pyrimido[5,6-g]quinoxaline-2,4-dione	45.75	0.19	
CS20	4-o-methyl-paeoniflorin_qt	56.70	0.43	HH13	beta-carotene	37.18	0.58	
CS21	8-debenzoylpaeonidanin	31.74	0.45	HH14	luteolin	36.16	0.25	
CS22	Paeoniflorigenone	65.33	0.37	HH15	safflomin-A	3.53	0.68	
CS23	9-ethyl-neo-paeoniaflorin A_qt	64.42	0.30	DL1	Dihydrocapsaicin	47.07	0.19	
CS24	evofolinB	64.74	0.22	DL2	arachidonate	45.57	0.20	
CS25	isobenzoylpaeoniflorin	31.14	0.54	DL3	Chlorambucil			
CX1	Mandenol	42.00	0.19	DL4	Fumaritine			
CX2	Myricanone	40.60	0.51	DL5	Hypoxanthine			
CX3	Perlolyrine	65.95	0.27	DL6	Lumefantrine			
CX4	senkyunone	47.66	0.24					

Tab.2 Repeated ingredients of Buyang Huanwu Decoction

Number	MOL ID	Ingredients	OB %	DL	Source of the drug				
A	MOL000296	hederagenin	36.91	0.75	Astragalus membranaceus	peach kernel			
B	MOL000422	kaempferol	41.88	0.24	Astragalus membranaceus	safflower			
C	MOL000098	quercetin	46.43	0.28	Astragalus membranaceus	safflower			
D	MOL000433	Folic Acid	68.96	0.71	Astragalus membranaceus	persimmon			
E	MOL000953	Cholesterol	37.87	0.68	safflower	Tyrannosaurus spp			
F	MOL002714	baicalein	33.52	0.21	Paeonia lactiflora	safflower			
G	MOL002776	Baicalin	40.12	0.75	Paeonia lactiflora	safflower			
H	MOL000359	sitosterol	36.91	0.75	Paeonia lactiflora	persimmon			
I	MOL000449	Stigmasterol	43.83	0.76	Paeonia lactiflora	Angelica sinensis	safflower		
J	MOL000358	beta-sitosterol	36.91	0.75	Paeonia lactiflora	Angelica sinensis	safflower	peach kernel	
K	MOL000675	Oleic Acid	33.13	0.14	Paeonia lactiflora	persimmon	safflower	Tyrannosaurus spp	
L	MOL000069	Palmitic acid	19.3	0.1	Paeonia lactiflora	persimmon	safflower	Astragalus membranaceus	Tyrannosaurus spp
M	MOL000131	Linoleic Acid	41.9	0.14	Paeonia lactiflora	persimmon	safflower	Astragalus membranaceus	peach kernel	Tyrannosaurus spp

2.2. Screening of CHF-related genes and construction and analysis of compound-one-disease-one-intersection target network

A total of 2908 CHF-related genes were screened based on GeneCards, TTD, OMIM, Drugbank, and PharmGkb databases, as shown in Fig.1. the Decoction and a total of 404 targets were intersected with CHF, as shown in Fig. 2.Cytoscape 3.8.0 was utilized to construct a "compound-disease-intersection-target network" for the treatment of CHF with tonifying Yang Renwu Tang, as shown in Figure 3.The network contains 508 nodes and 2838 edges, involving 104 active ingredients and 404 potential targets.
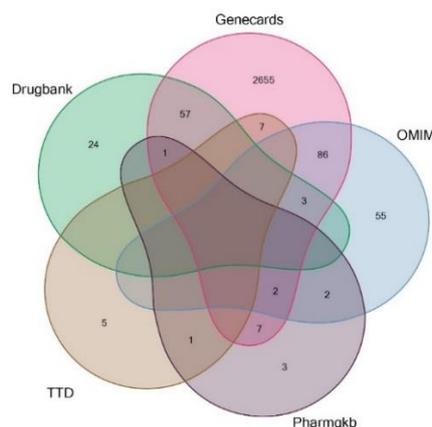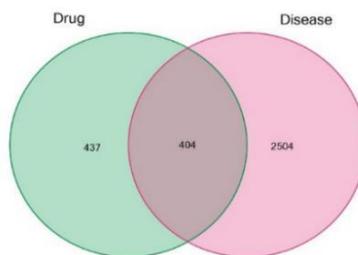
Fig.1 CHF related targets

Fig.2 Intersection targets of Buyang Huanwu Decoction and CHF

2.3. Construction and analysis of the intersection target protein interaction network

The highest confidence target protein PPI network for Buyang Huanwu Decoction treatment of CHF has a total of 288 nodes and 979 edges.After two filtrations, the target protein PPI core network was obtained, as shown in Fig. 4, with 28 nodes and 154 edges, i.e., a total of 28 targets in the network fulfilled the above cardinal value requirements, which can be used as the core targets for the treatment of CHF by the Decoction, as shown in Table3.

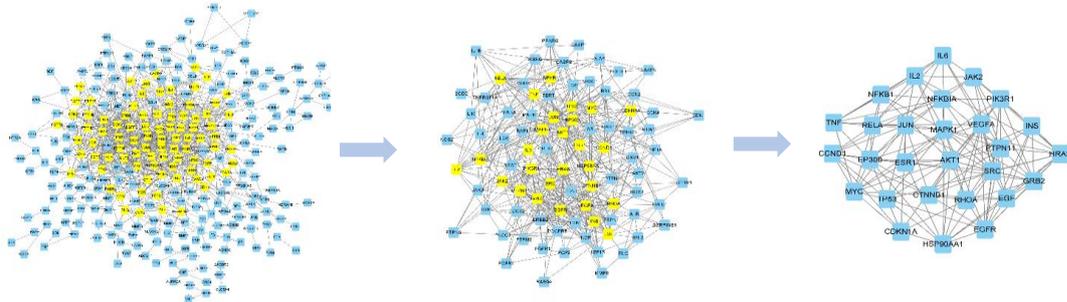Fig.3 Compound - disease - intersection target network diagram

Fig. 4 The core targets of Buyang Huanwu Decoction in the treatment of CHF

Tab. 3 The core targets of Buyang Huanwu Decoction in the treatment of CHF

NO.	target	Degree	NO.	target	Degree	
1	SRC	35	15	EGFR	23	
2	AKT1	34	16	HSP90AA1	22	
3	MAPK1	30	17	RELA	21	
4	JUN	28	18	JAK2	18	
5	EP300	26	19	IL6	17	
6	VEGFA	25	20	ESR1	17	
7	PIK3R1	25	21	NFKBIA	17	
8	TNF	24	22	RHOA	16	
9	GRB2	24	23	IL2	16	
10	CTNNB1	24	24	CCND1	15	
11	TP53	24	25	CDKN1A	15	
12	HRAS	23	26	MYC	14	
13	PTPN11	23	27	NFKB1	14	
14	EGF	23	28	INS	13	

2.4. Functional and pathway enrichment analysis of core targets

The GO biological enrichment results showed that there were 3964 GO entries, including 3520 biological processes (BP), 137 cellular components (CC) and 307 molecular functions (MF), of which the biological processes involved response to drug, response to lipopolysaccharide, response to molecule of bacte, response to lipopolysaccharide, response to molecule of bacterial origin, reactive oxygen species metabolic process, cellular response to oxidative stress, response to oxidative stress, peptidyl-tyrosine phosphorylation, and other factors. as shown in Figure 5.KEGG pathway enrichment analysis enriched a total of 191 pathways, as shown in Figure 6, including PI3K-Akt signaling pathway (hsa04151: PI3K-Akt signaling pathway), FoxO signaling pathway (hsa04068: FoxO signaling pathway), MAPK signaling pathway (hsa04010: MAPK signaling pathway), hypoxia-inducible factor-1 signaling pathway (hsa04066: HIF-1 signaling pathway), and tumor necrosis factor signaling pathway (hsa04668: TNF signaling pathway) are closely related to CHF, and can serve as an important pathway of Buyang Huanwu Decoction in the treatment of CHF.The PI3K-Akt signaling pathway (hsa04151: PI3K-Akt signaling pathway) was selected to

map the pathway, and 67 genes were seen to be involved in the regulation of the network, as shown in Figure 7.
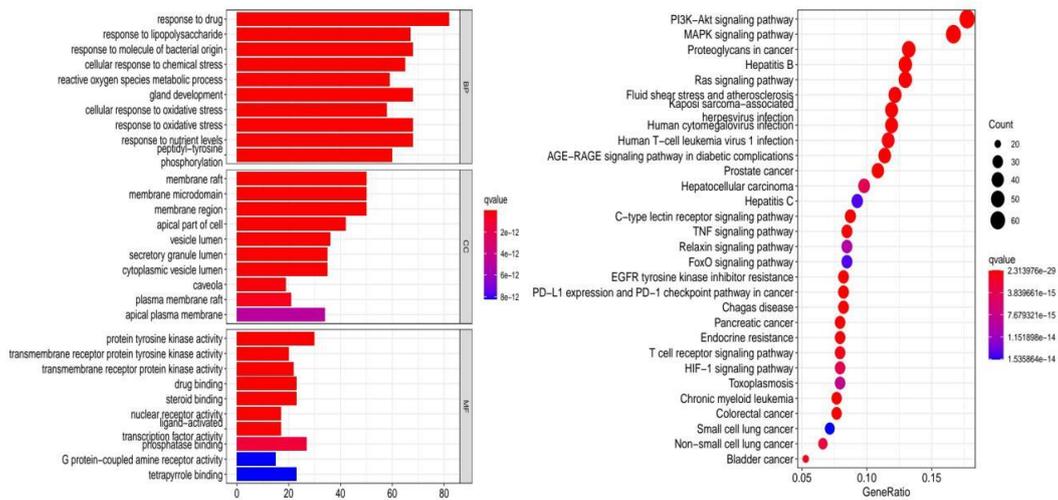

Fig.5 Histogram of GO biological enrichment results
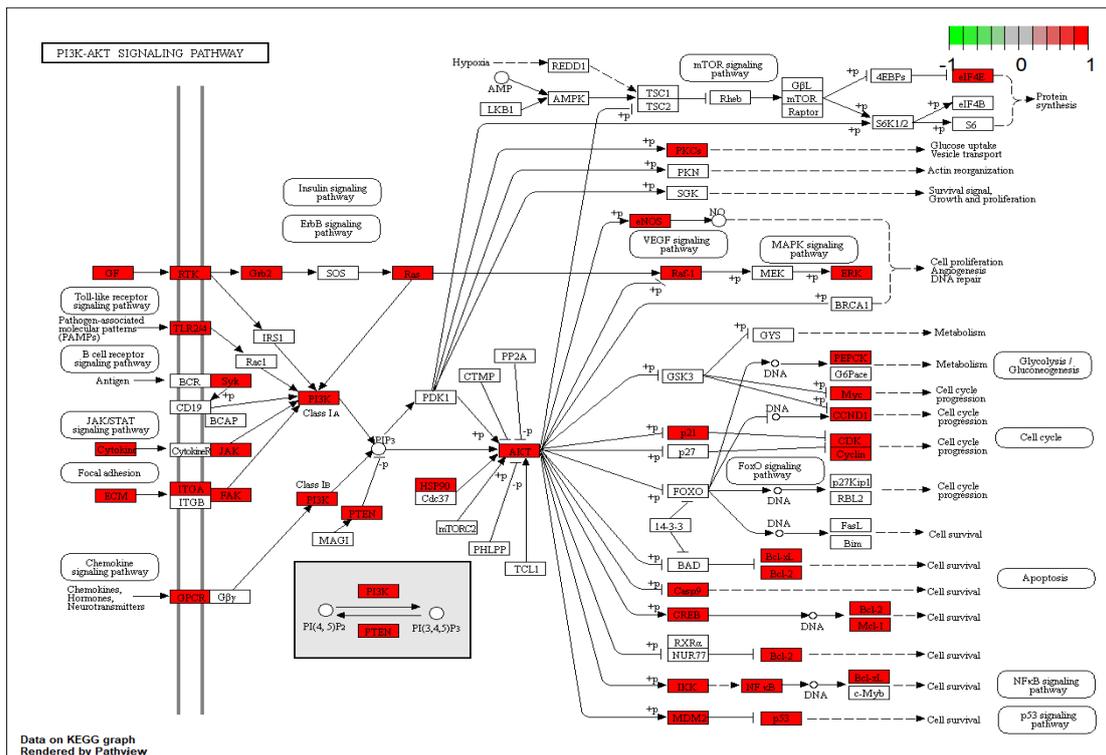

Fig.6 KEGG pathways enrichment analysis bubble diagram

Fig.7 PI3K-Akt signaling pathway

3. Discussion

3.1. Compositional analysis of Buyang Huanwu Decoction

As shown in the network diagram of "compound-disease-intersecting target", the active ingredients with more targets in the treatment of CHF in the Decoction include quercetin, paeoniflorin, baicalein, and lignocerotoxin.It is currently believed that activation of the RASS

system, sympathetic nerves, and the neuroendocrine system leads to the development of heart failure, and ventricular remodeling (VR) is the main pathological basis for it. myocardial tonus, hypertrophy, and fibrosis are the three main pathological changes.One of the main causes of deterioration and progression of HF is ventricular myofibrosis, and fibroblasts are the main cells that express collagen.An imbalance in the ratio of collagen I to collagen III expression triggers myocardial fibrotic changes and exacerbates ventricular remodeling in patients with HF.Quercetin, the active ingredient, can reduce collagen fibrillar protein deposition by down-regulating the expression of TGF-β1, Smad3, and p-Smad3 through the TGFβ1/Smad3 signaling pathway[10], and also activate the AKT/FOXO3 signaling pathway[11], reduce cardiomyocyte apoptosis, and thus inhibit ventricular remodeling.Zhang Huichao et al. showed that paeoniflorin effectively reversed the Ang-II-induced increase in cardiomyocyte apoptosis and the expression of cardiac hypertrophy markers ANP, BNP, and protected the myocardium by decreasing the level of Smad7 through miR-21 regulation [12].Paeoniflorin may also exert its protective effect on cardiomyocytes by inhibiting the production of ROS, reducing the release of mitochondrial cytochrome C, and down-regulating the expression and activity of Casapse-3 protein gene [13].Baicalein can inhibit myocardial fibrosis and delay myocardial aging by inhibiting p53-p21 Cip1/Waf1 signaling pathway[14] and TGF-β/Smads signaling pathway[15]. Liu Xin et al. showed that lignocaine could slow down the decrease of myocardial mitochondrial MMP, mitochondrial respiratory chain complex enzyme SDH and COX activity, inhibit the expression of mitochondrial apoptotic factors Bax, caspase3 and caspase9, improve mitochondrial respiratory function, and protect myocardial muscle by reversing the damage of mitochondrial DNA [16, 17].The above studies showed that most of the components had multiple effects and could mediate multiple signaling pathways to exert protective effects on the myocardium in order to improve ventricular remodeling, which also indicated that the Buyang Huanwu Decoction was synergistic with seven Chinese medicines to benefit qi, activate blood circulation and eliminate blood stasis.

3.2. Core target and pathway analysis

Through PPI and KEGG analysis, the top five core targets were SRC, AKT1, MAPK1, JUN, and EP300.Signaling pathways closely related to CHF include PI3K-Akt, FoxO, p38MAPK, HIF-1, TNF, etc.

Among these, the PI3K-Akt signaling pathway involves 67 target points, suggesting that the therapeutic effect of BuYang HuanWu Tang on CHF may primarily be achieved through this pathway. The PI3K-Akt (phosphoinositide-3-kinase/protein kinase B) signaling pathway can mediate the inhibition of cardiomyocytes by various degradative factors, such as the activation of the apoptotic factor Caspase-3 [18].PI3K is the primary regulatory factor in response to insulin action. Activation of the insulin/PI3K signaling pathway participates in various pathophysiological processes in cardiomyocytes, ranging from cardiac hypertrophic growth to increased cardiac contractility [19].Yin[20] et al. found that BuYang HuanWu Tang can inhibit TGF-β1-induced EMT and collagen accumulation in an in vitro PF model by suppressing the PI3K/Akt signaling pathway. It can not only inhibit the activation of PI3K, leading to downregulation of Akt, but also directly inhibit the activation of Akt, thus having potential anti-fibrotic effects. Multiple studies [21-23] have found that Bu Yang Huan Wu Tang can alter the levels of proteins characteristic of the PI3K-Akt signaling pathway, such as upregulating the expression levels of PI3K, p-Akt, and Bcl-2, and downregulating the level of Bax, thereby improving ischemic diseases.Class I PI3K can participate in the functional regulation of cardiomyocytes through IGF-1 signaling and calcium signaling [24]. The PI3K-Akt signaling pathway can also improve cardiomyocyte apoptosis and damage caused by hypertrophy [25-27].The FoxO family participates in the regulation of cellular

metabolic processes and is associated with various diseases such as diabetes and ischemia-reperfusion injury. PI3K/Akt can mediate the phosphorylation of Ser256 and Thr24 of the FoxO1 protein, causing nuclear exclusion, inhibiting the binding of transcription factors to DNA, and thereby achieving the effect of inhibiting cell apoptosis [28].

Additionally, the MAPK signaling pathway involves 63 target points. The MAPK (mitogen-activated protein kinase) family is one of the important signaling regulatory enzymes in the body. In mammals, the MAPK subfamilies primarily include ERK1/2, JNK, and p38. Their primary function is to mediate signal transduction between cell membrane receptors and the expression of target genes, participating in processes such as inflammatory responses and oxidative stress. Zheng et al. [29] found through in vitro experiments that BuYang HuanWu Tang can promote the differentiation of bone marrow mesenchymal stem cells into neuron-like cells by inhibiting the p38MAPK signaling pathway, thereby proving in vitro the regulatory effect of Bu Yang Huan Wu Tang on the p38MAPK signaling pathway.Chen[30] et al. also found that Bu Yang Huan Wu Tang can interfere with ERK signal transduction and inhibit vascular smooth muscle proliferation. Yu[31] et al. were the first to prove that BuYang HuanWu Tang has a protective effect against hypoxia/reoxygenation by upregulating the GLT-1/GS signaling pathway activated by p38MAPK in cultured astrocytes. Numerous studies have shown that p38MAPK can regulate cardiac remodeling and cardiac contractility [32], such as improving right ventricular function, inhibiting right ventricular fibrosis [33], and inhibiting myocardial infarction or ERS-induced myocardial cell apoptosis to prevent and treat post-infarction heart failure [34].HIF-1 (hypoxia-inducible factor-1) is a hypoxia-inducible factor that promotes angiogenesis, resists myocardial hypoxia, and improves myocardial metabolism. Under hypoxic conditions, it can protect the myocardium and is an important future treatment direction for heart failure [35].

Among the core targets, JUN (transcription factor AP-1) is a new transcription factor that can prevent cytoskeletal dysfunction, cardiomyocyte loss, and cardiac fibrosis, thereby inhibiting cardiac dilatation and failure [36].EP300 (histone acetyltransferase p300) controls cardiac development through chromatin remodeling mediated by histone acetylation and transcriptional regulation of genes required for cardiac development, including transcription factors, by increasing acetylation of specific lysines in histones and transcription factors, altering chromatin organization, increasing expression of hypertrophic and fibrotic genes, and accelerating cardiac aging under stress [37].

4. Conclusion

This study suggests that BuYang HuanWu Tang may act on multiple targets, including SRC, AKT1, MAPK1, JUN, and EP300, to regulate signaling pathways such as PI3K-Akt, FoxO, MAPK, HIF-1, and TNF. It may treat CHF by regulating mechanisms such as oxidative stress, inflammatory response, hypoxia, and cell apoptosis. Among these, SRC is the target with the highest degree value among the core targets, participating in signal transduction pathways that control various biological activities, including gene transcription, immune responses, cell adhesion, cell cycle progression, apoptosis, migration, and transformation. However, no studies have yet confirmed its association with CHF, which may provide insights for future research. This study provides guidance for further exploration of the mechanism of action of Bu Yang Huan Wu Tang on chronic heart failure. Since the results of this study are based on bioinformatics and extensive database calculations, further in vitro and in vivo studies are needed for validation.

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