Research on the Mechanism of Wuwei Yuganzi San in the Treatment of Coronary Heart Disease Based on Network Pharmacology

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Research

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Abstract

Background: Coronary heart disease (CHD) is a chronic cardiovascular disease across the world, which poses numerous threats to mankind. Wuwei Yuganzi San (WYS) is a famous traditional Tibetan medicine prescription. It has been confirmed effective in the treatment of CHD, but its specific mechanism remains still unclear.

Objective: To elucidate the main pharmacological action of WYS in treating CHD and investigate the underlying multiple mechanisms of its multi-ingredient-multi-target by network pharmacology.

Methods: Firstly, active ingredients of WYS and connected targets of five herbs were retrieved by using traditional Chinese medicine systems pharmacology (TCMSP) and screening literature. Then, genome explanation databases (OMIM and GeneCards) were used to acquire targets related to CHD. The protein-protein interaction (PPI) network was built using the mutual targets filtering genes through protein interaction. Next, a network diagram could be established with the help of Cytoscape 3.8.2. And, STRING platform was used to construct a protein interaction network. Finally, GO and KEGG analyses were analyzed to further elucidate biological process enrichment.

Results: After the screening, 36 active ingredients and 202 related targets in WYS in addition to 952 disease-related targets were acquired. A total of 37 key targets including AKT1, ESR1, and EGFR were screened in the PPI network. These targets were mostly concentrated on the transmembrane receptor protein tyrosine kinase signaling pathway, cellular response to growth factors stimulus, and response to growth factor. The KEGG enrichment demonstrated that the MAPK signaling pathway, P13K/AKT signaling pathway, Ras signaling pathway, and other corresponding signaling pathways were closely related to CHD.

Conclusions. WYS plays a significant role in the treatment of CHD. And this study provides a novel approach to disclose the therapeutic mechanisms of WYS on CHD.

Introduction

Over recent years, as a leading cause of death in the world, Coronary heart disease (CHD) remains one of the most epidemic health issues with a significant mortality and morbidity rate all over the world, which is caused by insufficiency in blood flow to cardiomyocyte because of coronary artery stenosis or myocardial infarction [1–2]. Consequently, percutaneous coronary intervention and drug therapy are very significant. Otherwise, major adverse cardiovascular events will happen. Nitrates, beta-blockers, and calcium antagonists are both used for the intervention of anti-anginal agents [1]. As CHD has an intricate process, these drugs can not treat complicated pathology well. However, traditional Tibetan medicine (TTM) has distinctive curative efficacy on cardiovascular diseases during clinical practice, mostly because of its multi-targeted functions [3].

Wuwei Yuganzi San (WYS) comes from MaDiYiZhuXuanJi, a well-known book in TTM, and is widely used in the treatment of CHD for a thousand years [4]. WYS consists of Yuganzi (*Phyllanthus Emblica* L. *YGZ*), Zangjinjier (*Caragana Jubata, ZJJE*), Saibeizijin (*Corydalis Impatiens, SBZJ*), Dahuang (*Rheum Palmatum* L, *DH*), and Ganjiang (*Zingiberis Rhizoma, GJ*). Our research has demonstrated that WYS has significant effects in protecting cardiomyocytes from myocardial ischemia-reperfusion injury [5]. However, the underlying molecular mechanisms of WYS in the therapy of CHD are still not well understood, which has become an obstacle to its research and development.

The network pharmacology provides a novel method for revealing the effect mechanism of TTM prescriptions, which is a significant part of systematic biology. And it also emphasizes the function of multi-ingredient-multi-target-multi-pathway in deep sight [6]. Consequently, network pharmacology strategies are performed to explore the mechanisms of WYS in the treatment of CHD. The purpose of this study is to provide a convincing scientific basis for WYS to treat CHD. Screening active ingredients in WYS and underlying targets in the treatment for CHD to construct a comprehensive network of multi-ingredient-multi-target-multi-pathway is an important method. What is more, KEGG and GO analysis also play a key role in analyzing this study. The flowchart of this study is shown in Fig. 1.

Materials And Methods

Active ingredients in WYS collection and screening.

Firstly, traditional Chinese medicine systems pharmacology (TCMSP: https://sm.nwsuaf.edu.cn/lsp/tcmsp.php.) and literature were used to collect the main active ingredients in the prescription of WYS [7]. Then, the main active chemical components of WYS were selected by absorption, distribution, metabolism, and excretion (ADME) [7]. Another part of the active ingredients was screened by SwissADME [8]. And oral bioavailability (OB) value was set as greater than or equal to 30%. Drug-likeness (DL) index was set as greater than or equal to 0.18 [7]. All components were confirmed by the PubChem database platform (http://pubchem.ncbi.nih.gov) [9]. Then, TCMSP and literature were used to acquire the effective chemical components in WYS. Both PharmMapper (http://www.lilab-ecust.cn/pharmmapper/) [10-12] and Swiss Target Prediction (http://www.swisstargetprediction.ch/index.php) were used to obtain the therapeutic target of active ingredients.

Identification of underlying targets for CHD

OMIM (http://omim.org/) [13] and GeneCards (http://www.gengcards.org/) [14] online websites were used to acquire CHD-related genes. All genes were retrieved and confirmed by the Uniprot database.

Construction of multi-ingredient-multi-target network

Cytoscape software 3.8.2 was used to construct a multi-ingredient-multi-target network to acquire the relationship between the active ingredients and underlying targets [15].

Construction of PPI Network Construction.

The related targets of WYS in the intervention of CHD were input into STRING (http://string-db.org/) online platform [16]. Firstly, “multiple proteins” were selected. Then, the mutual target genes of WYS and CHD were input into the blank, and the organism was set as Homo sapien. Finally, the interaction score was set as 0.7, and the PPI network was constructed.

Go and KEGG Analysis of Core Genes.

To further investigate the mechanism of WYS in the treatment of CHD. Go and KEGG analysis of potential targets were analyzed by Metascape (https://metascape.org/gp/index.html) [17]. THE Metascape online platform was used to elucidate the biological processes, molecular function, cellular components, and signaling pathways in the treatment of CHD.

Construction of drugs-targets-pathways-disease network

Cytoscape software 3.8.2 was used to construct a drugs-targets-pathways-disease network to elucidate specific mechanisms and targets of the function of WYS.

Results

Retrieving Results of Effective Ingredients of WYS

92 ingredients for YGZ, 92 ingredients for DH, and 148 ingredients for GJ were obtained from TCMSP online platform. 31 ingredients for SBZJ and 33 ingredients for ZJJE were acquired from the literature [18-22]. When ADME was set as OB≥ 30% and DL ≥ 0.18 in TCMSP online platform, the probability ≥ 0.88 in Swiss Target Prediction online platform, and the norm fit ≥ 0.88 in PharmMapper online platform, 13 ingredients and 370 targets for YGZ, 12 ingredients, and 353 targets for DH, 1 ingredient and 1 target for GJ, 1 ingredient and 2 targets for SBZJ, 9 ingredients and 34 targets for ZJJR. Finally, 36 active ingredients and 202 related targets in WYS (Table. 1). There are 37 core genes between WYS and CHD (Table. 2).

Table 1 36 active ingredients in WYS

No.	Mol ID/Pubchem Cid	Molecule Name	Degree	Herb
1	MOL000098	quercetin	69	YGZ
2	MOL001002	ellagic acid	45	YGZ
3	MOL006802	phyllaemblicin A	42	YGZ
4	MOL006793	mucic acid 1,4-lactone 2-0-gallate	40	YGZ
5	MOL000006	luteolin	36	YGZ
6	MOL006801	phyllaemblicacid methyl ester	36	YGZ
7	MOL006796	mucic acid 1,4-lactone 5-0-gallate	32	YGZ
8	MOL006806	Phyllanemblinin A	28	YGZ
9	MOL000422	kaempferol	18	YGZ
10	MOL000492	(+)-catechin	16	YGZ
11	MOL006821	(-)-epigallocatechin-3-gallate	16	YGZ
12	MOL000569	digallate	3	YGZ
13	MOL000358	beta-sitosterol	2	YGZ
14	MOL002293	Sennoside D_qt	85	DH
15	MOL002260	Procyanidin B-5,3'-O-gallate	65	DH
16	MOL002280	Torachrysone-8-O-beta-D-(6'-oxayl)-glucoside	38	DH
17	MOL000554	gallic acid-3-O-(6'-O-galloyl)-glucoside	38	DH
18	MOL002251	Mutatochrome	34	DH
19	MOL002276	Sennoside E_qt	33	DH
20	MOL002303	palmidin A	25	DH
21	MOL000096	(-)-catechin	16	DH
22	MOL002297	Daucosterol_qt	16	DH
23	MOL000471	aloe-emodin	10	DH
24	MOL002288	Emodin-1-O-beta-D-glucopyranoside	2	DH
25	MOL002293	Sennoside D_qt	2	DH
26	MOL000358	beta-sitosterol	2	GJ
27	439654	scoulerine	3	SBZJ
28	5281377	4',5, 7-Trihydroxyisoflavone	15	ZJJE
29	5281708	Daidzein	7	ZJJE
30	5280373	Biochanin A	7	ZJJE
31	8400	benzoin	3	ZJJE
32	10251	Flavanone	3	ZJJE
33	5280378	Formononetin	2	ZJJE

34	114829	Liquiritigenin	2	ZJJE
35	5281804	Prunetin	2	ZJJE
36	638278	isoliquiritigenin	2	ZJJE

Table 2 37 core genes between WYS and CHD

UniProt ID	Gene Symbol	Degree	UniProt ID	Gene Symbol	Degree	UniProt ID	Gene Symbol	Degree
P10636	MAPT	1	P00533	EGFR	3	P02652	APOA2	6
P05067	APP	2	P12931	SRC	2	P11310	ACADM	8
O14746	TERT	1	P35968	KDR	2	P00734	F2	1
P08253	MMP2	3	Q02763	TEK	1	P05164	MPO	1
P08183	ABCB1	3	P15056	BRAF	1	P45452	MMP13	1
P42224	STAT1	1	P47989	XDH	3	P08254	MMP3	1
P78536	ADAM17	17	P09917	ALOX5	1	P00519	ABL1	8
P31749	AKT1	14	P02766	TTR	1	P42574	CASP3	2
P10275	AR	12	P14780	MMP9	2	P04040	CAT	2
P04626	ERBB2	1	P12821	ACE	7	P03372	ESR1	3
P35916	FLT4	1	P00326	ADH1C	13	P60568	IL2	1
P06213	INSR	1	P02768	ALB	14	P28223	HTR2A	1
P12643	BMP2	1						

Potential Therapeutic Targets in CHD

Firstly, genes were retrieved from GeneCards, and the Inferred Functionality Score ≥30.34 was selected in GeneCards, which filtered genes in this database. 445 known therapeutic targets for CHD were acquired from the GeneCards database. Secondly, 548 known therapeutic targets for CHD were acquired from the OMIM database. In total, there were 951 therapeutic targets from CHD Finally, the target identification was performed by the Venny2.1.0 online system. And the results are displayed in Fig. 2.

Multi-ingredient-multi-target Interaction Network

36 ingredients of WYS and 202 interactive genes were connected to construct a complex PPI network using that included 243 nodes and 795 edges (Fig. 3).

PPI Network Diagram Construction

At the beginning, the 37 intersection targets of WYS in the treatment of CHD were input into the STRING database. And a protein interaction network diagram was acquired, with 37 nodes, 93 edges, and an average node degree of 5.03 (Fig. 4).

Results of Go Enrichment Analysis

Metascape online platform was used to perform KEGG analysis and GO analysis. There are three parts in GO enrichment analysis, including biological process, cellular component, and molecular function (Fig. 5).

From the results of biological process, it was significantly related to transmembrane receptor protein tyrosine kinase signaling pathway (GO: 0007169), cellular response to growth factor stimulus (GO: 0071363), and response to growth factor (GO: 0070848).

From the results of cellular component, it was closely correlated to membrane raft (GO: 0045121), membrane microdomain (GO: 0098857), and membrane region (GO: 0098589).

From the results of molecular function, it was closely correlated to protein kinase activity (GO: 0004672), phosphotransferase activity, alcohol group as acceptor (GO: 0016773), and kinase activity (GO: 0016301).

Results of KEGG Enrichment Analysis

The result demonstrated how WYS acts on the pathway. Thus, based on 37 core target genes, 20 key signaling pathways were acquired for analysis deeply, including MAPK signaling pathway(hsa04010), PI3K-Akt signaling pathway(hsa04151), Endocrine resistance(hsa01522), and Ras signaling pathway(hsa04014) (Fig. 6).

Drugs-targets- pathways-disease network

The Drugs-targets- pathways-disease network was shown in Fig. 7, which included 3 drugs, 22 core targets, 20 signaling pathways, 144 nodes. The light blue circle node is WYS; red node is CHD; green octagon node is significant signaling pathway; dark triangle node is core targets; purple diamond node is the drug, including YGZ, DH, and ZJJE. This network analysis demonstrated the characteristics of multiple drugs and multiple targets of WYS in the treatment of CHD.

Discussion

The definitions of “syndrome” and “disease” have been known in TTM. The recognition of the disease is based on the comprehensive condition of the disease. Consequently, the underlying occurrence and development of disease are known from a macro perspective. There is a comprehensive comprehension of the etiology, pathogenesis, and drug selection in the development of CHD [23]. However, the underlying mechanisms and pathways of TTM remain unclear. Recently, network pharmacology has been an optimized method to explore the “drug-component-target” of TTM or traditional Chinese medicine. In this study, our results showed that WYS has the effect of preventing CHD by regulating multi-ingredient-multi-targets with multi-pathways.

WYS consists of 5 herbs, including Yuganzi (*Phyllanthus Emblica* L. *YGZ*), Zangjinjier (*Caragana Jubata, ZJJE*), Saibeizijin (*Corydalis Impatiens, SBZJ*), Dahuang (*Rheum Palmatum* L*, DH*), and Ganjiang (*Zingiberis Rhizoma, GJ*). In this study, using the TCMSP and PubChem database at first, 36 active components and 202 drug targets were testified in WYS by OB and DL. Then, a multiple network diagram was constructed, including a multi-ingredient-multi-target interaction network, a PPI network diagram, and a drug-targets-pathways-disease network. Finally, GO and KEGG enrichment analyses were performed to explain the underlying mechanisms.

To date, many studies had found that YGZ and its extract could protect RAW264.7 cell from H_2O_2-induced toxicity, reduce high cholesterol and narrow the area of atherosclerotic plaque, and inhibits the expression of ET-1 gene [24-26]. And it also exerted anti-inflammatory effects by reducing the expression of NO and pro-inflammatory cytokines [27]. Moreover, it could protect β cells, scavenge free radicals, reduce inflammation and reduce advanced glycation end-products [28]. DH could reduce oxidative stress by regulating blood lipid metabolism and improving antioxidant capacity, thereby regulating mitochondrial apoptosis. Besides, DH could also regulate Fas/FasL-mediated apoptosis and inhibit the signal transduction pathway of β cell apoptosis [29]. The thesis showed that network pharmacology and metabolomics methods were carried out and found that Aconiti Lateralis Radix Praeparata combined with Zingiberis Rhizoma could treat chronic heart failure through mitochondria-mediated energy metabolism [30-31]. PPARα/PGC-1α/Sirt3 signal pathway played a significant role in the treatment of chronic heart failure [32]. There was an exerting anti-inflammatory effect, which SBZJ could inhibit the production of TNF-α, IL-6, and NO by down-regulating the activation of NF-κB, the phosphorylation of ERK1/2, and MAPK signaling pathway [33]. ZJJE had the effects of inhibiting TNF-α, scavenging free radicals, inhibiting lipid peroxidation, and having anti-thrombosis effects to achieve cardioprotection [34-36].

Above all, WYS had been used to be a typical and effective prescription for CHD for a long time. And our research team found that WYS had a protective effect on myocardial ischemia-reperfusion injury in rats. The mechanism might reduce serum LDH and CK levels, increase the activity of SOD and GSH-Px in myocardial tissue, and reduce MDA. It promoted the expression of Bcl-2 protein, increased Bcl-2/Bax, and inhibited the expression of Bax protein [4-5].

Analysis of active ingredients

In the network of multi-ingredient-multi-target, key ingredients with a higher degree contain quercetin, sennoside D_qt, procyanidin B-5,3'-O-gallate, ellagic acid, and phyllaemblicin A. Among them, quercetin is a flavonoid ingredient and exists widely in nature. Research showed that quercetin modulated AMPK/SIRT1/NF-κB signaling pathway [37] or JAK2/STAT3 pathway[38] to inhibit cell apoptosis and oxidative stress, reduce myocardial infarction size, improve ventricular remodeling and cardiac function-related biochemical indexes, and promote the recovery of cardiac blood flow. And a double-blind, placebo-controlled, randomized clinical trial demonstrated significantly elevated total antioxidant capacity [39]. Both two studies provided evidence for WYS treating CHD successfully.

Analysis of potential targets

The highest degree of the target was ADAM17. And the following targets were AKT1, ALB, ADH1C, AR in the network of multi-ingredient-multi-target. ADAM17, tumor necrosis factor-alpha converting enzyme, played a key role in cardiovascular. Increased shedding of ADAMs could induce various cardiovascular diseases, which are closely related to inflammation, tissue remodeling, and dysfunction. ADAMs may be promising therapeutic targets for hypertension and atherosclerosis [40].

GO analysis and KEGG analysis

Metascape online platform was used to perform KEGG analysis and GO analysis. From the results of GO analysis, the potential targets were enriched, which were connected with membrane raft(GO: 0045121), membrane microdomain(GO: 0098857), and membrane region (GO: 0098589) in biological process. Furthermore, from the results of KEGG analysis, 14 signaling pathways related to CHD as significant pathways from the 20 pathways of KEGG analysis were divided into three aspects: oxidative stress, metabolism, and immunity. As shown in Fig. 7: multi-targets and multi-pathways played a key role in the treatment of CHD. The pathways linked to oxidative stress contain MAPK signaling pathway, HIF-1 signaling pathway, Foxo signaling pathway, JAK/STAT signaling pathway, VEGF signaling pathway, Platelet activation. According to previous studies, CHD is a disease with complex mechanisms. When ischemia, blood oxygenation, and abnormal energy metabolism occurred, cardiomyocytes will deform or even die, which resulted in CHD. Metabolism included PI3K-Akt signaling pathway, Fluid shear stress and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, mTOR signaling pathway, Ras signaling pathway, Insulin resistance, Calcium signaling pathway. Abnormal changes in fluid shear stress [41], calcium [42], and insulin resistance [43] might be more likely to develop into CHD. Both PI3K-Akt signaling pathway and mTOR signaling pathway were involved in autophagy, which played a significant role in myocardial ischemia-reperfusion injury [44]. Immunity included Chemokine signaling pathway. Chemokines recruited inflammatory cells to the injured vascular endothelium and released inflammatory cytokines. Finally, the development of CHD is accelerating [45].

Conclusion

The mechanism of action of WYS in the treatment of CHD may be associated with multiple ingredients, targets, and signaling pathways. High-quality clinical research and basic research are needed to confirm these results.

Abbreviations

CHD: Chronic heart disease; WYS, Wuwei Yuganzi San; TCMSP: Traditional Chinese Medicine Systems Pharmacology; DL: Drug-likeness; OB: Oral bioavailability; GO: Gene ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes

Declarations

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Authors' Contributions

Qunhui Zhang, Yimei Li, and Dejun Zhang were involved in the study design and performed the experiments. The data were analyzed by Yang Guo, Qiqin Lu, Guoying Zhang, Jing Ma. Qunhui Zhang and Dejun Zhang reviewed this manuscript. Qunhui Zhang makes great contributions to this work and should be considered the first author. Dejun Zhang should be considered the corresponding author.

Availability of data and materials

All data are available in the manuscript and they are exhibited in figures and tables.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Authors have no conflict of interest.

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Figures

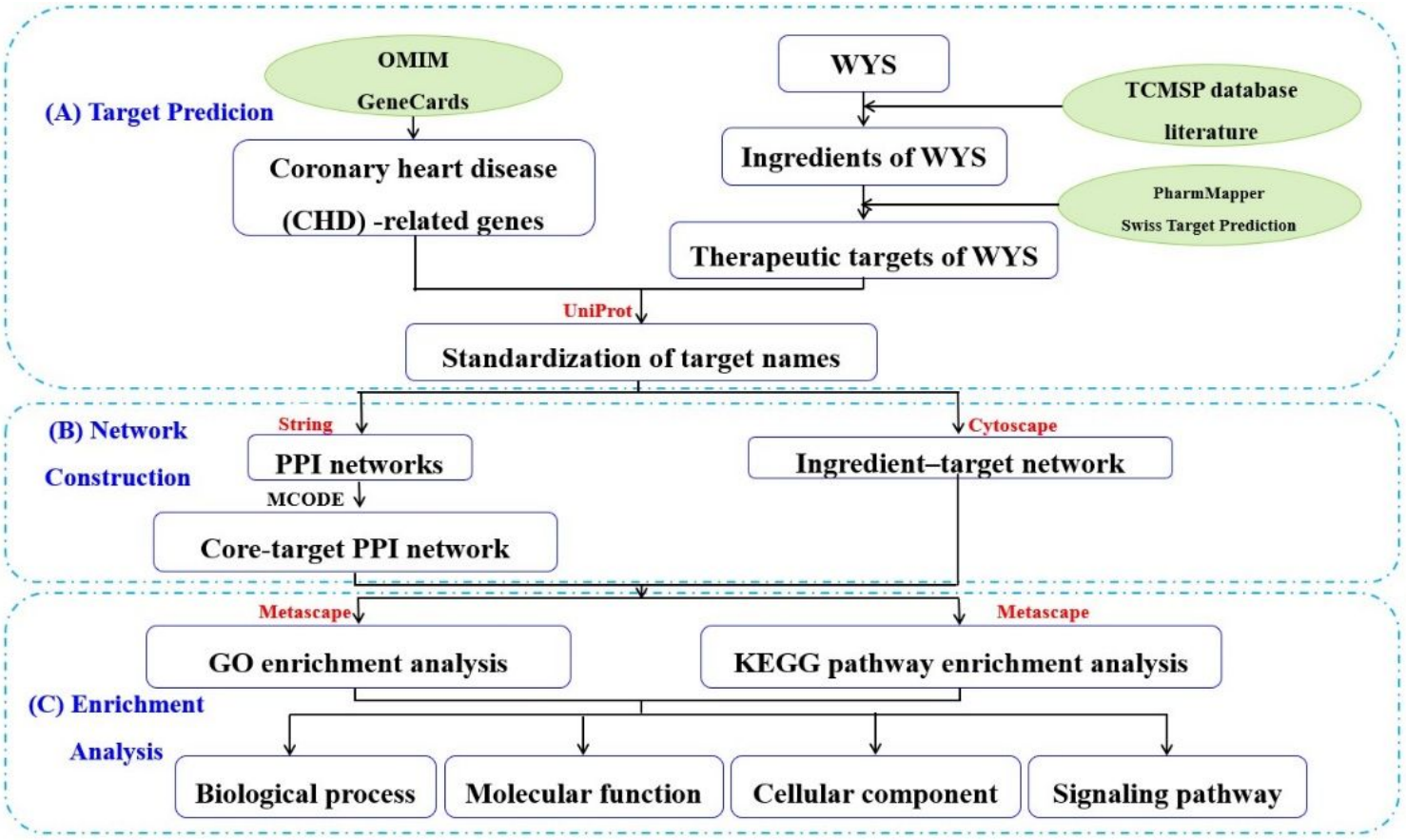

Figure 1

The flowchart of the network pharmacology for elucidating the mechanisms of WYS in CHD
Abbreviations: WYS: Wuwei Yuganzi San; TCMSP: Traditional Chinese Medicine Systems Pharmacology; OMIM: Online Mendelian Inheritance in Man; PPI: protein-protein interaction.

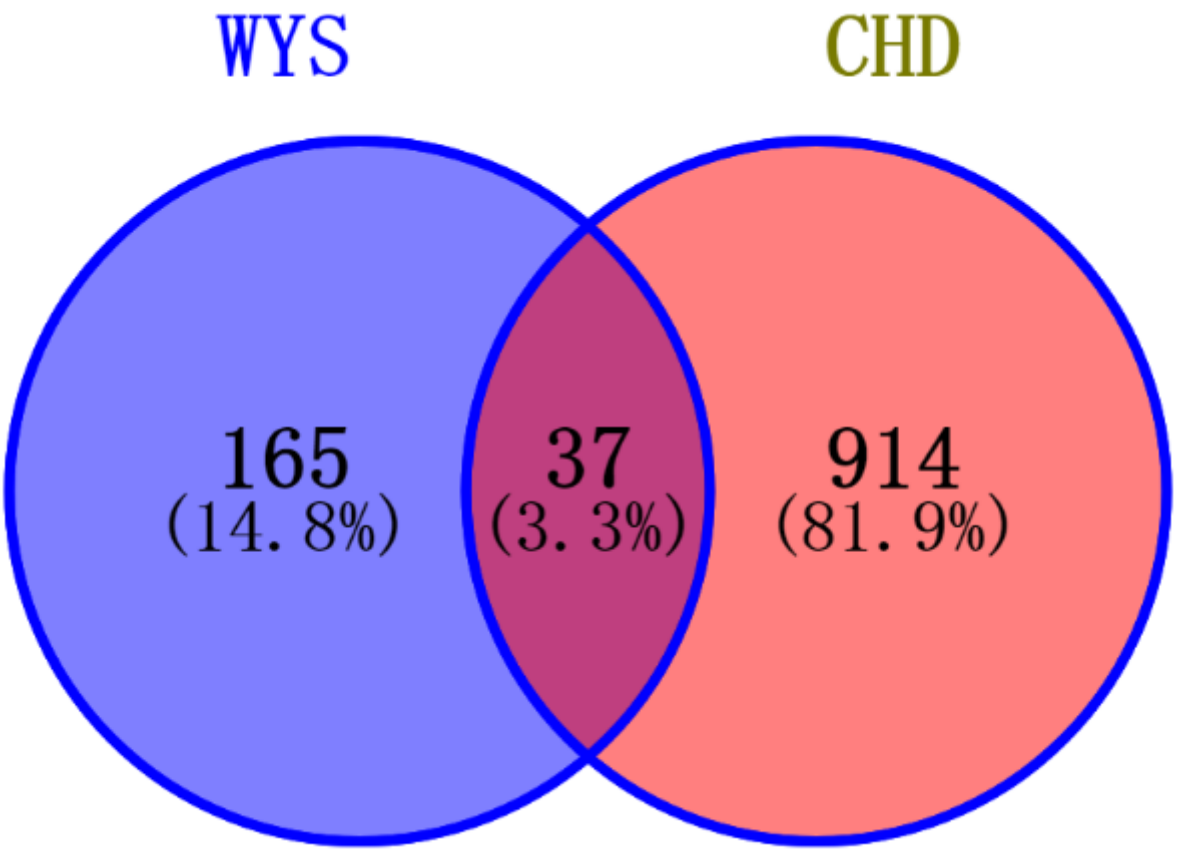

Figure 2

The potential therapeutic of Venn diagram of WYS in the treatment of CHD

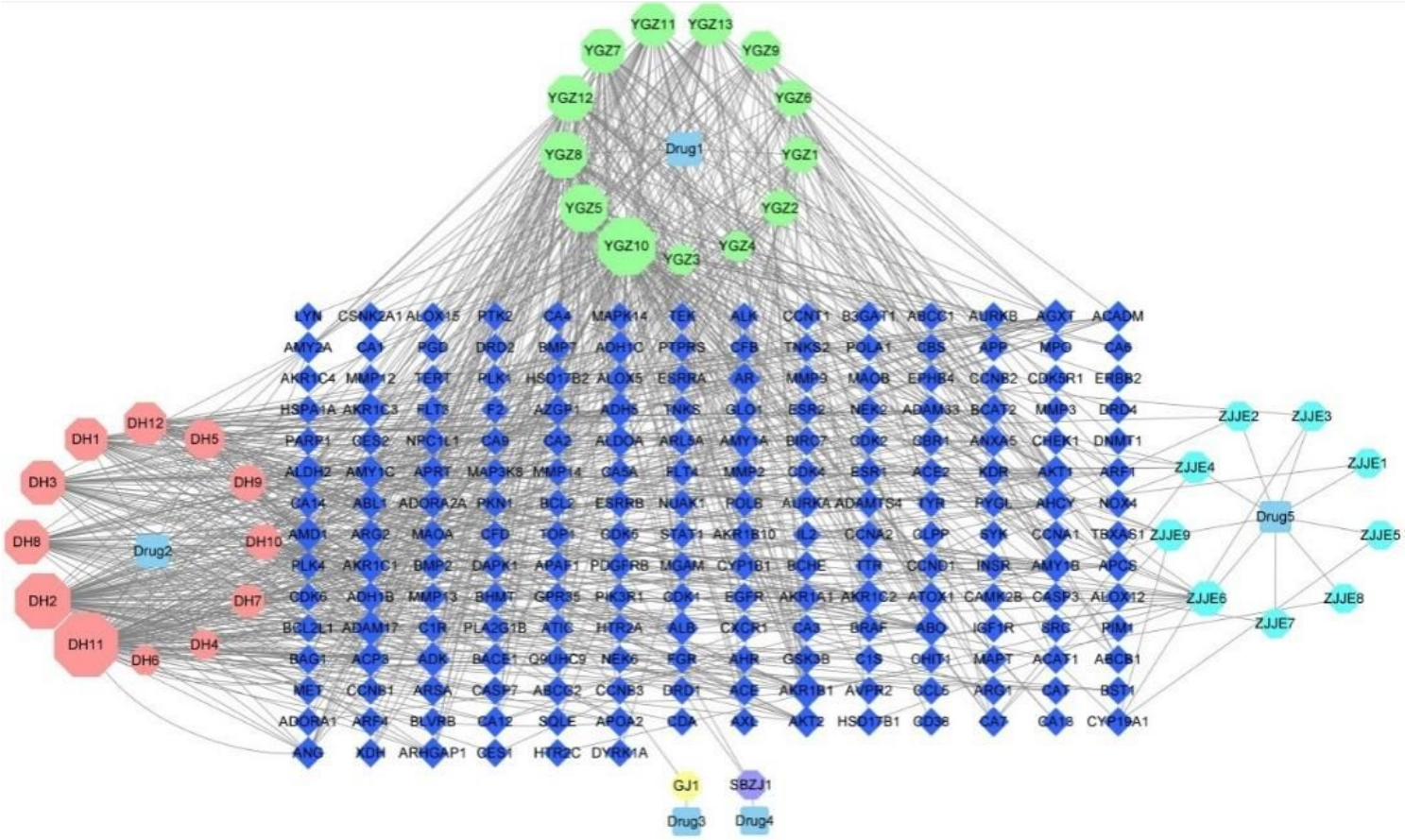

Figure 3

PPI by Cytospace

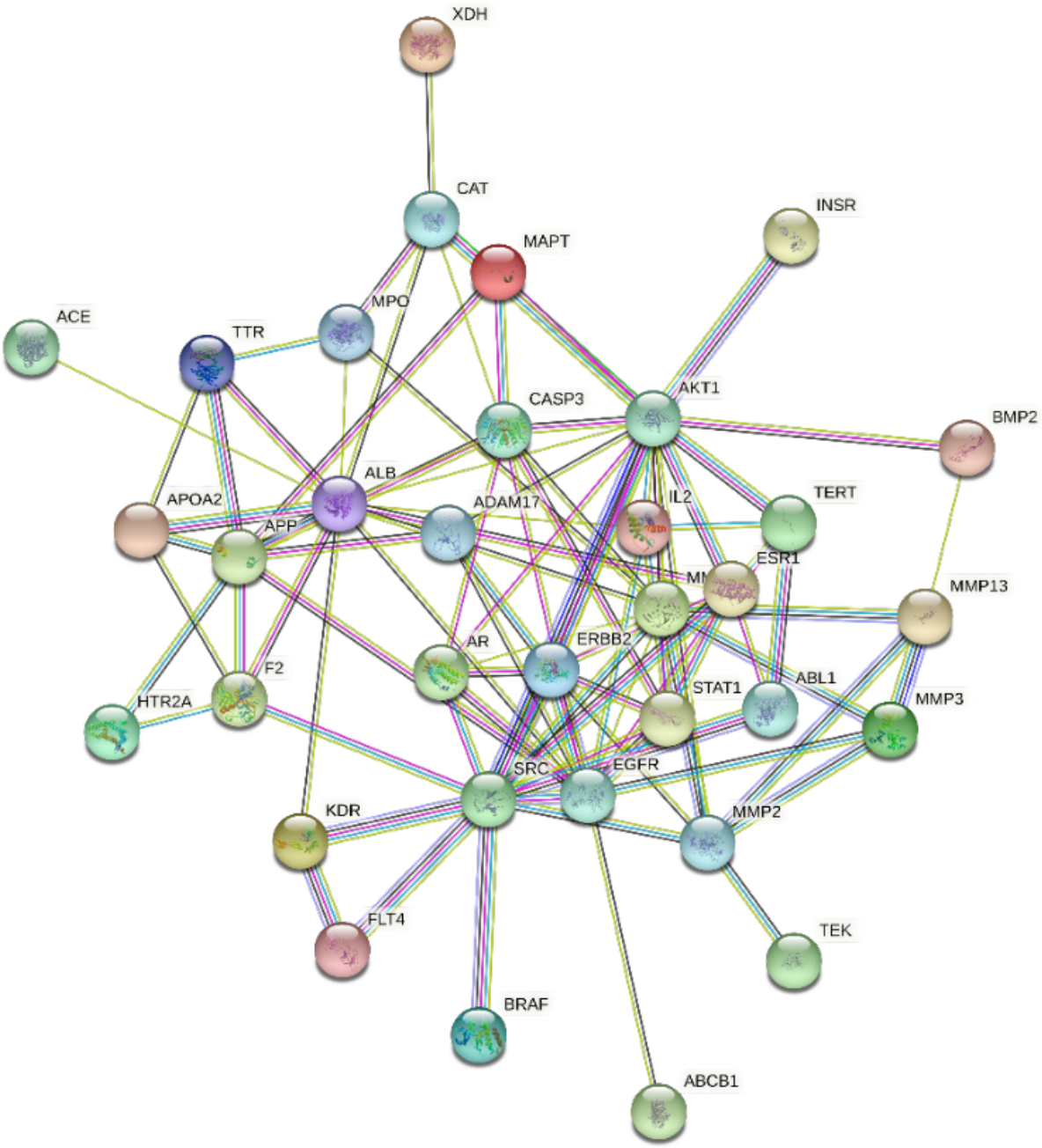

Figure 4

PPI by STRING

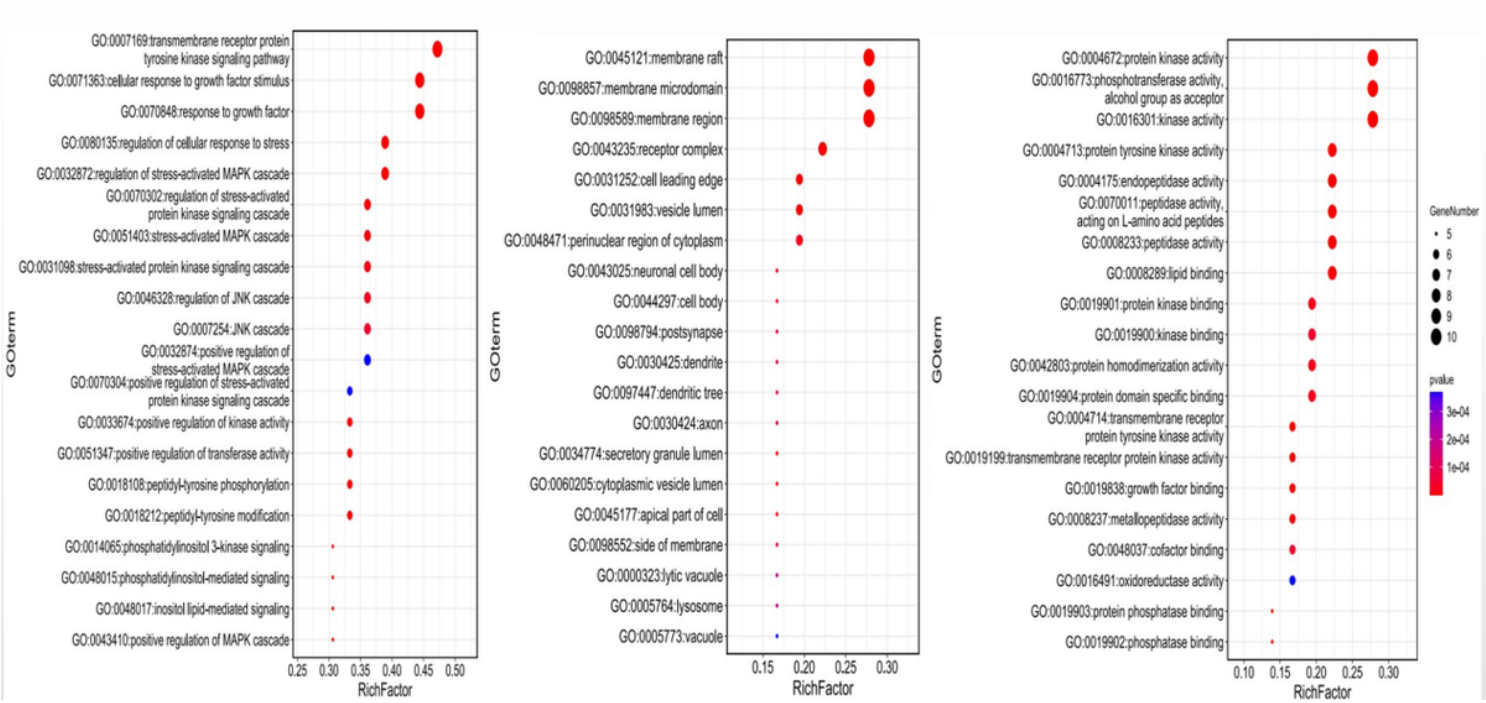

Figure 5

GO analysis results of WYS in the treatment of CHD

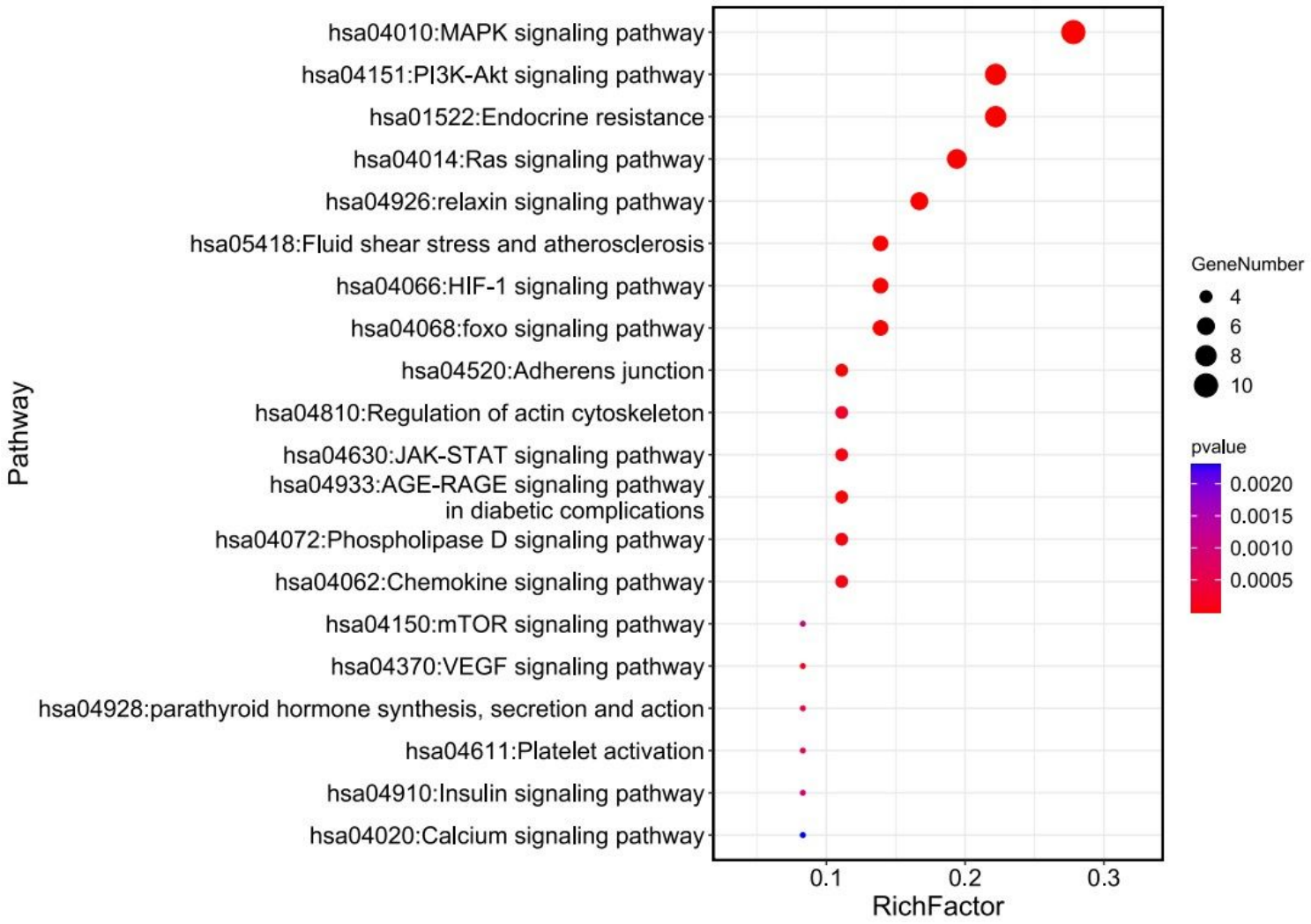

Figure 6

KEGG analysis results in the treatment of CHD

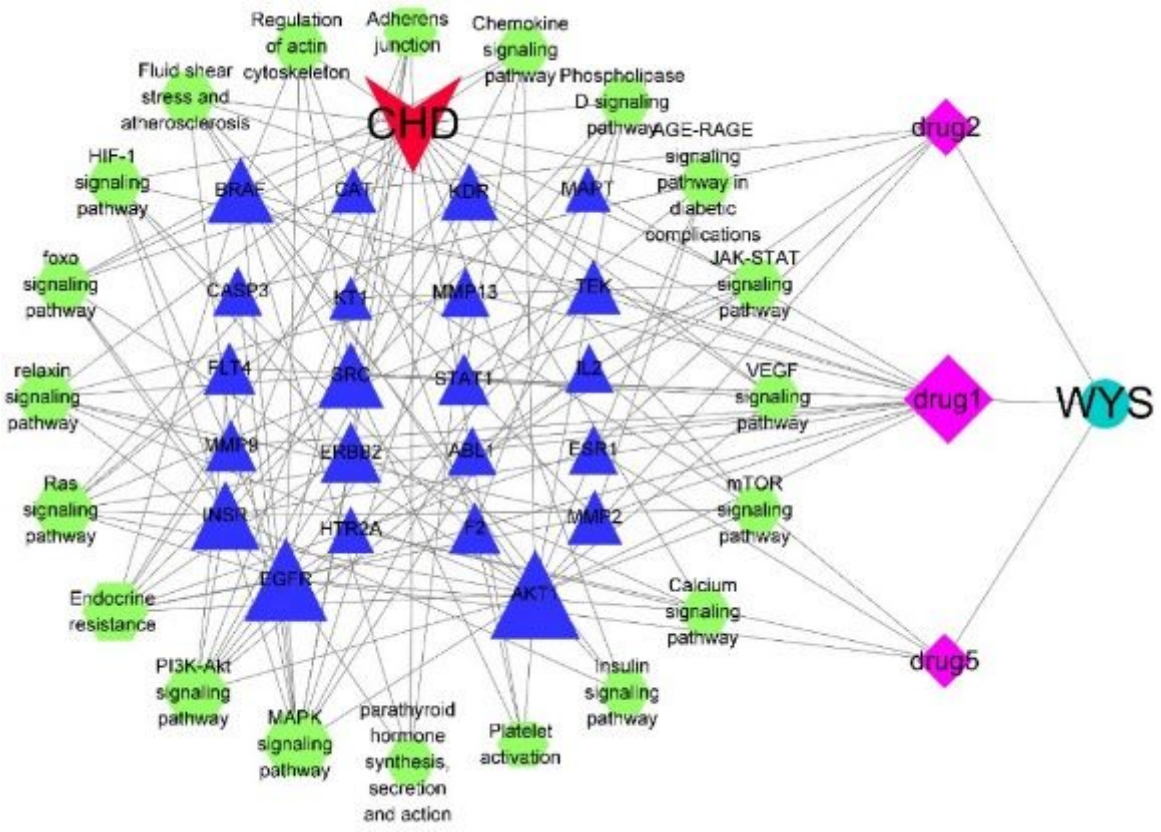

Figure 7

The drugs-targets-pathways-disease network