

Exploring the mechanism of Fu-Zi Decoction in treatment of chronic heart failure based on network pharmacology and molecular docking technology

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Abstract: In the present study, we aimed to explore the mechanism of Fu-Zi Decoction in the treatment of chronic heart failure (CHF) using network pharmacology. SymMap database was used to analyze the modern medical (MM) symptoms of various medicines. The chemical components of Fu-Zi Decoction were obtained through TCMSP, ETCM database, and previous results. The targets of Fu-Zi Decoction were obtained through STITCH, SwissTargetPrediction, TargetNET database, and literature. The targets for the treatment of CHF were obtained from the DisGeNET, GEO, and DrugBank databases, and the common parts of the Fu-Zi Decoction targets were screened out to construct the PPI network. The PPI network was decomposed modularly, its functions were analyzed, and the KEGG pathway enrichment analysis was performed. The key target was verified by SwissDock for molecular docking. A total of 205 chemical components of Fu-Zi Decoction, 551 drug targets, and 521 disease targets were collected. Functional enrichment analysis revealed that it was mainly involved in biological processes, such as negative regulation of cell death, oxidative stress, and G protein-coupled receptor regulation. KEGG enrichment findings mainly involved fluid shear stress and atherosclerosis, IL-17 signaling pathway, and so on. The results of molecular docking showed that benzoylaconitine, aconitine, mesaconitine, paeoniflorin, and atractylodes III all had a strong affinity with the core target CXCL8, suggesting that Fu-Zi Decoction could negatively regulate cell apoptosis and oxidative stress through fluid shear stress and atherosclerosis, IL-17 signaling pathway, and so on. Collectively, our data showed that Fu-Zi Decoction had a good effect on the treatment of CHF.

Keywords: Fu-Zi Decoction; Chronic heart failure; Network pharmacology; Molecular docking

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1. Introduction

Chronic heart failure (CHF) is a complex clinical syndrome, which is the end stage of all sorts of serious heart diseases, threatening human health seriously. For a long time, the primary drug treatments of CHF are diuretic, cardiotonic, angiotensin-converting enzyme inhibitors (ACE-I), and beta-blockers. However, these drugs are usually restricted due to a large number of taboos and adverse reactions in clinical application.

At present, CHF patients still have a poor prognosis and a high mortality rate^[1].

Traditional Chinese medicine (TCM) has a long history and a unique advantage in the treatment of cardiovascular diseases. Therefore, TCM has been widely used as an auxiliary therapy in combination with western medicine^[2]. CHF belongs to the categories of Chinese medicine “wheezing syndrome”, “edema”, “phlegm drinking”, “palpitation” and other disease categories. Derived from Treatise on Febrile Disease by Zhang Zhongjing, Fu-Zi Decoction is composed of five TCMS, including Fu Zi (*Aconitum carmichaelii* Debx.), Ren Shen (*Panax ginseng* C. A. Mey.), Fu Ling (*Poria cocos* (Schw.) Wolf), Bai Zhu (*Atractylodes macrocephala* Koidz.), and Bai Shao (*Paeonia lactiflora* Pall.). It is a representative prescription for warming

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the meridians to return Yang and strengthening and dehumidifying the spleen. Modern pharmacological studies have shown that Fu-Zi Decoction has an obvious protective effect on the myocardium of rats^[3], and clinical efficacy has shown that Fu-Zi Decoction has an excellent effect on CHF^[4].

Network pharmacology plays a special role in revealing the mechanism of action of multi-component and multi-target Chinese herbal compounds. In the present study, we aimed to use network pharmacology methods to study the potential material basis and targets of Fu-Zi Decoction in the treatment of CHF. Meanwhile, gene ontology (GO) function analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were combined to explore the potential molecular mechanism of Fu-Zi Decoction in treating CHF, and further application of molecular docking technology for affinity was adopted to validate key targets and chemical composition. In this way, the mechanism of action of Fu-Zi Decoction in the treatment of CHF was preliminarily clarified, providing a solid research basis and theoretical basis for future studies.

2. Experimental

2.1. Screening of modern medical (MM) symptoms of various medicines in Fu-Zi Decoction

All the TCMs in Fu-Zi Decoction were input into SymMap (<https://www.symmap.org/>) database in turn, the corresponding MM symptoms were searched, and MM symptoms belonging to CHF TCM disease and syndrome category were screened. The SymMap database included 499 TCM syndromes, and 17 top TCM experts matched 1717 TCM syndromes to 961 Western medicine symptoms.

2.2. Chemical composition and target collection of Fu-Zi Decoction

The chemical constituents of five TCMs, including Fu Zi, Ren Shen, Fu Ling, Bai Zhu, and Bai Shao, were obtained from TCMSP (<https://tcmispw.com/tcmisp.php>) and ETCM (<http://www.tcmip.cn/ETCM>) databases. According to the TCMSP database, compounds of oral bioavailability (OB) $\geq 30\%$ and drug-likeness (DL) ≥ 0.18 were selected as the active compounds. In ETCM database, the “medium” and “excellent” drug-like compounds were selected as the active compounds. In the early study, the research group has analyzed the chemical compositions of Fu-Zi Decoction by UHPLC-ESI-Q-Orbitrap-MS, and a total of 41 compounds have been obtained. The ingredients of each drug in *the Chinese Pharmacopeia* and those in the literature were added (Table 1), and the chemical components of Fu-Zi Decoction were composed together with the above active compounds.

Canonical SMILES structural formulas for the above chemical compositions of Fu-Zi Decoction were obtained from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/search/>). Confidence thresholds of 0.7, 0.7 and 1 were set in STITCH (<http://stitch.embl.de/>), SwissTargetPrediction (<http://www.swisstargetprediction.ch/>) and TargetNET (<http://targetnet.scbdd.com/>) databases, respectively, with a limit of species “Homo sapiens” to predict its targets, and the obtained targets were converted into gene names through Uniprot database (<https://www.uniprot.org/>). Among them, STITCH and SwissTargetPrediction databases predicted targets based on chemical similarity, and the TargetNET database predicted targets based on QSAR (quantitative structure-activity relationship) model.

Aconitine, mesaconitine, hypaconitine, benzoyleaconine, benzoylmesaconine, benzoylhypaconine, aconine,

Table 1. Experiment, *Chinese Pharmacopoeia*, and literature supplemented ingredient information.

Source	Components	Medicine	Source	Components	Medicine
Experiment	Karakolidine	Fu Zi	Experiment	Beiwutine	Fu Zi
Experiment	Lepenine	Fu Zi	Experiment	Benzoyldeoxyaconitine	Fu Zi
Experiment	Senbusine A	Fu Zi	Experiment	Benzylneoline	Fu Zi
Experiment	Mesaconine	Fu Zi	Experiment	Aconitine	Fu Zi
Experiment	16 β -Hydroxycardiopetaline	Fu Zi	Experiment	14- <i>O</i> -Anisoyleoline	Fu Zi
Experiment	Senbusine B	Fu Zi	Experiment	Hypaconitine	Fu Zi
Experiment	Chuanfumine	Fu Zi	Experiment	Delphinine	Fu Zi
Experiment	Talatizidine	Fu Zi	Experiment	3-Deoxyaconitine	Fu Zi
Experiment	Songorine	Fu Zi	Pharmacopoeia	Atractylone	Bai Zhu
Experiment	Aconine	Fu Zi	Literature	Atractylenolide	Bai Zhu
Experiment	Hetisine	Fu Zi	Literature	Atractylenolide III	Bai Zhu
Experiment	Fu-Ziline	Fu Zi	Experiment	Ginsenoside-Re	Ren Shen
Experiment	Hypaconine	Fu Zi	Experiment	Ginsenoside-Rf	Ren Shen
Experiment	Neoline	Fu Zi	Experiment	Ginsenoside-Ro	Ren Shen
Experiment	Talatizamine	Fu Zi	Experiment	Ginsenoside-Rb1	Ren Shen
Experiment	Chasmanine	Fu Zi	Experiment	Ginsenoside-Rb2	Ren Shen
Experiment	14- <i>O</i> -Acetyltalatizamine	Fu Zi	Pharmacopoeia	Ginsenoside-Rg1	Ren Shen
Experiment	Benzoylmesaconine	Fu Zi	Experiment	Poricoic acid F	Fu Ling
Experiment	Benzoylaconine	Fu Zi	Experiment	Poricoic acid B	Fu Ling
Experiment	Benzoyl-3,13-deoxyaconine	Fu Zi	Experiment	Poricoic acid BM	Fu Ling
Experiment	Benzoylhypaconine	Fu Zi	Experiment	6- <i>O</i> -Galloylsucrose	Bai Shao
Experiment	Mesaconitine	Fu Zi	Experiment	Benzoyl-oxypaeoniflorin	Bai Shao
Experiment	Penduline	Fu Zi	Pharmacopoeia	Paeoniflorin	Bai Shao

mesaconine, hypaconine, ginsenoside Rg1, ginsenoside Re, ginsenoside Rb1, paeoniflorin, poricoic acid, atractylenolide I, and atractylenolide III were selected to conduct a literature search in PubMed, and known targets were collected.

2.3. Collection of CHF-related genes

CHF-related genes were collected from DisGeNET (<https://www.disgenet.org/>) and GEO (<https://www.ncbi.nlm.nih.gov/geo/>) databases. In the DisGeNET database, the keyword “chronic heart failure” was searched. DisGeNET is a comprehensive gene-disease relational database with information from multiple database integrations, animal models, and literature. In the GEO database, the authors identified a gene expression profile (GSE9128) that differentiated CHF from the control groups. A total of 24 CHF patients

and 12 controls of similar age and sex were enrolled for analysis of peripheral mononuclear cells.

2.4. Collection of small molecule drugs and their target proteins to treat CHF

Small molecule drugs for CHF were used as a positive control to compare with Fu-Zi decoction. In the DrugBank database (<https://www.drugbank.ca/>), data were collected according to the drug Classification Number (ATC), and all FDA-approved small molecule drugs for CHF beginning with C03, C07, C08, and C09 and their target proteins were collected.

2.5. Identification of important targets of Fu-Zi Decoction for CHF and establishment of PPI network

The CHF-related genes collected in the database were combined with western drug target proteins to

form the disease gene set, the intersection with the targets of Fu-Zi decoction was obtained, and the important targets of Fu-Zi decoction in the treatment of CHF were obtained. The confidence threshold was set at 0.7 (high confidence) in the STRING database to build a PPI network of important targets. The core targets were screened by “Degree” and “Betweenness Centrality”, and ClusterMaker2 was used to decompose the network graph. ClusterMaker2 applies algorithms to break up large networks into topology modules, making the connections inside each module much larger than the connections outside.

2.6. Molecular docking verification

The key target in the PPI network was selected as a receptor, the active ingredient corresponding to this target was found from the Compound-target correspondence data, and then the two were verified by molecular docking. With the help of the PubChem database, the structure of compound 2D was obtained, and then it was converted to MOL2 format through Open Babel for subsequent analysis. With the help of the RCSB PDB database (<http://www.rcsb.org/>), the crystal structure of the target protein was obtained, and Pymol software was used to remove ligand molecules and water molecules in the target structure. SwissDock online platform (<http://www.swissdock.ch/>) was used for molecular docking verification, and the results were imported into UCSF Chimera analysis.

3. Results and discussion

3.1. Screening of chemical constituents and targets

Through screening of TCMSP and ETCM databases, preliminary experimental results, pharmacopeia, and literature supplement, 205 chemical components in

Fu-Zi Decoction were obtained, among which 63 were from Fu Zi, 25 from Fu Ling, 74 from Ren Shen, 19 from Bai Zhu, and 24 from Bai Shao. Among them, alkaloids accounted for most of the chemical constituents of Fu Zi, ginsenoside and other components were almost all reflected in the chemical constituents of Ren Shen, triterpene saponins, such as pachymic acid, occupied the majority of the chemical constituents of Fu Ling, the chemical constituents of Bai Zhu mainly included volatile oil and sesquiterpene lactones, and the chemical constituents of Bai Shao mainly included monoterpenoids, such as paeoniflorin, and flavonoids, such as kaempferol. A large number of studies have shown that the above-mentioned components are the main effective components of every single drug in Fu-Zi Decoction.

A total of 223 targets of the chemical components of Fu-Zi Decoction were collected from the database, 365 targets were obtained through literature search, and 551 targets were obtained after the combination and removal of duplicates.

3.2. Identification of disease genes

In the DisGeNET database, 223 CHF-related genes were obtained. In the GEO database, the genes with $P \leq 0.05$ were selected, and $\log FC = \pm 1$ was taken as the threshold to obtain 166 significantly differentially expressed genes. In the DrugBank database, 107 small molecule drugs for CHF and 159 targets were searched. After combining all target genes and removing duplicates, 521 disease genes were obtained.

3.3. Determination of important targets of Fu-Zi Decoction for CHF and decomposition of PPI network module

The targets of Fu-Zi Decoction were intersected with disease genes (Fig. 1), and a total of 104 important targets for the treatment of CHF were obtained. The network

was built through the STRING database, and Cytoscape software was imported to obtain a network diagram consisting of 86 nodes and 414 edges. After modular decomposition, the PPI network was decomposed into four modules (Fig. 2).

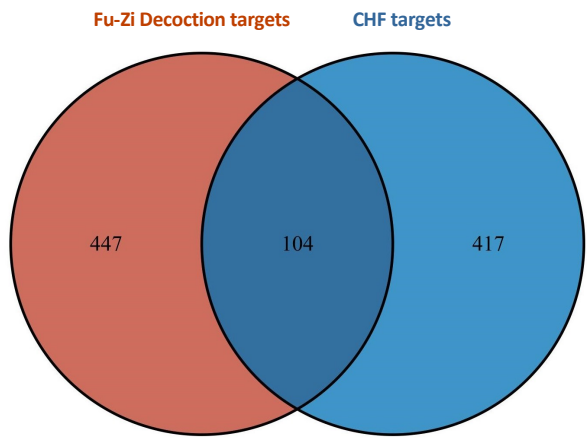


Figure 1. Venn diagram of Fu-Zi Decoction targets and CHF targets.

3.4. Analysis at the level of single-flavor medicine in Fu-Zi Decoction

SymMap database was used to screen MM symptoms corresponding to TCM syndromes, such as edema, asthmatic syndrome, phlegm, palpitation, and so on. It was found that Fu Zi could correspond to MM symptoms, such as edema, phlegm, angina pectoris, cardiac syncope, and so on. Ren Shen could be corresponding to sputum, palpitation, asthma, and other MM symptoms. Fu Ling could be corresponding to sputum, edema, palpitation, and other MM symptoms. Bai Zhu could correspond to MM symptoms, such as sputum, edema, and respiratory abnormalities.

“Chronic heart failure” and “Fu Zi”^[5], “Fu Ling”^[6], “Ren Shen”^[7], “Bai Zhu”^[8] and “Bai Shao”^[9] were used as keywords in literature retrieval, and all literature was reported. TCM compounds and preparations

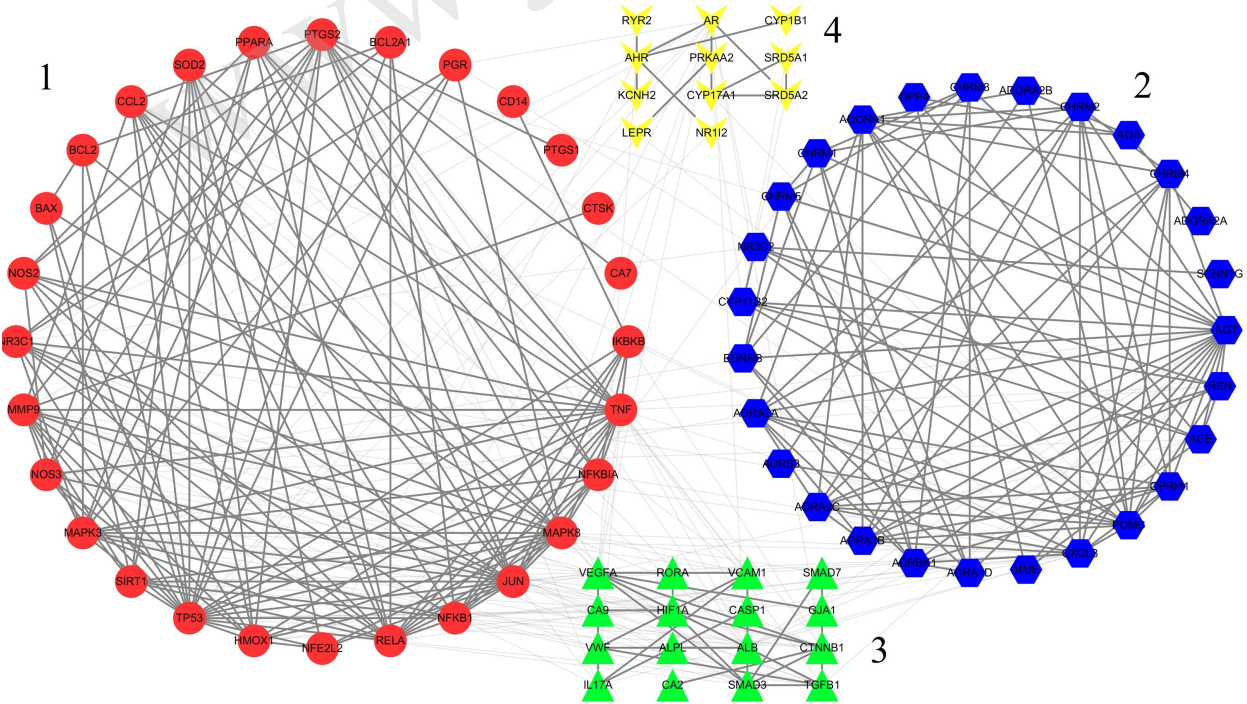


Figure 2. Module decomposition diagram of PPI network. (The modules are numbered from the largest to the smallest, 1–4, the main biological processes involved in each module are: 1. response to oxidative stress; 2. G protein-coupled receptor signaling pathway; 3. response to stress; 4. steroid metabolic process.)

containing every single drug, such as Shenmai injection^[10], Shenfu injection^[11], Shengmai SAN^[12], Zhenwu Tang^[13], and Qiliqiangxin capsule^[14], have also been reported in domestic and foreign literature, showing that they have good clinical effects on CHF.

3.5. Analysis of drug target level

Based on 104 therapeutic CHF targets obtained from the intersection of action targets of Fu-Zi Decoction and disease targets, the intersection of targets of Fu-Zi Decoction and CHF targets in the DisGeNet database was further calculated, and 50 intersection targets were obtained, accounting for 22.42% of all CHF targets in the database. The intersection of CHF targets from the GEO database was obtained, and 11 intersection targets were obtained, accounting for 6.63% of CHF targets obtained from this database. The intersection of CHF small-molecule drug targets collected from the DrugBank database yielded 60 intersection targets, accounting for 37.74% of CHF drug targets obtained from this database. After removing duplicates, all the intersection targets accounted for 19.06% of all the targets of Fu-Zi Decoction and 20.15% of all the disease targets.

Both the targets of Fu-Zi Decoction and the CHF targets obtained from each disease gene database had good overlap, and the overlapping targets occupied a high proportion in both the targets of Fu-Zi Decoction and the disease targets, suggesting that many targets in Fu-Zi Decoction jointly played a positive role in CHF.

3.6. PPI network analysis

After the construction of the STRING database, a network consisting of 86 nodes and 414 edges was obtained. The network was decomposed into four modules, and each module was numbered from 1 to 4 according to the number of nodes. GO enrichment analysis was performed on each module to determine

the biological processes of each module (Fig. 3). Module 1 mainly involved the negative regulation of the apoptotic process, response to oxidative stress, and other biological processes. Response to oxidative stress imbalance is the main pathological manifestation of CHF. The production of reactive oxygen species (ROS) is increased within the mitochondria when heart failure occurs, and the production of ROS in mitochondria is increased, activating a broad variety of hypertrophy signaling kinases and transcription factors and mediating apoptosis^[15]. Module 2 mainly involved G protein-coupled receptor signaling pathway, regulating blood vessel diameter, muscle contraction, muscle system process, and other biological processes. Slow stimulation of G protein-coupled receptors is associated with the development of CHF^[16]. Module 3 mainly involved biological processes, such as response to hypoxia, tissue morphogenesis, and stress, cytokine production, and blood vessel morphogenesis. The smallest module, module 4, dealt mainly with biological processes, such as steroid metabolic process, cellular response to xenobiotic stimulus, and drug. It was speculated that Fu-Zi Decoction was involved in reducing oxidative stress, inhibiting cardiomyocyte apoptosis, G protein-coupled receptor, and other processes.

3.7. Pathway enrichment analysis

A total of 20 core targets in the PPI network were selected with degree ≥ 14 and betweenness ≥ 0.01 , namely CXCL8, TP53, AGT, VEGFA, POMC, AR, JUN, PTGS2, NOS3, MAPK3, MAPK8, ALB, CTNNB1, MMP9, PPARG, TNF, NR3C1, RELA, CASP3, and HMOX1. Enrichment analysis of the KEGG pathway was carried out for the above-mentioned 20 targets. We found that the 10 pathways with the highest concentration (Fig. 4) were pathway in cancer, fluid shear stress and atherosclerosis, IL-17 signaling pathway, AGE-RAGE signaling pathway in diabetic complications,

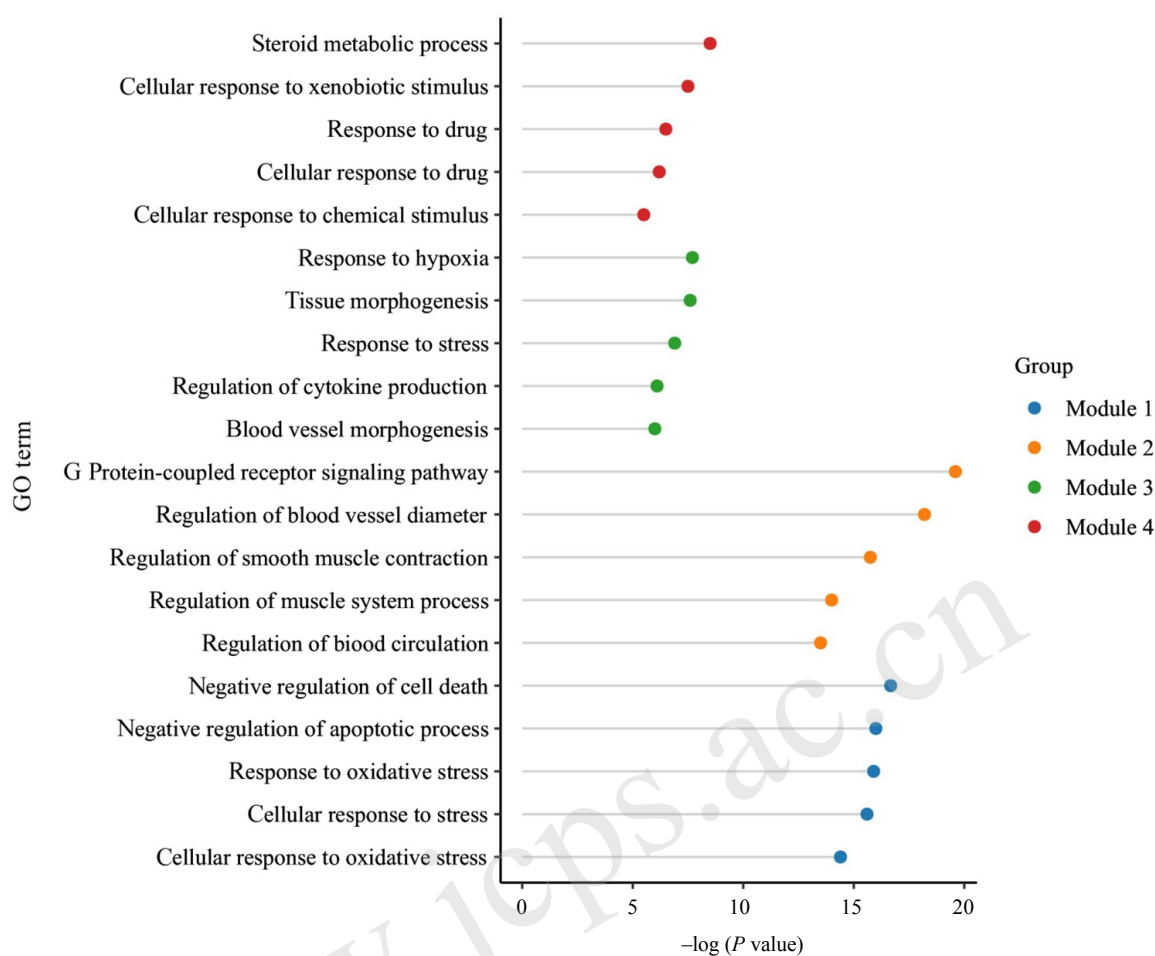


Figure 3. Results of GO function enrichment analysis.

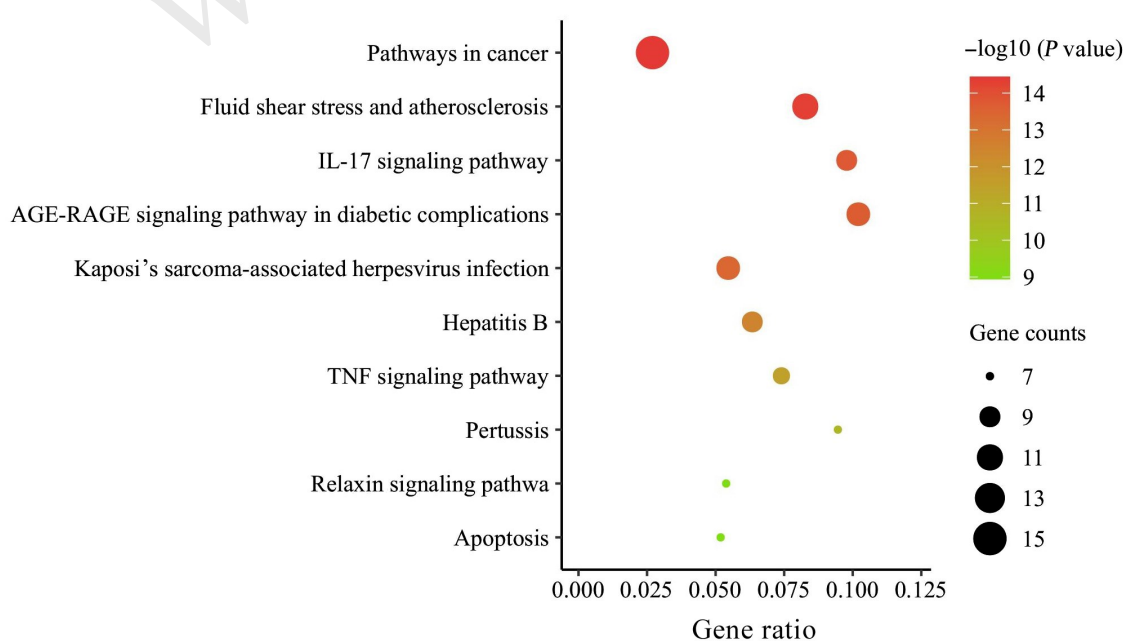


Figure 4. Results of KEGG pathway enrichment analysis.

Kaposi's sarcoma-associated herpesvirus infection, hepatitis B, TNF signaling pathway, pertussis, relaxin signaling pathway, and apoptosis.

According to the enrichment analysis of the pathway, the main pathways of Fu-Zi Decoction in the treatment of CHF were the blood flow shear stress and atherosclerosis pathway. Shear stress plays an important role in the cardiovascular system^[17] and simultaneously regulates many signal transduction molecules in endothelial cells, including G protein, Ca^{2+} channels, MAPKs, and so on. The Ca^{2+} circulation is an important physiological process to maintain the normal contraction of cardiomyocytes, and the disorder of the Ca^{2+} pump is an important aspect in the pathogenesis of heart failure^[18]. Studies have shown that IL-17 expression can increase the slope of the left ventricular recovery curve, prolong action potential duration, activate MAPK, and enhance TNF expression in patients with heart failure^[19]. AGEs are formed slowly in the aging process, accelerated formation occurs in the environment of high blood sugar and pro-oxidation, and intracellular signals are activated through RAGE, leading to the generation of free radicals and thus amplifying oxidative stress^[20]. The diagnostic and prognostic marker of CHF, NT-Pro BNP, may amplify inflammation through the AGE/RAGE system^[21].

3.8. Molecular docking

Selected by combining degree with betweenness, the most important target in the PPI network was

CXCL8, which was similar to the results of Li et al^[22]. The compounds corresponding to CXCL8 in Fu-Zi Decoction were aconitine, mesaconitine, benzoylaconine, paeoniflorin, and atractylenolide III. The molecular docking of the five compounds with CXCL8 was performed, and the binding energy Δ was -7.11 , -7.14 , -6.97 , -7.10 and -6.66 kcal/mol, respectively. The binding energy indicates the strength of the binding force between the compound and the target, and the smaller the binding energy is, the stronger the binding ability is. It is generally believed that molecules and ligands can bind effectively when the binding energy is lower than 0. When the binding energy is less than or equal to -7.00 kcal/mol, the molecules were closely bound to the targets. Therefore, all compounds had a good binding ability with CXCL8. Figure 5 shows the molecular docking diagram of each compound and CXCL8.

At present, clinicians are aware that heart failure is an inflammatory response, and more and more evidence shows that inflammation plays an important role in the occurrence and development of heart failure^[23]. CXCL8, a cytokine in the chemokine family, is involved in neutrophil chemotaxis, angiogenesis, and many other processes, and it can be induced by stimulation of shear stress, ischemia, hypoxia, and (NF)-KB pathways^[24]. Studies have found that the CXCL8 pathway is involved in the inflammatory response of CHF, and the level of CXCL8 is increased in CHF patients^[25].

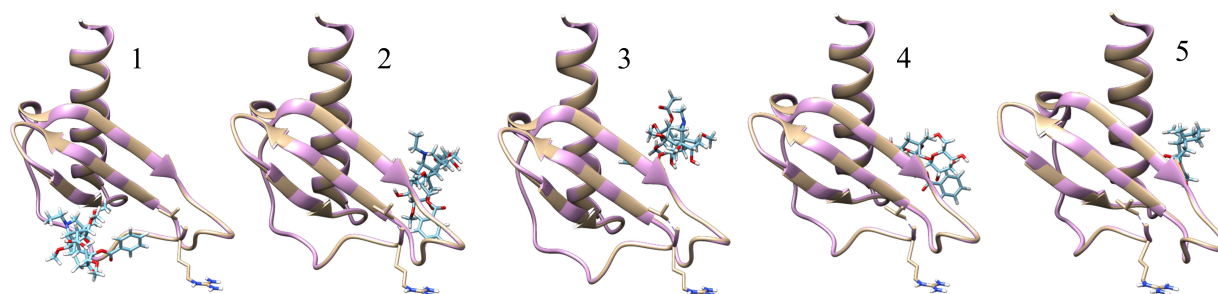


Figure 5. Molecular docking diagram of each compound and CXCL8 (1 to 5 is benzoylaconine, aconitine, mesaconitine, paeoniflorin, and atractylenolide III, respectively).

In addition, we found that CXCL8 binding compounds were important chemical components in Fu Zi, Bai Zhu, and Bai Shao.

4. Conclusions

In the present study, network pharmacology technology was applied to explore the mechanism of Fu-Zi Decoction in the treatment of CHF from the aspects of a single medicine, target, PPI network module function and pathway, and the binding ability of compounds and targets was verified by molecular docking. In terms of data collection, multiple databases were combined, and preliminary experimental results were added to make the data more complete. In terms of target prediction, targets with high confidence were selected, and targets determined experimentally in the literature were added to make target prediction data more reliable.

In the present study, we analyzed the potential targets and pathways of Fu-Zi Decoction in the treatment of CHF using network pharmacology, revealed the complex network mechanism of Fu-Zi Decoction in its efficacy, and laid a foundation for further research on the mechanism of action of Fu-Zi Decoction.

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基于网络药理学和分子对接技术 探讨附子汤治疗慢性心力衰竭的作用机制

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摘要: 采用网络药理学方法探讨附子汤治疗慢性心力衰竭的作用机制。首先利用SymMap数据库分析各味药的现代医学症状, 然后通过TCMSP、ETCM数据库和前期结果得到附子汤化学成分, 并结合STITCH、SwissTargetPrediction、TargetNET数据库及文献获得附子汤作用靶点。在DisGeNET、GEO和DrugBank数据库中获取治疗慢性心力衰竭的靶点, 筛选出与附子汤靶点共同部分构建PPI网络, 对PPI网络模块化分解分析其功能并进行KEGG通路富集分析。最后对关键靶点由SwissDock进行分子对接验证。结果收集到附子汤化学成分205个, 药物靶点551个, 疾病靶点521个。功能富集分析发现主要参与细胞凋亡负调控、氧化应激和G蛋白偶联受体调节等生物过程。KEGG富集发现主要涉及血流剪切应力与动脉粥样硬化、IL-17信号通路等。分子对接结果显示苯甲酰乌头原碱、乌头碱、新乌头碱、芍药苷、白术内酯III均与核心靶点CXCL8具有较强亲和力。提示附子汤可能通过血流剪切应力与动脉粥样硬化、IL-17信号通路等发挥负调控细胞凋亡、氧化应激等作用, 起到治疗慢性心力衰竭的疗效。

关键词: 附子汤; 慢性心力衰竭; 网络药理学; 分子对接

