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Discussion on the Mechanism of Wushenyin in the Treatment of Premature Ventricular Contractions of Coronary Heart Disease Based on the Network Pharmacology

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Abstract: **Objective:** To explore the mechanism of Wushenyin in the treatment of premature ventricular contractions (PVCs) of coronary heart disease (CHD) by TCMSP. **Methods:** The main chemical components of Wushen Decoction were retrieved and the target sites of the active components were predicted by using TCMSP. The targets related to PVCs of CHD were obtained from OMIM and Genecards databases, and the intersection targets were obtained by mapping the drug component targets with the disease targets using Venn diagram. String database and Cytoscape3.8.2 software were used to construct a protein interaction network for the main targets. Metascape was used to analyze the biological functions and metabolic pathways of the main targets and visualize them. **Results:** Finally, 140 active components of Wushenyin were obtained, corresponding to 241 targets, 2238 targets related to PVCs, and 150 targets shared by drugs and diseases. **Conclusion:** Through multiple targets such as STAT3, TP53 and MAPK1, the multiple components represented by quercetin in Wushenyin regulate multiple signaling pathways including PI3K-AKT, play a role in reducing inflammatory response, improving immune function, regulating cardiomyocyte metabolism and apoptosis, intervening vascular remodeling, improving myocardial blood supply and regulating bioelectrical conduction. So as to treat PVCs.

1. Introduction

Coronary heart disease is a common cardiovascular disease, which is caused by vascular lumen stenosis or obstruction caused by coronary atherosclerosis, thereby causing ischemia and hypoxia of cardiomyocytes [1], and causing patients to have palpitation, chest tightness, chest pain, shortness of breath, and even fainting outside, which may threaten life in severe cases. Premature ventricular beats is one of the common complications of coronary atherosclerotic heart disease. About 20% of

patients with coronary heart disease can have premature contractions, among which premature ventricular beats are the most common [2-3]. In recent years, traditional Chinese medicine has a synergistic effect with conventional western medicine in the treatment of PVCs [4-6]. Clinical studies have shown [7-8] that Wushenyin is effective in the treatment of PVCs, which can significantly reduce clinical symptoms, stabilize cardiac electrical activity, increase left ventricular ejection fraction, improve cardiac systolic function and reduce the frequency of premature contractions. However, the molecular mechanism of Wushenyin in the treatment of PVCs is still unclear. Therefore, this study explored the main active components, targets, signaling pathways and potential network relationships of Wushenyin in the treatment of PVCs through network pharmacology method, in order to clarify the potential molecular mechanism of its intervention in PVCs and provide theoretical basis for subsequent research.

2. Materials and Methods

2.1. Screening of active constituents and related targets of Wushenyin

Through TCMSP (https://tcmspw.com/tcmsp.php) [9] database, retrieving the codonopsis pilosula, straight ladybell, radix scrophulariae, Sophora flavescens and salvia miltiorrhiza. Oral bioavailability (OB)≥30% and drug-likeness (DL)≥0.18 were set as the conditions for screening the main active components and protein targets. With the aid of UniProt database (https://tcmspw.com/tcmsp.php) [10] the effective components of protein targets for gene name standardization, and remove duplicates.

2.2. Construction of compound component-target network diagram

Excel software was used to construct the files and type attribute files of the correspondence between drugs and active components, active components and target sites, which were imported into Cytoscape3.8.2 software to construct the drug-compound target network diagram. Use the built-in tool "Network Analyse" the Network topology data of the drug and target, and select the effective active ingredients of Wushen Decoction according to Degree centrality (DC).

2.3. Prediction of targets related to premature ventricular contractions in coronary heart disease

In GeneCards (https://www.genecards.org), OMIM database (http://omim.org) with "Premature Ventricular beats of coronary heart disease" was searched for the disease search term, and the disease targets corresponding to PVCs were obtained after integrating the obtained disease targets and eliminating the repeated targets.

2.4. Prediction of common targets of drugs and diseases

The active component targets of Wushenyin were mapped with key targets of PVCs by Venny 2.1.0 software to obtain intersection targets, which were potential target genes of Wushenyin in the treatment of PVCs, and the Venn diagram was drawn.

2.5. Drug and Disease Common Target Protein Interaction Network Construction (PPI)

The interaction network diagram of drug and disease common target protein was established by String database (https://string-db.org/) [11]. Among them, the species is "Homo sapiens", the minimum interaction threshold is set as "highest confidence >0.9", the rest is set as the default value,

and the free nodes are hidden to obtain PPI network relationship information, and then Cytoscape is imported in the form of TSV file. The built-in plug-in CytoNCA was used to analyze the network topology of the obtained PPI network relations, and the key protein interaction modules in the network were screened out.

2.6. GO and KEGG enrichment analysis

TO enter common targets of drug and disease protein Metascape [12] (http://metascape.org/gp/index.html) platform, analyzes the main biological processes and metabolic pathways and enrichment analysis, secondly by means of microscopic letter platform (http://www.bioinformatics.com.cn/) for data visualization processing.

3. Result

3.1. Screening of active constituents and related targets of Wushenyin

A total of 148 active compounds were screened through the TCMSP database platform, including 21 codonopsis,8 Radix Shariana,9 Radix Shariana,45 Radix sophora flavescens and 65 Radix salvia miltiorrhiza.140 active compounds were left after deleting duplicated compounds. The 140 active ingredients in Wushenyin were retrieved again on the TCMSP platform and matched with potential targets one by one. After removing duplicate values,251 targets were left. With the help of UniProt database, the Gene names of protein targets of active components were standardized, and 241 effective targets of Gene Symbol were obtained after conversion.

3.2. Construction of active ingredient-target network diagram of Wushenyin

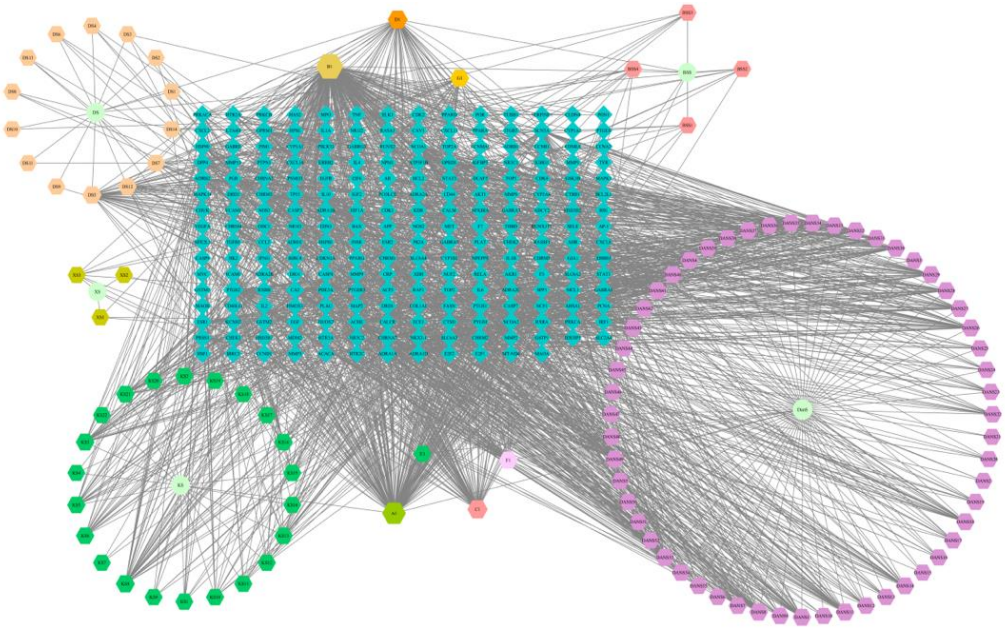

Figure 1: Compound component-target network diagram

Cytoscape software was used to construct the active ingredient-target network diagram of Wushenyin as shown in Figure 1. The network consists of 332 nodes and 1965 edges. The hexagonal nodes with different colors respectively represent the corresponding drug compounds, the lines between nodes represent the interactions between biomolecules, and the blue diamond

represents the target sites. The larger the node in the figure, the higher the degree of interaction (DC), indicating the greater the therapeutic effect of the compound. The topological properties of the Network were analyzed by using the "Network Analyze" function in Cytoscape software, and the top 5 compounds with degree values were screened out, which were quercetin, luteolin, β-sitosterol, stigmasterol and formonontin.

3.3. Potential target of Wushenyin in the treatment of PVCs

In GeneCards and OMIM database with "Ventricular premature beats of coronary heart"Disease" was searched separately for disease search terms. Among them, 1073 targets of PVCs were obtained from GeneCards database, and 1200 targets were obtained from OMIM database. After integrating the disease targets obtained from the two databases and eliminating the repeated targets, 2238 corresponding disease targets were obtained. The potential mapping intersection targets of Wushenyin and PVCs were obtained, a total of 150 intersection targets were obtained, and the Venn diagram was obtained (FIG.2), which may be the potential targets of Wushenyin in the treatment of PVCs.

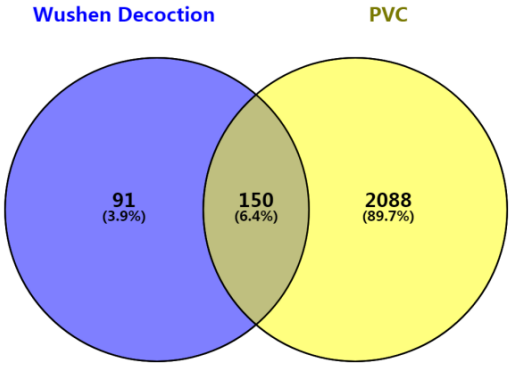

Figure 2: Venn diagram of common target of Wushenyin and PVCs

3.4. Construction of Drug and Disease Common Target Protein Interaction Network (PPI)

The common targets were imported into String database for analysis, and the PPI network diagram was obtained. The obtained data files were imported into Cytoscape for network topology analysis, and the core cluster proteins were analyzed by CytoNCA built-in plug-in. Six values such as Degree, Eigenvector, LAC, Betweenness, Closeness and Network are taken as the screening conditions, and the screening process is shown in Figure 3.

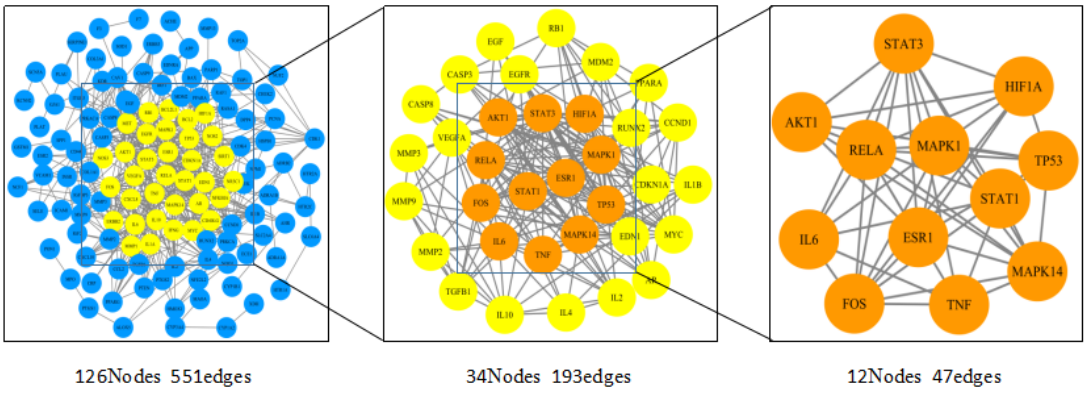

Figure 3: CytoNCA screening process

3.5. GO enrichment analysis

Metascape data platform was used to analyze the signal pathway of potential targets of Wushenyin in the treatment of ventricular premature contractions of coronary heart disease, and Weisheng data platform was used to visualize the results. Among them, the bioinformation process (BP) of WUShenyin in the treatment of ventricular premature contractions of coronary heart disease mainly involves the cellular response to nitrogen compounds, hormone response, cellular response to organic nitrogen compounds, and cellular response to inorganic substances. The top 10 GO functional enrichment analysis are presented in bar chart, as shown in Figure 4.

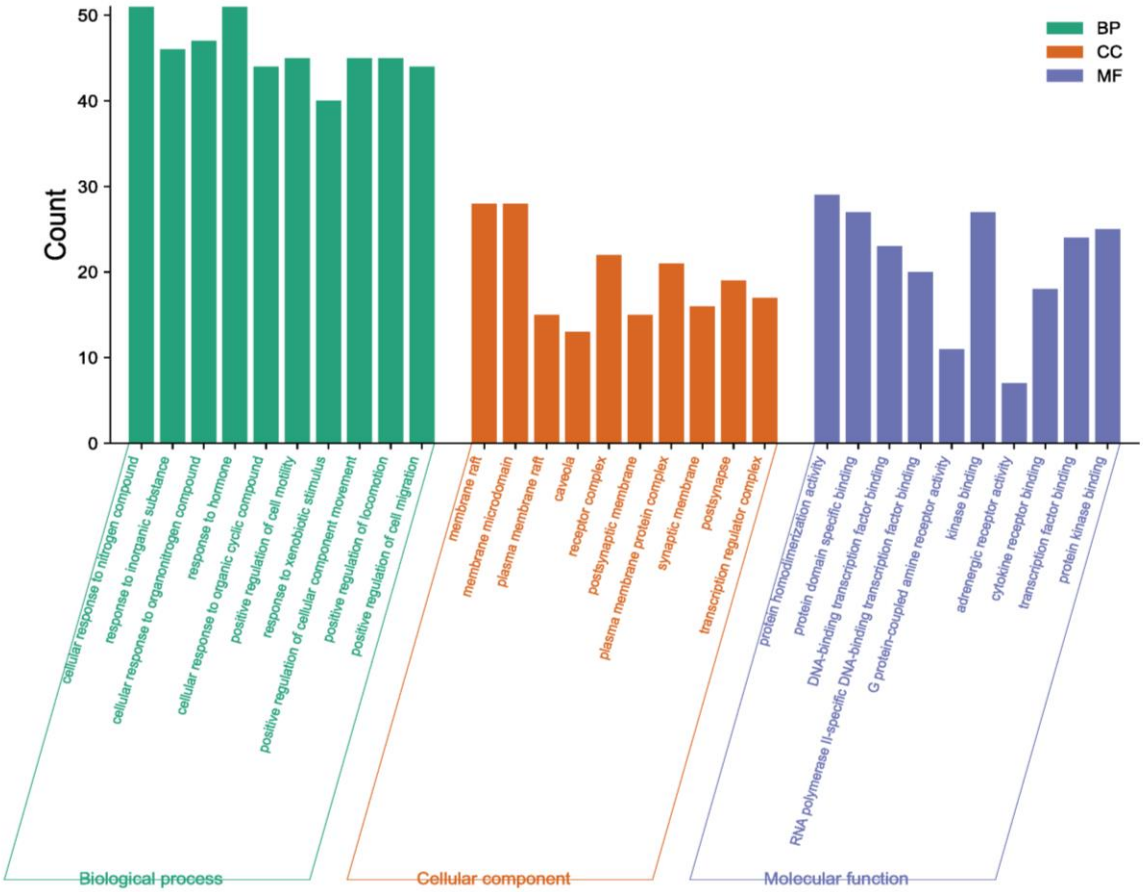

Figure 4: GO enrichment analysis

3.6. KEGG pathway analysis

KEGG pathway enrichment analysis of intersection targets was performed using Metascape database, which mainly involved 251 signaling pathways. The top 20 KEGG pathways were shown in FIG. 5 bubble chart. The results of signaling pathway showed that the genes were mainly enriched in PI3K-Akt signaling pathway, AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, MAPK signaling pathway, relaxin signaling pathway, IL-17 signaling pathway and so on.

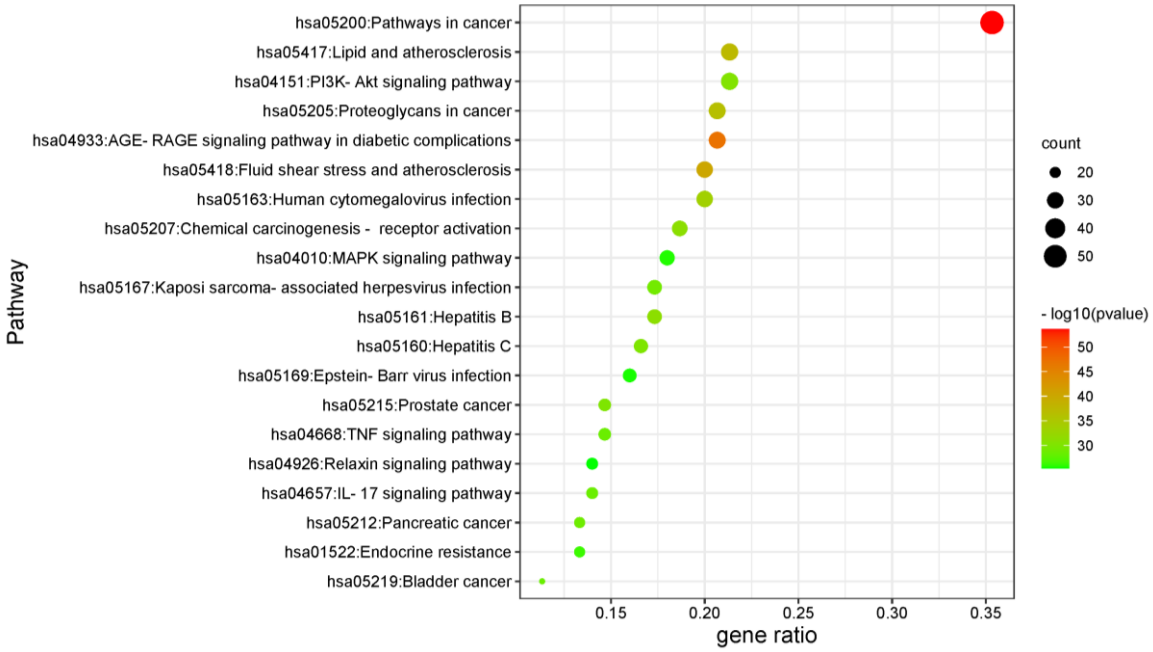

Figure 5: GO enrichment analysis

4. Discussion

In this study, through searching relevant databases and literature, and analyzing the collected chemical components and targets, 140 possible main active components were screened out, and then 150 targets related to ventricular premature contractions in coronary heart disease were screened out. The results of component-target map and protein interaction network diagram showed that Wushenyin has the characteristics of multi-component and multi-target in the treatment of ventricular premature contraction of coronary heart disease. In KEGG pathway enrichment analysis, it was found that Wushenyin may treat premature ventricular contractions by interfering PI3K-Akt signaling pathway, TNF signaling pathway, MAPK signaling pathway and so on. PI3K-Akt has biological functions such as regulating cell growth, proliferation, differentiation and migration, interfering with inflammatory response and regulating autophagy [13]. Phosphatidylinositol-3,4, 5-triphosphate (PIP3) activates the downstream signal transduction factor AKT to regulate the growth, proliferation and survival of cells, which has a certain protective effect on cardiomyocytes. If the activity of PIP3 signal transduction decreases, arrhythmias can be induced [14]. Previous studies have confirmed that resveratrol can up-regulate the content and activity of connexin 43 through the activation of PI3K-Akt signaling pathway, thereby preventing the occurrence of reperfusion arrhythmias [15]. PI3K-Akt pathway can be used as the key experimental research object in the future.

5. Conclusion

Through network pharmacology method, this study found that multiple components represented by quercetin in Wushenyin regulate multiple signaling pathways including PI3K-AKT through multiple targets such as STAT3, TP53 and MAPK1. It can reduce inflammation, improve immune function, regulate cardiomyocyte metabolism and apoptosis, intervene vascular remodeling, improve myocardial blood supply and regulate bioelectrical conduction, so as to treat ventricular premature beats of coronary heart disease. This study for the clinical application of five and water

treatment of coronary heart disease (CHD) of ventricular premature beat provides the theory basis of molecular level, and to further develop coronary heart disease (CHD) ventricular premature beat pharmacology research and basic research provides a theoretical reference, and about five ginseng drink intervention mechanism of coronary heart disease etiology and pathology of ventricular premature beat, concentration-response relationship, problems such as adverse drug reactions, remains to be verified further research in the future.

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