

Research Article

Network Pharmacology Study on Molecular Mechanisms of Zhishi Xiebai Guizhi Decoction in the Treatment of Coronary Heart Disease

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Background. Coronary heart disease is characterized by the formation of arterial plaque. If not taken seriously, it will cause serious consequences such as myocardial infarction and heart failure. Zhishi Xiebai Guizhi Decoction first appeared in "Synopsis of Prescriptions of the Golden Chamber" and is a representative prescription for the treatment of coronary heart disease. This study aims to explain the mechanism of Zhishi Xiebai Guizhi Decoction in the treatment of coronary heart disease through network pharmacology and clinical trials. Methods. We first identified the core compounds of Zhishi Xiebai Guizhi Decoction and their potential targets through TCMSP. Then, We analyzed the molecular targets of Zhishi Xiebai Guizhi Decoction in coronary heart disease with OMIM and GeneCards databases. After the common targets were screened out, we manage to figure out the pathways of these target genes through STRING. Finally, we verify the treatment results in clinical trials. Results. Through network pharmacology analysis, we discovered that several core compounds of Zhishi Xiebai Guizhi Decoction have anti-inflammatory effects and are of great significance to treatment of cardiovascular diseases. The mechanism may be closely related to PPARy, inflammation, TNF signaling pathway, AMPK signaling pathway, and PI3K-Akt signaling pathway. Clinical trials have also proved the key role of inflammation. Conclusions. Zhishi Xiebai Guizhi Decoction may play a role in treating coronary heart disease by activating PPARy. TNF signaling pathway, AMPK signaling pathway, and PI3K-Akt signaling pathway are potential mechanisms as well. The application of network pharmacology can provide a novel method for the research of Chinese herbal medicine. We hope that Zhishi Xiebai Guizhi Decoction will be recognized as a complementary or alternative treatment for coronary heart disease.

1. Introduction

Coronary heart disease (CHD) is characterized by formation of arterial plaques which are mainly comprised of lipids, calcium, and inflammatory cells [1]. These plaques narrow the lumen of coronary arteries leading to episodic or persistent angina. Rupture of these plaques results in the appearance of thrombus, which, brought about by cessation of blood flow, causes myocardial infarct and death [2]. CHD is one of the leading causes of death worldwide [3, 4]. The increasing number of CHD patients will lay a heavy economic burden on society [5]. Currently, the drugs commonly used in clinic to treat coronary heart disease are statins, nitrate esters, etc., with which the residual risk of cardiovascular events cannot be completely eliminated after treatment [6, 7]. Given this, many doctors have been seeking alternative medicines to treat CHD. Traditional Chinese medicine (TCM), as a type of alternative drug, displays the merits of low side effects and less irritation to the gastrointestinal tract [8, 9]. It has been demonstrated that TCM works an outstanding clinical effect when treating CHD [10]. Zhishi Xiebai Guizhi Decoction is effective. This prescription contains Aurantii Fructus Immaturus ("ZhiShi" in Chinese, ZS), Allium Azureum Ledeb. ("XieBai" in Chinese, XB), Cinnamomi Ramulus ("GuiZhi" in Chinese, GZ), Trichosanthes Kirilowii Maxim ("GuaLou" in Chinese, GL), and Magnolia Officinalis Rehd Et Wils. ("HouPo" in Chinese, HP). Multidrug compatibility is regarded as the essence of TCM theory [11]. However, due to the complex components and numerous targets involved, fully elucidating its mechanism using traditional methods is challenging. Therefore, it is necessary to reveal the potential mechanism of Zhishi Xiebai Guizhi Decoction in the treatment of CHD at the systemic level.

With the continuous innovation and development of systems biology and computer technology, the network pharmacology has been confirmed as a feasible choice to explicate the substance composition and molecular mechanism of TCM effectively and systemically [12, 13]. In 2008, Hopkins proposed the concept of network pharmacology [14]. Because network pharmacology can provide a full or partial understanding of the principles of network theory and systems biology, it has been considered the next paradigm in drug discovery. In addition, the network pharmacology approach has been used to study "compoundproteins/genes-disease" pathways, which are capable of describing complexities among biological systems, drugs, and diseases from a network perspective, sharing a similar holistic philosophy as TCM [15]. The application of systems biology methods to study the pharmacological effects, mechanism of action, and safety of TCM is of great significance to modern research and development of TCM. Thus, a new interdisciplinary method termed TCM network pharmacology has been proposed, which has initiated a new research paradigm for transforming TCM from an experience-based to evidence-based medicine. Furthermore, with recent advances in molecular biology and genomic technologies, an increasing amount of data has become available [16], for example, TCMSP [17], STRING [18], OMIM [19], and DisGeNET [20].

In this study, we used network pharmacology to predict the potential mechanism of Zhishi Xiebai Guizhi Decoction in the treatment of CHD. The workflow is displayed in Figure 1.

2. Methods

2.1. Screening the Chemical Components of Zhishi Xiebai Guizhi Decoction and Predicting the Component-Targets. The chemical ingredients of Zhishi Xiebai Guizhi Decoction were screened from TCMSP (http://lsp.nwu.edu.cn/ tcmsp.php). Based on a previously reported model, we screened the various compounds in Zhishi Xiebai Guizhi Decoction according to their pharmacokinetic absorption, distribution, metabolism, and excretion, which is known as ADME process. TCMSP database details the ADME parameters of each component, including oral bioavailability (OB), druglikeness (DL), and blood-brain barrier (BBB). Ingredients meeting the demands of both $OB \ge 30\%$ and $DL \ge 0.18$ were selected to find the effective components of this prescription [21]. OB represents the oral availability of pharmaceutical ingredients, and DL refers to the similarity between a component and a known drug. Subsequently, the components in the prescription were selected (Table 1).

2.2. Predicting the Target Proteins of the Selected Compounds. All the active ingredients were input into the TCMSP database to obtain their known targets, and the Cytoscape3.8.2 tool was used to draw a network diagram of the compound and the target protein (Figure 2).

The blue nodes represent Zhishi, Xiebai, Guizhi, Gualou, and Houpo. The red nodes represent the compounds shared by Guizhi and Xiebai. The dark purple nodes represent the compounds of Houpo. The orange nodes represent the compounds of Zhishi. The light purple nodes represent the compounds of Xiebai. The pink nodes represent the compounds of Gualou. The yellow nodes represent the compounds of Guizhi. The green nodes represent the targets related to Zhishi Xiebai Guizhi Decoction.

2.3. Seeking Out Disease-Related Targets. With "coronary heart disease" as the keywords, OMIM (https://www.omim. prg/) and GeneCards (https://www.genecards.org/) were used to search and screen the known disease-targets for the subsequent study, and the repeated targets in the search results were discarded. UniProt knowledge base [22, 23] (https://www.uniprot.org/) was used to get the standard targets' names with the organism selected as "Homo sapiens."

2.4. Searching for Common Targets and Key Targets of Zhishi Xiebai Guizhi Decoction and CHD. The common targets of drug and disease were found, and a Venn diagram was drawn (Figure 3).

The obtained intersection target was used as the drug effect target, and Cytoscape3.8.2 was employed to construct the drug effect target-component interaction network (Figure 4). The network was analyzed to get its degree value and get the key drug effect target (Table 2).

The green nodes represent the compounds of Zhishi Xiebai Guizhi Decoction. The blue nodes represent the key targets related to Zhishi Xiebai Guizhi Decoction.

2.5. Construction of the Protein-Protein Interaction Network. Using the STRING (Search Tool for the Retrieval of Interacting Gene/Proteins) database containing known and predicted PPIs [24], we constructed a protein-protein interaction (PPI) network of potential target genes of Zhishi Xiebai Guizhi Decoction in CHD (Figure 5).



FIGURE 1: The whole framework based on an integration strategy of network pharmacology.

2.6. Enrichment Analysis. To identify the biological process and signaling pathways in which the main hub target genes are involved, Database for Annotation, Visualization, and Integrated Discovery (David) were used for pathway enrichment analysis. The target genes of Zhishi Xiebai Guizhi Decoction in CHD were input into David for Gene Ontology (GO) biological process analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. GO biological processes with $P \le 0.01$ and KEGG pathways with $P \le 0.01$ were considered to be significantly enriched.

2.7. Clinical Index Changes of Zhishi Xiebai Guizhi Decoction in Treating Coronary Heart Disease Patients. A total of 176 patients with coronary heart disease were included in the clinical study. According to the random number table, the enrolled patients were divided into control group (88 cases) and the test group (88 cases). During the treatment, 7 cases were dropped from the two groups, and final effective cases were 81 cases in each group. This study was approved by the Ethics Committee of Wuxi Hospital of Traditional Chinese Medicine and registered in the Chinese Clinical Trial Registration Center (ethics number: 2018022736, registration number: ChiCTR1800019814). Before entering the group, patients and their family members were informed of all the research content and interests, were fully aware of them, and signed an informed consent form on the premise of voluntary participation. The diagnostic criteria for patients with coronary heart disease enrolled in this trial were based on the "2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology [25]," and the most diagnosed patients were patients with stable coronary artery disease. After admission, both groups were given standardized treatment for stable coronary heart disease. The test group was treated with Zhishi Xiebai Guizhi Decoction on the basis of the control group.

Both groups were treated for 2 months and finally got inflammations such as Neutrophil to lymphocyte ratio (NLR), Monocyte of lymphocyte ratio (MLR), Monocyte to highdensity lipoprotein ratio (MHR), and C-reaction protein (CRP) factor level changes, and preliminary exploration of the mechanism of the prescription on the inflammatory response provided a clinical basis for the later confirmation of its molecular mechanism in vitro and in vivo.

3. Results

3.1. Identification of Targets of Zhishi Xiebai Guizhi Decoction and CHD in Various Databases. The database retrieved 139 relevant targets of the active ingredient, and the active ingredient-target interaction network was constructed using Cytoscape 3.8.2 (Figure 2). Through keyword search, 1991 related targets of coronary heart disease were obtained in GeneCards database and OMIM database. The Venny diagram constructs the intersection of active ingredient-target and disease-target. A total of 85 intersection targets are used for subsequent network pharmacological analysis.

3.2. Seeking Key Targets and Built PPI Networks. The obtained intersection target was used as the drug effect target, and Cytoscape 3.8.2 was used to construct the drug effect target-component interaction network (Figure 4). The network was analyzed to get its degree value. The top 20 pharmacodynamic targets with degree value include estrogen receptor (ESR1), androgen receptor (AR), prostaglandin G/H synthase 2(PTGS2), and peroxisome proliferator activated receptor (PPARG) (Table 2).

3.3. Enrichment Analysis by GO and KEGG. According to P value, the important items of BP of GO analysis were regulation of blood pressure, regulation of inflammatory

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MOL000073 Ent-epicatechin 48.95984 0.2416. MOL000358 Beta-sitosterol 36.91391 0.7512 MOL000492 (+)-catechin 54.82643 0.2416 MOL000359 Quercetin 46.4335 0.27525 MOL000332 n-coumaroyltyramine 85.62883 0.20237 MOL000358 (2)-3-(4-Hydroxy-3-methoxy-phenyl)-N-[2.(4-hydroxyphenyl) ethyl] acrylamide 118.3477 0.2039 MOL000137 Coumaroyltyramine 112.2016 0.20234 MOL000138 (2)-3-(4-Hydroxy-3-methoxy-phenyl)-N-[2.(4-hydroxyphenyl) ethyl] acrylamide 118.3477 0.2039 MOL000137 Sitosteryl acetate 40.38964 0.82102 MOL0002341 Hesperetin 70.31209 0.22234 MOL000760 PGA (sup 1) 43.98251 0.24344 MOL000761 Prostaglandin B1 40.02777 0.2334 MOL0007651 Prostaglandin B1 40.20777 0.2334 MOL0001803 Sinenestin 50.5685 0.4454 MOL0001804 Sinenestin 50.5685 0.4454 <td>111</td> <td>MOL005980</td> <td>Neohesperidin</td> <td>57.44074</td> <td>0.27085</td>	111	MOL005980	Neohesperidin	57.44074	0.27085
MOL000358 Beta-sitosterol 36,9139 07,512 MOL000359 Sitosterol 36,9139 0,7512 MOL000736 (-)-Taxifolin 60,5062 0,27342 MOL000352 (-)-Taxifolin 60,5062 0,27342 MOL000332 n-coumaroyltyramine 86,6283 0,20237 MOL000433 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl) ethyl] acrylamide 118,3477 0,2034 MOL000431 Coumaroyltyramine 112,9016 0,20234 MOL000432 Naringenin 50,2399 0,21252 MOL000432 Naringenin 50,2399 0,21252 MOL007640 Macrostemonoide e_qt 35,9559 0,87216 MOL007650 PGA (sup 1) 43,98251 0,2534 MOL0007650 Prostaglandin B1 40,20777 0,2534 MOL0007650 Prostaglandin B1 40,20777 0,2534 MOL000768 Neohesperidin_qt 71,1688 0,22355 MOL001798 Neohesperidin_qt 71,6886 0,22355 MOL000160 5,7-Dihy		MOL000073	Ent-epicatechin	48.95984	0.24162
GZ MOL000359 Sitosterol 36.91391 0.7512 MOL000492 (+)-catechin 54.82643 0.24164 MOL000736 (-)-Taxifolin 60.50622 0.27342 MOL000038 Quercetin 46.43335 0.27352 MOL000332 n-coumaroyltyramine 85.62838 0.20287 MOL0000518 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl) ethyl] acrylamide 118.3477 0.26339 MOL000631 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl) ethyl] acrylamide 118.3016 0.20234 XB MOL001973 Sitosteryl acetate 40.38964 0.85102 MOL002341 Hesperetin 70.31209 0.27252 MOL007650 PGA (sup 1) 33.98251 0.25437 MOL007651 Prostaglandin B1 40.20777 0.25384 MOL001798 Neohesperidin_qt 71.16886 0.22355 MOL001798 Neohesperidin_qt 41.5043 0.24364 MOL001798 Neohesperidin_qt 41.5043 0.24364 MOL0002914 Eriodyctiol (flavanoe)		MOL000358	Beta-sitosterol	36.91391	0.75123
MOL000492 (+)-catechin 54.82643 0.24164 MOL001736 (-)-Taxifolin 60.5062 0.27342 MOL000038 Quercetin 46.4335 0.27525 MOL0000358 Beta-sitosterol 36.9139 0.75123 MOL0000483 (Z)-3-(4-Hydroxy-3-methoxy-phenyl-N-12-(4-Hydroxyphenyl) ethyl] acrylamide 118.3477 0.26399 MOL0000431 Coumaroyltyramine 112.9016 0.20234 MOL0002341 Hesperetin 70.31200 0.27252 MOL007640 Macrostemonoside e_qt 35.259 0.87216 MOL007650 PGA (sup 1) 43.98251 0.25437 MOL007651 Prostaglandin B1 40.0277 0.25384 MOL001798 Neohesperidin_qt 71.16886 0.27055 MOL001914 Ammidin 34.5485 0.24552 MOL002944 Eriodyctiol (flavanone) 41.35043 0.24552 MOL002194 Eriodyctiol (flavanone) 41.35043 0.24364 MOL002849 Didymin 38.5519 0.2308 MOL0007879 5	GΖ	MOL000359	Sitosterol	36.91391	0.7512
MOL001736 (-)-Taxifolin 60.50622 0.27342 MOL000038 Quercetin 46.43333 0.7525 MOL000332 n-coumaroyltyramine 85.62883 0.20247 MOL000358 Beta-sitosterol 36.91391 0.75123 MOL000631 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-12-(4-hydroxyphenyl) ethyl] acrylamide 118.3477 0.26399 MOL000631 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-12-(4-hydroxyphenyl) ethyl] acrylamide 10.839747 0.26399 MOL000433 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-12-(4-hydroxyphenyl) ethyl] acrylamide 10.83910 0.20239 MOL000231 Cumaroyltyramine 112.9016 0.202342 0.83102 MOL000328 Naringenin 59.2939 0.21128 0.27252 MOL007640 Macrostemonoside e_qt 35.259 0.87216 MOL007651 Prostaglandin B1 40.20777 0.25343 MOL001798 Neohesperidin_qt 7.1686 0.27085 MOL001803 Sinensetin 50.5565 0.46444 MOL002914 Eriodyctiol (flavanone) 47.3644 0.27226 <td></td> <td>MOL000492</td> <td>(+)-catechin</td> <td>54.82643</td> <td>0.24164</td>		MOL000492	(+)-catechin	54.82643	0.24164
MOL00098Quercetin46.433350.27525MOL000358n-coumaroyltyramine85.62880.20287MOL000438(Z)-3-(4-Hydroxy-Beta-sitosterol36.9190.75123MOL000631(Z)-3-(4-Hydroxy-phenyl)-N-[2-(4-hydroxyphenyl) ethyl] acrylamide118.3470.26399MOL001973Coumaroyltyramine112.9010.20234XBMOL001973Sitosteryl acetate40.88960.85102MOL001341Hesperetin70.312090.27252MOL007650PGA (sup 1)43.982510.25437MOL007651Prostaglandi B140.20770.25384MOL007651Prostaglandi B140.20770.25437MOL001941Ammidin36.162630.24555MOL001941Sinensetin50.56680.4434MOL002104Sinensetin50.55680.4434MOL002104Si.7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one47.736440.27226MOL0051005,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one47.736440.27226MOL0058249Didymin38.55190.329890.21128MOL007857Tetramethoxyluteolin43.684760.3709MOL007858MOL007877Sosienesetin50.55140.3948MOL007852Poncirin36.54610.74202MOL003277Sosienesetin-7-rutinoside41.240130.7616MOL013277Sosienesetin-7-rutinoside41.240130.7616MOL013428Poncirin36.34230.24362MOL013428Isosakurane		MOL001736	(–)-Taxifolin	60.50622	0.27342
MOL000332 n-coumaroyltyramine 85.62883 0.20287 MOL000433 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)N-[2-(4-hydroxyphenyl) ethyl] acrylamide 118.3477 0.26399 MOL000631 Coumaroyltyramine 112.9016 0.20234 MOL000334 Hesperetin 70.31209 0.27252 MOL002341 Hesperetin 70.31209 0.27252 MOL00750 PGA (sup 1) 43.98251 0.25437 MOL007650 PGA (sup 1) 43.98251 0.25437 MOL007651 Prostaglandin B1 40.20777 0.25384 MOL001798 Neohesperidin_qt 71.1686 0.24755 MOL001798 Neohesperidin_qt 71.1686 0.24755 MOL001803 Sinensetin 50.5565 0.44634 MOL001991 Ammidin 34.54856 0.22355 MOL0019214 Eriodyctiol (flavanone) 41.35043 0.2349 MOL005828 Naringenin 59.2939 0.21128 MOL005849 Didymin 38.8513 0.3309 MOL00787 Tetramethoxyluteolin </td <td></td> <td>MOL000098</td> <td>Quercetin</td> <td>46.43335</td> <td>0.27525</td>		MOL000098	Quercetin	46.43335	0.27525
MOL000358 Beta-sitosterol 36.91391 0.75123 MOL000433 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl) etryl] acrylamide 118.3477 0.20334 XB MOL000531 Coumaroyltyramine 112.0016 0.20234 XB MOL001973 Sitosteryl acetate 40.38964 0.85102 MOL004328 Naringenin 59.2939 0.21128 MOL007640 Macrostemonoside e_qt 35.259 0.87216 MOL007650 PGA (sup 1) 43.98251 0.24352 MOL0007651 Prostaglandin B1 40.2077 0.25384 MOL0001798 Neohesperidin_qt 71.1688 0.24552 MOL001303 Sinensetin 50.5568 0.44634 MOL00141 Ammidin 34.5456 0.22355 MOL002510 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.7564 0.27226 MOL005828 Nobiletin 61.66944 0.51652 0.37009 MOL005829 Fetramethoxyluteolin 36.5619 0.37069 MOL0005820 5,7-Dihydroxy-2-(3-hydroxy		MOL000332	<i>n</i> -coumaroyltyramine	85.62883	0.20287
MOL000483 (Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl) ethyl] acrylamide 118.3477 0.26394 MOL000631 Coumaroyltyramine 112.9016 0.20234 MOL001973 Sitosteryl acetate 40.38966 0.85102 MOL002341 Hesperetin 70.31209 0.27252 MOL007640 Marrostermonoside e_qt 35.259 0.87216 MOL007650 PGA (sup 1) 43.98251 0.2534 MOL007651 Prostaglandin B1 40.2077 0.2584 MOL0010798 Neohosperidin_qt 71.16886 0.27055 MOL00191798 Neohesperidin_qt 71.16886 0.27055 MOL002914 Eriodyctiol (flavanone) 41.35043 0.24352 MOL002914 Eriodyctiol (flavanone) 41.35043 0.24356 MOL005100 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.7364 0.27226 MOL005849 Didymin 36.5139 0.2305 0.24052 MOL005849 Eteramethoxyluteolin 41.626,381-5-[(E)-3-Hydroxyr-2-(3-hydroxy-3-methylol-2,3-dihydrobenzofurara-2 50.5516 0.37069		MOL000358	Beta-sitosterol	36.91391	0.75123
MOL000631 Coumaroyltyramine 112.9016 0.20234 XB MOL001973 Sitosteryl acetate 40.38964 0.85102 MOL002341 Hesperetin 70.31209 0.27252 MOL007640 Macrostemonoside e_qt 35.259 0.87216 MOL007650 PGA (sup 1) 43.98251 0.25437 MOL007651 Prostaglandin B1 40.20777 0.25384 MOL001978 Neohesperidin_qt 71.1688 0.27055 MOL001908 Sinensetin 50.55865 0.44534 MOL0019141 Ammidin 34.54856 0.22355 MOL00102914 Eriodyctiol (flavanone) 41.35043 0.24128 MOL005100 5,7-Dihydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27226 MOL005100 5,7-Dihydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27226 MOL005828 Nabiletin 61.66944 0.51625 MOL007879 Tetramethoxylutcolin 43.68476 0.37009 XB MOL007879 Tetramethoxylutcolin 43.68476 0.37029		MOL000483	(Z)-3-(4-Hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl) ethyl] acrylamide		0.26399
XBMOL001973Sitosteryl acetate40,389640.85102MOL002341Hesperetin70.312090.27252MOL007640Macrostemonoside e_qt35.2590.21128MOL007650PGA (sup 1)43,982510.25437MOL007650Prostaglandin B10.0207770.25384MOL001798Neohesperidin_qt71.16860.27855MOL001979Neohesperidin_qt71.16860.27855MOL001979Neohesperidin_qt71.16860.27855MOL001979Neohesperidin_qt1.450430.24351MOL001941Ammidin34.548560.22355MOL002914Eriodyctiol (flavanone)41.350430.2436MOL0051005,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one47.736440.27226MOL005828Nobiletin61.669440.37094MOL005829Didymin38.55130.23908MOL005829Yel-(25,3R)-5-[(E)-3-Hydroxyprop-1-enyl]-7-methoxy-3-methylol-2,3-dihydrobenzofuran-2-50.755140.3948MOL013276Poncirin36.546010.4149MOL013277Isosinensetin51.15160.44149MOL0132795,7,4'-Trimethylapigenin39.832720.9363MOL013330Prangenin hydrate43.268470.27363MOL013430Prangenin hydrate72.634010.29428MOL013433Prangenin hydrate63.20760.3136MOL013434Isoponcimarin63.20760.3136MOL013435Poncimarin R63.20760.3136		MOL000631	Coumaroyltyramine		0.20234
MOL002341 Hesperetin 70.31209 0.27252 MOL007640 Naringenin 59.2939 0.21128 MOL007650 PGA (sup 1) 43.98251 0.25437 MOL007651 Prostaglandin B1 40.20777 0.25384 MOL0017681 Prostaglandin B1 40.20777 0.25384 MOL001798 Neohesperidin_qt 71.1688 0.27655 MOL0011798 Neohesperidin_qt 71.1688 0.27855 MOL001914 Ammidin 35.459 0.23355 MOL0004328 Naringenin 59.2939 0.2128 MOL005100 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.3644 0.27226 MOL005828 Nobiletin 61.66944 0.3109 MOL005849 Didymin 38.5139 0.23948 MOL007579 Tetramethoxyluteolin 43.68476 0.3709 MOL013276 Poncirin 36.5401 0.7402 MOL013277 Isosinensetin 51.516 0.44149 MOL013320 Obacunone 3.885139 0.29	XB	MOL001973	Sitosteryl acetate	40.38964	0.85102
MOL004328 Naringenin 59.2939 0.21128 MOL007640 Macrostemonoside e_qt 35.259 0.87216 MOL007650 PGA (sup 1) 43.9821 0.25334 MOL007651 Prostaglandin B1 40.20777 0.25384 MOL001798 Neohesperidin_gt 71.16886 0.24552 MOL001941 Ammidin 34.54856 0.22355 MOL002914 Eriodyctiol (flavanone) 41.35043 0.2436 MOL005828 Naringenin 59.2939 0.21128 MOL005828 Nobiletin 61.66944 0.2152 MOL007879 Tetramethoxyluteolin 43.68476 0.3709 XIS YI]-2-methoxy-phenol 50.75614 0.3404 MOL007879 4-[(25,3R)-5-[(E)-3-Hydroxy-pro-1-enyl]-7-methoxy-shenol 50.75514 0.3948 MOL013277 Isosinensetin 51.15169 0.4149 MOL013277 5,7,4'-Trimethylapigenin 39.8327 0.2908 MOL013275 5,7,4'-Trimethylapigenin 39.8327 0.29248 MOL013352 Obacunone </td <td></td> <td>MOL002341</td> <td>Hesperetin</td> <td>70.31209</td> <td>0.27252</td>		MOL002341	Hesperetin	70.31209	0.27252
MOL007640 Macrostemonoside e_qt 35.259 0.87216 MOL007650 PGA (sup 1) 43.98251 0.25437 MOL007651 Prostaglandin B1 40.2077 0.25384 MOL00006 Luteolin 36.16263 0.24552 MOL001798 Neohesperidin_qt 71.16886 0.27085 MOL0019141 Ammidin 34.54856 0.223552 MOL0019214 Eriodyctiol (flavanore) 41.35043 0.2436 MOL001803 Sinensetin 59.2939 0.21128 MOL001810 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27256 MOL005828 Nobiletin 61.66944 0.51652 MOL007879 Tetramethoxyluteolin 43.68476 0.37009 MOL007879 Tetramethoxyluteolin 50.75514 0.3948 MOL003277 Isosinensetin 51.5159 0.41419 MOL013276 Poncirin 36.5401 0.74202 MOL013279 5,7,4'-Trimethylapigenin 39.83272 0.29636 MOL013352 Obacunore		MOL004328	Naringenin	59.2939	0.21128
MOL007650 PGA (sup 1) 43.98251 0.25437 MOL007651 Prostaglandin B1 40.20777 0.25384 MOL000006 Luteolin 36.1623 0.24552 MOL001798 Neohesperidin_qt 71.16886 0.27085 MOL001941 Ammidin 34.54856 0.22355 MOL002914 Eriodyctiol (flavanone) 41.35043 0.24362 MOL00328 Naringenin 59.2939 0.21128 MOL005100 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27326 MOL005828 Nobiletin 61.66944 0.51652 MOL007879 Tetramethoxyluteolin 38.55139 0.23908 MOL007879 Tetramethoxyluteolin 43.68476 0.37009 MOL007879 Tetramethoxyluteolin 36.54601 0.74202 MOL0013276 Poncirin 50.7514 0.3948 MOL013276 Poncirin 36.54601 0.74202 MOL013279 5,7,4' Trimethylapigenin 39.83272 0.29636 MOL013432 Poncirin		MOL007640	Macrostemonoside e_qt	35.259	0.87216
MOL007651 Prostaglandin B1 40.20777 0.25384 MOL000006 Luteolin 36.16263 0.24552 MOL001798 Neohesperidin_qt 71.16886 0.27085 MOL001901 Sinensetin 50.5685 0.44634 MOL001914 Ammidin 44.54856 0.22355 MOL0019214 Eriodyctiol (flavanone) 41.35043 0.2436 MOL005828 Naringenin 59.2939 0.21128 MOL005828 Nobiletin 61.6944 0.51652 MOL005829 Didymin 38.55139 0.23908 MOL005709 Tetramethoxyluteolin 43.68476 0.37009 XS MOL009053 4-[(2S,3R)-5-[(E)-3-Hydroxyr-1-enyl]-7-methoxy-3-methylol-2,3-dihydrobenzofuran-2- yl]-2-methoxy-phenol 50.75514 0.3948 MOL013276 Poncirin 36.54601 0.74202 MOL013352 Obacunone 43.28625 0.76724 MOL013430 Prangenin 43.59734 0.29488 MOL013433 Prangenin hydrate 72.63401 0.28463 MOL013433<		MOL007650	PGA (sup 1)	43.98251	0.25437
MOL000006 Luteolin 36.16263 0.24552 MOL001798 Neohesperidin_qt 71.16886 0.27085 MOL001803 Sinensetin 50.5568 0.44634 MOL001941 Ammidin 34.5486 0.22355 MOL001428 Naringenin 59.2939 0.21128 MOL005100 5,7-Dihydroxy-2(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.22355 MOL005100 5,7-Dihydroxy-2(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.22398 MOL005100 5,7-Dihydroxy-2(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.22398 MOL005828 Noblotistin 38.5139 0.23908 MOL005849 Didymin 38.5139 0.3909 MOL007879 Tetramethoxyluteolin 43.68476 0.3709 MOL013276 Poncirin 36.54001 0.74202 MOL013279 5,7,4'/ Trimethylapigenin 39.83272 0.2963 MOL013352 Obacunone 43.28625 0.76724 MOL013433 Prangenin hydrate 72.63401 0.29428		MOL007651	Prostaglandin B1	40.20777	0.25384
MOL001798 Neohesperidin_qt 71.16886 0.27085 MOL001803 Sinensetin 50.55685 0.44634 MOL001941 Ammidin 34.54856 0.22355 MOL002914 Eriodyctiol (flavanone) 41.35043 0.2436 MOL005100 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27226 MOL005828 Nobiletin 61.66944 0.51652 MOL005849 Didymin 38.55139 0.23908 MOL007879 Tetramethoxylucolin 43.68476 0.37009 MOL013276 Poncirin 36.54601 0.74202 MOL013277 Isosinensetin 51.15169 0.44149 MOL013279 5,7,4'-Trimethylapigenin 39.83272 0.29428 MOL013279 S,7,4'-Trimethylapigenin 39.83272 0.29428 MOL013430 Prangenin hydrate 72.63401 0.28463 MOL013433 Prangenin hydrate 72.63401 0.28463 MOL013433 Prangenin hydrate 72.63401 0.28463 MOL013433 Pran		MOL000006	Luteolin	36.16263	0.24552
MOL001803 Sinensetin 50.55685 0.44634 MOL001941 Ammidin 34.54856 0.22355 MOL002914 Eriodyctiol (flavanone) 41.35043 0.2436 MOL001328 Naringenin 59.2939 0.21128 MOL005100 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27226 MOL005828 Nobiletin 61.66944 0.51652 MOL007879 Tetramethoxyluteolin 38.55139 0.23908 MOL007879 4-[(2S,3R)-5-[(E)-3-Hydroxyrd-1-emyl]-7-methoxy-3-methylol-2,3-dihydrobenzofuran-2- yl]-2-methoxy-1-emothoxy-3-methylol-2,3-dihydrobenzofuran-2- yl]-2 50.75514 0.3948 MOL0013276 4-[(2S,3R)-5-[(E)-3-Hydroxyrop-1-emyl]-7-methoxy-3-methylol-2,3-dihydrobenzofuran-2- yl]-2-methoxy-phenol 50.75514 0.3948 MOL013277 Isosinensetin 51.15169 0.44149 MOL013279 5,7,4'-Trimethylapigenin 39.83272 0.29636 MOL013428 Isosakuranetin-7-rutinoside 41.24013 0.71616 MOL013430 Prangenin 43.59734 0.29428 MOL013433 Prangenin hydrate 72.63		MOL001798	Neohesperidin_qt	71.16886	0.27085
MOL001941 Ammidin 34.54856 0.22355 MOL002914 Eriodyctiol (flavanone) 41.35043 0.2436 MOL004328 Naringenin 59.2939 0.21128 MOL005100 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27226 MOL005828 Nobiletin 61.66944 0.51652 MOL007879 Tetramethoxyluteolin 43.68476 0.37009 MOL013276 Poncirin 43.68476 0.37049 MOL013277 Isosiensetin 51.5169 0.44149 MOL013282 Sor,7,4'-Trimethylapigenin 39.83272 0.29636 MOL013279 5,7,4'-Trimethylapigenin 39.83272 0.29636 MOL013428 Isosakuranetin-7-rutinoside 41.24013 0.7166 MOL013430 Prangenin hydrate 72.63401 0.28863 MOL013435 Poncimarin 63.62093 0.34942 MOL013435 Poncimarin 63.62093 0.34942 MOL013435 Poncimarin 63.62093 0.34942 MOL013436 Isopo		MOL001803	Sinensetin	50.55685	0.44634
MOL002914 Eriodyctiol (flavanone) 41.35043 0.2436 MOL004328 Naringenin 59.2939 0.21128 MOL005100 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27226 MOL005828 Nobiletin 61.66944 0.51652 MOL007879 Tetramethoxyluteolin 38.55139 0.23908 MOL009053 4-[(2S,3R)-5-[(E)-3-Hydroxyprop-1-enyl]-7-methoxy-3-methylol-2,3-dihydrobenzofuran-2- yl]-2-methoxy-phenol 50.75514 0.3948 MOL013276 Poncirin 36.54601 0.74202 MOL013279 5,7,4'-Trimethylapigenin 39.83272 0.29636 MOL013428 Isosakuranetin-7-rutinoside 41.24013 0.71616 MOL013430 Prangenin 43.59734 0.29428 MOL013433 Prangenin hydrate 72.63401 0.28863 MOL013433 Prangenin hydrate 72.63401 0.28863 MOL013435 Poncimarin 63.2076 0.31316 MOL013437 6-Methoxy aurapten 31.23777 0.3008 MOL0134340 Gitrusin B 40.7971		MOL001941	Ammidin	34.54856	0.22355
MOL004328 Naringenin 59.2939 0.21128 MOL005100 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one 47.73644 0.27226 MOL005828 Nobiletin 61.66944 0.51652 MOL007879 Didymin 38.55139 0.23908 MOL009053 4-[(2S,3R)-5-[(E)-3-Hydroxyprop-1-enyl]-7-methoxy-3-methylol-2,3-dihydrobenzofuran-2- yl]-2-methoxy-phenol 50.75514 0.3948 MOL013276 Poncirin 36.54601 0.74202 MOL013279 5,7,4'-Trimethylapigenin 39.83272 0.29636 MOL013428 Isosiaensetin 51.15169 0.44149 MOL013430 Prangenin 43.28625 0.76724 MOL013433 Prangenin hydrate 72.63401 0.28863 MOL013433 Prangenin hydrate 72.63401 0.28863 MOL013434 Isoponcimarin 63.2276 0.31316 MOL013437 6-Methoxy aurapten 31.23777 0.3008 MOL0134340 Gitrusin B 40.70717 0.71331		MOL002914	Eriodyctiol (flavanone)	41.35043	0.2436
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		MOL013440	Citrusin B	40.79717	0.71331

TABLE 1: Effective components of Zhishi Xiebai Guizhi Decoction that meet the demands of both $OB \ge 30\%$ and $DL \ge 0.18$ were obtained from TCMSP.

response, blood circulation, cellular response to lipid, cellular response to peptide, response to hormone, negative regulation of apoptotic process, regulation of immune response, regulation of acute inflammatory response, regulation of cytokine production involved in inflammatory response, and positive regulation of acute inflammatory response (Figure 6). The results showed that Zhishi Xiebai Guizhi Decoction is closely related to inflammatory reaction in the treatment of CHD.

According to the *P* value, a total of 29 pathways were screened by KEGG analysis, including pathways in cancer, adrenergic signaling in cardiomyocytes, IL-17 signaling



FIGURE 2: The network diagram of the compound and the target protein.



FIGURE 3: Venn diagram of targets of Zhishi Xiebai Guizhi Decoction in treating coronary heart disease.



FIGURE 4: Network diagram of intersection targets of Zhishi Xiebai Guizhi Decoction in the treatment of coronary heart disease.

pathway, T cell receptor signaling pathway, PI3K-Akt signaling pathway, and AMPK signaling pathway (Figure 7).

3.4. Clinical Trial Results. The CRP of the two groups of patients before and after treatment showed a skewed distribution, so the median (interquartile range) was used to describe the difference, and nonparametric tests were used to compare the differences (Figure 8). The comparison of CRP in the two groups before and after treatment was statistically significant (P < 0.05), and the CRP levels in both the test group and the control group decreased after treatment. After rank sum test, there was no statistically significant difference between the two groups before treatment (P > 0.05), and there was no significant difference in CRP between the two groups after treatment (P > 0.05) (Table 3).

Teseb = before treatment in the test group; Testa = after treatment in the test group

Controlb = before treatment in the control group; Controla = after treatment in the control group.

The NLR of the two groups of patients before and after treatment showed a skewed distribution, so the median (interquartile range) was used to describe the difference, and the difference was compared with nonparametric tests (Table 4). The comparison of NLR in the two groups before and after treatment was statistically significant (P < 0.05), and the NLR levels in both the test group and the control

UniP-ID	Protein names	Degree
P03372	Estrogen receptor (ESR1)	41
P10275	Androgen receptor (AR)	40
P35354	Prostaglandin G/H synthase 2 (PTGS2)	35
P37231	Peroxisome proliferator activated receptor gamma (PPARG)	32
P27487	Dipeptidyl peptidase IV (DPP4)	32
P35228	Nitric oxide synthase, inducible (NOS2)	30
P23219	Prostaglandin G/H synthase 1 (PTGS1)	28
P49841	Glycogen synthase kinase-3 beta (GSK3B)	28
Q16539	Mitogen-activated protein kinase 14 (MAPK14)	27
P24941	Cell division protein kinase 2 (CDK2)	27
P20248	Cyclin-A2 (CCNA2)	26
P00918	Carbonic anhydrase II (CA2)	26
P18031	mRNA of protein-tyrosine phosphatase, nonreceptor type 1 (PTPN1)	23
P11309	Protooncogene serine/threonine-protein kinase Pim-1 (PIM1)	23
P00734	Thrombin (F2)	22
P0DP23	Calmodulin (CALM1)	17
P48736	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit, gamma isoform (PIK3CG)	15
Q14524	Sodium channel protein type 5 subunit alpha (SCN5A)	14
P07550	Beta-2 adrenergic receptor (ADRB2)	14
P00742	Coagulation factor Xa (F10)	9

TABLE 2: Top 20 targets of Zhishi Xiebai Guizhi Decoction in the treatment of coronary heart disease.



FIGURE 5: The protein-protein interaction network of Zhishi Xiebai Guizhi Decoction in the treatment of coronary heart disease.

group decreased after treatment. After the rank sum test, there was no statistical difference between the two groups before treatment (P > 0.05), and the difference in NLR between the two groups after treatment was statistically significant (P < 0.05).

The MLR of the two groups of patients before and after treatment showed a skewed distribution, so the median (interquartile range) was used to describe the difference, and the difference was compared with nonparametric tests (Table 5). The comparison of MLR in the two groups before and after treatment was statistically significant (P < 0.05), and the MLR levels in both the test group and the control group decreased after treatment. After the rank sum test, there was no statistical difference between the two groups before treatment (P > 0.05), and the difference in MLR between the two groups after treatment was statistically significant (P < 0.05).

The MHR of the two groups of patients before and after treatment showed a skewed distribution, so the median

(interquartile range) was used to describe the difference, and the difference was compared with nonparametric tests (Table 6). The comparison of MHR in the two groups before and after treatment was statistically significant (P < 0.05), and the MHR levels in both the test group and the control group decreased after treatment. After the rank sum test, there was no statistical difference between the two groups before treatment (P > 0.05), and the difference in MHR between the two groups after treatment was statistically significant (P < 0.05).

4. Discussion

4.1. Summary of Findings. Coronary heart disease is a common cardiovascular disease, caused by coronary atherosclerosis. If not taken seriously, it will cause serious consequences such as myocardial infarction and heart failure [26]. In our study, Zhishi Xiebai Guizhi Decoction was used to treat coronary heart disease. However, illuminating the complex mechanisms of Zhishi Xiebai Guizhi Decoction in the treatment of CHD using traditional methods is challenging. Therefore, the integration of network pharmacology is essential sense based on big data bioinformatics into the study of the molecular mechanisms of TCM in the treatment of diseases [27, 28]. In the present study, network pharmacology was used to explore the material basis and molecular mechanism of Zhishi Xiebai Guizhi Decoction for treatment of CHD.

From the network of herbs, natural compounds, and targets, we found the core compounds of this prescription were quercetin, naringenin, luteolin, (+)-catechin, hesperetin, etc. Quercetin, a flavonoid, is one of the polyphenols characterized as the compounds containing large multiples of phenol structural units [29]. It can reduce blood pressure and promote angiogenesis through antiinflammatory, antioxidant, immune, and other ways [30]. It is a potential protector of coronary heart disease,



¢	positive regulation of acute inflammatory
申	regulation of cytokine production involve
申	regulation of acute inflammatory response
¢	cellular response to peptide
¢	negative regulation of apoptotic process
	regulation of blood pressure
¢.	regulation of immune response
÷.	blood circulation
¢.	cellular response to lipid
白	regulation of inflammatory response
¢	response to hormone

FIGURE 6: GO biological process enrichment analysis.

cancers, and inflammatory bowel disease [31]. It exhibits significant heart related benefits as inhibition of LDL oxidation, endothelium-independent vasodilator effects, and other inflammatory effects [32]. Naringenin has the functions of lowering lipid, anti-inflammatory, antiallergic, antithrombotic effects, and promoting atherosclerosis regression [33–35]. Luteolin administration improved cardiac function, attenuated the inflammatory response, alleviated mitochondrial injury, decreased oxidative stress, inhibited cardiac apoptosis, and enhanced autophagy [36, 37]. Studies have shown that it can attenuate isoproterenol-induced myocardial injury and fibrosis in mice [38].

85 common targets were found for drugs and diseases, which might be targets for this prescription when treating CHD. Based on the topological analysis, we further found the 20 critical targets from the 85 common targets for subsequent study, including estrogen receptor (ESR1), androgen receptor (AR), prostaglandin G/H synthase 2(PTGS2), and peroxisome proliferator activated receptor gamma (PPARG). A number of studies also provide evidence for an inhibitory role of PPAR γ in atherosclerosis and that it may exert atheroprotective effects [39]. The human PPAR γ gene is located on chromosome 3 at



FIGURE 7: KEGG enrichment analysis.

position 3p25 and gives rise to three different mRNAs isoforms, y1, y2, and y3. Among them, PPARy3 is predominantly expressed in macrophages, the large intestine, and adipose tissue [40]. The pleiotropic effects of PPARs show the potential of this drug class in terms of treating atherosclerotic disease in the future [41-43], including their ability to decrease thrombosis, cell recruitment, cell activation, foam cell formation, and inflammatory responses, and their concurrent ability to improve plaque stability, endothelial function, endothelial progenitor cell biology, and C efflux. In human atherosclerotic lesions, PPARy activation has been reported to promote differentiation of proatherogenic M1 macrophages into an alternative antiinflammatory phenotype, M2, which could protect against the development of atherosclerosis. There is accumulating evidence suggesting that activated PPAR has powerful antiatherosclerotic properties, which not only directly affects the blood vessel wall but also indirectly affects systemic inflammation [42]. A combination of our GO analysis, clinical trials, and other modern studies has confirmed the important role of inflammation in CHD. KEGG enrichment analysis shows the important position of AMPK, TNF, and PI3K-Akt signaling pathway in CHD [44–46]. PPARy plays a vital role in these pathways.



TABLE 3: Comparison of CRP between two groups (median (interquartile)).

CRP	Before treatment	After treatment	Z value	P value
Test group	1.3 (2.65)	1.3 (1.05)	-2.979	0.003
Control group	1 (1.7)	1.5 (1.1)	-3.498	≤0.001
Z value	-1.447	-1.590		
P value	0.148	0.112		

TABLE 4: Comparison of NLR between two groups (median (interquartile)).

NI D	Before	After	7 valua	Druslara	
INLK	treatment	treatment	Z value	P value	
Test group	2.02 (1.19)	1.27 (0.4)	-7.751	≤ 0.001	
Control group	2.26 (1.14)	1.76 (0.89)	-6.151	≤0.001	
Z value	-1.603	-6.844			
P value	0.109	≤0.001			

TABLE 5: Comparison of MLR between two groups (median (interquartile)).

MID	Before	After	7 value	Drealers	
MLK	treatment	treatment	Z value	P value	
Test group	0.18 (0.09)	0.13 (0.05)	-7.568	≤0.001	
Control group	0.19 (0.14)	0.17 (0.10)	-2.935	0.003	
Z value	-0.59	-5.061			
P value	0.555	≤0.001			

TABLE 6: Comparison of MHR between two groups (median (interquartile)).

мнр	Before	After	7 valua	Duralua	
WIIIK	treatment	treatment	Z value	r value	
Test group	0.32 (0.19)	0.23 (0.14)	-6.796	≤ 0.001	
Control	0.31 (0.25)	0.25 (0.12)	-4.066	≤0.001	
group	0.020	0.000			
Z value	-0.039	-2.686			
P value	0.969	0.007			

4.2. Implication for Clinical Trial. As we all know, inflammatory is of great essence in the pathogenesis of

CHD [2]. Among the various inflammatory factors, besides the CRP that has been widely used in clinical practice, it has been generally recognized. In addition, clinical studies have confirmed that white blood cells and their subtypes are closely related to cardiovascular disease caused by atherosclerosis [47]. White blood cells are an important marker of inflammation. In recent years, experts have integrated various subtypes and recently proposed three indicators: Monocyte to lymphocyte ratio (MLR), Neutrophil to lymphocyte ratio (NLR), and Monocyte to high-density lipoprotein ratio (MHR) [48-52]. They can all be regarded as a kind of inflammatory markers and are related to coronary heart disease [53]. Almost all the compounds in Zhishi Xiebai Guizhi Decoction have anti-inflammatory effects, so we speculate that Zhishi Xiebai Guizhi Decoction treats CHD through inflammation.

4.3. Limitations. The key targets and/or pathways found in network pharmacology have not been verified in clinical trials, but NLR, NHR, and MHR can all be regarded as a kind of inflammatory markers and are related to coronary heart disease. The key targets and pathways also play an important role in inflammation. In the future, we need to verify our conjecture through animal experiments.

5. Conclusions

This study combined network pharmacology and clinical trials to explore the mechanism of Zhishi Xiebai Guizhi Decoction in the treatment of CHD. The results showed that Zhishi Xiebai Guizhi Decoction may exert antiatherosclerosis effect through PPARy. In addition, TNF, AMPK, and PI3K-Akt signaling pathway may also be its potential mechanisms. We hope that computer biology can provide a method for the modern research of Chinese medicine, and Zhishi Xiebai Guizhi Decoction can be recognized as a complementary or alternative treatment for CHD.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All human experiments were approved by the Ethics Committee of Wuxi Hospital of Traditional Chinese Medicine and registered in the Chinese Clinical Trial Registration Center (ethics number: 2018022736, registration number: ChiCTR1800019814).

Disclosure

J. Gao and Y.-J. Pan are the co-first authors.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

H. Chen contributed to conception and design and administrative support. X.-D. Tan contributed to the provision of study materials or patients. J. Gao and Y.-J. Pan contributed to the collection and assembly of data and data analysis and interpretation. All authors contributed to manuscript writing and final approval of the manuscript. All authors contributed equally to this work.

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