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Research Article

Using Network Pharmacology to Explore the Mechanism of Panax notoginseng in the Treatment of Myocardial Fibrosis

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Objective. The mechanism of Panax notoginseng in treating myocardial fibrosis (MF) was investigated using network pharmacology. *Methods*. Effective ingredients and potential targets of Panax notoginseng were screened in relevant databases to construct a compound-target network. Targets of MF were then screened to select common targets and construct a protein-protein interaction network. This was followed by Gene Ontology and pathway enrichment analyses. Molecular docking then verified the results of network analysis. *Results*. A total of 14 effective ingredients and 119 potential targets for MF were predicted. Quercetin, beta-sitosterol, and gossypetin were speculated to be the main active ingredients. The mechanism of action may be related to AGE-RAGE, proteoglycans, and IL-17 signaling pathways. Five key targets (IL6, ALB, AKT1, TNF, and VEGFA) may be involved in the treatment of MF using Panax notoginseng. *Conclusions*. This study embodies the complex network relationship of multicomponents, multitargets, and multipathways of Panax notoginseng in treating MF and provides a novel method for further research on this herb's mechanism.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, and it is estimated that CVD will result in more than 23 million deaths by 2030 [1]. Diabetes mellitus is widely known as a major risk factor for CVD. When glucose is not well-controlled in either type 1 or 2 diabetes, vascular and nerve damage can occur over time [2–4]. Damage to the heart vessels can lead to CVD. Myocardial fibrosis (MF) is a pathophysiologic process of many cardiovascular diseases [5, 6]. MF is the result of persistent and/or repeated damage and stress from various causes. These can include myocardial ischemia and hypoxia due to coronary atherosclerotic stenosis resulting from diabetes mellitus [7, 8]. Drugs such as angiotensin-converting enzyme inhibitors, beta-blockers, statins, and agents that target fibrosis have some beneficial effects. However, they cannot prevent the progression of MF and have certain side effects [9]. Thus, alternative therapies such as traditional Chinese medicine may be a treatment option for MF with fewer side effects and lower cost.

Panax notoginseng (Burk.) F.H. Chen (notoginseng) is an herb commonly used in Chinese medicine. Its traditional application is to promote blood circulation and dispel blood stasis. Records of Panax notoginseng date to the *Compendium of Materia Medica* (*Ben Cao Gang Mu*) compiled by Li Shizhen in the Ming dynasty. Modern research has revealed that the main components of Panax notoginseng include saponins, volatile oils, flavonoids, and polysaccharides. Its pharmacologic effects are mainly reflected in its

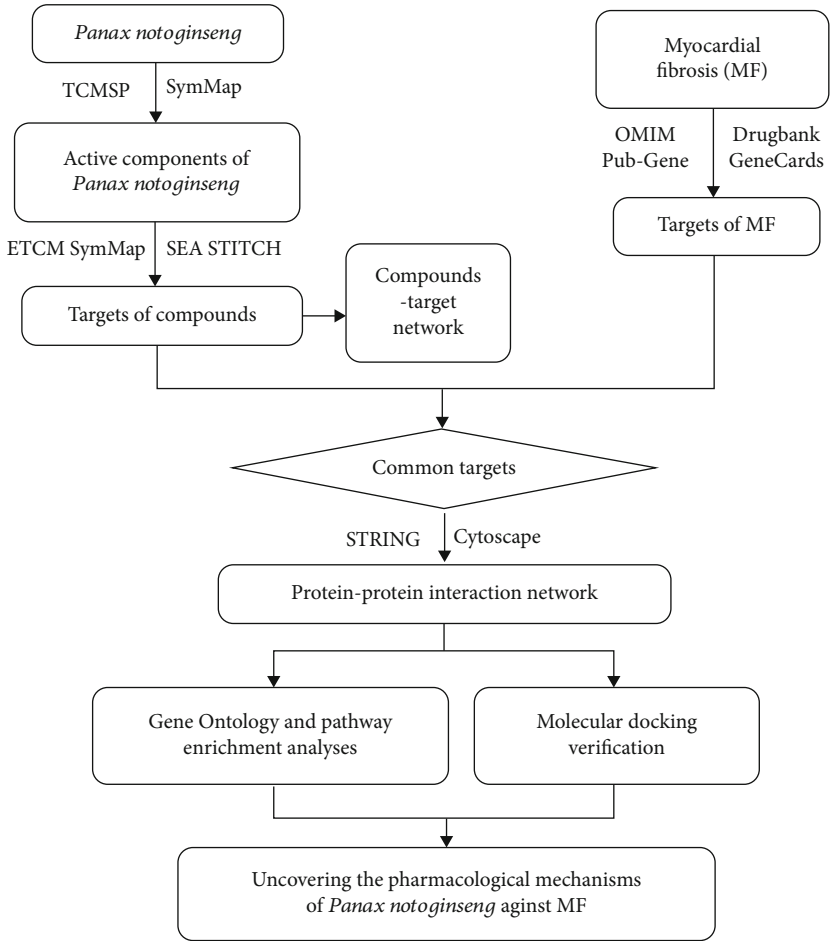


Figure 1: Flow diagram of the pharmacology-based study of Panax notoginseng used in treating MF.

actions on the circulatory and cerebrovascular systems. In murine experiments, Panax notoginseng has been found to have a therapeutic effect on MF [10–12]. However, its mechanism of action remains unclear.

Network pharmacology is a systematic research methodology that combines laboratory and clinical inquiries with data processing to guide drug discovery and development. It is an effective method for studying the complex relationship between Chinese herbal medicines and diseases [13]. This current study uses network pharmacology methods to elucidate the potential mechanism of Panax notoginseng in the treatment of MF and provides a basis for subsequent pharmacologic experimental studies (Figure 1).

2. Materials and Methods

2.1. Screening of Compound Components. The keywords "Panax notoginseng" were used to retrieve the compound components in the SymMap database (http://www.symmap.org) and in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) database (https://tcmspw.com/tcmsp.php). The screening criteria were oral bioavailability (OB) ≥ 30% and drug-like (DL) ≥ 0.18.

2.2. Construction of the Component-Target Network. The targets of the compounds were searched through the Encyclopedia of Traditional Chinese Medicine (ETCM) database (http://www.nrc.ac.cn:9090/ETCM/index.php/Home/Index/index.html), the SymMap database, the Similarity Ensemble Approach (SEA) database (http://sea.bkslab.org), and the STITCH database (http://stitch.embl.de). The UniProt ID of the target was then searched through the Universal Protein Resource (UniProt) database (https://www.uniprot.org), with the species defined as "Homo sapiens." All gene names were assigned their official gene symbol. Then, targets that did not meet the screening criteria were eliminated. Next, the network mapping software Cytoscape 3.8.0 (http://www.cytoscape.org) was used to construct networks for the compounds and their targets. In the network, a node represents a target, gene, molecule, or protein, and the connections between nodes represent the interactions between the targets, genes, molecules, or proteins. The "degree" value of a node represents the number of connections between the nodes in the network; the larger the value, the more likely the target is to become the key target of compounds.

2.3. Acquisition of Disease Targets. The keyword "myocardial fibrosis" was searched in the Online Mendelian Inheritance in Man (OMIM) database (https://omim.org), GeneCards

database (https://www.genecards.org), Drugbank database (https://www.drugbank.ca), and Pub-Gene database (https://www.ncbi.nlm.nih.gov/pubmed) to obtain the disease targets.

2.4. Construction and Analysis of the Protein-Protein Interaction (PPI) Network. The potential targets of the retrieved compounds and disease targets were intersected, and the overlapping targets were selected and imported into the STRING database (https://string-db.org) to obtain the protein interaction relationship. The results were then imported into Cytoscape 3.8.0 software to construct and analyze the interaction network.

2.5. Screening of Core Clusters and Key Targets. Cytoscape plugin MCODE was applied for cluster analysis, and the filter conditions were set as degree cutoff: 2, *k*-core: 2 to select the core cluster with the closest relationship in the network. Then, the plugin CytoHubba was applied to analyze the PPI network and core cluster to obtain the network topology parameters. The targets shared by both the PPI network and core cluster with a high degree were selected as the key targets, which were retrieved in the DisGeNET database (http://www.disgenet.org/search) to obtain the protein class of key targets.

2.6. Gene Ontology and Pathway Enrichment Analyses. The Gene Ontology (GO) database (http://geneontology.org) includes various functions of genes including biologic process (BP), molecular function (MF), and cellular component (CC) and can be applied to the analysis of potential biologic molecular mechanisms. The KEGG database (https://www.kegg.jp) is used to identify biologic functions and candidate targets. In this study, ClusterProfiler (https://bioconductor.org/packages/release/clusterProfiler.html) in R package was applied to GO functional annotation and KEGG pathway analysis, and the enrichment analysis results were visualized.

2.7. Molecular Docking Verification. The Ligand Docking module in Schrödinger software was used to verify the reliability of the results, and the binding activity of the compound to the key targets was evaluated by the docking score. The structures of all the compounds were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and the three-dimensional structures of the key targets were downloaded from the Protein Database (PDB) (http://www.rcsb.org/pdb/home/home.do). The higher the absolute value of the docking score, the stronger the binding ability of small molecules to protease targets.

3. Results and Analysis

3.1. Compound Screening. Ten compounds were screened through the SymMap and TCMSP databases. The OB and DL values of notoginsenoside R1, ginsenoside Rg1, ginsenoside Rb1, and ginsenoside Rb2 were smaller than the screening criteria and were deleted by the system. However, through searching the literature, we found that these compounds are related to myocardial fibrosis and diabetes and thus included the compounds [11, 14–16]. Therefore, a total of 14 compounds were eventually contained in the follow-up study (Table 1).

3.2. Target Prediction and Network Analysis of Compounds. Potential targets of compounds through ETCM, SymMap, SEA, and STITCH databases were searched, and 829 targets of Panax notoginseng were obtained after deleting duplicates.

Using Cytoscape 3.8.0, we constructed a network relationship among compounds and predicted targets (Figure 2). The resulting network included 451 nodes and 829 interaction edges. The degree values of compounds in the compound-target network were then obtained (Table 2). Quercetin has 238 potential targets, followed by beta-sitosterol with 121, gossypetin with 102, and stigmasterol with 96. These higher-degree compounds are likely to be involved in treatment of MF by Panax notoginseng.

3.3. Results of Disease Target Retrieval. With "myocardial fibrosis" as the keyword, a combined total of 601 myocardial fibrosis disease targets were found in the OMIM, Pub-Gene, Drugbank, and GeneCards databases after deleting duplicates.

3.4. Screening of Drug-Disease Targets. The intersections of potential targets of Panax notoginseng and disease targets resulted in 119 potential treatment targets for MF.

3.5. PPI Network of Panax notoginseng in the Treatment of MF and Key Target Analysis. The PPI network was mapped using common potential targets of Panax notoginseng and MF, consisting of 119 nodes and 2597 interaction edges (Figure 3(a)). The CytoHubba plug-in was used to analyze the PPI network to obtain core clusters (Figure 3(b)) and key targets (degree > 90). The following are the five targets with the largest degree value: interleukin 6 (IL6), albumin (ALB), AKT serine/threonine kinase 1 (AKT1), tumor necrosis factor (TNF), and vascular endothelial growth factor A (VEGFA), whose protein class involves transfer/carrier protein, calcium-binding protein, kinase, transferase, and signaling molecule (Table 2). The network of key targets was constructed based on the STRING database (Figure 3(c)). In the network, the key targets interacted with each other through known (from curated databases and experimentally determined), predicted (gene neighborhood, gene fusions, and gene cooccurrence), and other (text mining, coexpression, and protein homology) interactions.

3.6. GO and KEGG Enrichment Analysis. GO functional annotation and KEGG pathway analysis were performed on 119 targets of the PPI network. The top 20 were then visualized as bubble charts (Figure 4). In the biological process, Panax notoginseng has great influence on nutrient levels, lipopolysaccharide, and molecule of bacterial origin (Figure 4(a)). At the molecular level, the function of drug components of Panax notoginseng is mainly related to cytokine receptor binding, receptor ligand activity, and cytokine activity (Figure 4(b)). Targets in the cellular components are closely related to membrane raft, membrane microdomain, and membrane region (Figure 4(c)).

Table 1: Potential effective compounds of Panax notoginseng.

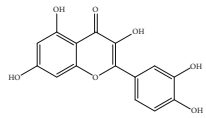
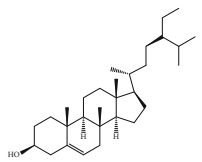
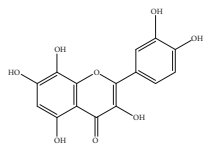
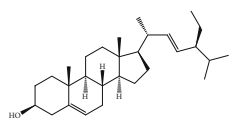
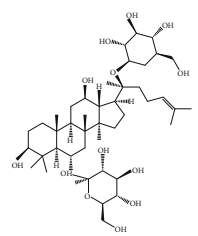
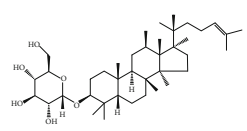
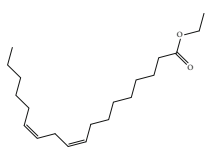
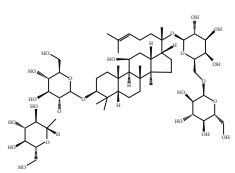
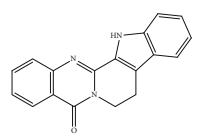
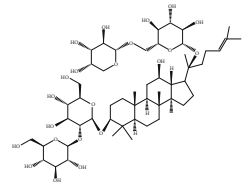
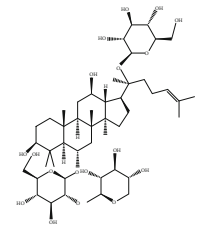
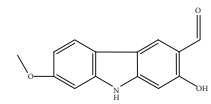
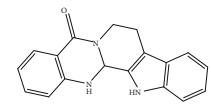
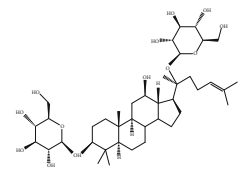
	Compound	OB%	DL	Degree	Structure
1	Quercetin	46.43	0.28	238	
2	Beta-sitosterol	36.91	0.75	121	
3	Gossypetin	35	0.31	102	
4	Stigmasterol	43.83	0.76	96	
5	Ginsenoside Rg1	9.03	0.28	46	
6	Ginsenoside Rh2	36.32	0.56	41	
7	Mandenol	42	0.19	40	
8	Ginsenoside Rb1	6.24	0.04	38	
9	Rutaecarpine	40.3	0.6	36	
10	Ginsenoside Rb2	6.02	0.04	28	

Table 1: Continued.

	Compound	OB%	DL	Degree	Structure
11	Notoginsenoside R1	4.27	0.13	26	
12	2-Hydroxy-3-formyl-7-methoxycarbazole	83.08	0.18	10	
13	Dihydrorutaecarpine	42.27	0.6	4	
14	Ginsenoside F2	36.43	0.25	3	

A total of 230 enrichment results were obtained by KEGG pathway analysis. The first 20 pathways were screened according to adjusted $p < 0.05$ (Figure 5) and consisted of 101 nodes and 419 interaction edges, which mainly involve signaling pathways such as the advanced glycation end products-receptor for advanced glycation end product (AGE-RAGE) signaling pathway in diabetic complications, proteoglycans in cancer, fluid shear stress and atherosclerosis, and interleukin-17 (IL-17) signaling pathway, thus indicating that the effective components of Panax notoginseng might treat MF by acting on these pathways.

3.7. Verification of Results by Molecular Docking. The key targets IL6, ALB, AKT1, TNF, and VEGFA were used for molecular docking with the effective compounds of Panax notoginseng, and a heat map was drawn based on the results (Figure 6). All bioactive components of Panax notoginseng had good binding with key targets, suggesting that Panax notoginseng has a strong tendency as a therapeutic strategy for MF via these key targets.

Results showed that rutaecarpine has a strong binding ability with ALB (docking score = −10.526), AKT1 (docking score = −8.277), and TNF (docking score = −4.689) (Figure 7). Dihydrorutaecarpine has a strong binding ability to IL6 (docking score = −3.345) and ginsenoside Rb1 with VEGFA (docking score = −6.188).

4. Discussion

This study used network pharmacology to systematically analyze the mechanism of action of Panax notoginseng in the treatment of myocardial fibrosis (MF). The resulting PPI network has 119 targets, accounting for one-third of the target number of Panax notoginseng. Five key targets, IL6, ALB, AKT1, TNF, and VEGFA, have high network value. Thus, we speculate that the effective components of Panax notoginseng may have pharmacologic activities in the treatment of MF through these targets.

Fibrosis is the final stage of a chronic inflammatory response, which can be caused by many factors. IL6 is a potent proinflammatory cytokine involved in MF [17]. Fibroblasts maintain this potential pathogenic change by regulating the production of IL6. Overexpression of IL6 is sufficient to induce myofibroblast proliferation, differentiation, and fibrosis. IL6 is involved in ischemic myocardial remodeling by upregulating the TGF-β1 signaling pathway [18–20]. TNF-α is also a proinflammatory cytokine with a wide range of biologic effects and is involved in the pathophysiology of various cardiovascular diseases. Low-level expression of TNF-α in normal myocardium has a protective effect on myocardial cells. However, its increased expression can cause myocardial fibroblast proliferation, myocardial cell death, systolic dysfunction, cardiac fibrosis, and ventricular remodeling [21–23].

In this network pharmacology study, we found that ALB, VEGFA, and AKT1 are also involved in MF. Jäntti et al. found a close relationship between the ALB level and cardiac function. When the plasma ALB level of hemodialysis patients was increased, cardiac function of patients improved, thus effectively raising their quality of life [24]. Studies have found that VEGFA can induce angiogenesis, and in infarcted hearts, VEGFA-mediated cardiac stem cell engraftment resulted in a reduction in fibrosis [25, 26]. The Akt signaling pathway is involved in cardiac hypertrophy

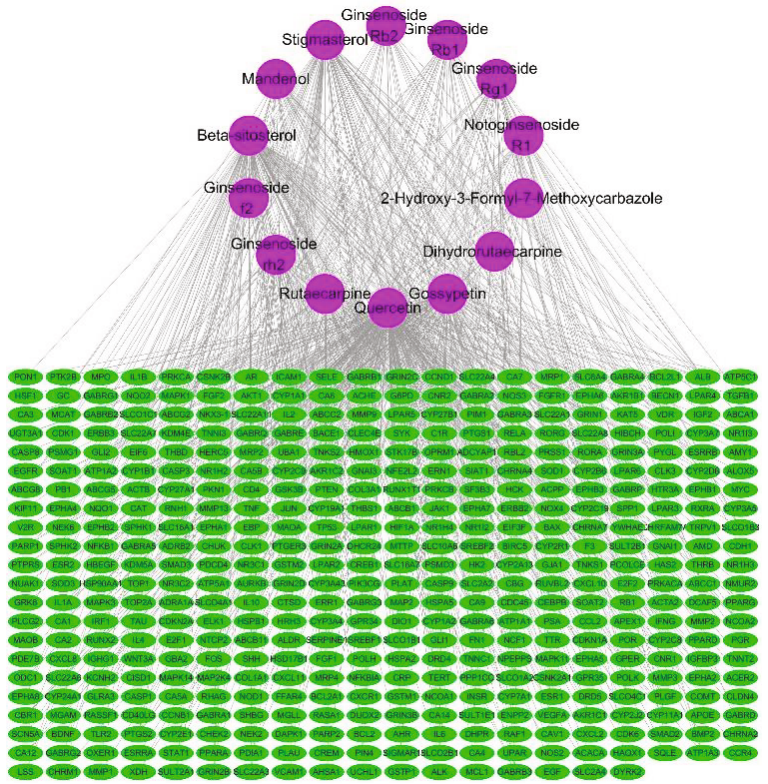


Figure 2: Effective component-target network. Violet nodes represent compounds of Panax notoginseng, and green nodes represent predicted targets.

Table 2: Protein classes of key targets.

Gene name	Target	UniProt ID	Protein class	Degree
IL6	Interleukin 6	P05231	None	106
ALB	Albumin	P02768	Transfer/carrier protein	100
AKT1	AKT serine/threonine kinase 1	P31749	Calcium-binding protein; kinase; transfer/carrier protein; transferase	98
TNF	Tumor necrosis factor	P01375	Signaling molecule	98
VEGFA	Vascular endothelial growth factor A	P15692	Signaling molecule	95

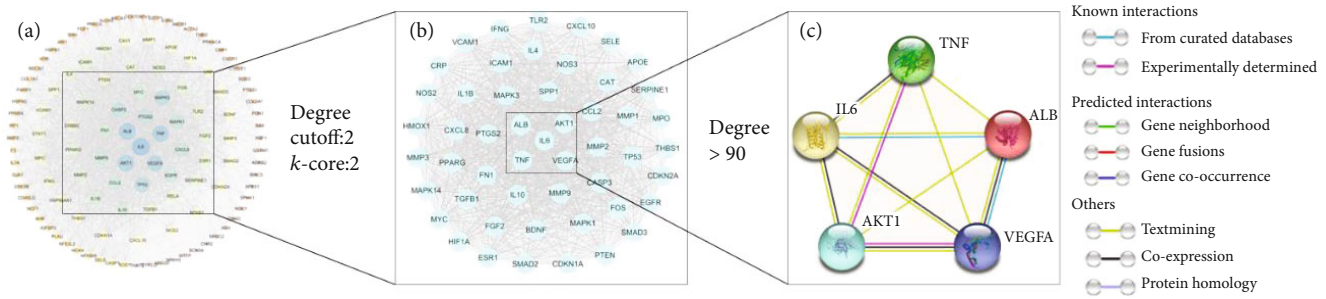
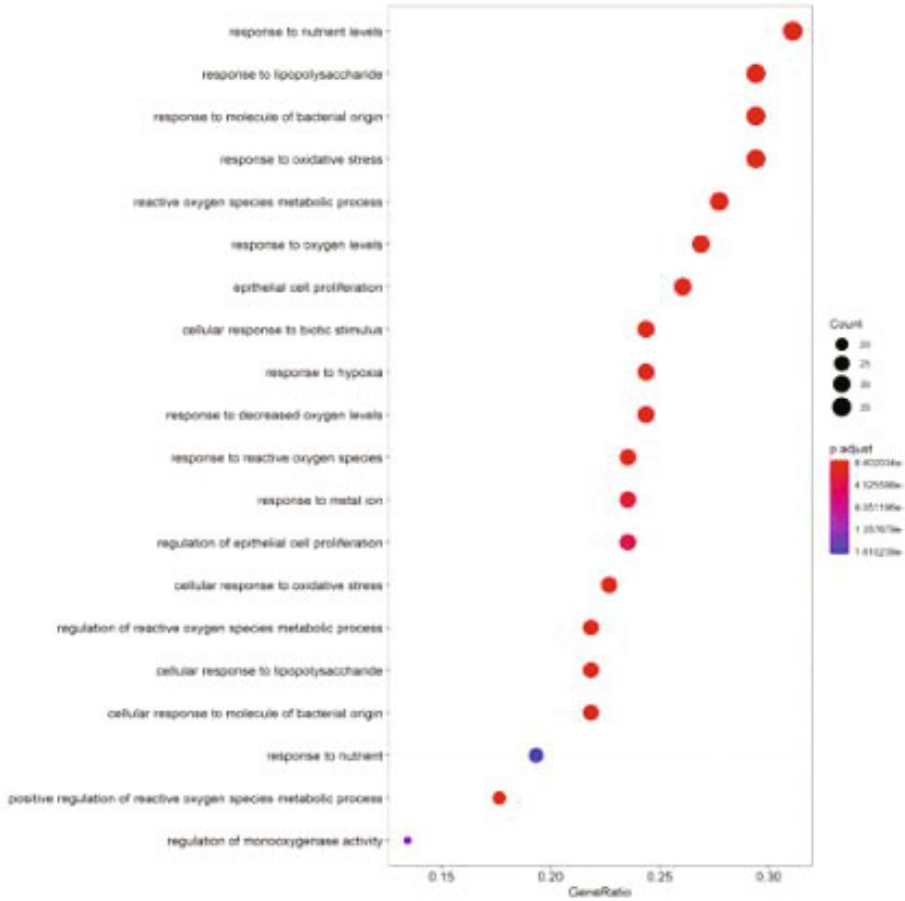
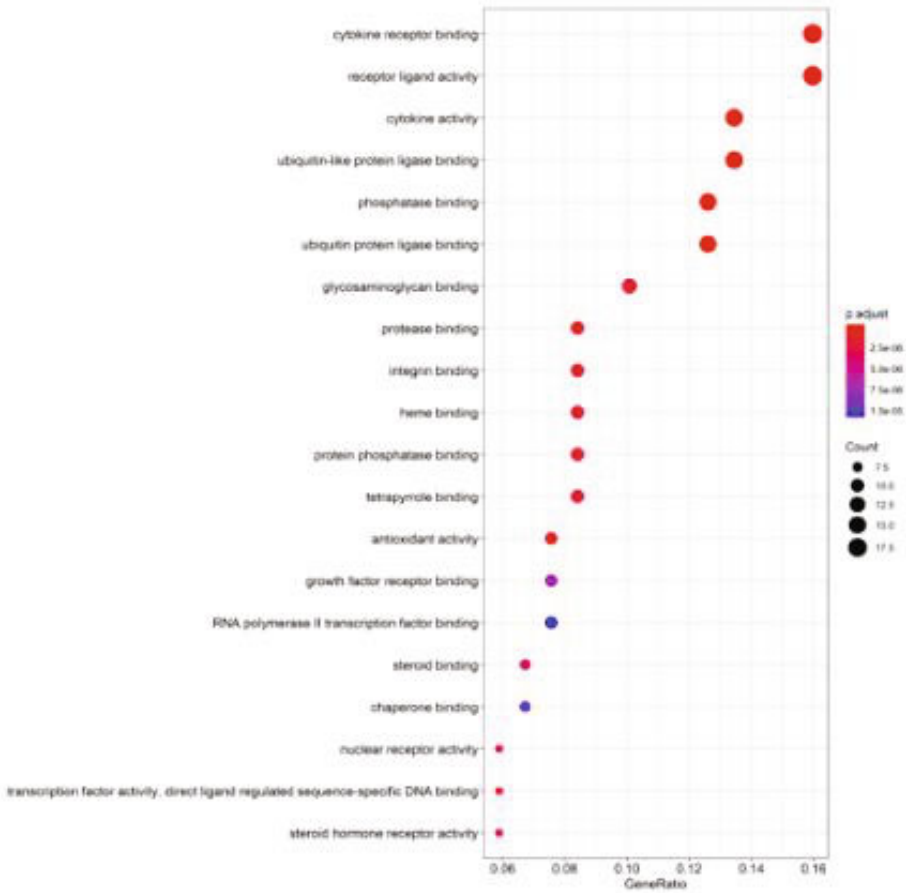


Figure 3: Network diagram of the PPI network, core clusters, and key targets: (a) PPI network; (b) core clusters; (c) key targets.



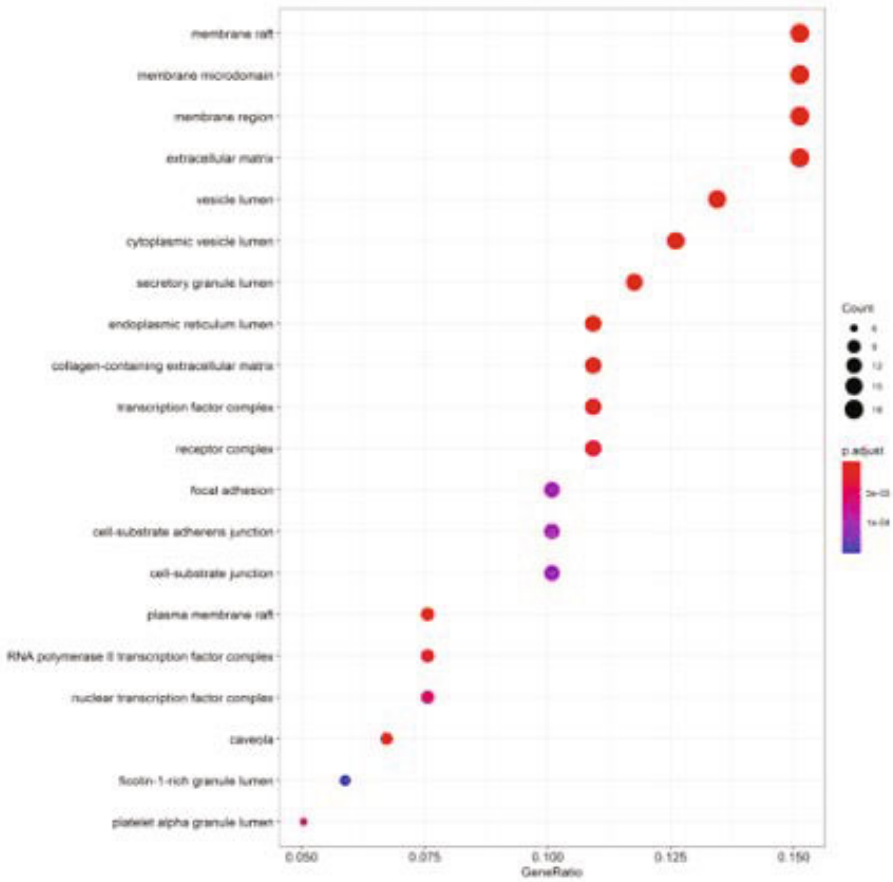
(a)

Figure 4: Continued.



(b)

Figure 4: Continued.



(c)

Figure 4: GO function enrichment analysis of potential targets from active ingredients of Panax notoginseng: (a) biological process; (b) molecular function; (c) cellular component.

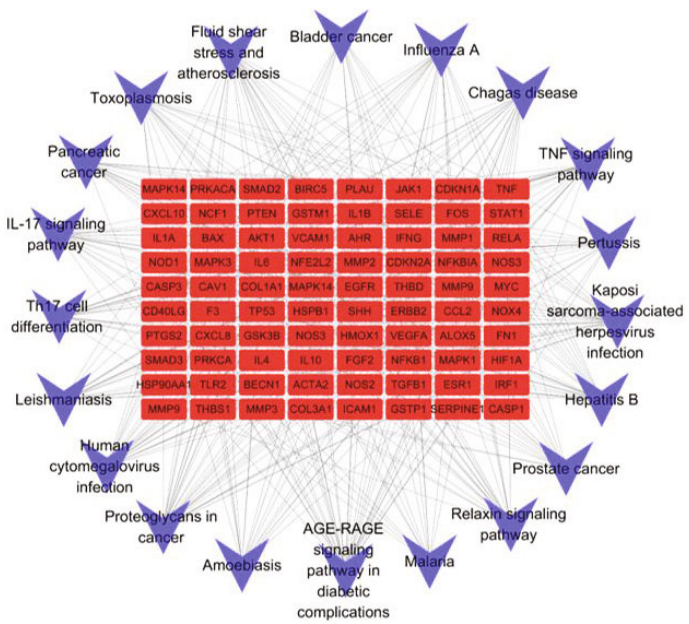


Figure 5: Target-KEGG pathway network. Blue nodes represent 20 KEGG pathways, and red nodes represent common targets.

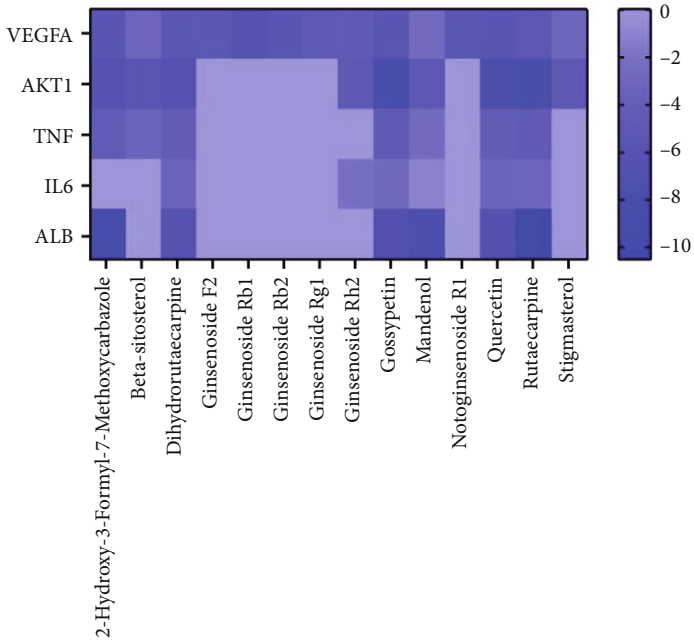


Figure 6: Heat maps of the docking scores of key targets combining with bioactive compounds in Panax notoginseng.

and remodeling. Short- and medium-term overexpression of AKT1 leads to physiologic hypertrophy, but long-term activation of AKT1 can lead to pathologic hypertrophy, such as systolic dysfunction [27]. Knockdown of AKT1 in macrophages can reduce transdifferentiation of fibroblasts, suggesting that AKT1, as an important signaling molecule, may regulate fibroblast transdifferentiation by promoting an inflammatory reaction [28].

Through this network pharmacology study, we found that Panax notoginseng in treating MF mainly involves the AGE-RAGE signaling pathway in diabetic complications, proteoglycans in cancer, and IL-17 signaling pathways. Cardiovascular complications are the leading cause of death in diabetic patients. The AGE-RAGE signaling pathway of myocardial fibrosis in diabetic complications has been widely studied. It regulates the pathogenesis of cardiovascular disease and promotes increased collagen deposition leading to tissue fibrosis [29, 30]. Therefore, targeting the AGE-RAGE signaling pathway is a potential therapeutic strategy for ameliorating CVDs in diabetes.

Recent studies have shown that proteoglycans are promising diagnostic biomarkers for cardiac fibrosis and may provide new treatment strategies for heart disease [31]. Proteoglycans are a nonstructural component of the extracellular matrix and regulate many aspects of the immune response [32, 33]. Decorin, a well-investigated proteoglycan, inhibits both bioactivity and gene expression of TGF-β, a powerful fibrogenic factor [34]. Furthermore, decorin gene transfer significantly attenuates interstitial fibrosis and cardiac hypertrophy [35]. In various forms of cardiac fibrosis, the expression of the four-membered family of transmembrane proteoglycans, syndecan-1 to syndecan-4, is upregulated in response to proinflammatory stimuli and regulating fibrosis [36].

IL-17 has also been found to be involved in MF. In diabetic mice, IL-17 can reduce MF and improve cardiac function by inhibiting long-term noncoding RNA-AK081284 [37]. Studies have found that IL-17 contributes to MF through the protein kinase C (PKC) β/Erk1/2/NF-κB (nuclear factor κappa B) pathway [38, 39]. Thus, it can be inferred that AGE-RAGE, proteoglycans, IL-17, and other signaling pathways appear to be closely related to the mechanism of Panax notoginseng in the treatment of MF.

We found that rutaecarpine and ginsenoside Rb1 are the prime binding compounds to the key targets through molecular docking. Rutaecarpine exhibits a number of pharmacologic effects on the cardiovascular system including cardiac protective, vasodilator, and antiatherosclerotic activities [40, 41]. Rutaecarpine has been found to significantly improve cardiac function and decrease the content of TNF-α in myocardial tissues [42]. Ginsenoside Rb1, an active saponin of Panax notoginseng, has anti-inflammatory and antioxidative functions. It decreases the heart rate, improves cardiac function, and attenuates histologic changes induced by heart failure. Furthermore, ginsenoside Rb1 has also been shown to protect cardiomyocytes by targeting microRNA-21 and reverse the imbalance between apoptosis and autophagy in atherosclerosis [43–45]. While research on the above compounds has revealed their potential effects on the heart muscle, the specific mechanisms of their antimyocardial fibrotic actions remain unclear and need further study.

5. Conclusion

Panax notoginseng has a wide range of clinical applications in treating MF, but there are few reports on its pharmacologic activities. In this network pharmacology study, a multicomponent, multitarget, and multipathway treatment of MF

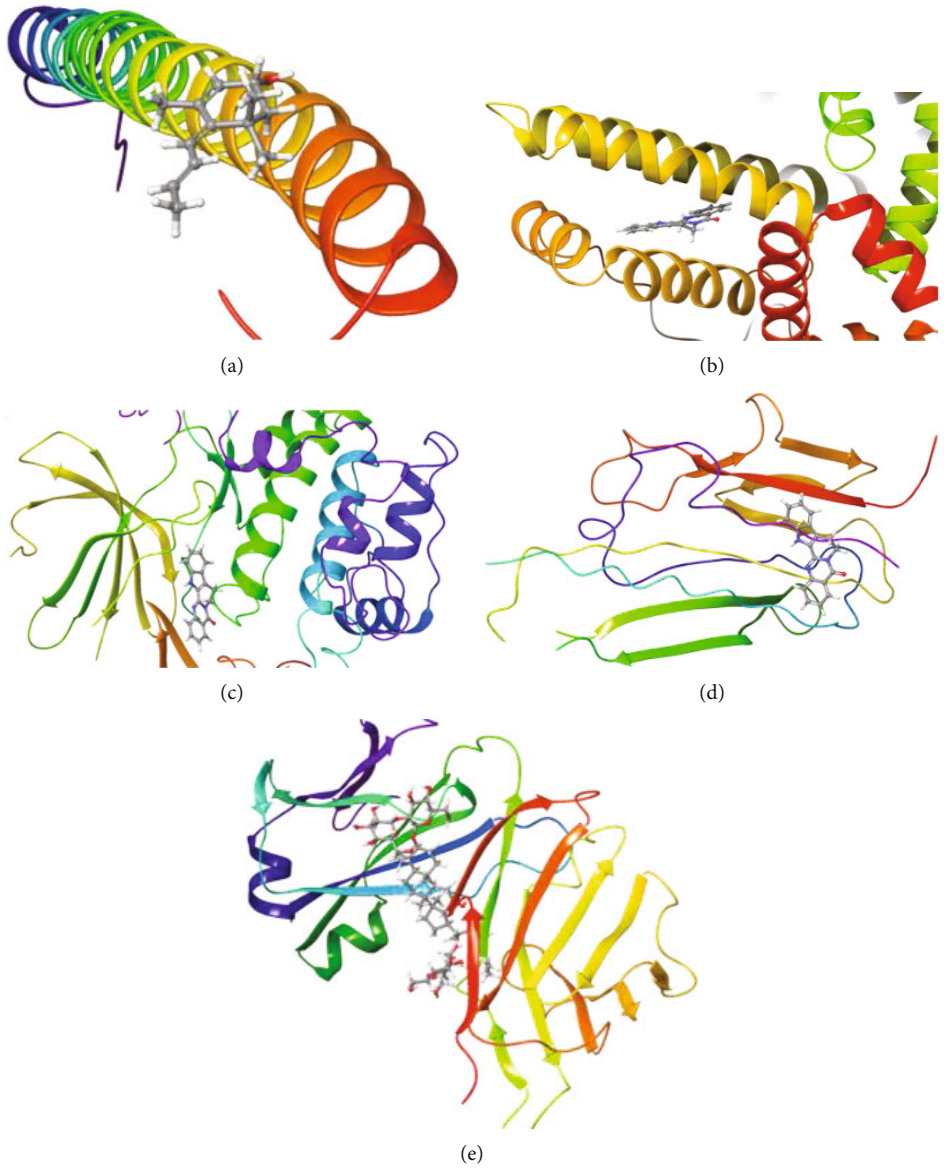


Figure 7: Molecular docking simulation of bioactive compound-key target: (a) IL6-dihydrorutaecarpine; (b) ALB-rutaecarpine; (c) AKT1-rutaecarpine; (d) TNF-rutaecarpine; (e) VEGFA-ginsenoside Rb1.

using Panax notoginseng was established and provides a theoretical basis for clinical treatment of MF. However, the results of this study are based on data analysis and have only a certain predictive effect, which needs to be verified by further in vitro and in vivo experiments.

Data Availability

The data used to support the findings of the study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Tingting Zhao and Xinwei Wang conceived and designed the study. Jingxue Han, Jingyi Hou, Yu Liu, and Peng Liu performed the data analysis. Jingxue Han wrote the paper. All authors have read and approved the final manuscript.

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References

[1] World Health Organization, "Projections of mortality and burden of disease, 2004–2030," August 2020, https://wwwwhoint/healthinfo/global_burden_disease/projections2004/en.

[2] G. Rodriguez-Araujo, "Pathophysiology of cardiovascular disease in diabetes mellitus," *Cardiovascular Endocrinology & Metabolism*, vol. 7, no. 1, pp. 4–9, 2018.

[3] R. J. King and P. J. Grant, "Diabetes and cardiovascular disease: pathophysiology of a life-threatening epidemic," *Herz*, vol. 41, no. 3, pp. 184–192, 2016.

[4] B. Brannick and S. Dagogo-Jack, "Prediabetes and cardiovascular disease: pathophysiology and interventions for prevention and risk reduction," *Endocrinology and Metabolism Clinics of North America*, vol. 47, no. 1, pp. 33–50, 2018.

[5] J. G. Travers, F. A. Kamal, J. Robbins, K. E. Yutzey, and B. C. Blaxall, "*Cardiac fibrosis: the fibroblast awakens*," *Circulation Research*, vol. 118, no. 6, pp. 1021–1040, 2016.

[6] P. Kong, P. Christia, and N. G. Frangogiannis, "The pathogenesis of cardiac fibrosis," *Cellular and Molecular Life Sciences*, vol. 71, no. 4, pp. 549–574, 2014.

[7] U. Kim, J. A. Leipsic, S. L. Sellers et al., "Natural history of diabetic coronary atherosclerosis by quantitative measurement of serial coronary computed tomographic angiography: results of the PARADIGM study," *JACC: Cardiovascular Imaging*, vol. 11, no. 10, pp. 1461–1471, 2018.

[8] A. C. Armstrong, B. Ambale-Venkatesh, E. Turkbey et al., "Association of cardiovascular risk factors and myocardial fibrosis with early cardiac dysfunction in type 1 diabetes: the diabetes control and complications trial/epidemiology of diabetes interventions and complications study," *Diabetes Care*, vol. 40, no. 3, pp. 405–411, 2017.

[9] S. Hinderer and K. Schenke-Layland, "Cardiac fibrosis – a short review of causes and therapeutic strategies," *Advanced Drug Delivery Reviews*, vol. 146, pp. 77–82, 2019.

[10] L. Liu, B. Ning, J. Cui, T. Zhang, and Y. Chen, "miR-29c is implicated in the cardioprotective activity of Panax notoginseng saponins against isoproterenol-induced myocardial fibrogenesis," *Journal of Ethnopharmacology*, vol. 198, pp. 1–4, 2017.

[11] J. Xiao, T. Zhu, Y.-z. Yin, and B. Sun, "Notoginsenoside R1, a unique constituent of Panax notoginseng, blinds proinflammatory monocytes to protect against cardiac hypertrophy in ApoE-/- mice," *European Journal of Pharmacology*, vol. 833, pp. 441–450, 2018.

[12] C.-y. Li, W. Deng, X.-q. Liao, J. Deng, Y.-k. Zhang, and D.-x. Wang, "The effects and mechanism of ginsenoside Rg1 on myocardial remodeling in an animal model of chronic thromboembolic pulmonary hypertension," *European Journal of Medical Research*, vol. 18, no. 1, 2013.

[13] G. Yu, Y. Zhang, W. Ren et al., "Network pharmacology-based identification of key pharmacological pathways of Yin-Huang-Qing-Fei capsule acting on chronic bronchitis," *International Journal of Chronic Obstructive Pulmonary Disease*, vol. 12, pp. 85–94, 2017.

[14] Y. Gao, S. Chu, Z. Zhang, and N. Chen, "Hepataprotective effects of ginsenoside Rg1 - A review," *Journal of Ethnopharmacology*, vol. 206, pp. 178–183, 2017.

[15] P. Zhou, X. Zhang, M. Guo et al., "Ginsenoside Rb1 ameliorates CKD-associated vascular calcification by inhibiting the Wnt/β-catenin pathway," *Journal of Cellular and Molecular Medicine*, vol. 23, no. 10, pp. 7088–7098, 2019.

[16] K.-T. Lee, T. W. Jung, H.-J. Lee, S.-G. Kim, Y.-S. Shin, and W.-K. Whang, "The antidiabetic effect of ginsenoside Rb2 via activation of AMPK," *Archives of Pharmacal Research*, vol. 34, no. 7, pp. 1201–1208, 2011.

[17] M. D. Marques, V. Nauffal, B. Ambale-Venkatesh et al., "Association between inflammatory markers and myocardial fibrosis," *Hypertension*, vol. 72, no. 4, pp. 902–908, 2018.

[18] J.-H. Wang, L. Zhao, X. Pan et al., "Hypoxia-stimulated cardiac fibroblast production of IL-6 promotes myocardial fibrosis via the TGF-β1 signaling pathway," *Laboratory Investigation*, vol. 96, no. 8, pp. 839–852, 2016.

[19] C.-H. Chou, C.-S. Hung, C.-W. Liao et al., "IL-6 trans-signalling contributes to aldosterone-induced cardiac fibrosis," *Cardiovascular Research*, vol. 114, no. 5, pp. 690–702, 2018.

[20] S. Kumar, G. Wang, N. Zheng et al., "HIMF (hypoxia-induced mitogenic factor)-IL (interleukin)-6 signaling mediates cardiomyocyte-fibroblast crosstalk to promote cardiac hypertrophy and fibrosis," *Hypertension*, vol. 73, no. 5, pp. 1058–1070, 2019.

[21] C.-F. Lin, C.-J. Su, J.-H. Liu, S.-T. Chen, H.-L. Huang, and S.-L. Pan, "Potential effects of CXCL9 and CCL20 on cardiac fibrosis in patients with myocardial infarction and isoproterenol-treated rats," *Journal of Clinical Medicine*, vol. 8, no. 5, 2019.

[22] N. A. B. Ntusi, J. M. Francis, E. Sever et al., "Anti-TNF modulation reduces myocardial inflammation and improves cardiovascular function in systemic rheumatic diseases," *International Journal of Cardiology*, vol. 270, pp. 253–259, 2018.

[23] C. Zhang, G. Zhou, Y. Chen et al., "Human umbilical cord mesenchymal stem cells alleviate interstitial fibrosis and cardiac dysfunction in a dilated cardiomyopathy rat model by inhibiting TNF α and TGF β1/ERK1/2 signaling pathways," *Molecular medicine reports*, vol. 17, no. 1, 2017.

[24] T. Jäntti, T. Tarvasmäki, V.-P. Harjola et al., "Hypoalbuminemia is a frequent marker of increased mortality in cardiogenic shock," *PLoS One*, vol. 14, no. 5, article e0217006, 2019.

[25] J.-M. Tang, B. Luo, J.-h. Xiao et al., "VEGF-A promotes cardiac stem cell engraftment and myocardial repair in the infarcted heart," *International Journal of Cardiology*, vol. 183, pp. 221–231, 2015.

[26] Y. Du, Y. Ge, Z. Xu et al., "Hypoxia-inducible factor 1 alpha (HIF-1α)/vascular endothelial growth factor (VEGF) pathway participates in angiogenesis of myocardial infarction in muscone-treated mice: preliminary study," *Medical Science Monitor*, vol. 24, pp. 8870–8877, 2018.

[27] S. Ock, W. S. Lee, H. M. Kim et al., "Connexin43 and zonula occludens-1 are targets of Akt in cardiomyocytes that correlate with cardiac contractile dysfunction in Akt deficient hearts," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1864, no. 4, Part A, pp. 1183–1191, 2018.

[28] Q. Ding, J. Sun, W. Xie, M. Zhang, C. Zhang, and X. Xu, "Stemona alkaloids suppress the positive feedback loop between M2 polarization and fibroblast differentiation by inhibiting JAK2/STAT3 pathway in fibroblasts and CXCR4/PI3K/AKT1 pathway in macrophages," *International Immunopharmacology*, vol. 72, pp. 385–394, 2019.

[29] T.-W. Lee, Y.-H. Kao, Y.-J. Chen, T.-F. Chao, and T.-I. Lee, "Therapeutic potential of vitamin D in AGE/RAGE-related

cardiovascular diseases," *Cellular and Molecular Life Sciences*, vol. 76, no. 20, pp. 4103–4115, 2019.

[30] J. Zhao, R. Randive, and J. A. Stewart, "Molecular mechanisms of AGE/RAGE-mediated fibrosis in the diabetic heart," *World Journal of Diabetes*, vol. 5, no. 6, pp. 860–867, 2014.

[31] G. Christensen, K. M. Herum, and I. G. Lunde, "Sweet, yet underappreciated: proteoglycans and extracellular matrix remodeling in heart disease," *Matrix Biology*, vol. 75-76, pp. 286–299, 2019.

[32] X. Wang, Y. Lu, Y. Xie, J. Shen, and M. Xiang, "Emerging roles of proteoglycans in cardiac remodeling," *International Journal of Cardiology*, vol. 278, pp. 192–198, 2019.

[33] J. R. Warford, A.-C. Lamport, D. R. Clements et al., "Surfen, a proteoglycan binding agent, reduces inflammation but inhibits remyelination in murine models of multiple sclerosis," *Acta Neuropathologica Communications*, vol. 6, no. 1, p. 4, 2018.

[34] C. O. Heras-Bautista, N. Mikhael, J. Lam et al., "Cardiomyocytes facing fibrotic conditions re-express extracellular matrix transcripts," *Acta Biomaterialia*, vol. 15, no. 89, pp. 180–192, 2019.

[35] S. M. Faust, G. Lu, S. C. Wood, and D. K. Bishop, "TGFβ neutralization within cardiac allografts by decorin gene transfer attenuates chronic rejection," *Journal of Immunology*, vol. 183, no. 11, pp. 7307–7313, 2009.

[36] I. G. Lunde, K. M. Herum, C. C. Carlson, and G. Christensen, "Syndecans in heart fibrosis," *Cell and Tissue Research*, vol. 365, no. 3, pp. 539–552, 2016.

[37] Y. Zhang, Y.-Y. Zhang, T.-T. Li et al., "Ablation of interleukin-17 alleviated cardiac interstitial fibrosis and improved cardiac function via inhibiting long non-coding RNA-AK081284 in diabetic mice," *Journal of Molecular and Cellular Cardiology*, vol. 115, pp. 64–72, 2018.

[38] Y. Liu, H. Zhu, Z. Su et al., "IL-17 contributes to cardiac fibrosis following experimental autoimmune myocarditis by a PKCβ/Erk1/2/NF-κB-dependent signaling pathway," *International Immunology*, vol. 24, no. 10, pp. 605–612, 2012.

[39] S. Ahmed, D. P. Misra, and V. Agarwal, "Interleukin-17 pathways in systemic sclerosis-associated fibrosis," *Rheumatology International*, vol. 39, no. 7, pp. 1135–1143, 2019.

[40] W.-Q. Li, X.-H. Li, J. Du et al., "Rutaecarpine attenuates hypoxia-induced right ventricular remodeling in rats," *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 389, no. 7, pp. 757–767, 2016.

[41] K.-m. Tian, J.-j. Li, and S.-w. Xu, "Rutaecarpine: a promising cardiovascular protective alkaloid from Evodia rutaecarpa (Wu Zhu Yu)," *Pharmacological Research*, vol. 141, pp. 541–550, 2019.

[42] S. Jia and C. Hu, "Pharmacological effects of rutaecarpine as a cardiovascular protective agent," *Molecules*, vol. 15, no. 3, pp. 1873–1881, 2010.

[43] X. Zheng, S. Wang, X. Zou et al., "Ginsenoside Rb1 improves cardiac function and remodeling in heart failure," *Experimental Animals*, vol. 66, no. 3, pp. 217–228, 2017.

[44] C. Yang, B. Li, Y. Liu, and Y. Xing, "Ginsenoside Rb1 protects cardiomyocytes from oxygen-glucose deprivation injuries by targeting microRNA-21," *Experimental and Therapeutic Medicine*, vol. 17, no. 5, pp. 3709–3716, 2019.

[45] P. Zhou, W. Xie, Y. Luo et al., "Inhibitory effects of ginsenoside Rb1 on early atherosclerosis in ApoE-/- mice via inhibition of apoptosis and enhancing autophagy," *Molecules*, vol. 23, no. 11, p. 2912, 2018.