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# Network Pharmacology and Molecular Docking Reveal Wenxin Granule's Anti-Atrial Fibrillation Mechanisms

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**Abstract:** *Objective:* Wenxin Granules (WXG) is a Chinese medicine preparation made from five traditional Chinese medicines, including *Polygonal circumscribe*, *Synopsis peninsula*, *Panax nothingness*, Succinct, and *Chardonnays chines*, clinically used for the treatment of atrial fibrillation. The specific components and molecular mechanisms of WXG in treating atrial fibrillation have not been fully clarified. This study will further elucidate the mechanism of action of WXG in treating atrial fibrillation through network pharmacology research and molecular docking techniques. Methods: The components corresponding to the five Chinese herbs were searched in the Herb database and the active components of OB 30%, DL 0.18 were screened according to the TCMSP database, and the relevant targets of the active components were retrieved in Symmap. The above "metacentric particle-active component-target" data were imported into the Cytoscape software to build an intuitive map of the "metacentric particle-active component-target" network. In the GeneCards database, "atrial fibrillation" was used as the keyword to obtain disease-related targets of atrial fibrillation, and the intersection targets of metacellular particles and atrial fibrillation in the Venny 2.1.0 platform. These targets were initially considered to be the targets of metacellular particles in the treatment of atrial fibrillation. The intersection targets were imported into the protein intercorrelation analysis platform, STRING website, to get the PPI to further analyze the relationship between these intersection targets. PPI data were imported into Cytoscape software for more accurate analysis to obtain core targets. The intersection targets were analyzed by the David database and obtained as enrichment analysis for KEGG and GO. Finally, the molecular docking of the core target and the active component was scored with AutoDock series software, and the results were imported into PyMOL display. *Conclusion:* This study provides a reference for further investigation of the mechanism of antiarrhythmic action, and defines the core targets of the drug phase and selects 191 intersection targets of cardiac particles and atrial fibrillation. The core targets were TP 53, AKT 1, JUN, STAT 3, TNF and IL 6, and the main signaling pathways involved were the PI3K-Akt signaling pathway. KEGG enrichment analysis identified TP 53, AKT 1 and STAT 3 as core targets of metacentric granule (WXG) modulation of atrial fibrillation (AF) through the PI3K-AKT pathway, lipid metabolism and anti-inflammatory signaling pathway. Molecular docking revealed that Acacetin, the major bioactive component of WXG, stabilizes atrial electrophysiology by selectively inhibiting

potassium currents, consistent with established antiarrhythmic effects.
**Keywords:** Wenxin granules; Atrial fibrillation; P13K-Akt; Pharmacology; Molecular docking

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# 1. Introduction

Atrial fibrillation (AF) is recognized as the most common clinical arrhythmia, with incidence increasing with age [1], imposing a substantial healthcare burden due to its elevated morbidity and mortality rates. AF induces characteristic atrial remodeling involving fibrosis, inflammation, and molecular-cellular alterations [2], which reciprocally enhance arrhythmogenic susceptibility. Wenxin Granule (WXG), a Chinese herbal formulation comprising *Polygonati rhizoma*, *Codonopsis radix*, *Notoginseng radix*, Succinum, and *Nardostachyos radix* [3], has demonstrated clinical efficacy in early-stage AF intervention through symptom alleviation, establishing its role in conservative arrhythmia management. Despite its recognized therapeutic benefits and safety profile, the underlying mechanisms remain undefined. This investigation employs systems biology approaches to elucidate WXG's anti-AF mechanisms and identify bioactive constituents. Network pharmacological analysis was conducted with theoretical validation through molecular docking simulations [4].

# 2. Materials and methods

## 2.1. Collection of active ingredients and action targets of WXG

The experiment leverages the similarity of small molecule structures to predict drug targets. By integrating multi-source data and algorithms through the natural medicine database platform "HERB," it reduces the bias of single-source data and enhances the specificity of target prediction to determine the mechanism of action of WXG particles. It analyzes the complex network relationships between traditional Chinese medicine components, targets, and diseases, excluding components that do not meet the OB 30% and DL 0.18 criteria. The final remaining components are identified as the ultimate targets of WXG particles. The Human Gene Database-Gene Card (https://www.genecards.org/) automatically integrates gene-centric data from 150 network sources, including genomics, transcriptomics, proteomics, genetics, clinical and functional information. Using "atrial fibrillation" in the GeneCards database, the atrial fibrillation-related disease target [5].

## 2.2. Construction of the intersection target of WXG and AF

The corresponding target of WXG and the disease target related to atrial fibrillation were introduced into the Venny 2.1 platform. After the platform analysis, the intersection target of WXG was obtained. These targets were initially considered as the targets of WXG in the treatment of atrial fibrillation.

## 2.3. Constructing Protein Interaction networks

The intersection targets of WXG-AF were introduced into the protein interaction analysis platform, String Database

(https://string-db.org/). The relationships between proteins corresponding to these intersection targets were analyzed to obtain their PPI network information, which was then imported into Cytoscape 3.8.0 software for network relationship analysis. The results were further visualized as color graphs. The degree values were used to rank the obtained results, selecting the core targets for WXG in atrial fibrillation treatment.

## 2.4. Gene Ontology bioenrichment analysis and pathway analysis with Kyoto Encyclopedia of Genes and Genomes

The obtained core targets were imported into GO and KEGG pathway enrichment analysis to provide information about the function of gene products [6] to obtain biological processes, cellular components, molecular functions and metabolic pathways, and the intersection genes were introduced into (DAVID) (https://david-d.ncifcrf.gov/tools.jsp) for analysis [7]. Determine that the pathway was significantly active in the experimental data and screen out key molecules associated with therapeutic response.

## 2.5. Molecular docking

Docking of the active components and the core targets by molecular docking techniques [8].To further verify the binding activity of the core targets of the preliminary network pharmacology, Docking validation of the screened molecules and the screened key protein targets. In the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) and the protein database (https://www.rcsb.org), And using Chem3D (https://library.bath.ac.uk/chemistry-software/chem3d) were converted to 3D structures. Compounds were converted into ligands for future molecular docking using Auto Dock Tools 1.5.7. The protein sequence database Uniprot (https://www.uniprot.org) was used to identify the core targets. In PyMol, the 3D structure is opened and excess chains, ions, and water molecules are removed. Proteins were then converted to the pdbqt format for molecular docking using AutoDock Tools 1.5.7. Core target proteins and ligands were sequentially introduced into AutoDock Tools, docking parameters were configured, molecular docking was performed using Vina, and the final results were presented with PyMol. The docking parameters use Vina for molecular docking and display the final results in PyMol.

# 3. Results

## 3.1. Components, targets of WXG and AF related disease targets

After screening, 18 potential active components of the steady particles were obtained (**Table 1**). Meanwhile, 4295 related targets were found for AF. The GIFtS values were screened, and 623 genes with a GIFtS value of 50 were selected as targets for AF-related diseases. A total of 191 genes are targets related to drugs and diseases, and are displayed in the Wayne diagram (**Figure 1**). The blue part on the left is the number of target targets, and the red part on the right is the number of targets corresponding to atrial fibrillation. The intersection genes were fed into the STRING database to obtain the protein interaction networks, and the PPI data imported into the Cytoscape software for visual analysis.

**Table 1.** The active ingredients of Wenxin granules

| CAS ID | Compounds | OB (%) | DL |
|---|---|---|---|
| 480-44-4 | Acacetin | 34.97 | 0.24 |
| 34079-22-6 | Camptothecin | 61.04 | 0.81 |
| 35825-57-1 | Cryptotanshinone | 52.34 | 0.4 |
| 5779-62-4 | Sitosterol | 36.91 | 0.75 |
| 727409-30-5 | Baicalein | 33.52 | 0.21 |
| 64997-52-0 | Beta-sitosterol | 36.91 | 0.75 |
| 518-17-2 | Evodiamine | 86.02 | 0.64 |
| 28283-45-6 | Oleanolic acid | 45.57 | 0.20 |
| 19666-76-3 | Panaxadiol | 33.09 | 0.79 |
| 117-39-5 | Quercetin | 46.43 | 0.28 |
| 470-82-6 | Eucalyptol | 60.62 | 0.32 |
| 23455-43-8 | α-spinasterol | 42.98 | 0.76 |
| 83-48-7 | Beta-stigmasterol | 43.83 | 0.76 |
| 19865-96-4 | Friedelin | 29.16 | 0.76 |
| 40957-83-3 | Glycitein | 50.48 | 0.24 |
| 481-18-5 | Spinasterol | 42.98 | 0.76 |
| 83-48-7 | Stigmasterol | 43.83 | 0.76 |
| 127-22-0 | Taraxerol | 38.40 | 0.77 |
| 480-44-4 | Acacetin | 34.97 | 0.24 |
| 34079-22-6 | Camptothecin | 61.04 | 0.81 |

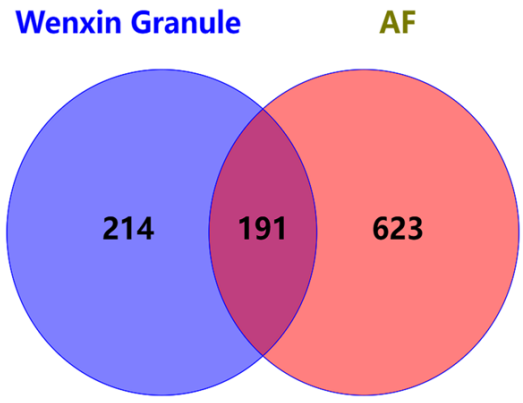


**Figure 1.** Wayne diagram of WXG and AF1.

The results of PPI data are shown in **Figure 2.** As the Degree increases, the importance of this node in the PPI network also increases, and its role in biological function may also increase accordingly. As the area increases, the Degree value also shows a trend of gradually increasing. Six targets were selected as core targets for AF treatment, namely TP 53, AKT 1, JUN, STAT 3, TNF and IL 6 (**Table 2**) [9].

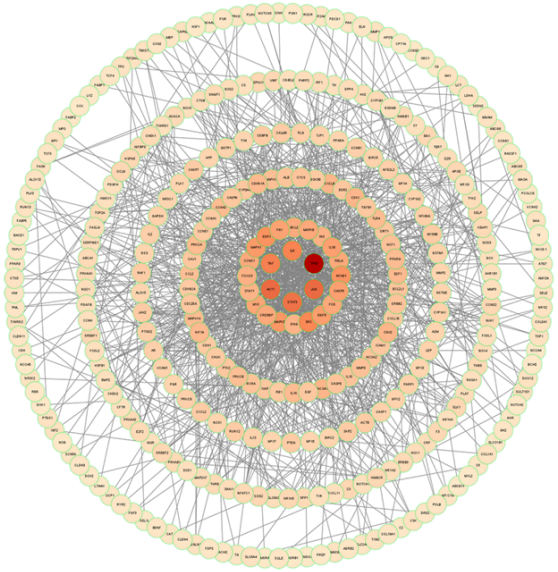

**Figure 2.** Centre-steady granule-target-AF.

**Table 2.** Core targets information

| UniProt ID | Gene | Degree | Protein | PDB ID |
|---|---|---|---|---|
| P04637 | TP53 | 67 | Cellular tumor antigen p53 | 1A1U |
| P31749 | AKT1 | 42 | RAC-alpha serine/threonine-protein kinase | 1H10 |
| P05412 | JUN | 42 | Transcription factor Jun | 1A02 |
| P40763 | STAT3 | 40 | Signal transducer and activator of transcription 3 | 5AX3 |
| P01375 | TNF | 37 | Tumor necrosis factor | 1A8M |
| P05231 | IL6 | 36 | Interleukin-6 | 1ALU |

## 3.2. GO functional enrichment analysis and KEGG pathway enrichment analysis

The results of GO functional enrichment analysis include 990 biological processes (BP), 122 cell components (CC), and 175 molecular functions (MF). Select the top 10 enrichment results with Count values and create color bubble plots. Among them, there are 4 enrichment results with Count values of 26 in MF, sorted according to *P* values. As the *P* value increases and the color turns red, the degree of enrichment represented also increases. As shown in **Figure 3**, the BF of intersection target design mainly includes positive regulation of translation from the RNA polymerase II promoter, positive regulation of gene expression, positive regulation of translation, DNA template, etc. The CC mainly involves Cytosol, Cytoplast, Nucleus, etc., while the MF mainly involves Protein binding, Identity protein binding, Enzyme binding, etc. According to the analysis of KEGG signaling pathway enrichment, there are up to 181 pathways involved in the intersection of stable cardiac granules and atrial fibrillation. The main signaling pathways involved are lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic applications, fluid shear stress and atherosclerosis, Kaposi sarcoma associated herpesvirus infection, HIF-1 signaling pathway, etc, filter the top 30 signal pathways with count values and draw a bar chart (**Figure 4**), sort them according to *P* values. As the *P* value increases and the color turns red, the degree of enrichment represented also increases.

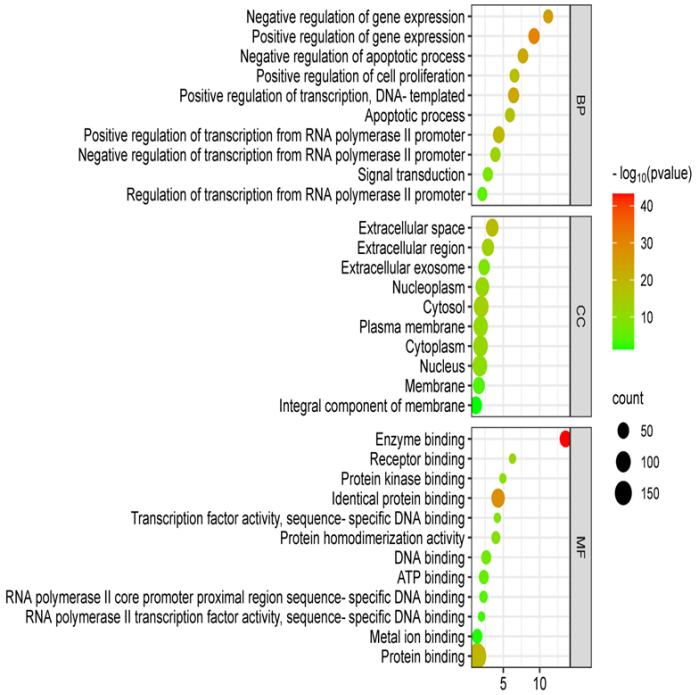


**Figure 3.** Analysis GO of WXG and AF core targets in bubble figure.

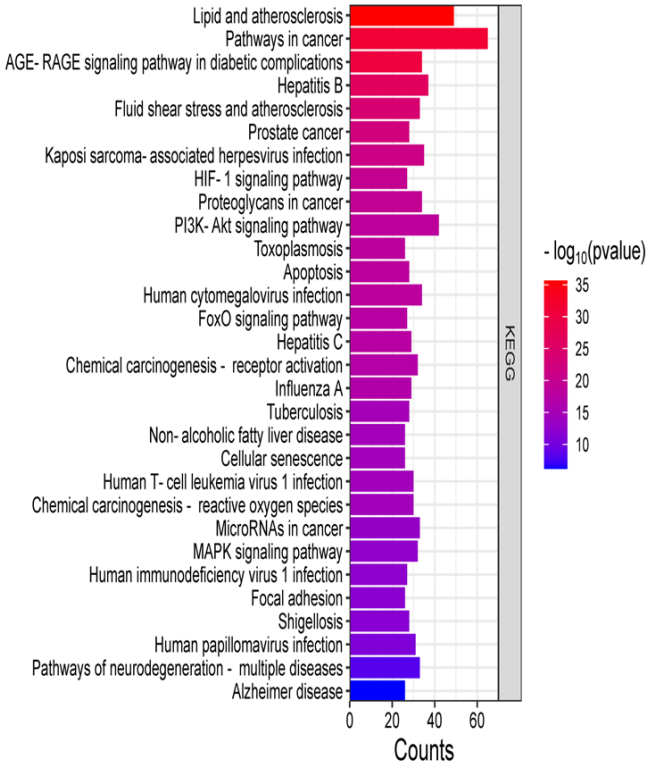


**Figure 4.** Analysis KEGG of WXG and AF core targets in bubble figure.

## 3.3. Molecular docking results

The study selected six representative active components from the 18 active ingredients, consisting of acacetin, camptothecin, cryptotanshinone, panaxadiol, friedelin, taraxerol, and docked them with 36 core targets, TP 53, AKT 1, JUN, STAT 3, TNF, and IL 6. The scoring function of Score 5 is the threshold, and the smaller the binding free energy, the more stable the ligand binding to the receptor, and the larger the Total Score value, indicating the better binding effect of the active component to the target protein [10]. The results showed that the six representative components docked better with the core target, which was better than friedelin and taraxerol. The specific docking data are shown in **Figure 5**.

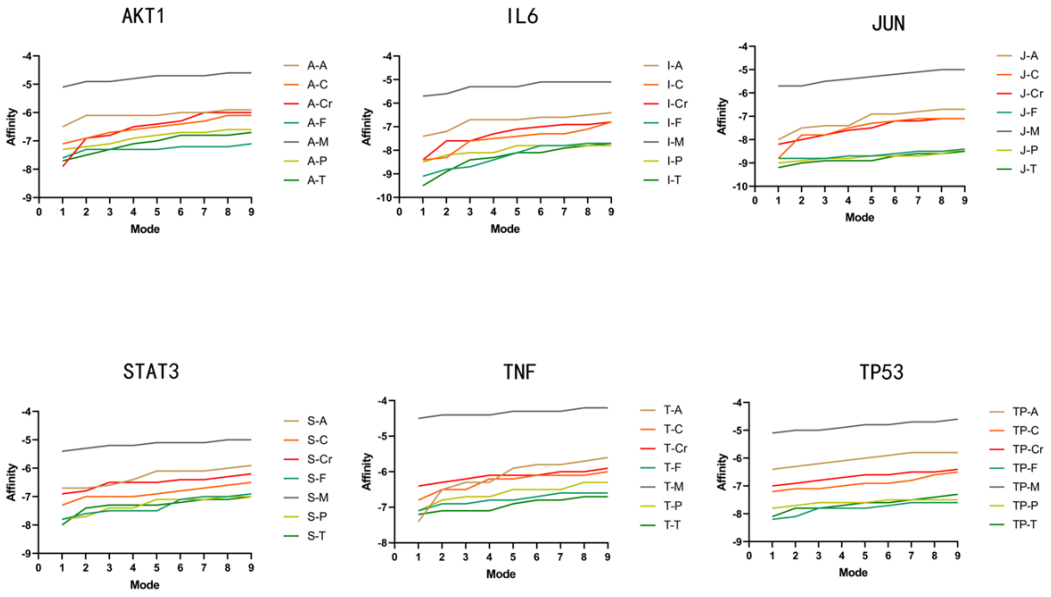


**Figure 5**. Racentric particles docking with AF core target molecules.

## 4. Discussion

In this study, the mechanism of cardientrtry therapy for AF was initially revealed, involving several targets including TP 53, AKT 1, JUN, STAT 3, TNF, IL 6 and other signaling pathways such as AGE-RAGE, HIF-1, and Lipid / AS. The molecular docking structure shows that, in cardiocentric granules, the representative drug Acacetin has a stronger target binding force for AF treatment, acacetin is a natural flavanone and a potential drug candidate for the treatment of AF [11]. As shown by Li *et al*., acacetin can selectively inhibit the human atrial repolarization potassium current, to prevent atrial fibrillation from the acacetin treatment [12] of atrial fibrillation may be a newly informative [13] by binding to the P-loop filter helix and S6 domain to inhibit the closed channel and block the open state of the channel. Some studies believe that the heart stabilizing particles can selectively affect the atrial muscle action potential time limit (P wave time limit) [14], has a significant inhibitory effect on the atrial fibrillation induced by

acetylcholine [15], can inhibit the matrix remodeling and proactive effect of inflammatory factors after atrial ablation, and play a protective effect on the damaged myocardium. Hu [16] believes that the inflammatory response plays an important role in the mechanism of atrial fibrillation. IL-6 is a proinflammatory factor synthesized by monocytes, which can promote the synthesis of acute phase proteins such as CRP, increase inflammatory response, cause inflammatory damage to atrial muscle cells and induce interstitial fibrocell hyperplasia, leading to left atrial remodeling [17]. Other components have been less studied in atrial fibrillation.

The prothrombotic state in AF is the result of a multifaceted interaction called the triad of hypercoagulability in Virchow, structural abnormalities and blood stasis. Recently, increasing evidence suggests that lipoproteins are involved in this process, going beyond their traditional role in atherosclerosis [18]. An observational and Mendelian randomization study showed that lipoprotein is a potential causal agent in the development of AF [19], in addition, a community cohort study showed that HDL cholesterol and triglycerides are associated with atrial fibrillation risk [20], these findings are associated with Lipid and atherosclerosis enriched in KEGG signaling pathway, suggesting that cardiac particles may improve AF by regulating lipid metabolism. Studies have shown that the occurrence of diabetes and AF found correlation, insulin resistance even before the development of diabetes is considered a risk factor for AF [21], the formation of advanced glycosylation end products (AGEs) and accumulation is closely related to the occurrence of AF [22], HIF1α is essential for the maturation of DCs and T cell activation. It is induced in LPS-activated macrophages [23], where it actively participates in the induction of glycolysis and pro-inflammatory genes, with metformin via activation. It is a common component of the pathway involved in the control of cell metabolism, plays a role in regulating immune cell effector function, which is related to the enrichment of AGE-RAGE signaling pathway in diabetic complications.

## Disclosure statement

The author declares no conflict of interest.

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