Journal of Biosciences and Medicines, 2026, 14(2), 92-113
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Exploring Potential Mechanisms of Insect-Derived Drugs in Treating Atrial Fibrillation Based on Data Mining, Network Pharmacology and Molecular Docking Techniques

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How to cite this paper: Leng, T., Zhao, J., Nie, Q. and Xie, W. (2026) Exploring Potential Mechanisms of Insect-Derived Drugs in Treating Atrial Fibrillation Based on Data Mining, Network Pharmacology and Molecular Docking Techniques. *Journal of Biosciences and Medicines*, **14**, 92-113.
https://doi.org/10.4236/jbm.2026.142009

Received: December 31, 2025
Accepted: January 31, 2026
Published: February 3, 2026

Abstract

This study uses data mining, network pharmacology, and molecular docking to explore the potential mechanisms of insect-derived traditional Chinese medicines against atrial fibrillation (AF). We systematically screened 11 insect-derived medicines from multiple databases and identified 49 active compounds targeting 1038 unique genes. Cross-analysis with 645 known AF-related targets revealed 61 common targets. Key pathways involved include arrhythmogenic right ventricular cardiomyopathy and atherosclerosis. Molecular docking confirmed strong binding between core compounds (e.g., ergotamine) and targets (e.g., CACNA1C). Our findings suggest that these drugs exert anti-AF effects through multi-component, multi-target, and multi-pathway mechanisms, providing novel insights into their potential clinical applications.

Keywords

Insect-Derived Drug, Atrial Fibrillation, Network Pharmacological

1. Introduction

Atrial fibrillation (AF) is a prevalent form of rapid arrhythmia, distinguished by disorganized atrial activation that impedes normal atrial function. Serious com-

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plications may ensue, with potential consequences including thromboembolism and heart failure [1]. These complications can have a significant impact on patients' physical and mental health, as well as their quality of life. Projections indicate that by 2050, the number of AF patients in China will reach 52 million, while in the United States, the number of AF patients will exceed 8 million [2] [3]. This places a significant strain on healthcare systems. The pathogenesis of AF is associated with various factors [4] [5], including but not limited to: smoking, alcohol consumption, social stress, obesity, hypertension, diabetes, and coronary heart disease. Additionally, genetic predisposition plays a significant role in the development of AF [6]. The treatment of this condition primarily involves pharmacological interventions, such as the administration of antiarrhythmics and anticoagulants, as well as non-pharmacological approaches, including radiofrequency ablation and pulsed-field ablation (PFA) [4]. It is imperative to note that for elderly patients afflicted with multiple comorbidities, the safety of antiarrhythmic medications and the judicious administration of oral anticoagulants to mitigate thromboembolic events and bleeding risks remain critical considerations. Although surgical intervention offers the potential for a "cure", studies indicate that traditional ablation methods achieve approximately 50% success rates for persistent AF [7]. Although PFA has been shown to improve success rates and reduce intraoperative complications in comparison with conventional methods, the findings of the latest ADVANTAGE AF study [8] indicate that PFA's primary efficacy at one year is 63.5% (lower confidence limit: 57.3%), with an asymptomatic AF rate of 85.3%. It is important to note that these outcomes are significantly influenced by operator skill. Consequently, the limited success rate of ablation procedures, in conjunction with the high rate of recurrence, constitutes pressing issues that demand urgent resolution. Consequently, the exploration of safer alternative therapeutic strategies with multi-target efficacy remains crucial.

Medicines derived from insects represent a distinctive category within the framework of traditional Chinese medicine. As detailed in the *Lin Chuang Zhi Nan Yi An* [9]: An examination of Zhang Zhongjing's methodologies for addressing blood stasis resulting from overwork and injury reveals a recurrent utilization of swift-moving insects and ants in his approach to unblocking meridians. The principle of yin and yang asserts that movement facilitates the circulation of vital energy, thereby preventing stagnation and promoting the flow of qi. This approach contrasts with methodologies that exclusively target accumulations, remove hardened masses, or penetrate viscera. Medicinal preparations derived from insects possess dual characteristics, exhibiting both attacking and nourishing properties, due to their origin from living creatures. These substances have been demonstrated to exhibit potent antibacterial properties, while concurrently augmenting the body's vital energy, thereby fortifying and reinforcing its fundamental structures. The efficacy of these treatments is demonstrated by their ability to unblock and nourish meridians, invigorate blood, and resolve stasis. Additionally, they have been observed to attack toxins and disperse nodules. Historically, these treatments have

been frequently used to address chronic conditions such as blood stasis, rheumatic pain, and persistent numbness. Additionally, they have been widely applied in the domain of cardiovascular diseases. For instance: The *Yi Lin Zuan Yao Tan Yuan* [10] notes that the use of whole scorpions is primarily indicated for the treatment of various wind disorders, with additional benefits reported for the heart. Similarly, Tao Hongjing's Compendium of Famous Physicians from the *Ming Yi Bie Lu: Ji Jiao Ben* [11] notes the use of cicada molt for the treatment of palpitations. Contemporary pharmacological research has demonstrated that pharmaceuticals derived from insects exhibit a variety of bioactivities, including but not limited to anticoagulant effects (e.g., hirudin), antifibrotic properties (e.g., chitinase from centipedes [12]), and ion channel modulation (e.g., antiepileptic peptides in scorpion venom [13]). These properties are closely associated with the fundamental pathophysiological mechanisms underlying atrial fibrillation. Consequently, the development of pharmaceuticals derived from insects represents a highly promising area for the treatment of AF, demonstrating broad potential.

However, the therapeutic potential of insect-derived drugs for treating atrial fibrillation has yet to be fully validated through rigorous scientific research. The complexity of their chemical composition and the multi-target characteristics of these compounds pose significant challenges to traditional reductionist approaches, which are often insufficient for elucidating their mechanisms of action. Network pharmacology, an emerging discipline integrating systems biology and multi-target pharmacology, provides a powerful tool for deciphering the "multi-component, multi-target, multi-pathway" therapeutic model of traditional Chinese medicine [14]. By constructing compound-target and target-pathway networks, this approach can predict potential active components and their synergistic effects within disease-specific networks. Molecular docking simulations provide further validation of the binding affinity and interactions between key compounds and targets at the atomic level, thereby revealing the structural basis of pharmacological actions [15].

The objective of this study is to establish a comprehensive framework for understanding the complex mechanisms underlying the insect-derived drug's prevention of atrial fibrillation, thereby revealing its potential as a multi-target therapeutic agent. These findings provide a scientific foundation for future clinical applications and drug development inspired by traditional Chinese medicine.

2. Materials and Methods

2.1. Data Mining

2.1.1. Source

Collect insect-derived medicinal substances from the 2020 edition of the *Pharmacopoeia of the People's Republic of China* [16], the *Zhong Hua Ben Cao* [17], and prescriptions by renowned traditional Chinese medicine practitioners indexed in China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Information, and the Chinese Biomedical Literature Service System (SinoMed/CBM).

Focus particularly on insect-derived substances documented in the literature as possessing anticoagulant, antifibrotic, and ion channel regulatory activities.

2.1.2. Inclusion Criteria

1) The drug origin is clearly identified as an insect species (Insecta) or its secretion, and clinical or pharmacological studies confirm its cardiovascular protective activity; 2) Possesses explicit pharmacological activity data support in either the TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform) or BATMAN-TCM (Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine) databases; 3) The active drug components (e.g., toxins, protein peptides, small-molecule compounds) exhibit relatively well-defined structural characterization and mechanism studies.

2.1.3. Exclusion Criteria

1) Animal-derived drugs not sourced from insects; 2) Drugs with unclear pharmacological mechanisms or lacking support from modern pharmacological research data; 3) Drugs with only traditional usage but no evidence of anticoagulant, antifibrotic, or ion channel-modulating activities.

2.1.4. Data Entry and Verification

The collected data were then processed using Microsoft Excel 2016 software, where they were organized and deduplicated to identify eligible drugs. These drugs were subsequently standardized in accordance with the *Pharmacopoeia of the People's Republic of China* and the *Zhong Hua Ben Cao*. The uniformity in the documentation of drugs of the same species, irrespective of regional variations or alternative names, is noteworthy. The collection and standardization of the data were carried out independently by two researchers. A third researcher was tasked with the verification of the data and the resolution of any disputes that arose, with the objective of ensuring the accuracy of the data.

2.2. Network Pharmacology

2.2.1. Ingredient Collection and Screening

Utilizing oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 as screening criteria, the Traditional Chinese Medicine System Pharmacology Database and Analysis Platform (TCMSP database, https://www.tcmsp-e.com/molecule.php?qn=12744) was employed. The analysis of online data identified 11 traditional Chinese medicines as search terms, leading to the detection of qualifying active components and their corresponding targets. For drugs not identified in the TCMSP database, screening was conducted using the BATMAN-TCM database (http://bionet.ncpsb.org.cn/batman-tcm/#/home). The selection of BATMAN-TCM targets was guided by a stringent set of criteria, including a minimum score threshold of 20% and an adjusted p-value of 0.05, which is a Benjamini-Hochberg corrected p-value for multiple tests. Subsequently, genetic data related to these targets were retrieved from the Uniprot database, and human

genetic information concerning these targets was searched for gene annotation.

2.2.2. AF Target Acquisition

Using the GeneCards database (https://www.genecards.org) with a relevance score ≥10 as the criterion, combined with the OMIM database (https://www.omim.org) and the PharmGKB database (https://www.pharmgkb.org), potential disease target genes associated with AF were identified using "Atrial Fibrillation" as the keyword. Then, duplicate data were removed using an Excel spreadsheet.

2.2.3. Drug-Disease Intersection Targets and Venn Diagram Mapping

Import the obtained drug active ingredient targets and disease genes into the online Venn diagram creation tool Venn 2.1.0 (https://www.bioinformatics.com.cn). Obtain the target genes representing the intersection of drug targets and disease genes, and generate a Venn diagram.

2.2.4. Drug-Disease Protein-Protein Interaction Network

The STRING database (https://cn.string-db.org/) can be utilized to set the following parameters. The search yielded multiple proteins, the species Homo sapiens, a minimum required interaction score of high confidence (0.700), and network display options that include the ability to hide disconnected nodes in the network. It is imperative that all other parameters remain at their default settings. The following steps are required to create the drug-disease protein interaction network diagram. Maintain the aforementioned settings and other parameters unchanged. Import the intersecting target genes from the "List of Names" to obtain the drug-disease protein interaction network diagram. Export the diagram as a TSV format file. Using Cytoscape 3.10.2 software and the cytoNCA plugin, screen the TSV file obtained from the STRING database for genes exhibiting protein-protein interaction network topology to identify core drug-disease target genes. Subsequently, perform molecular docking analysis on these core target genes.

2.2.5. GO Biofunction and KEGG Signaling Pathway Enrichment Analysis

The drug-disease cross-target genes that were identified in the previous step were then imported into the DAVID database (https://davidbioinformatics.nih.gov/). Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed using the filters "OFFICIAL_GENE_SYMBOL", "Homo sapiens", and "Gene List". The top ten enriched functions with a P-value less than 0.01, the KEGG pathways with a P-value less than 0.01, and the top twenty enriched genes were selected for annotation. These pathways were annotated via the Microbial Information Platform (https://www.bioinformatics.com.cn/). Visual analysis was performed by generating combined two-sided bar charts and bubble charts for Biological Process (BP), Cellular Component (CC), and Molecular Function (MF).

2.3. Molecular Docking

Perform molecular docking between the top 5 core targets ranked by Degree val-

ues and the top 5 drug active ingredients: Download the 2D structures of core targets via the TCMSP database and PubChem software, optimize them using Chem3D software, convert them into 3D structures, and use them as ligands. In the UniProt database (https://www.uniprot.org/), enter the core target name with species source restricted to human to identify the corresponding Entry ID. Input this ID into the PDB Protein Network (https://www.rcbs.org/) to locate the receptor protein. Then, use PyMOL and AutoDockTools software to perform operations such as dehydration, residue removal, and hydrogenation on the receptor protein before using it as the receptor. Perform molecular docking between the receptor and ligand structures using AutoDockTools and Vinna software. Finally, visualize the docking results using PyMOL software.

3. Results and Analysis

3.1. Screening of Insect-Derived Drugs

3.1.1. Data Collection

The 2020 edition of the *Pharmacopoeia of the People's Republic of China* includes 51 animal-derived medicines, while the *Chinese Materia Medica* lists a total of 1,047 animal species. Database searches (CNKI, Wanfang, VIP, SinoMed) employing keywords such as "insect medicines & insect-based drugs & formulas & prescriptions & compound preparations" yielded 11,542 initial prescription records.

3.1.2. Data Aggregation and Deduplication

The integration of drug names and prescription information from the aforementioned sources is imperative, followed by the standardization of these data elements. Following a thorough process of merging and deduplication, a total of 28 insect-derived drugs were identified (after removing duplicate literature, reviews, and irrelevant clinical reports).

3.1.3. Data Inclusion and Exclusion

First, based on the established criteria: 1) clearly belonging to the insect class with cardiovascular activity; 2) possessing explicit pharmacological data in TCMSP/BATMAN-TCM; 3) having clearly identified active components as inclusion standards, the initial screening of the aforementioned 28 insect-derived medicines yielded 23 remaining candidates. A second screening was then conducted using exclusion criteria: 1) Non-insect origin; 2) Unclear pharmacological mechanism; 3) Lack of evidence for anticoagulant/anti-fibrotic/ion channel regulatory activity as exclusion criteria. This yielded 11 insect-derived medicines meeting all criteria: *Coridius chinensis*, ground beetle, gallnut, mantis egg-case, blister beetle, centipede, cicada slough, *Bufonis venenum*, leech, cordyceps sinensis, earthworm.

3.2. Network Pharmacology Analysis

3.2.1. Screening Results for Active Ingredients and Targets in Insecticides

The screening of 11 insect-derived medicinal materials yielded 49 active compo-

nents: the following components were utilized: two active components from the *Coridius chinensis*, one active component from the ground beetle, two active components from the gallnut, two active components from the mantis egg-case, two active components from the blister beetle, five active components from the centipede, three active components from the cicada slough, one active component from *Bufonis venenum*, 13 active components from leeches, 12 active components from cordyceps sinensis, and seven active components from earthworms (Correction: The initial count for cordyceps sinensis was 16; after re-checking against the TCMSP filters (OB ≥ 30%, DL ≥ 0.18), four components were removed, resulting in 12. This adjustment corrects the total from 54 to 49). The UNIPROT database was utilized to identify all corresponding genes for these active components, yielding a total of 2,084 target genes. Following the elimination of 1,046 duplicate targets, the final dataset was composed of 1,038 target genes.

3.2.2. Disease Targets for AF

A comprehensive search for "Atrial fibrillation" in the OMIM database, Gene Cards database, and PharmGKB database yielded a total of 723 disease target genes. Following the elimination of redundant data through the utilization of an Excel spreadsheet, a total of 645 unique disease target genes was identified.

3.2.3. Drug-Disease Cross-Target

The 1038 effect target genes of the obtained insect-derived drugs and the 723 disease target genes of atrial fibrillation were imported into the online tool Venny 2.1.0. By setting the two datasets as the intersection, 61 overlapping target genes were identified and visualized in the Venn diagram (Figure 1).

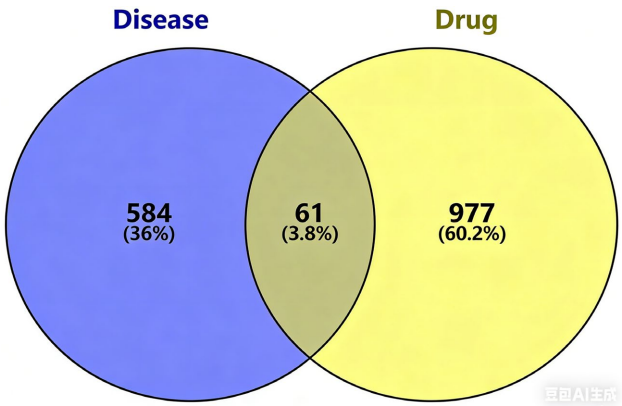

Figure 1. Venn diagram of cross-targets between drugs and diseases. Yellow represents drugs, blue represents diseases.

3.2.4. Constructing Drug-Disease Protein-Protein Interaction Network Maps

The importation of 61 intersecting target genes into the STRING database was followed by the removal of disconnected nodes from the network. A high confidence threshold of 0.700 was selected for the construction of the protein-protein interaction (PPI) network diagram (Figure 2 and Figure 3). The graph under

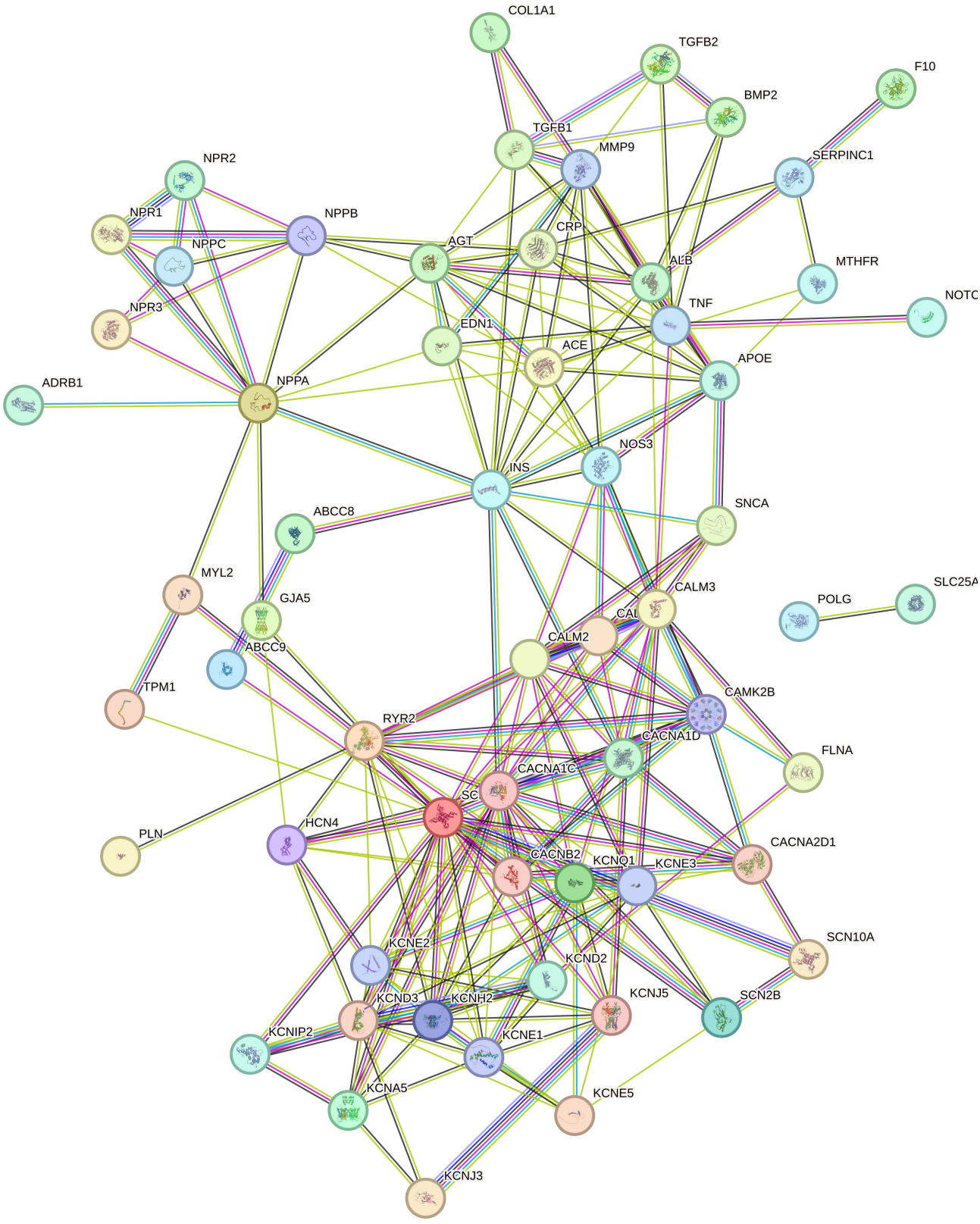

Figure 2. Protein interaction network diagram.

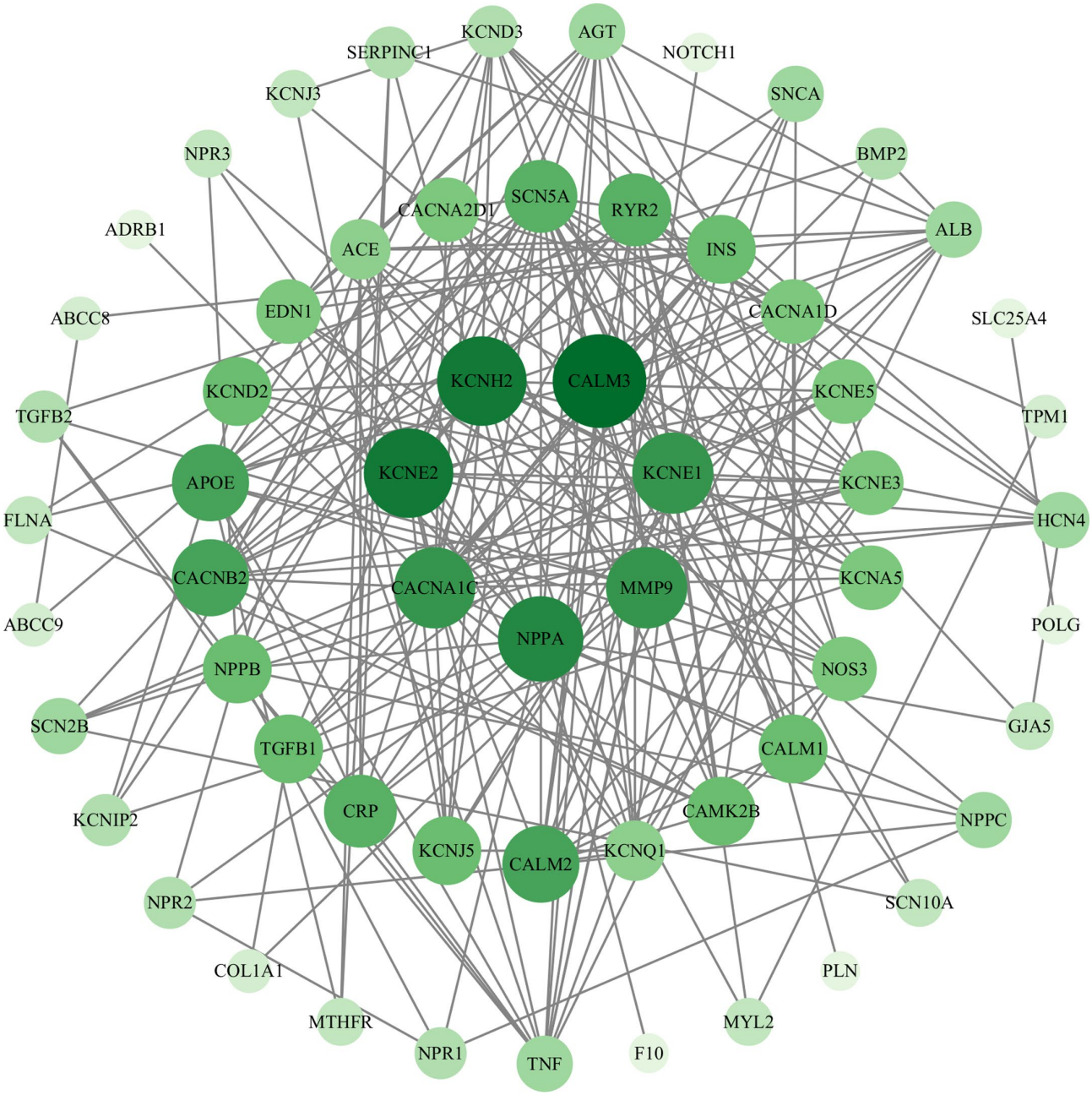

Figure 3. Protein interaction network diagram. The higher the degree, the darker the color.

consideration contained 61 nodes and 464 edges, with an average node degree of 15.2. The TSV file that was extracted from the STRING database was subsequently imported into Cytoscape 3.10.2 software. The cytoNCA plugin was utilized for core gene screening by calculating the median values of betweenness, closeness, degree, eigenvector, and network6. The selection of core genes is accomplished by employing node parameters that exceed the centrality median. Following two rounds of screening, five core genes were identified: Calmodulin-2 (CALM2), Voltage-dependent L-type calcium channel subunit alpha-1C (CACNA1C), Calmodulin-3 (CALM3), Sodium channel protein type 5 subunit alpha (SCN5A), and

Ryanodine receptor 2 (RYR2). Subsequently, molecular docking was performed on these five core genes.

3.2.5. Constructing a Visual Network Diagram of Traditional Chinese Medicine-Active Ingredients-Interacting Genes-Disease Networks

The construction of a network diagram for the 61 intersecting genes was performed using Cytoscape 3.10.0 software, thereby facilitating the mapping of relationships among traditional Chinese medicine, active components, intersecting genes, and diseases (**Figure 4**). The network under consideration contains a total of 96 nodes, including 9 traditional Chinese medicines, 25 active molecules, 61 genes, and 1 disease. The network also comprises 255 edges. The top five active molecules by degree were guanidine, crocetin, D-mannitol, canthaxanthin, and tyrosin. The top 10 target genes by degree were RYR2, KCNH2, NPPA, CACNA1C, KCNQ1, KCNJ2, CALM3, SCN5A, KCND3, and KCNJ5.

Clarification regarding the number of drugs in the network visualization: All 11 screened insect-derived drugs were included in the full computational pipeline. However, in the specific network visualization generated by Cytoscape (**Figure 4**), two drugs ("gallnut" and "mantis egg-case") were excluded because they did not contribute active components that directly linked to the final 61 intersecting targets through the applied screening filters (OB ≥ 30%, DL ≥ 0.18). Their exclusion from the final visual network is solely for the purpose of visual clarity and interpretability, as disconnected nodes do not contribute to the topological analysis. It is important to note that their inclusion in the initial pool of 11 drugs remains essential for the comprehensiveness of our target prediction.

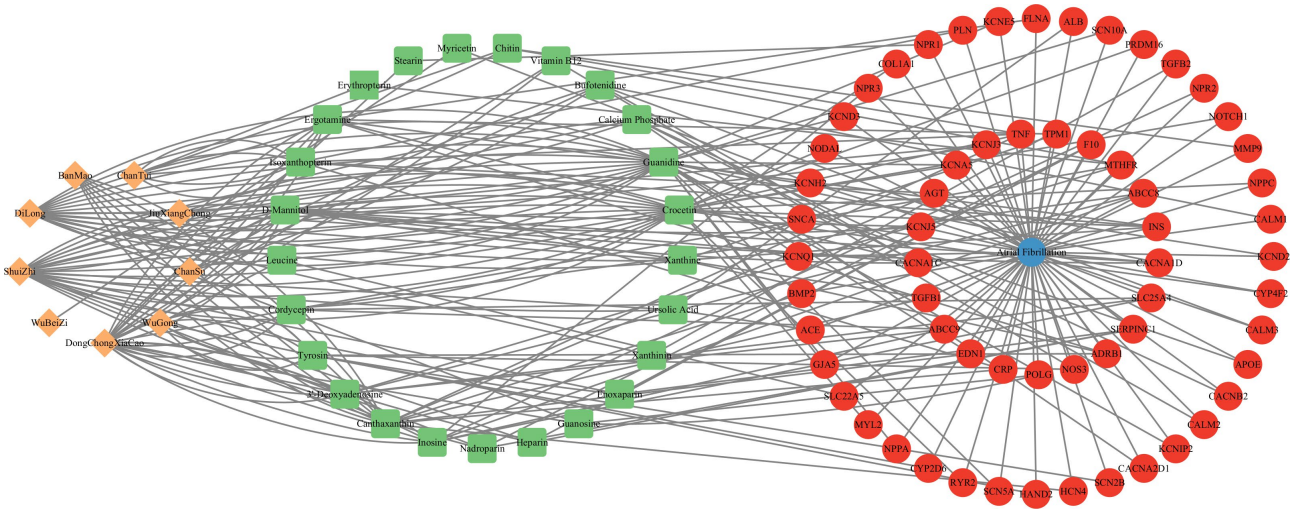

Figure 4. The yellow diamond on the far left represents insecticides with intersecting genes. The green square in the middle denotes the active ingredient of the drug. The red circle on the right indicates intersecting target genes, while the blue circle in the middle right represents the disease. The greater the number of lines in the diagram, the stronger the interactions within the network.

3.2.6. GO Biological Function and KEGG Signaling Pathway Enrichment Analysis Results

The intersecting target genes were subsequently imported into the DAVID data-

base for GO and KEGG analysis. The GO molecular function enrichment analysis yielded a total of 438 enriched results, including 323 BP, 49 CC, and 66 MF. The P-values for all three categories were less than 0.01. The top 10 genes, as determined by functional annotation counts in the microbial information platform analysis, were represented in the form of a trivalent bilateral bar chart for BP, CC, and MF (**Figure 5**). The left axis of the figure displays the statistical value –log10(p), while the right axis shows the number of enriched genes. Results indicate that biological processes primarily encompass regulation of heart rate by cardiac conduction, membrane repolarization during ventricular cardiac muscle cell action potential, and regulation of atrial cardiac muscle cell membrane repolarization. Cellular components mainly include the voltage-gated potassium channel complex, plasma membrane, and extracellular region. Molecular functions were primarily reflected in voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization, transmembrane transporter binding, and gated potassium channel activity.

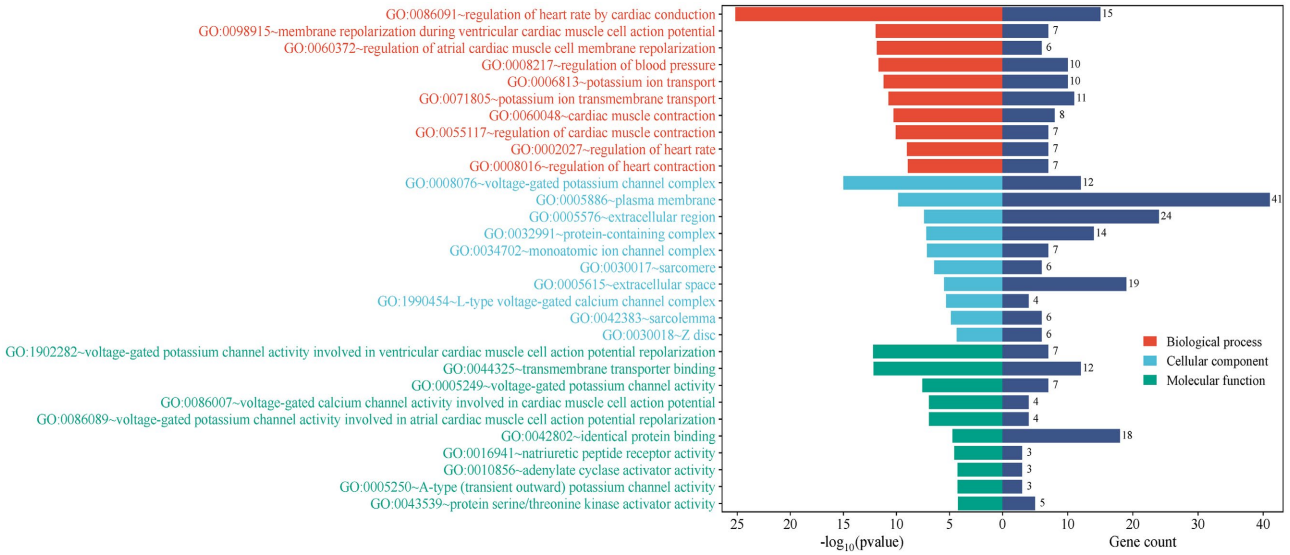

Figure 5. The figure illustrates the significant GO enrichment terms for drugs and diseases. Red indicates biological processes, blue indicates cellular components, green indicates molecular functions, and GO denotes Gene Ontology.

In the KEGG signaling pathways, pathways with $P < 0.01$ and the top 20 ranked genes were selected for analysis, and a pathway enrichment bubble plot was generated (**Figure 6**). The left panel of the figure illustrates the genes contained within each pathway, while the right panel displays a standard bubble chart. The size of each bubble corresponds to the number of genes belonging to a specific pathway, while the color of each bubble represents the P-value. The results of this study indicate that among the significantly enriched pathways, several are directly relevant to cardiac pathophysiology, including the cAMP signaling pathway, arrhythmogenic right ventricular cardiomyopathy (ARVC), and the calcium signaling pathway. The enrichment of the "Malaria" pathway is likely a statistical artifact resulting from shared genes involved in general inflammatory or endothelial dys-

function processes (e.g., IL6, TNF), rather than indicating a direct therapeutic link between insect-derived drugs and malaria. This is a known phenomenon in KEGG enrichment analysis when gene sets overlap across multiple biological contexts.

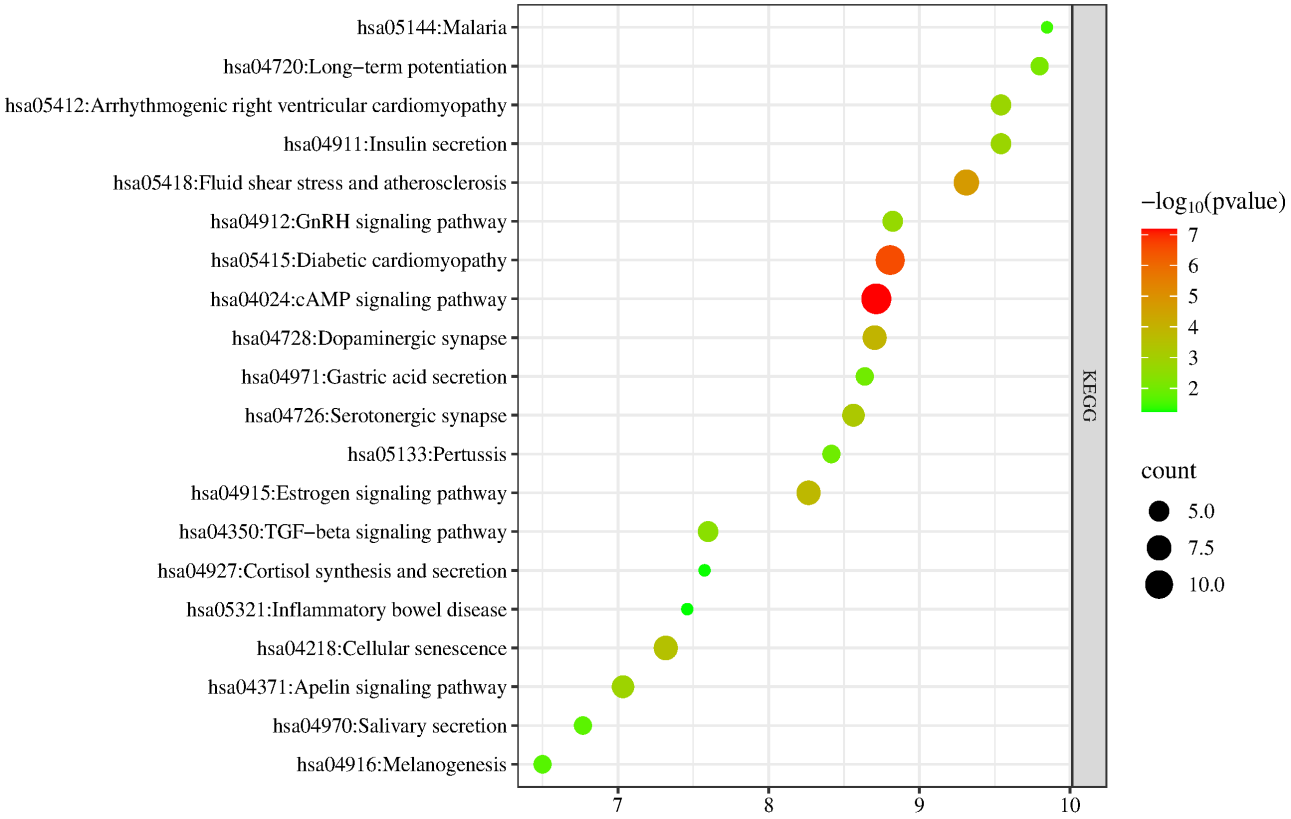

Figure 6. KEGG enrichment bubble plot.

3.2.7. Molecular Docking Results

The five core intersecting target genes obtained were used as protein receptors to identify their corresponding small-molecule ligands (active components). Molecular docking technology was employed to dock each core gene with the active components individually. The docking binding energy results are presented in Table 1. The visualization process was facilitated by the utilization of the PyMOL software. Typically, absolute docking scores greater than 4.25 are indicative of moderate activity, scores between 5.0 and 7.0 are indicative of good binding activity, and scores above 7.0 are indicative of strong binding activity. To provide a benchmark for the docking results, we included verapamil, a known L-type calcium channel blocker clinically used in arrhythmia management, as a positive control. Verapamil exhibited a binding energy of −7.2 kcal/mol with CACNA1C, confirming the reliability of our docking protocol. In comparison, ergotamine showed a stronger binding affinity (−8.5 kcal/mol) with the same target. The top three lowest binding energies were: Crocetin formed hydrogen bonds with RYR2 at GLN-38 and ASP-83; bufotenidine formed hydrogen bonds with CALM2 at ASP-372 and GLN-297 (Figure 7).

Table 1. Results of docking between core genes and corresponding active component molecules.

Core gene	Uniprot ID	PDB ID	Active ingredient	Docking binding energy (kcal/mol)
CALM2	P0DP24	6XXF	Bufotenidine	−5.3
CACNA1C	Q13936	5V2Q	D-Mannitol	−4.7
CACNA1C	Q13936	5V2Q	Ergotamine	−8.5
CACNA1C	Q13936	5V2Q	Calcium Phosphate	−3.0
CALM3	P0DP25	6K67	Bufotenidine	−4.6
SCN5A	Q14524	4DJC	Guanidine	−3.8
RYR2	Q92736	6Y4O	Crocetin	−5.5

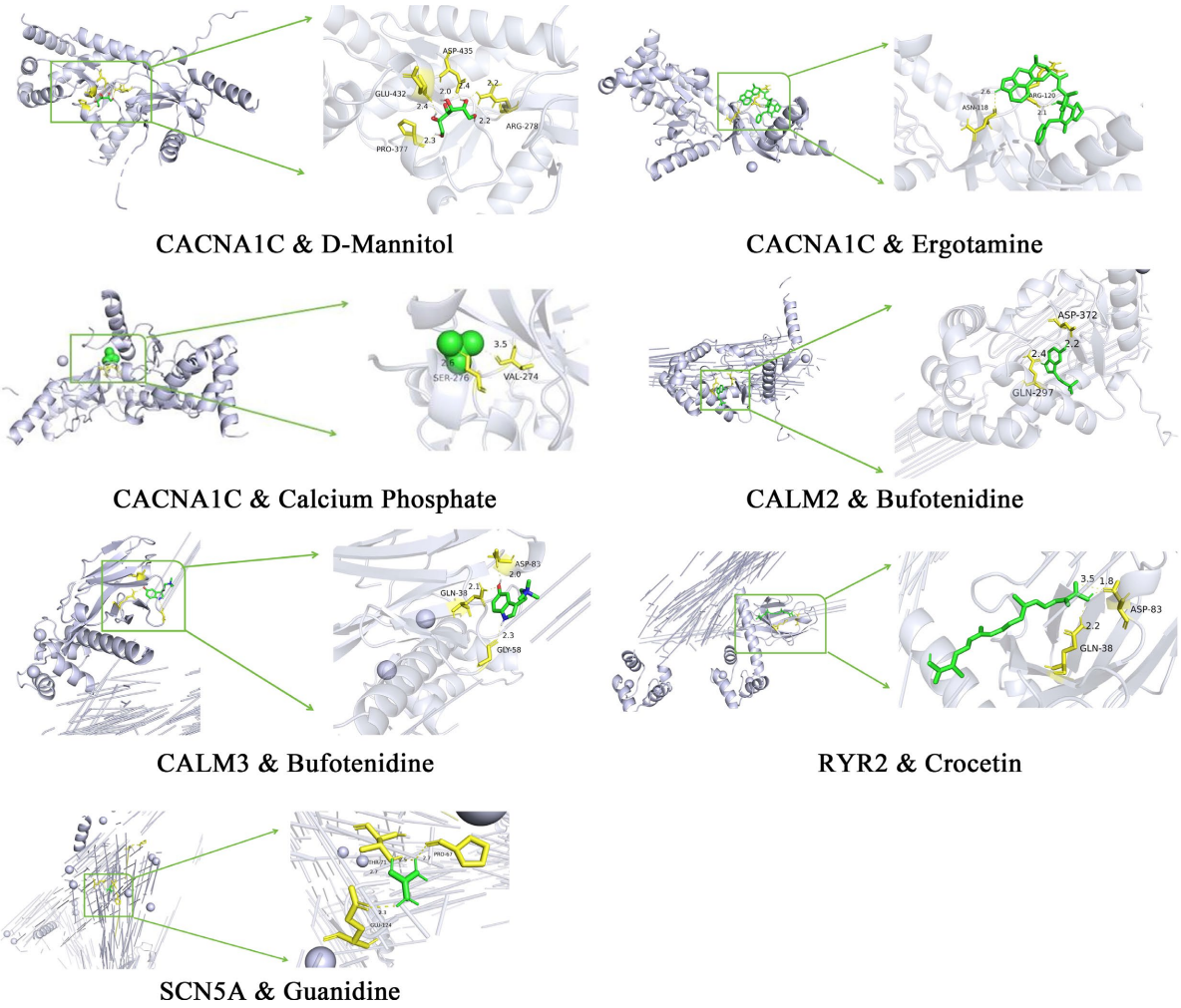

Figure 7. Molecular docking model diagram.

Note regarding Calcium Phosphate: In Table 1, "Calcium Phosphate" is listed as an active component interacting with CACNA1C. It is important to clarify that calcium phosphate is included here as a representative ionic ligand to model the

binding interaction of inorganic calcium ions (Ca^{2+}) within the channel pore, given the central role of calcium influx via CACNA1C in AF pathophysiology. Its docking score provides a reference point for comparing the binding modes and relative strengths of the organic compounds (e.g., ergotamine) at the same site.

4. Discussion

AF is the most prevalent arrhythmia in clinical practice and is regarded as a progressive condition [18]. The majority of patients initially experience brief episodes of AF that terminate spontaneously. However, in the presence of appropriate triggers and substrate, these episodes may progressively evolve into more persistent and permanent forms. Consequently, AF is clinically categorized into three distinct classifications: paroxysmal AF, long-standing persistent AF, and permanent AF [4]. The pathogenesis of this condition is complex and involves the interplay of multiple factors, including electrophysiological disturbances, structural remodeling, and autonomic dysregulation [6] [19] [20]. The efficacy and safety of current antiarrhythmic medications are limited, and surgical treatments carry a high risk of long-term recurrence, underscoring the necessity for the exploration of novel therapeutic strategies. Traditional Chinese medicine (TCM), particularly in the domain of insect-derived drugs, boasts a long history and unique advantages in the treatment of arrhythmias. This study, integrating data mining, network pharmacology, and molecular docking techniques, systematically investigates for the first time the multi-component, multi-target, and multi-pathway mechanisms of 11 insect-derived drugs (*Pheretima aspergillum*, *Eupolyphaga sinensis*, Gallnut, *Cynoglossus*, *Mylabris phalerata*, *Scolopendra subspinipes*, Cicada molt, toad venom, leech, cordyceps, and earthworm) against atrial fibrillation. The findings of this study indicate that toad venom, leech, cordyceps, nine-spice beetle, and earthworm may offer novel therapeutic approaches for AF by synergistically regulating calcium handling, sodium channel function, and cardiac electrophysiological processes.

In the course of our network pharmacology analysis, we constructed a visual network diagram linking drugs, active ingredients, diseases, and targets. This analysis yielded the identification of critical active ingredients associated with AF, including bufotenidine, D-mannitol, ergotamine, calcium phosphate, guanidine, and crocetin. Research [21] [22] indicates that the hyperosmolar properties of mannitol and its effective scavenging of free radicals may exert myocardial protection by regulating ROS levels during ischemia and reperfusion. Katharina Feige's study [23] confirmed that mannitol activates the mitochondrial ATP-sensitive potassium (mKATP) channel to exert cardioprotective effects. A notable decrease in the activity of mitochondrial ATP synthase in atrial tissue has been observed in patients with AF, resulting in inadequate ATP production [24], as evidenced by the activation of the mKATP channel. The excessive opening of mKATP channels has been demonstrated to be a primary factor in the progression of AF dysfunction, operating through the mechanisms of shortening the action

potential duration (APD) and promoting calcium overload [25]. Regarding D-Mannitol, while conventionally used as an osmotic agent, its inclusion here is supported by emerging pharmacological insights. Beyond osmolarity, mannitol has demonstrated free radical scavenging properties [21] [22] and the ability to activate mitochondrial mKATP channels [23], contributing to cardioprotection during ischemia-reperfusion. Although its oral bioavailability is low, its potential direct cardiac effects, possibly through modulation of ion channels or signaling pathways in a localized manner, warrant further investigation. In our study, D-mannitol showed moderate docking affinity with CACNA1C (−4.7 kcal/mol), suggesting a possible direct interaction that complements its known indirect protective roles. Future studies should validate whether mannitol or its metabolites can achieve sufficient concentration at cardiac targets to exert antiarrhythmic effects. Crocin, a predominant active ingredient in gardenia yellow pigment, demonstrates hypoglycemic [26] and hypolipidemic [27] properties, along with anti-thrombotic, anti-myocardial ischemia, antioxidant stress, and anti-apoptotic actions [28] [29]. According to the findings of Jun Cai's research [30], crocin has the potential to reduce fibrosis and collagen synthesis by obstructing the MEK-ERK1/2 signaling pathway. This suggests that crocin may offer a novel therapeutic approach to decelerate the progression of AF. Guanidine and its derivatives or synthetic compounds exhibit a diverse array of biological activities, including antitumor, antibacterial, antifungal, antipathogenic, and antiviral effects [31]. Among these, guanidine derivatives (e.g., ME10092 [32]) have been demonstrated to dose-dependently inhibit reperfusion-induced arrhythmias, significantly improve animal survival rates, and reduce infarct size. The cardioprotective effects of these substances may be associated with their ability to mitigate oxidative damage. Guanidine derivatives (e.g., KR-32568 [33]) act as sodium-hydrogen exchanger-1 (NHE-1) inhibitors, significantly reducing the incidence and duration of ventricular premature beats, ventricular tachycardia, and ventricular fibrillation in rat ischemia/reperfusion models. This finding suggests that the antiarrhythmic effects of these compounds are achieved through the regulation of ion homeostasis.

Utilizing a combination of PPI and core target screening methodologies, we have identified CALM2, CACNA1C, CALM3, SCN5A, and RYR2 as occupying pivotal roles within the network architecture. These targets have demonstrated significant enrichment in critical pathways, thereby substantiating their potential as vital targets for the development of insect-derived therapeutic agents for the management of AF. As core components of the calmodulin complex, CALM2 and CALM3 dynamically regulate downstream kinases (e.g., CaMKII) and phosphatase activity by binding calcium ions, thereby forming calcium-dependent signaling cascades [34]. In AF, disrupted calcium homeostasis is a hallmark of the pathological condition [35]. Abnormal phosphorylation at the S2808/S2814 [36] [37] sites of RYR2 has been demonstrated to lead to diastolic calcium leakage, which in turn triggers delayed afterdepolarizations (DADs) and action potential initiation. Overactivation of CACNA1C has been demonstrated to increase cal-

cium influx, exacerbating calcium overload and activating CaMKII, thus establishing a self-perpetuating cycle [38] [39]. The SCN5A gene is responsible for encoding the cardiac sodium channel Nav1.5, which is responsible for action potential initiation and propagation. Abnormal sodium currents have been demonstrated to influence intracellular calcium concentrations via the sodium-calcium exchanger (NCX). SCN5A gain-of-function mutations (e.g., R1193Q [40]) have been demonstrated to increase sustained inward sodium currents, which in turn enhance calcium influx via NCX. This results in an accumulation of calcium within the cell, leading to the initiation of activity and, consequently, the formation of a substrate conducive to arrhythmias. Furthermore, aberrant calcium signaling has been shown to promote collagen deposition by activating fibroblasts (e.g., via the TGF-β1/Smad3 pathway), resulting in myocardial fibrosis—a pivotal mechanism sustaining AF [41].

GO enrichment analysis results reveal that the potential biological processes underlying the anti-AF effects of insect-derived drugs primarily focus on cardiac electrophysiological regulation: regulation of heart rate by cardiac conduction, membrane repolarization during ventricular cardiac muscle cell action potential, and regulation of atrial cardiac muscle cell membrane repolarization. These processes are directly related to the electrophysiological mechanisms of AF, particularly as abnormalities in the repolarization processes of atrial and ventricular muscle cells form a crucial basis for arrhythmia occurrence. A molecular function analysis indicates that these drugs primarily affect three processes: the activity of voltage-gated potassium channels involved in ventricular cardiac muscle cell action potential repolarization, transmembrane transporter binding, and gated potassium channel activity. This finding suggests that drugs derived from insects may influence action potential duration and effective refractory period by modulating potassium channel function, thereby reducing reentry formation—a key mechanism sustaining AF. It is noteworthy that while the present study concentrated on AF, a significant number of enriched items pertained to ventricular myocytes. This observation indicates the potential for insect-derived drugs to exhibit a comprehensive antiarrhythmic effect that extends beyond the scope of atrial arrhythmias.

KEGG pathway enrichment analysis revealed a significant association between the candidate targets and pathways such as ARVC and the cAMP signaling pathway. ARVC is a hereditary cardiomyopathy characterized by progressive fibrofatty infiltration of the right ventricular myocardium [42]. The pathological manifestation of this condition is characterized by the replacement of normal myocardial tissue with fibrofatty tissue, resulting in ventricular electrophysiological disturbances and contractile dysfunction. Molecular studies indicate that ARVC-associated desmin gene mutations compromise myocardial structural integrity and directly induce electrophysiological abnormalities. For instance, desmoplakin [43] dysfunction has been demonstrated to disrupt the function and localization of voltage-gated sodium channels (Nav1.5), thereby diminishing inward sodium

currents (I_{Na}) and markedly slowing atrial conduction velocity. This phenomenon engenders a milieu conducive to the initiation and progression of AF. The cAMP signaling pathway, a pivotal component of the second messenger system, exerts a direct regulatory influence on the opening of L-type calcium channels and the subsequent release of calcium from the sarcoplasmic reticulum. In pathological conditions, aberrant activation of the cAMP-PKA signaling pathway results in excessive phosphorylation of RyR2, leading to diastolic calcium leakage and DADs. These phenomena, in turn, trigger and sustain AF [44] [45]. Of particular interest is the observation that these pathways are associated with calcium signaling regulation, a finding that aligns closely with our core target analysis. Furthermore, molecular docking indicates that CACNA1C & Ergotamine, CALM2 & Bufotenidine, and RYR2 & Crocetin exhibit strong binding affinity, suggesting effective interaction between insect-derived drugs and specific AF-related proteins.

The present study is subject to several limitations: Firstly, the reliability of the results is contingent upon the completeness and accuracy of the databases. Discrepancies in nomenclature and delays in updates across various databases have the potential to compromise the comprehensiveness of target predictions. Secondly, the findings of the present study are contingent upon experimental validation; at this juncture, the available evidence consists of computational biology predictions, devoid of in vitro and in vivo experimental verification. In addition, the majority of insect-derived drugs demonstrate toxicity and possess complex chemical compositions, with related research remaining limited. It is important to note that multiple components may act on the same target, thereby producing synergistic or antagonistic effects. Future studies should employ orthogonal experimental designs to identify key active constituents and validate synergistic interactions through optimized component combinations. The objective of this research is to broaden the scope of the existing work, thereby establishing a foundation for future investigations and the clinical utilization of insect-derived drugs in the treatment of AF.

5. Conclusion

This study systematically elucidates the multi-component, multi-target, and multi-pathway mechanisms of insect-derived drugs in treating atrial fibrillation by integrating data mining, network pharmacology, and molecular docking approaches. The findings suggest that these traditional Chinese medicines may possess anti-atrial fibrillation properties by modulating core targets such as CALM2, CACNA1C, CALM3, SCN5A, and RYR2. This influence may be exerted through the regulation of cardiac electrophysiology, calcium handling, and multiple signaling pathways. These findings provide scientific rationale for the conventional utilization of these medications and suggest novel avenues for the development of antiarrhythmic pharmaceuticals. It is imperative that future experimental studies be conducted to validate these computational predictions and to explore their potential for clinical translation.

Authors' Contributions

L.T. conceived and designed the study, performed data mining, and analyzed the data. J.Z. conducted the network pharmacology analysis. Q.N. carried out the molecular docking studies. Q.N. and W.X. supervised the entire project, interpreted the results, and revised the manuscript. All authors read and approved the final manuscript.

Funding

The authors acknowledge key funding support from the Scientific Research Project of the Sichuan Provincial Administration of Traditional Chinese Medicine (Grant No.: 51000025T000013799606) and the Innovation Fund of Chengdu University of Traditional Chinese Medicine (Grant No.: WXLH202403248).

Data and Materials Acquisition

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

Acknowledgements

The authors would like to thank all authors for the references.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Brundel, B.J.J.M., Ai, X., Hills, M.T., Kuipers, M.F., Lip, G.Y.H. and de Groot, N.M.S. (2022) Atrial Fibrillation. *Nature Reviews Disease Primers*, **8**, Article No. 21. https://doi.org/10.1038/s41572-022-00347-9

[2] Cheng, S., He, J., Han, Y., Han, S., Li, P., Liao, H., *et al.* (2024) Global Burden of Atrial Fibrillation/Atrial Flutter and Its Attributable Risk Factors from 1990 to 2021. *Europace*, **26**, euae195. https://doi.org/10.1093/europace/euae195

[3] Shi, S., Tang, Y., Zhao, Q., Yan, H., Yu, B., Zheng, Q., *et al.* (2022) Prevalence and Risk of Atrial Fibrillation in China: A National Cross-Sectional Epidemiological Study. *The Lancet Regional Health- Western Pacific*, **23**, Article 100439. https://doi.org/10.1016/j.lanwpc.2022.100439

[4] Joglar, J.A., Chung, M.K., Armbruster, A.L., Benjamin, E.J., Chyou, J.Y., Cronin, E.M., *et al.* (2024) 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, **149**, e1-e156. https://doi.org/10.1161/cir.0000000000001193

[5] Morseth, B., Geelhoed, B., Linneberg, A., Johansson, L., Kuulasmaa, K., Salomaa, V., *et al.* (2021) Age-Specific Atrial Fibrillation Incidence, Attributable Risk Factors and Risk of Stroke and Mortality: Results from the MORGAM Consortium. *Open Heart*, **8**, e001624. https://doi.org/10.1136/openhrt-2021-001624

[6] Ninni, S., Dombrowicz, D., de Winther, M., Staels, B., Montaigne, D. and Nattel, S. (2024) Genetic Factors Altering Immune Responses in Atrial Fibrillation. *Journal of*

the American College of Cardiology, **83**, 1163-1176. https://doi.org/10.1016/j.jacc.2023.12.034

[7] Hu, X., Biase, L.D., Hou, X. and Liu, X. (2025) Persistent Atrial Fibrillation Ablation: Glimpsing the Light Ahead? *Europace*, **27**, euaf037. https://doi.org/10.1093/europace/euaf037

[8] Reddy, V.Y., Gerstenfeld, E.P., Schmidt, B., Nair, D., Natale, A., Saliba, W., *et al.* (2025) Pulsed Field Ablation for Persistent Atrial Fibrillation. *Journal of the American College of Cardiology*, **85**, 1664-1678. https://doi.org/10.1016/j.jacc.2025.03.515

[9] Ye, T.-S. (2017) A Guide to Clinical Case Studies. People's Medical Publishing House.

[10] Wang, F. (2015) An Exploration of the Origins of Medical Compilations. In: Jiang, L.-Z., Ed., *China Press of Traditional Chinese Medicine*, 123-125.

[11] Tao, H.-J. (2013) Supplementary Records of Renowned Physicians: A Collated Edition. China Press of Traditional Chinese Medicine.

[12] Lian, X., Liu, B., Li, D., Wang, X., Long, C., Feng, X., *et al.* (2025) An Elastase Inhibitor ShSPI from Centipede Attenuates Bleomycin-Induced Pulmonary Fibrosis. *Toxins*, **17**, Article 213. https://doi.org/10.3390/toxins17050213

[13] Lu, W., Cheng, X., Chen, J., Wang, M., Chen, Y., Liu, J., *et al.* (2021) A Buthus Martensii Karsch Scorpion Sting Targets $Na_v1.7$ in Mice and Mimics a Phenotype of Human Chronic Pain. *Pain*, **163**, e202-e214. https://doi.org/10.1097/j.pain.0000000000002397

[14] Luo, T., Lu, Y., Yan, S., Xiao, X., Rong, X. and Guo, J. (2020) Network Pharmacology in Research of Chinese Medicine Formula: Methodology, Application and Prospective. *Chinese Journal of Integrative Medicine*, **26**, 72-80. https://doi.org/10.1007/s11655-019-3064-0

[15] Paggi, J.M., Pandit, A. and Dror, R.O. (2024) The Art and Science of Molecular Docking. *Annual Review of Biochemistry*, **93**, 389-410. https://doi.org/10.1146/annurev-biochem-030222-120000

[16] National Pharmacopoeia Commission (2020) Pharmacopoeia of the People's Republic of China: Volume I. China Medical Science Press.

[17] State Administration of Traditional Chinese Medicine (1999) Zhong Hua Ben Cao: Volume 1. Shanghai Science and Technology Press.

[18] Heijman, J., Voigt, N., Nattel, S. and Dobrev, D. (2014) Cellular and Molecular Electrophysiology of Atrial Fibrillation Initiation, Maintenance, and Progression. *Circulation Research*, **114**, 1483-1499. https://doi.org/10.1161/circresaha.114.302226

[19] Pikunov, A.V., Syunyaev, R.A., Ali, R., Prakosa, A., Gams, A., Boyle, P.M., *et al.* (2025) Role of Structural versus Cellular Remodeling in Atrial Arrhythmogenesis: Insights from Personalized Digital Twins. *Circulation: Arrhythmia and Electrophysiology*, **18**, e013898. https://doi.org/10.1161/circep.125.013898

[20] Meng, S., Huang, T., Zhou, Z., Yu, L. and Wang, H. (2025) Chronic Mild Stress Exacerbates Atrial Fibrillation and Neutrophil Extracellular Traps Formation through S100A8/A9 Signaling. *Signal Transduction and Targeted Therapy*, **10**, Article No. 108. https://doi.org/10.1038/s41392-025-02199-7

[21] Chen, M., Zhang, X.P., Fan, Y.Y. and Zhang, M.S. (2016) Mannitol Preconditioning Alleviates Hypoxia/Reoxygenation Injury in H9c2 Cells. *Chinese Journal of Clinical Pharmacology*, **32**, 1011-1013.

[22] Magovern, G.J., Bolling, S.F., Casale, A.S., Bulkley, B.H. and Gardner, T.J. (1984) The Mechanism of Mannitol in Reducing Ischemic Injury: Hyperosmolarity or Hydroxyl Scavenger? *Circulation*, **70**, I91-I95.

[23] Feige, K., Rubbert, J., Raupach, A., Stroethoff, M., Heinen, A., Hollmann, M.W., *et al.* (2021) Cardioprotective Properties of Mannitol—Involvement of Mitochondrial Potassium Channels. *International Journal of Molecular Sciences*, **22**, Article 2395. https://doi.org/10.3390/ijms22052395

[24] Ozcan, C., LI, Z., Kim, G., Jeevanandam, V. and Uriel, N. (2019) Molecular Mechanism of the Association between Atrial Fibrillation and Heart Failure Includes Energy Metabolic Dysregulation Due to Mitochondrial Dysfunction. *Journal of Cardiac Failure*, **25**, 911-920. https://doi.org/10.1016/j.cardfail.2019.08.005

[25] Mauriello, A., Correra, A., Molinari, R., Del Vecchio, G.E., Tessitore, V., D'Andrea, A., *et al.* (2024) Mitochondrial Dysfunction in Atrial Fibrillation: The Need for a Strong Pharmacological Approach. *Biomedicines*, **12**, Article 2720. https://doi.org/10.3390/biomedicines12122720

[26] Asdaq, S.M.B. and Inamdar, M.N. (2010) Potential of Crocus Sativus (Saffron) and Its Constituent, Crocin, as Hypolipidemic and Antioxidant in Rats. *Applied Biochemistry and Biotechnology*, **162**, 358-372. https://doi.org/10.1007/s12010-009-8740-7

[27] Yu, L., Gao, R., Song, X., Li, X. and Zhu, J. (2021) Cardio-Protective and Anti-Atherosclerosis Effect of Crocetin on Vitamin D3 and HFD-Induced Atherosclerosis in Rats. *Journal of Oleo Science*, **70**, 1447-1459. https://doi.org/10.5650/jos.ess21168

[28] Su, X., Yuan, C., Wang, L., Chen, R., Li, X., Zhang, Y., *et al.* (2021) The Beneficial Effects of Saffron Extract on Potential Oxidative Stress in Cardiovascular Diseases. *Oxidative Medicine and Cellular Longevity*, **2021**, Article ID: 6699821. https://doi.org/10.1155/2021/6699821

[29] Higashino, S., Sasaki, Y., Giddings, J.C., Hyodo, K., Fujimoto Sakata, S., Matsuda, K., *et al.* (2014) Crocetin, a Carotenoid from *Gardenia jasminoides* Ellis, Protects against Hypertension and Cerebral Thrombogenesis in Stroke-prone Spontaneously Hypertensive Rats. *Phytotherapy Research*, **28**, 1315-1319. https://doi.org/10.1002/ptr.5130

[30] Cai, J., Yi, F., Bian, Z., Shen, D., Yang, L., Yan, L., *et al.* (2009) Crocetin Protects against Cardiac Hypertrophy by Blocking MEK-ERK1/2 Signalling Pathway. *Journal of Cellular and Molecular Medicine*, **13**, 909-925. https://doi.org/10.1111/j.1582-4934.2008.00620.x

[31] Gomes, A.R., Varela, C.L., Pires, A.S., Tavares-da-Silva, E.J. and Roleira, F.M.F. (2023) Synthetic and Natural Guanidine Derivatives as Antitumor and Antimicrobial Agents: A Review. *Bioorganic Chemistry*, **138**, Article 106600. https://doi.org/10.1016/j.bioorg.2023.106600

[32] Dambrova, M., Veveris, M., Cirule, H., Pugovichs, O., Post, C., Lundstedt, T., *et al.* (2002) The Novel Guanidine ME10092 Protects the Heart during Ischemia-Reperfusion. *European Journal of Pharmacology*, **445**, 105-113. https://doi.org/10.1016/s0014-2999(02)01596-0

[33] Roh, H., Jung, I., Park, J., Yun, Y., Yi, K., Yoo, S., *et al.* (2005) Cardioprotective Effects of [5-(2-Methyl-5-Fluorophenyl)Furan-2-Ylcarbonyl]Guanidine (KR-32568) in an Anesthetized Rat Model of Ischemia and Reperfusion Heart Injury. *Pharmacology*, **75**, 37-44. https://doi.org/10.1159/000086192

[34] Hussey, J.W., Limpitikul, W.B. and Dick, I.E. (2023) Calmodulin Mutations in Human Disease. *Channels*, **17**, Article 2165278. https://doi.org/10.1080/19336950.2023.2165278

[35] Chang, Y. and Zou, Q. (2025) Mitochondrial Calcium Homeostasis and Atrial Fibrillation: Mechanisms and Therapeutic Strategies Review. *Current Problems in Cardiology*, **50**, Article 102988. https://doi.org/10.1016/j.cpcardiol.2025.102988

[36] Walweel, K., Gomez-Hurtado, N., Rebbeck, R.T., Oo, Y.W., Beard, N.A., Molenaar, P., *et al.* (2019) Calmodulin Inhibition of Human RyR2 Channels Requires Phosphorylation of RyR2-S2808 or RyR2-S2814. *Journal of Molecular and Cellular Cardiology*, **130**, 96-106. https://doi.org/10.1016/j.yjmcc.2019.03.018

[37] Wehrens, X.H.T., Lehnart, S.E., Reiken, S., Vest, J.A., Wronska, A. and Marks, A.R. (2006) Ryanodine Receptor/Calcium Release Channel PKA Phosphorylation: A Critical Mediator of Heart Failure Progression. *Proceedings of the National Academy of Sciences*, **103**, 511-518. https://doi.org/10.1073/pnas.0510113103

[38] Ronkainen, J.J., Hänninen, S.L., Korhonen, T., Koivumäki, J.T., Skoumal, R., Rautio, S., *et al.* (2011) Ca^{2+}-Calmodulin-Dependent Protein Kinase II Represses Cardiac Transcription of the L-Type Calcium Channel α_{1C}-Subunit Gene (*Cacna1c*) by DREAM Translocation. *The Journal of Physiology*, **589**, 2669-2686. https://doi.org/10.1113/jphysiol.2010.201400

[39] Sato, D., Ghayoumi, B., Fasoli, A., Ko, C.Y. and Bers, D.M. (2025) Positive Feedback between RyR Phosphorylation and Ca^{2+} Leak Promotes Heterogeneous Ca^{2+} Release. *Biophysical Journal*, **124**, 717-721. https://doi.org/10.1016/j.bpj.2025.01.023

[40] Huang, H., Zhao, J., Barrane, F., Champagne, J. and Chahine, M. (2006) NAV1.5/R1193Q Polymorphism Is Associated with Both Long QT and Brugada Syndromes. *Canadian Journal of Cardiology*, **22**, 309-313. https://doi.org/10.1016/s0828-282x(06)70915-1

[41] Kittana, N. (2025) Calcium Signaling in Cardiac Fibroblasts: Roles in Fibrosis and Therapeutic Implications. *Cardiovascular Drugs and Therapy*. https://doi.org/10.1007/s10557-025-07699-w

[42] Sinagra, G., Cappelletto, C., DE Luca, A., Romani, S., Paldino, A., Korcova, R., *et al.* (2020) Focus on Arrhythmogenic Right Ventricular Cardiomyopathy. *European Heart Journal Supplements*, **22**, L129-L135. https://doi.org/10.1093/eurheartj/suaa152

[43] Zhang, Q.H., Deng, C.Y., Rao, F., Liu, X.Y., Mai, L.P., Zhu, J.N., *et al.* (2013) Down-Regulation of Desmosomal Gene Expression Impairs $Na_v1.5$ Function in HL-1 Cardiomyocytes. *Journal of Southern Medical University*, **33**, 983-989.

[44] Dridi, H., Kushnir, A., Zalk, R., Yuan, Q., Melville, Z. and Marks, A.R. (2020) Intracellular Calcium Leak in Heart Failure and Atrial Fibrillation: A Unifying Mechanism and Therapeutic Target. *Nature Reviews Cardiology*, **17**, 732-747. https://doi.org/10.1038/s41569-020-0394-8

[45] Landstrom, A.P., Dobrev, D. and Wehrens, X.H.T. (2017) Calcium Signaling and Cardiac Arrhythmias. *Circulation Research*, **120**, 1969-1993. https://doi.org/10.1161/circresaha.117.310083

Abbreviation

AF	Atrial fibrillation
APD	Action potential duration
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ATP	Adenosine triphosphate
BB	Biological Process
CACNA1C	Voltage-dependent L-type calcium channel subunit alpha-1C
CALM2	Calmodulin-2
CALM3	Calmodulin-3
cAMP	Cyclic adenosine monophosphate
CaMKII	Calcium/calmodulin-dependent protein kinase II
CC	Cellular Component
DADs	Delayed afterdepolarizations
I_{Na}	Inward sodium currents
MF	Molecular Function
mKATP	Mitochondrial ATP-sensitive potassium
Nav1.5	Voltage-gated sodium channels
NCX	Sodium-calcium exchanger
NHE-1	Sodium-hydrogen exchanger-1
PFA	Pulsed-field ablation
RYR2	Ryanodine receptor 2
SCN5A	Sodium channel protein type 5 subunit alpha
TCM	Traditional Chinese medicine