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Network Pharmacology and Molecular Docking Analysis of Mahuang Fuzi Xixin Decoction for Arrhythmia

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Abstract: This study employed integrated network pharmacology and molecular docking to elucidate how Mahuang Fuzi Xixin Decoction (MFXD) counters cardiac arrhythmia. Bioactive compounds and targets of Ephedra sinica, Aconitum carmichaelii, and Asarum heterotropoides were retrieved from BATMAN-TCM, while arrhythmia-related genes were compiled from GeneCards, DisGeNET, and NCBI. Overlapping targets defined the MFXD–arrhythmia set used to construct an arrhythmia–MFXD–compound–target network in Cytoscape and a STRING protein–protein interaction (PPI) network; functional annotation used GO and KEGG enrichment in R, and representative interactions were evaluated with AutoDock Vina. In total, 273 bioactive compounds and 78 shared targets were identified; PPI analysis highlighted six hubs (INS, TNF, IL6, ALB, TP53, PPARG). GO analysis yielded 2,048 significant terms and KEGG identified 158 pathways, prominently oxytocin signaling, hypertrophic cardiomyopathy, and cAMP signaling. Docking showed broadly favorable affinities (mostly ≤ -6.0 kcal·mol^{-1}), with the most favorable scores for TP53–3beta-Hydroxyurs-12-En-28-Syre (-8.2 kcal·mol^{-1}), ALB–quercetin (-8.1 kcal·mol^{-1}), and PPARG–quercetin (-7.9 kcal·mol^{-1}). Collectively, these findings indicate that MFXD exerts anti-arrhythmic effects through coordinated, multi-component modulation of inflammatory, metabolic, and ion-channel processes across convergent signaling pathways, providing a pharmacological rationale for its clinical application in arrhythmia management.

1. Introduction

Cardiac arrhythmias are heterogeneous disorders of cardiac electrical activity ranging from benign premature beats to life-threatening ventricular fibrillation, contributing substantially to morbidity and mortality [1]. Their pathophysiology involves abnormal automaticity, triggered

activity, and reentry, often on a substrate of structural heart disease, electrolyte imbalance, or autonomic dysregulation [2]. Although current antiarrhythmic drugs can be effective, their use is limited by proarrhythmic risk, interactions, and systemic toxicity, underscoring the need for alternative strategies [3].

Mahuang Fuzi Xixin Decoction (MFXD), recorded in Zhang Zhongjing's "Shang Han Lun," is clinically used for cardiovascular disorders, particularly bradyarrhythmias such as sick sinus syndrome and atrioventricular block [4]. MFXD comprises three medicinal herbs: *Ephedra sinica Stapf* (Mahuang), *Aconitum carmichaelii Debx* (Fuzi), and *Asarum heterotropoides Fr. Schmidt var. mandshuricum (Maxim.) Kitag.* (Xixin). Clinical observations reported that MFXD can significantly improve heart rate and rhythm disturbances within a relatively short treatment period [5]. The formula's therapeutic effects are attributed to its ability to warm Yang, disperse cold, and restore cardiovascular homeostasis according to Traditional Chinese Medicine (TCM) theory. Recent studies have suggested that MFXD's cardiovascular benefits may involve modulation of ion channels, autonomic nervous system regulation, and anti-inflammatory mechanisms [6]. Despite its widespread clinical application, the molecular mechanisms underlying MFXD's anti-arrhythmic effects remain incompletely elucidated, limiting its integration into evidence-based cardiovascular therapeutics.

Network pharmacology, an emerging paradigm in drug discovery and mechanistic research, provides a systems-level framework for analyzing "drug–compound–target–disease" interactions [7]. It offers insights into the multi-component and multi-target properties of traditional Chinese medicine (TCM) [8], and enables systematic exploration of synergistic effects among herbal constituents within disease-related molecular networks [9].

In this study, an integrated strategy combining network pharmacology and molecular docking was employed to elucidate the therapeutic mechanisms of MFXD against cardiac arrhythmia, aiming to advance its modernization as an anti-arrhythmic therapy.

2. Materials and Methods

2.1. Network Pharmacology Analysis

2.1.1. Compound and Target Identification

Bioactive constituents and predicted targets of Mahuang, Fuzi, and Xixin were retrieved from BATMAN-TCM 2.0 database (*http://bionet.*ncpsb.*org.cn/batman-tcm/*) [10]. Filters were set to Score cutoff ≥ 0.86 and $P < 0.05$. Targets were standardized to official gene symbols via UniProt database (*https://www.uniprot.org/*).

Arrhythmia-associated genes were collected using the term "Arrhythmia" from: GeneCards (*https://www.genecards.org/*) with a relevance score > 10, DisGeNET (https://www.disgenet.org/) with a score > 0.1, and NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/), followed by deduplication and symbol harmonization to form a comprehensive disease target set [11]. The overlap between MFXD targets and arrhythmia targets was computed.

2.1.2. Network Construction and Analysis

An "arrhythmia–MFXD–compound–target" interaction network was constructed in Cytoscape [12]. Topological metrics (degree, betweenness, closeness) were calculated to prioritize compounds and targets. Common targets were imported into STRING database (*https://www.string-db.org/*) to build a PPI network [13]. The species was limited to "Homo sapiens" with a minimum interaction confidence score of 0.4. The resulting PPI network was visualized and analyzed using Cytoscape.

2.1.3. Functional Enrichment Analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the clusterProfiler package in R software [14]. GO analysis encompassed biological process (BP), cellular component (CC), and molecular function (MF) categories. The organism was set to Homo sapiens. P values were adjusted by Benjamini-Hochberg; terms with adjusted $P < 0.05$ were considered significant.

2.2. Molecular Docking Validation

Three-dimensional structures of the hub proteins were obtained from the Protein Data Bank (PDB, *https://www.rcsb.org/*). Protein structures were prepared in PyMOL by removing water molecules, extraneous heteroatoms and nonessential chains. The cleaned models were exported in PDB format for docking. Chemical structures of core compounds were downloaded from PubChem (*https://pubchem.ncbi.nlm.nih.gov/*) in SDF format for docking.

Docking was performed with AutoDock Vina [15]. For each protein, the search box covered the known active site to ensure adequate sampling. Binding affinities were ranked by binding energy ($kcal \cdot mol^{-1}$), where more negative values indicate stronger predicted binding. Top poses were visualized in PyMOL and inspected for hydrogen bonds, hydrophobic contacts and key interactions.

3. Results

3.1. Network Pharmacology Results

3.1.1. Identification of Bioactive Compounds and Targets

The systematic screening of MFXD components yielded 273 unique bioactive compounds (202 from Mahuang, 32 from Fuzi, 87 from Xixin) and 1,116 unique drug targets (after deduplication: 2,860 from Mahuang, 468 from Fuzi, 1,148 from Xixin). From database mining, we retrieved 393 unique arrhythmia-associated targets (257 from GeneCards, 190 from DisGeNET, and 102 from NCBI, with overlap removed). Intersection analysis revealed 78 shared targets (5.5 % of the union) between MFXD (1,116) and arrhythmia (393). The remainder comprised 1,038 MFXD-specific targets (72.5 %) and 315 arrhythmia-specific targets (22.0 %). These 78 common targets represent the core molecular nodes through which MFXD may exert anti-arrhythmic effects.

3.1.2. Network Topology Analysis

The “arrhythmia–MFXD–compound–target” network is shown in Figure 1. Network topology analysis identified six key bioactive compounds with the highest degree values: Ethanol (Mahuang, 22), Quercetin (Mahuang, 21), Estradiol (Xixin, 17), Acetaldehyde (Mahuang, 13), 3beta-Hydroxyurs-12-En-28-Syre (Mahuang, 12), and honokiol (Fuzi, 10). These compounds likely represent the principal constituents contributing to MFXD’s anti-arrhythmic effects.

After applying the confidence cutoff, PPI analysis of the shared targets produced a densely connected network (76 nodes, 665 edges) with an average degree of 17.3 and a mean local clustering coefficient of 0.637 (Figure 2). This high connectivity suggests coordinated regulation of multiple proteins in MFXD’s therapeutic mechanism. The top six hub proteins based on degree values were: INS (insulin, 48), TNF (tumor necrosis factor, 42), IL-6 (interleukin-6, 40), ALB (albumin, 38), TP53 (tumor protein p53, 37), and PPARG (peroxisome proliferator-activated receptor gamma, 36).

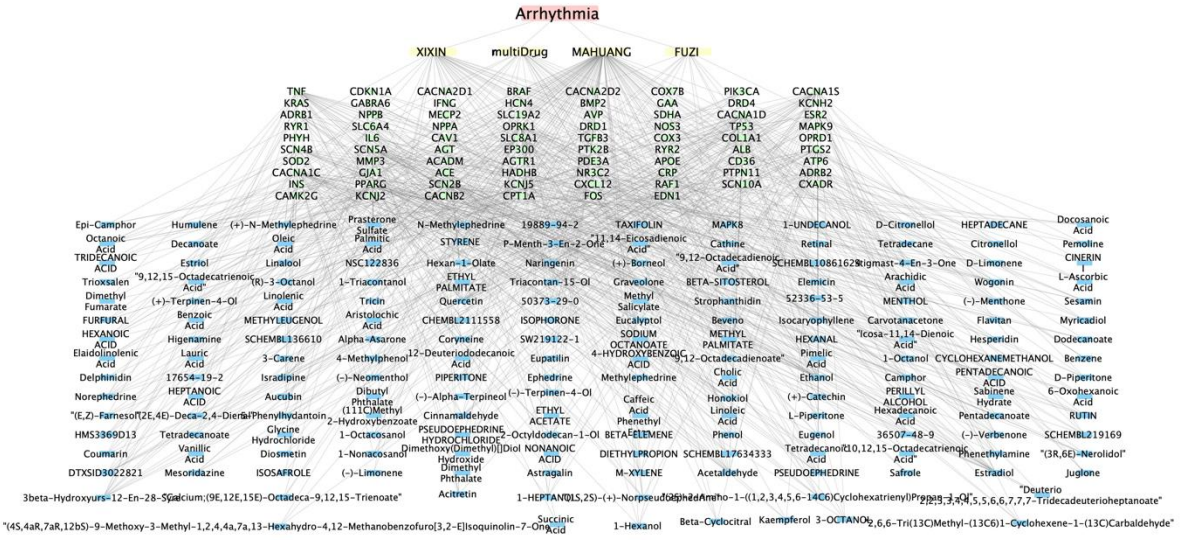

Figure 1. Network diagram of “arrhythmia-MFXD-compound-target” interactions. Red node represents arrhythmia; yellow nodes represent herbs; green nodes represent common targets; blue nodes represent bioactive compounds.

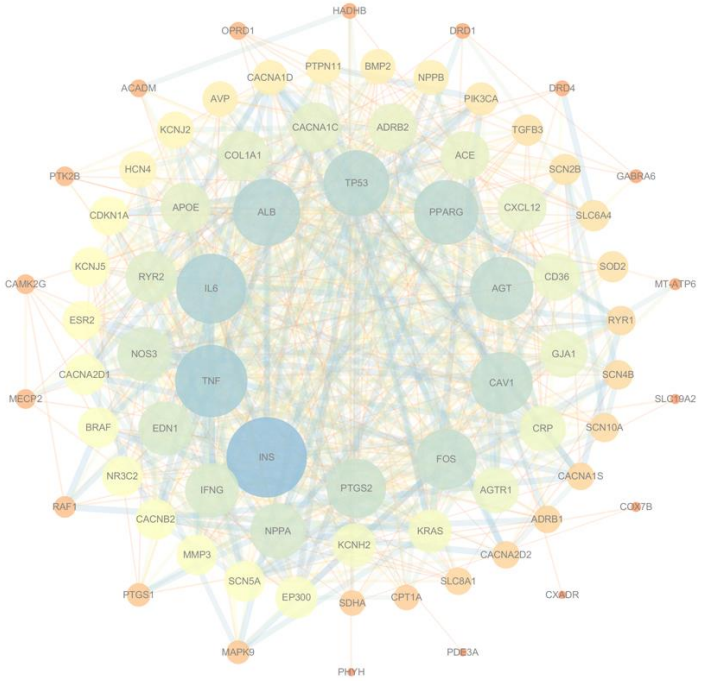

Figure 2. Protein-protein interaction network of MFXD-arrhythmia common targets. Darker blue and larger nodes indicate higher degree. Thicker and bluer edges represent stronger interactions.

3.1.3. Functional Enrichment Analysis

GO analysis identified 2,048 significantly terms (adjusted P < 0.05), comprising 1,876 biological process (BP), 74 cellular component (CC), and 98 molecular function (MF) terms (Figure 3A). Key terms included: BP—regulation of membrane potential, regulation of blood circulation and regulation of heart contraction; CC—cation channel complex, T-tubule and monoatomic ion channel complex; MF—monoatomic cation channel activity, monoatomic ion channel activity and

metal ion transmembrane transporter activity. KEGG pathway analysis identified 158 significantly enriched pathways (Figure 3B), highlighting pathways including Oxytocin signaling pathway, Hypertrophic cardiomyopathy and cAMP signaling pathway.

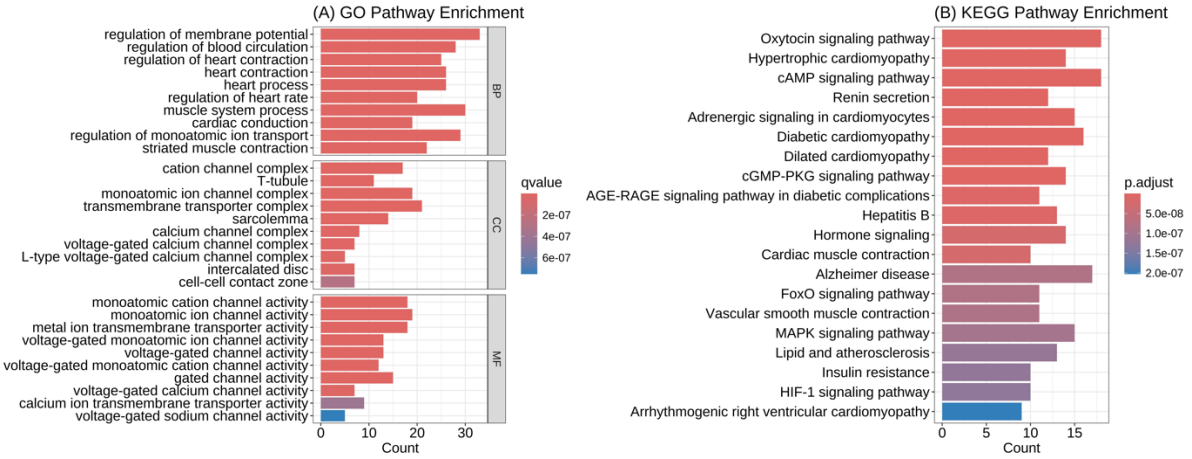

Figure 3. Functional enrichment analysis of MFXD-associated targets. (A) Top 10 Gene Ontology (GO) terms; (B) Top 20 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

3.2. Molecular Docking Results

Molecular docking simulations were performed between the six hub proteins (INS, TNF, IL-6, ALB, TP53, PPARG) and six core compounds (Ethanol, Quercetin, Estradiol, Acetaldehyde, 3beta-Hydroxyurs-12-En-28-Syre, Honokiol). The docking results demonstrated favorable binding affinities across multiple compound-target pairs (Figure 4). The strongest binding affinity was observed between TP53 and 3beta-Hydroxyurs-12-En-28-Syre (-8.2 kcal mol^{-1}), followed by ALB-Quercetin (-8.1 kcal mol^{-1}) and PPARG-Quercetin (-7.9 kcal·mol^{-1}). Most docking pairs exhibited binding energies ≤ -6.0 kcal mol^{-1}, indicating stable compound-target interactions.

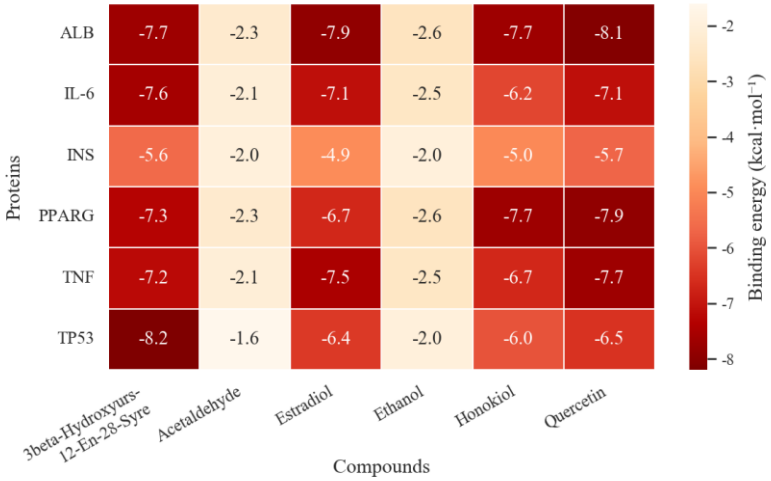

Figure 4. Molecular docking results showing binding affinities.

Representative molecular docking conformations of the top three protein–ligand pairs are shown in Figure 5. From left to right, each column presents the overall protein structure with the bound ligand, a magnified view of the binding pocket, and a schematic diagram of molecular interactions. These results visualize the key binding features, including hydrogen bonds and hydrophobic contacts, which contribute to the stability and specificity of protein–ligand interactions.

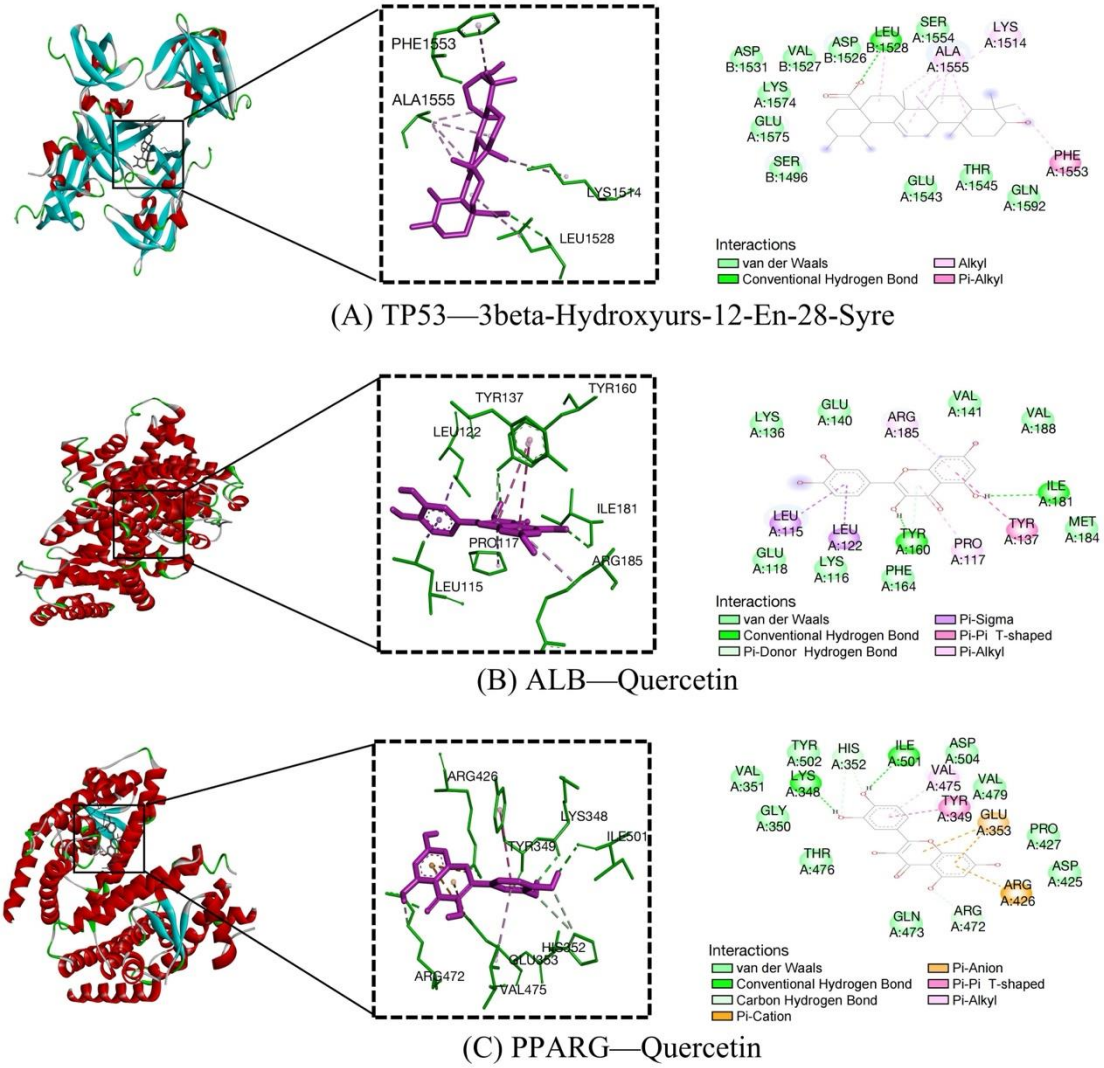

Figure 5. Representative molecular docking conformations of the top three protein–ligand pairs. (A) TP53–3beta-Hydroxyurs-12-En-28-Syre; (B) ALB–Quercetin; (C) PPARG–Quercetin. Left: protein structure; Middle: binding site; Right: interaction diagram.

4. Discussion

4.1. Core Bioactive Compounds and Pharmacological Significance

Network pharmacology and docking highlight quercetin, honokiol, and ursolic-acid–type triterpenoids as principal contributors to MFXD's anti-arrhythmic activity. Quercetin, a hub compound, modulates ion channels, reduces reactive oxygen species, and suppresses inflammatory signaling; its strong docking to ALB and PPARG supports roles in distribution, metabolic control, and inflammation [16]. Honokiol inhibits L-type Ca^{2+} channels, attenuates hypertrophy [17], and improves atrial metabolism via Sirt3-dependent mechanisms [18], consistent with reduced triggered activity and fibrosis. 3beta-Hydroxyurs-12-En-28-Syre, structurally related to ursolic acid, interacts with TP53; such triterpenoids provide anti-inflammatory and antioxidant protection against ischemic/oxidative injury relevant to arrhythmogenesis [19]. Ethanol and acetaldehyde, despite high network degrees, showed weak binding and likely represent extraction artifacts. Estradiol remains

notable, as estrogen receptors regulate Ca^{2+} channels and mitochondrial function, helping explain sex-related differences in arrhythmia risk and stabilizing electrophysiology through genomic and non-genomic actions [20].

4.2. Hub Proteins and Therapeutic Targets

High-degree PPI nodes indicate pathogenic control points and likely mechanisms of MFXD. Insulin (INS) showed the greatest connectivity, reflecting metabolic regulation of excitability; insulin signaling shapes substrate use and ion-channel function, whereas insulin resistance associates with electrical instability and sudden death [21][22]. Modulating INS may restore metabolic homeostasis and reduce arrhythmic susceptibility in diabetes or metabolic syndrome. TNF-alpha and IL-6 also emerged as hubs; these cytokines downregulate gap junctions, disrupt Ca^{2+} handling, and promote fibrosis, favoring arrhythmia [23]. Docking suggests quercetin and other constituents bind these cytokines, supporting mitigation of inflammation-driven electrical remodeling. TP53 coordinates cardiomyocyte stress responses, and excess activity promotes apoptosis and adverse remodeling [24]. PPARG integrates lipid metabolism with inflammatory tone; agonism tends to reduce cytokines and fibrosis, yet excessive activation may disturb ion currents [25]. Identification of PPARG—together with quercetin docking—suggests a capacity to fine-tune this axis. Albumin (ALB), though not a receptor, may enhance bioavailability and antioxidant buffering via high-affinity quercetin binding, indirectly stabilizing myocardium.

4.3. Signaling Pathways and Mechanistic Insights

Enrichment analyses emphasize cAMP–PKA and Ca^{2+} signaling central to pacemaking, L-type channel phosphorylation, and arrhythmia susceptibility [26]. Gene Ontology terms for calcium signaling and ion-channel complexes indicate convergence on Ca^{2+} handling and voltage-gated conductances, implying stabilization of intracellular Ca^{2+} and excitation–contraction coupling. Adrenergic signaling enrichment points to limiting sympathetic overdrive, with potential normalization of rate and ectopy. Structural and stress-response pathways—including hypertrophic cardiomyopathy, hypoxia-inducible factor-1, and PI3K–Akt—suggest constraints on fibrotic or hypertrophic substrate formation and improved stress adaptation, survival signaling, and connexin43 regulation reminiscent of preconditioning [27]. Overall, these pathways align with hub targets and docking results, indicating a multipronged mechanism that harmonizes ion-channel function, dampens stress responses, and counters maladaptive remodeling.

4.4. Integration with Previous Research and Clinical Implications

The multi-target profile identified here offers a mechanistic basis for reported clinical benefits of MFXD in arrhythmia. Clinical and experimental evidence indicates improved sinus node function and atrioventricular conduction in sick-sinus syndrome and atrioventricular block [5], often after short courses. Our predicted targets and pathways are concordant with these observations: modulation of cAMP and Ca^{2+} signaling by quercetin and honokiol plausibly contributes to correction of bradyarrhythmias. The pronounced anti-inflammatory and metabolic signatures also argue for utility in systemic-driven arrhythmias. Elevations in TNF-alpha or IL-6 are implicated in postoperative atrial fibrillation [28][29] and in arrhythmias accompanying viral myocarditis [30][31]; by inhibiting these cytokine pathways, MFXD may lessen inflammation-triggered electrical remodeling. Similarly, insulin resistance and metabolic syndrome increase arrhythmia risk [32]; targeting INS and PPARG suggests potential benefit in diabetes, where ventricular arrhythmias are common [33]. Together, these links imply that patients with inflammatory or

metabolic substrates may derive particular advantage from MFXD. More broadly, the data indicate that a traditional warming-Yang formula can act through contemporary molecular targets, helping to bridge TCM theory with evidence-based cardiology.

5. Conclusion

This study employing network pharmacology and molecular docking approaches has elucidated the multi-dimensional therapeutic mechanisms of MFXD against cardiac arrhythmia. The identification of 273 bioactive compounds, 78 therapeutic targets, and multiple enriched pathways demonstrates that MFXD exerts anti-arrhythmic effects through coordinated modulation of inflammatory responses, metabolic regulation, ion channel function, and cellular signaling cascades. The strong binding affinities observed between core compounds and hub proteins provide molecular evidence supporting MFXD's therapeutic efficacy. These findings not only provide scientific justification for the clinical application of MFXD in arrhythmia management but also offer a paradigm for investigating complex traditional medicine formulations using modern computational approaches. The multi-target therapeutic strategy exemplified by MFXD may offer advantages over single-target approaches, particularly in complex arrhythmias with multiple underlying mechanisms. This research establishes a foundation for further experimental validation and clinical translation of MFXD as an evidence-based anti-arrhythmic therapy.

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