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Research article

Molecular targets and mechanisms of resveratrol in alleviating arrhythmia based on network pharmacology and bioinformatics ☆

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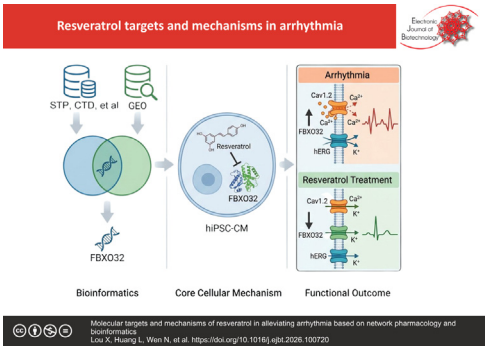
GRAPHICAL ABSTRACT

Molecular targets and mechanisms of resveratrol in alleviating arrhythmia based on network pharmacology and bioinformatics



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ABSTRACT

Background: Arrhythmia refers to a disorder in which abnormal cardiac electrical activity leads to irregular heart rhythm and conduction. Resveratrol (Res), a natural polyphenol compound extracted from medicinal plants, plays an important role in the treatment of arrhythmia, but its precise molecular mechanisms remain unclear.

Results: The intersection of Res targets and arrhythmia yielded 78 common targets, including F-box protein 32 (FBXO32). These targets were significantly enriched in cardiac conduction system development, protein-containing complex, vascular endothelial growth factor (VEGF) signaling pathway, cyclic adenosine monophosphate (cAMP) signaling pathway, and forkhead box O (FoxO) signaling pathway. Molecular docking confirmed that FBXO32 could stably bind to Res. Res treatment increased cell viability in the arrhythmia cell model. FBXO32 was highly expressed in the arrhythmia cell model, but its expression was significantly reduced under Res treatment. Knockdown of FBXO32 increased cell viability, decreased apoptosis, and increased protein levels of calcium voltage-gated channel subunit alpha1 C (CACNA1C) and human ether-à-go-go-related gene (hERG), whereas Res treatment partially modulated these effects.

Conclusions: Res inhibits the expression of FBXO32, thereby suppressing the malignant phenotypes of arrhythmia.

☆ Audio abstract available in Supplementary material.

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1. Introduction

Arrhythmia refers to a pathological condition resulting from abnormalities in the cardiac pacing and conduction system, which lead to disturbances in heart rhythm, frequency, or pacemaker activity [1,2,3]. It typically manifests as tachycardia, bradycardia, or irregular heartbeat. Several contributing factors, such as coronary artery disease [4], cardiomyopathy [5], or excessive vagal nerve activity, have been recognized as major causes of arrhythmia [6]. Moreover, chronic psychological tension or prolonged exposure to stressful conditions [7], along with external stimulants such as caffeine [8], sleep deprivation, and fatigue, can trigger or exacerbate arrhythmic episodes [9,10]. The occurrence of arrhythmia is not limited by gender and can affect individuals across nearly all age groups [11,12]. Persistent palpitations and irregular cardiac rhythms may lead to dizziness, fatigue, and even syncope [13], increasing psychological stress and potentially resulting in anxiety and depression [14], or in severe cases, stroke and sudden cardiac death [15,16].

Naturally occurring polyphenol resveratrol (Res) occurs in a variety of plant-based foods, including peanuts, berries, red wine, and red grape skins [17,18]. Reports have indicated its antioxidant, anti-inflammatory, and cardioprotective effects [19,20,21,22]. Extensive investigations have verified the involvement of Res in combating a range of disorders, including those affecting the cardiovascular and nervous systems, as well as multiple malignancies [23,24,25]. In addition, emerging evidence has shown that Res can modulate signaling pathways and ion channels involved in cardiac remodeling, thereby directly influencing heart rhythm and function. Res has also been identified as a potential regulator in the treatment of arrhythmia [26,27,28]. Previous studies further indicated that Res could mitigate arrhythmia in rat models by modulating the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) cascade [29], act as a Ca^{2+}-mobilizing regulator to improve cardiac performance [30], and modulate mitochondrial function via the sirtuin3 pathway, partially reversing cardiac electrophysiological dysfunction [31]. However, current understanding of how Res affects arrhythmic development at the molecular level is still quite limited, and its precise signaling routes have not been comprehensively clarified, highlighting the need for additional research. Therefore, an integrative analysis combining network pharmacology with bioinformatics was conducted to clarify how Res may modulate arrhythmia progression, offering fresh insights and potential preventive as well as therapeutic strategies.

Accordingly, this study systematically integrates the potential targets of Res with arrhythmia-associated genes, identifies pivotal regulatory elements and signaling pathways, and clarifies how Res influences cardiac rhythm abnormalities, thereby laying a theoretical groundwork for its clinical use and for devising innovative treatment approaches.

2. Materials and methods

2.1. Data download and differential analysis

The structure of Res was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov) and depicted using ChemDraw Professional 20. To ensure comprehensiveness, potential targets of Res were compiled from multiple public resources, including HERB (https://herb.ac.cn/), SwissTargetPrediction (https://www.swisstargetprediction.ch/), and CTD (https://ctdbase.org). CTD-predicted targets were filtered using an interaction count ≥ 5. Meanwhile, arrhythmia-associated genes were assembled based on data from GeneCards (https://www.genecards.org), CTD, and OMIM (https://www.omim.org). GeneCards targets were selected with a relevance score ≥ 5. Additionally, transcriptomic datasets related to arrhythmia were downloaded from the GEO repository (https://www.ncbi.nlm.nih.gov/geo). Specifically, GSE41177 was used, which was based on the GPL570 platform and included left atrial appendage tissues from 6 healthy individuals and 32 atrial fibrillation patients. Differentially expressed genes (DEGs) were identified using thresholds of adjusted p value < 0.05 and $|\log_2$ fold change$| \geq 1.5$. All data processing and analysis were conducted according to these criteria.

2.2. Construction of the drug-disease-target network

Interaction data were acquired by submitting the identified Res targets, arrhythmia-associated targets, and their shared targets to the search tool for the retrieval of interacting genes (STRING, https://string-db.org). Afterward, Cytoscape 3.9 was employed to visualize the resulting network.

2.3. Gene ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis

The 24 shared targets between Res and arrhythmia were subjected to GO functional annotation and KEGG enrichment analysis using the clusterProfiler package in R. The GO annotation was categorized into three main modules: biological process (BP), cellular component (CC), and molecular function (MF). The results were visualized using the ggplot2 package.

2.4. Molecular docking and molecular dynamics simulation

The structural data for Res were obtained from pubchem (https://pubchem.ncbi.nlm.nih.gov/), and those for F-box protein 32 (FBXO32) were downloaded from the protein data bank (PDB, https://www.rcsb.org). Molecular docking illustrations were generated using AutoDock 4.2, and the resulting models were visualized with PyMOL 2.5.

To further evaluate the stability and collective motions of the Res-FBXO32 complex, molecular dynamics simulations were conducted using the iMODs server (https://imods.iqf.csic.es/), a tool based on normal mode analysis (NMA) in internal coordinates. This approach was employed to describe the protein's flexibility through coordinates that naturally represent its collective movements. The simulation parameters were kept at default settings, and the structural stability was assessed via the main chain deformability, B-factor analysis, and the covariance matrix. The residue index-based correlation analysis was also performed to examine the local and global stability of the protein–ligand system.

2.5. Cell culture and treatment

Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) (Merck, Darmstadt, Germany) underwent cultivation in line with the guidelines supplied by the manufacturer. Subsequently, the cells were subjected to Res (Sigma-Aldrich, St. Louis, Missouri, USA) at four distinct doses: 2 μM, 5 μM, 10 μM, and 20 μM. In addition, 2 μM aconitine (Sigma-Aldrich) was applied to the cells for 24 h to establish an arrhythmia model for subsequent experiments.

2.6. Cell transfection

Small interfering RNA targeting FBXO32 (siFBXO32) and a non-targeting control siRNA (siNC) were obtained from Genechem (Shanghai, China) and employed for gene knockdown. Plasmid constructs for FBXO32 overexpression, along with an empty vector serving as the negative control, were also designed and generated by Genechem Co., Ltd. All transfections of plasmids and siRNAs into cells were performed using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) in strict accordance with the manufacturer's protocol.

2.7. Cell counting kit-8 (CCK-8) assay

Cells in the logarithmic growth phase were adjusted to 5×10^3 and evenly seeded into 96-well plates. Ten microliters of CCK-8 reagent (GeneCopoeia, Rockville, Maryland, USA) were added to each test well, and the plates were gently mixed before being incubated at 37°C with 5% CO_2 for 3 h. Subsequently, the absorbance (OD value) at 450 nm was measured using a microplate reader (Tiangen, Beijing, China).

2.8. Western blot (WB) analysis

The total protein content of the samples was determined using the bicinchoninic acid (BCA) Protein Assay Kit (Elabscience, Wuhan, China). Proteins were then separated via sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and subsequently transferred onto polyvinylidene fluoride (PVDF) membranes (Elabscience). The membranes were blocked with 5% bovine serum albumin (BSA) (Elabscience) for 2 h. After blocking, the membranes were incubated overnight at 4°C with primary antibodies targeting the proteins of interest: Beta-actin (β-actin) (ab8226, 1:1000, Abcam, Cambridge, UK); FBXO32 (ab68372, 1:1000, Abcam); Calcium Voltage-Gated Channel Subunit Alpha1 C (CACNA1C) (ab81980, 1:1000, Abcam); and human Ether-à-go-go-Related Gene (hERG) (ab192500, 1:1000, Abcam).

Subsequently, membranes were exposed to HRP-conjugated secondary antibodies (ab97051, 1:5000, Abcam) at room temperature for 1 h. Protein bands were visualized using enhanced chemiluminescence (ECL) chemiluminescent substrate (Elabscience) and quantified with ImageJ software version 1.53.

2.9. Flow cytometry

Cells from each group were digested with trypsin (Bioss, Beijing, China) and subsequently collected. After being washed twice with phosphate-buffered saline (PBS, Bioss), the cell suspensions were centrifuged, and the resulting pellets were gathered. The cells were then stained using an Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) kit (BD Biosciences, Franklin Lakes, New Jersey, USA) following the manufacturer's instructions and incubated at room temperature in the dark for 15 min. Immediately afterward, the fluorescence signals of Annexin V-FITC and PI were measured by flow cytometry to discriminate between early apoptotic, late apoptotic, and viable cells. Data were analyzed using FlowJo 10.

2.10. Statistical analysis

Independent biological replicates ($n \geq 3$) provided the basis for all findings, which are reported as mean ± standard deviation (SD). Statistical disparities were determined via GraphPad Prism 8.0; specifically, *t*-tests addressed two-group data, while ANOVA handled multi-group sets. Significance was defined by $p < 0.05$.

3. Results

3.1. Res structure and target screening

Res molecule contained hydroxyl groups (–OH), benzene rings, and carbon–carbon double bonds, and exhibited strong molecular bioactivity, potentially possessing multi-target and multi-pathway characteristics (Fig. 1A). After screening, merging, and deduplication through the CTD, HERB, and SwissTargetPrediction databases, a total of 605 Res-related targets were obtained (Fig. 1B), indicating that Res molecules have multi-target properties.

3.2. Preliminary screening of Res targets related to arrhythmia

After screening and deduplication through the GeneCards, CTD, and OMIM databases, a total of 589 arrhythmia-related targets were obtained (Fig. 2A). Then, the 605 Res targets were intersected with the 589 arrhythmia targets, yielding 78 common targets

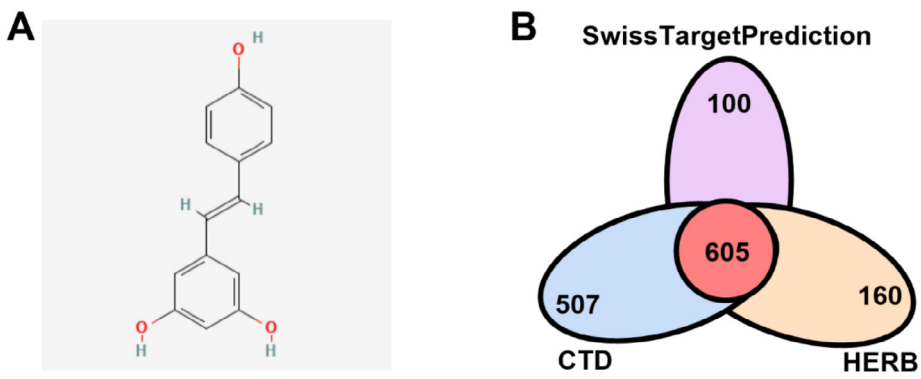

Fig. 1. Screening of potential targets of Res. (A) Structural formula of the Res molecule. (B) Venn diagram of Res targets obtained from the GeneCards, OMIM, and CTD databases, where the overlapping section represents the shared targets among the three databases.

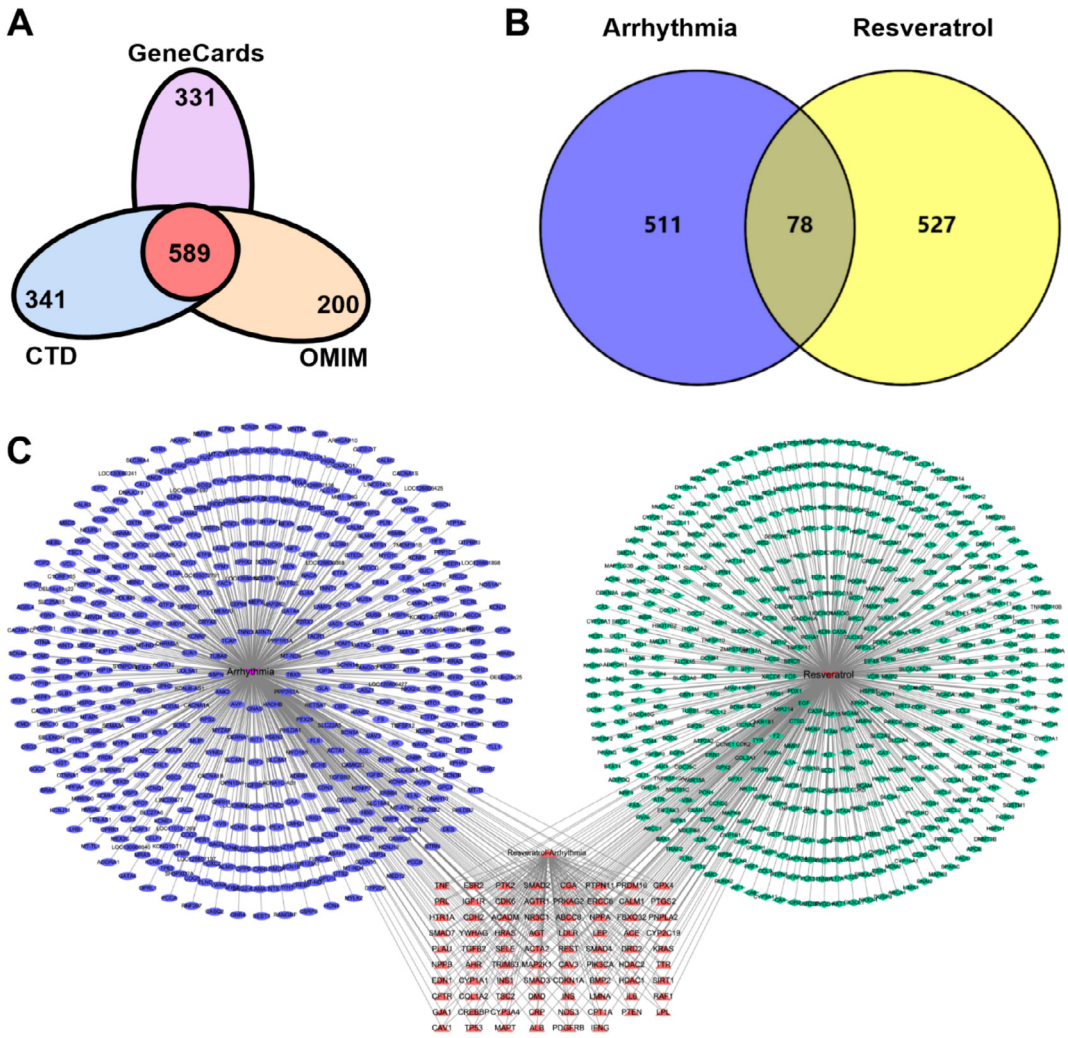

Fig. 2. Screening of targets related to Res in the treatment of arrhythmia. (A) Venn diagram of arrhythmia-related targets obtained from the GeneCards, OMIM, and CTD databases, where the overlapping section represents the shared targets among the three databases. (B) Venn diagram showing the intersection between Res targets and arrhythmia targets, with the overlapping section indicating the number of shared targets. (C) Network diagram of common targets between Res and arrhythmia, including Res-specific and arrhythmia-specific targets.

(Fig. 2B). Subsequently, network diagrams were constructed for the 605 Res targets, 589 arrhythmia targets, and 78 common targets (Fig. 2C). These results indicate that Res may act through the 78 common targets associated with arrhythmia, providing clues for its potential therapeutic mechanism.

3.3. Screening of key targets of Res in arrhythmia treatment

Based on arrhythmia transcriptome data analysis, 3180 arrhythmia-related targets were identified, and the intersection with the aforementioned 78 common targets yielded 24 key targets of Res for treating arrhythmia (Fig. 3A). Most of these 24 key genes showed a significant upregulation trend, suggesting that these genes might promote the malignant progression of arrhythmia (Fig. 3B). GO functional annotation of these genes revealed that pathways such as cardiac conduction system development (BP) and protein-containing complex (CC) were successfully annotated (Fig. 3C). KEGG enrichment analysis indicated that the vascular endothelial growth factor (VEGF) signaling pathway, cyclic adenosine monophosphate (cAMP) signaling pathway, and forkhead box O (FoxO) signaling pathway were significantly enriched (Fig. 3D). This suggests that these genes and pathways may be crucial in regulating arrhythmia progression. Moreover, since FBXO32 was highly expressed in arrhythmia and was significantly enriched in the FoxO signaling pathway, many studies showed that this pathway participated in the regulation of various diseases [32,33], and some reports indicated that it was involved in the regulation of cardiomyocytes [34]; therefore, this study particularly focuses on the regulatory role of FBXO32.

3.4. Molecular docking analysis of Res with the key target FBXO32

Molecular docking was performed to evaluate the binding affinity and interaction mode between Res and FBXO32. The results demonstrated that Res could stably bind to FBXO32, with a calculated binding energy of −5.9 kcal/mol and a ligand RMSD of 0.754 Å. Specifically, the stability of the complex was maintained by 4 hydrogen bonds involving residues ASP, TYR, and THR (donor–acceptor distances: 2.23–3.22 Å, 4 hydrophobic interactions with residues ASP, TYR, and ARG (3.41–3.93 Å), and a T-shaped π-stacking interaction (4.97 Å) (Fig. 4A). Molecular dynamics simulations were further conducted using the iMODs server, which utilizes NMA in internal coordinates to assess the structural flexibility and stability of the complex. The results indicated that a prominent peak appeared at atom index 50, suggesting that this flexible region might be the binding site for the stable interaction

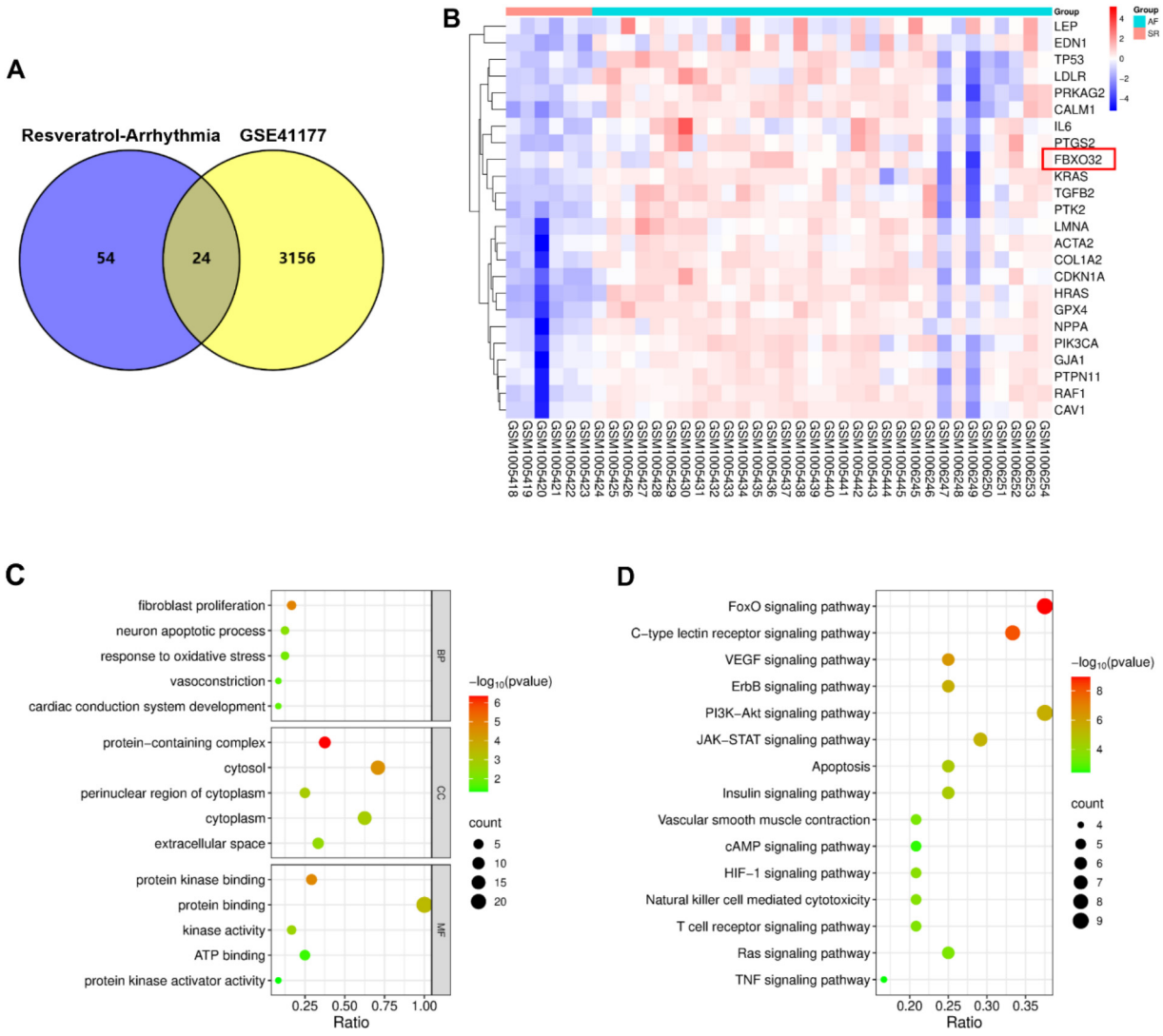

Fig. 3. Further screening of targets for Res in the treatment of arrhythmia based on transcriptomic data. (A) Venn diagram showing the intersection of DEGs from the GSE41177 dataset with the common targets of Res and arrhythmia, with the overlapping section displaying the number of key targets identified. (B) Heatmap of differential expression of key targets, where red indicates upregulation and blue indicates downregulation. (C) GO functional annotation of key targets. (D) KEGG enrichment analysis of key targets. "Count" represents the number of genes enriched in a given function, and a smaller −log10 (*p* value) indicates higher enrichment significance. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

between Res and FBXO32. In addition, B-factor analysis showed that the overall model quality was good, and residue index analysis indicated that the local protein structure was stable (Fig. 4B). These results indicate that Res formed a stable complex with FBXO32, while both the overall and local protein structures maintained high stability throughout the simulation, supporting the reliability of this interaction.

3.5. In vitro validation of Res's therapeutic effects on arrhythmia

Normal hiPSC-CMs were treated with Res at concentrations of 2 μM, 5 μM, 10 μM, and 20 μM. It was observed that when the Res concentration was below 10 μM, cell viability gradually decreased with increasing Res concentration, whereas when the Res concentration exceeded 10 μM, cell viability showed a significant decline (Fig. 5A). However, in the aconitine-induced hiPSC-CM arrhythmia model, cell viability increased with increasing Res concentration (Fig. 5B). Moreover, in the arrhythmia model, FBXO32 protein expression exhibited a significant decreasing trend as Res concentration increased (Fig. 5C). These results indicate that Res exerts an inhibitory effect on normal cardiomyocytes at high concentrations, whereas it shows a protective effect in the aconitine-induced arrhythmia model, possibly alleviating cell damage by downregulating FBXO32 expression.

3.6. Modulation of cell function by FBXO32 knockdown or overexpression in Res-treated arrhythmia models

WB analysis confirmed the successful knockdown and overexpression of FBXO32 (Fig. 6A, B). In the arrhythmia cell model, both FBXO32 knockdown and Res treatment alone significantly increased cell viability and reduced apoptosis, whereas FBXO32 overexpression in the presence of Res treatment markedly decreased cell viability and increased apoptosis (Fig. 6C, D). Moreover, the expression levels of CACNA1C and hERG proteins were significantly upregulated following FBXO32 knockdown or Res treatment alone, while FBXO32 overexpression combined with Res treatment resulted in a pronounced reduction (Fig. 6E). These results indicate that Res enhances cell viability and inhibits apoptosis by downregulating FBXO32 expression and upregulating

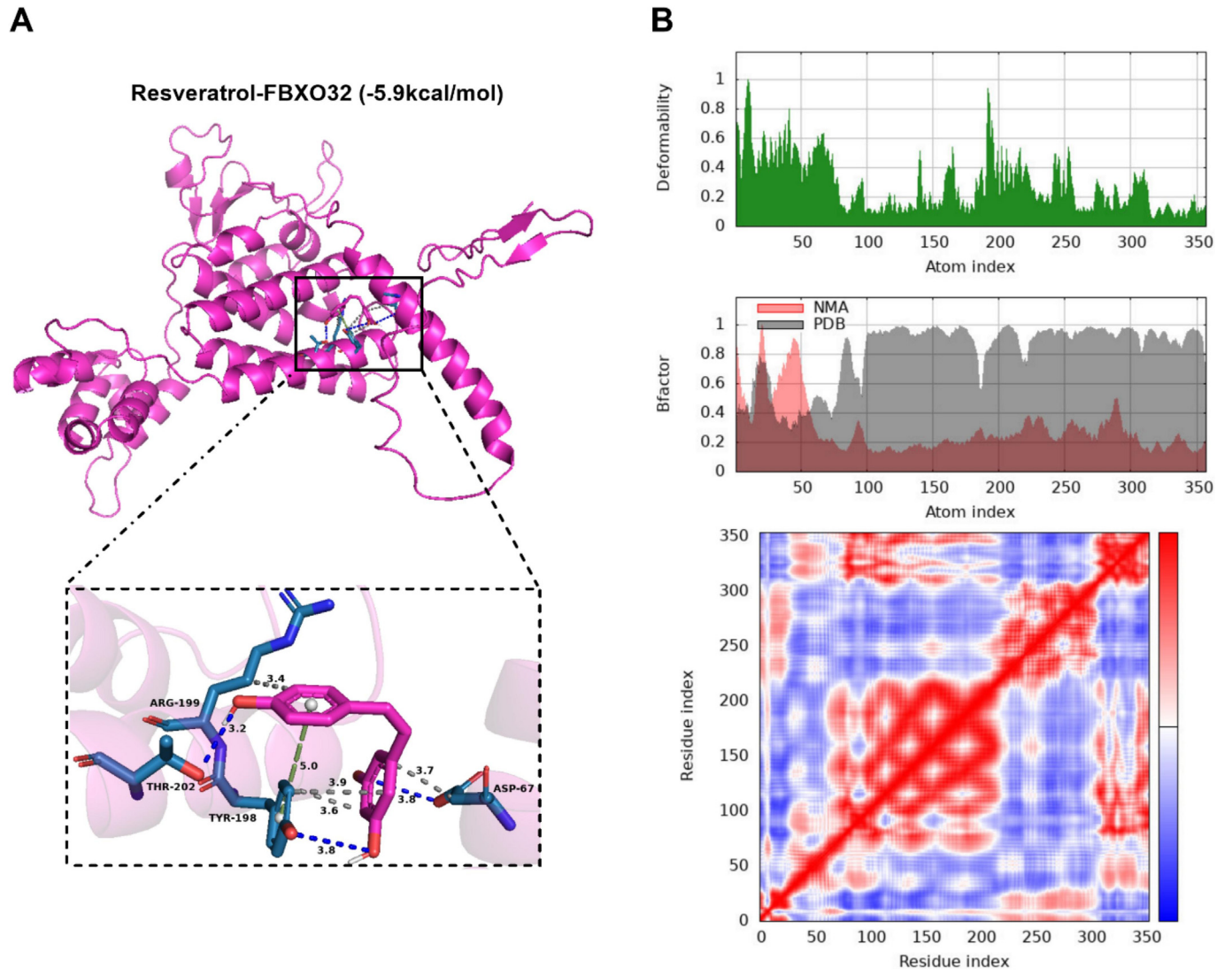

Fig. 4. Molecular docking between Res and its key target FBXO32 in the treatment of arrhythmia. (A) Molecular docking of Res with FBXO32, showing the docking sites and binding energy. (B) Molecular dynamics simulation of Res with FBXO32.

CACNA1C and hERG levels, suggesting that FBXO32 plays a key regulatory role in the process by which Res ameliorates arrhythmia.

4. Discussion

Res had been recognized for its antioxidant, anti-inflammatory, anti-aging, and cardioprotective properties [35]. Recent investigations also identified its involvement in the therapeutic modulation of arrhythmia [36]. Evidence suggested that Res alleviated the malignant progression of arrhythmia by regulating potassium ion channels [37], which was considered of great significance in preventing the exacerbation of arrhythmic conditions [38,39]. These findings were consistent with previous reports, which indicated that Res exerted cardioprotective effects and modulated ion channel activity in cardiac models [40,41]. In the present study, Res was found to exhibit strong biological activity and possess therapeutic targets associated with arrhythmia. Treatment with Res enhanced the viability of arrhythmic cell models while reducing apoptosis, thereby confirming its regulatory effect on arrhythmia. Interestingly, Res at concentrations above 10 μM decreased the viability of normal cardiomyocytes but increased the viability of arrhythmic cells, indicating a concentration-dependent biphasic effect. These observations suggested that the therapeutic window of Res was limited, with lower to moderate concentrations exerting protective effects while higher concentrations may induce cytotoxicity in normal cells. Such biphasic responses have been reported in other cardiac cellular studies and emphasize the need for careful dose optimization to balance efficacy and safety [42].

Moreover, FBXO32 had been implicated in promoting the development of multiple tumor types. It exerted pivotal control over several pathological pathways, notably in pancreatic, lung, and hepatocellular carcinomas [43,44,45]. FBXO32 has been shown in previous research to contribute to the regulation of arrhythmia [34]. The current study revealed that FBXO32 was significantly upregulated in arrhythmia and served as a pivotal target in the regulation of its malignant phenotypes. Furthermore, earlier research identified the FoxO signaling pathway as an essential regulator in atrial fibrillation [46], while the VEGF signaling pathway was also shown to participate in the modulation of arrhythmic processes [47]. Mechanistic analysis indicated that FBXO32 silencing led to upregulation of key ion channel genes CACNA1C and hERG, whereas FBXO32 overexpression suppressed their expression, suggesting a direct modulatory role of FBXO32 in cardiac electrophysiology. These results support a causal link between FBXO32 and

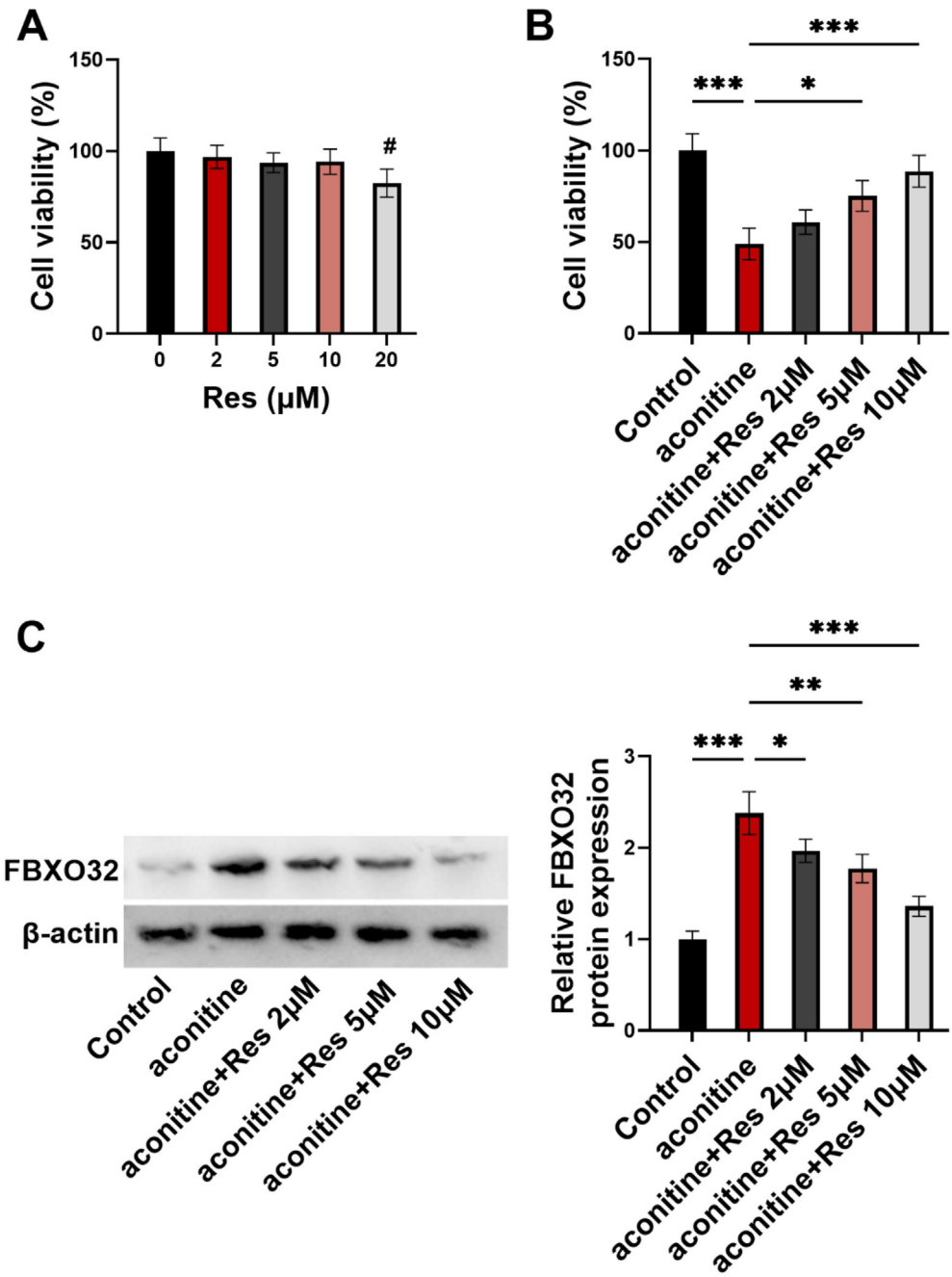

Fig. 5. *In vitro* validation of the therapeutic effects of Res on arrhythmia. (A) CCK-8 assay assessing the effects of different concentrations of Res on the viability of hiPSC-CMs (n = 3), $^{\#}p < 0.05$. (B) CCK-8 assay assessing the effects of different concentrations of Res on cell viability in the arrhythmia model (n = 3). (C) WB analysis of FBXO32 protein expression in the arrhythmia cell model treated with different concentrations of Res (n = 3). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

arrhythmic phenotypes through regulation of ion channel expression and cardiomyocyte electrical stability, consistent with prior cardiac studies [48,49]. In this study, FBXO32 was enriched in the FoxO signaling pathway, and significant enrichment was also observed in the VEGF signaling pathway, indicating that these pathways played important roles in the regulation of arrhythmia, consistent with previous reports.

Moreover, the findings demonstrated that the Res molecule could stably bind to FBXO32 and suppress its expression, thereby modulating the malignant phenotypes of arrhythmia. To date, no studies have elucidated the mechanism by which Res regulates arrhythmia progression via FBXO32 modulation, marking this as one of the innovative aspects of the present work. Aconitine, known for its cardiotoxicity, primarily targets voltage-gated Na^{+} channels in cardiomyocytes, inducing abnormal depolarization and calcium overload, thereby reproducing the electrophysiological features of arrhythmia *in vitro*. Hence, it has been widely employed to establish cellular models of arrhythmia [50,51,52]. Additionally, CACNA1C and hERG are two essential ion channel genes associated with arrhythmia, both of which are vital for maintaining normal cardiac rhythm and suppressing arrhythmic activity, contributing significantly to the stability of cardiac electrophysiology [53,54]. In the present study, silencing FBXO32 led to increased expression of CACNA1C and hERG, whereas

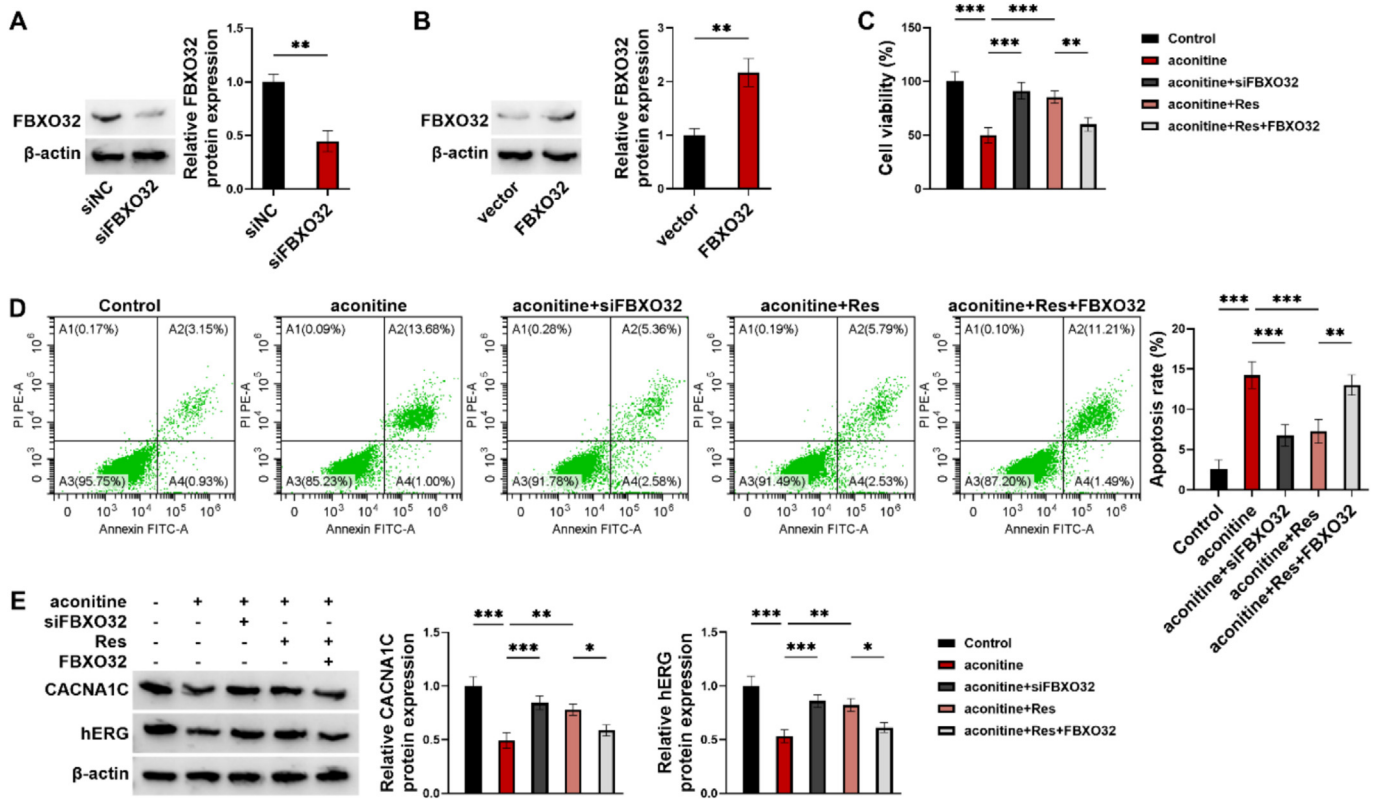

Fig. 6. Effects of FBXO32 knockdown and overexpression on cell function in the Res-treated arrhythmia cell model. (A) WB verification of FBXO32 knockdown efficiency ($n = 3$). (B) WB verification of FBXO32 overexpression efficiency ($n = 3$). (C) CCK-8 assay assessing the effects of FBXO32 knockdown and overexpression on cell viability in the Res-treated arrhythmia model ($n = 3$). (D) Flow cytometry analysis of the effects of FBXO32 knockdown and overexpression on cell apoptosis in the Res-treated arrhythmia model ($n = 3$). (E) WB analysis of CACNA1C and hERG protein expression after FBXO32 knockdown and overexpression in the Res-treated arrhythmia model ($n = 3$). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

FBXO32 overexpression resulted in the opposite effect. Treatment with Res elevated the expression levels of CACNA1C and hERG, supporting the cardioprotective roles of Res, CACNA1C, and hERG in maintaining rhythmic stability, while highlighting FBXO32 as a promoter of arrhythmic malignant phenotypes.

Nevertheless, this study had certain limitations. All experiments were conducted *in vitro* using hiPSC-CMs, which, although human-derived and physiologically relevant, cannot fully recapitulate the complex systemic and multi-level regulatory mechanisms involved in arrhythmia *in vivo*. Therefore, the observed effects of Res on FBXO32 expression, ion channel regulation, and electrophysiological homeostasis require further validation in animal models to confirm their translational relevance.

In summary, this study combines network pharmacology, bioinformatics, and cellular experiments to reveal that Res regulates arrhythmia by downregulating FBXO32 expression, thereby upregulating ion channel genes such as CACNA1C and hERG, ultimately improving electrophysiological homeostasis and cellular viability in arrhythmic models. The observed cytotoxicity at higher concentrations also emphasizes the importance of dose optimization for safe therapeutic application. This finding provides new insights into the molecular mechanism by which Res prevents arrhythmia and offers promising avenues for identifying novel targets and approaches in the creation of safe and effective anti-arrhythmic agents, with significant theoretical and translational implications.

CRediT authorship contribution statement

Xiuping Lou: Writing – original draft, Supervision, Resources, Project administration. **Leilei Huang:** Methodology, Data curation. **Nonghao Wen:** Formal analysis. **Yan Wang:** Validation, Software. **Jiayin Yu:** Writing – review & editing, Visualization, Investigation, Funding acquisition, Conceptualization.

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Data availability

The data are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejbt.2026.100720.

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