

Unraveling the Mechanism of Higenamine in the Treatment of Right Heart Failure via Computational Drug Discovery and Molecular Simulation Technology

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Abstract: Right heart failure (RHF) represents a multifactorial and clinically challenging syndrome characterized by complex pathophysiology and a persistent unmet therapeutic need. Despite an extensive body of literature delineating diverse putative determinants capable of modulating disease susceptibility and progression, the precise molecular mechanisms continue to be inadequately elucidated. The purpose of this study was to identify mechanisms underlying higenamine (HIG)-mediated therapy for RHF by combining network pharmacology with molecular dynamics (MD) techniques. Based on drug-likeness properties, HIG was identified as a promising phytoconstituent against RHF. It is predicted to exert its effects by modulating pathways related to pro-growth, angiogenesis and inflammation, all of which are associated with ESR1, PPARG and TGFBR1. Molecular docking and MD were subsequently employed to further confirm the binding of HIG to ESR1. Finally, HIG is considered to hold potential in modulating key pathological pathways of RHF, offering a promising experimental basis for the future development of novel therapeutics against RHF.

Keywords: right heart failure; higenamine; network pharmacology; molecular docking; molecular dynamics

1. Introduction

Over the past decade, right heart failure (RHF) has attracted intensifying clinical scrutiny, principally because this syndrome confers a disproportionately high incidence and case-fatality rate. RHF, alternatively termed right ventricular failure, is defined as a clinical syndrome characterized by impaired right ventricular systolic function, such that the ventricle is unable to deliver adequate blood flow to the pulmonary circulation at normal central venous pressures, resulting in systemic venous congestion and low cardiac output [1,2].

Despite substantial recent advances in RHF research, critical knowledge chasms persist. The development of pharmacological agents whose molecular targets are explicitly situated within the right ventricular myocardium lags markedly behind. Consequently, the rational design of novel therapeutics, particularly compounds capable of conferring direct, structure- and function-selective benefit to the right ventricle (RV), constitutes an urgent translational imperative for ameliorating the dismal clinical trajectory afflicting RHF patients.

Right heart failure (RHF) should not be viewed as a single disease entity. Instead, it arises as a cumulative outcome of distinct yet interrelated pathological processes, including pressure overload, volume stress, ischemia, metabolic dysregulation, and systemic inflammation, that all converge on a shared, maladaptive program of right ventricular remodeling [3]. This inherent complexity extends to the molecular level, where transcriptional, post-transcriptional, and epigenetic networks work in parallel to regulate cardiomyocyte hypertrophy, fibroblast activation, endothelial dysfunction, and immune cell infiltration [4,5]. To overcome this impasse, there is an urgent need for a systems-level map: one that connects druggable targets to the multi-omic drivers of RHF. This need, in turn, provides the rationale for the network pharmacology and systems-pharmacology analyses.

Higenamine (HIG), the principal bioactive constituent accountable for the “restoring yang and reversing collapse” action of *Aconiti Lateralis Radix Praeparata*, exerts β -adrenergic-receptor-mediated positive inotropy,



positive chronotropy [6] and systemic arteriolar vasodilatation [7] that specifically rectify the low cardiac output, venous stasis and peripheral hypoperfusion characteristic of right-sided heart failure [8]. This modern cardiotoxic profile establishes an evidence-based “syndrome–effect–component” correspondence with the traditional therapeutic principle of “warming and unblocking heart-yang to invigorate blood flow”, thereby furnishing a scientific rationale for the clinical deployment of the “restoring yang and reversing collapse” strategy in the treatment of right ventricular failure [9]. However, despite its well-characterized β -adrenergic agonistic activity, it remains uncertain whether the therapeutic effects of HIG in RHF can be fully explained by classical receptor-mediated inotropic stimulation alone. Current evidence regarding HIG primarily derives from general cardiovascular models, whereas its target spectrum and pathway-specific actions in the context of RHF have not been systematically delineated. Given the multi-component and multi-target pharmacological nature of bioactive natural compounds, it is plausible that HIG may exert broader regulatory effects beyond canonical β -adrenergic signaling. The absence of a systems-level mechanistic framework therefore represents a key limitation in understanding its precise role in RHF.

To address this gap, we adopted a network pharmacology–based strategy to characterize the interaction landscape between HIG and RHF-associated molecular targets. By integrating metabolite–target prediction, protein–protein interaction analysis, pathway enrichment, molecular docking, and molecular dynamics (MD) simulations, we aimed to identify potential core regulatory nodes and signaling cascades underlying the therapeutic actions of HIG in RHF. This integrative computational approach provides a rational and systematic means to decode the multi-target pharmacological mechanisms of HIG and supports the modernization and mechanistic clarification of the “restoring yang and reversing collapse” strategy.

2. Methods and Materials

2.1. Data Acquisition: Disease-Associated and Compound-Target Genes

Human genes associated with RHF were identified by querying the GeneCards (<http://www.genecards.org/>, accessed on 9 September 2025) and OMIM (<http://www.omim.org> (accessed on 9 September 2025)) databases using the keyword “Right heart failure”. To ensure high disease relevance, only entries with a GeneCards relevance score ≥ 10 were retained [10]. The results from both databases were merged and deduplicated to form a consolidated, high-confidence RHF gene set.

To comprehensively map the potential protein targets of HIG, we aggregated predictions from three complementary resources: (1) SwissTargetPrediction (<http://www.swisstargetprediction.ch/> (accessed on 9 September 2025)); (2) the full list of potential targets returned by the PharmMapper (<https://www.lilab-ecust.cn/> (accessed on 9 September 2025)) [11–13], and (3) genes documented to interact with HIG in the Comparative Toxicogenomics Database (CTD) (<https://ctdbase.org> (accessed on 9 September 2025)). The union of these three sources constituted the putative target repertoire of HIG.

The intersection of disease-related genes and compound-associated targets was computed, yielding a consensus gene set that was retained for downstream analyses.

2.2. Protein–Protein Interaction (PPI) Network Generation and Subsequent Evaluation

The intersecting proteins of RHF and HIG genes were uploaded to STRING (<https://cn.string-db.org> (accessed on 11 September 2025)) with the organism limited to “Homo sapiens” to retrieve known and predicted interactions. The resulting network data was imported into Cytoscape software (version 3.10.0, Cytoscape Consortium, San Diego, CA, USA) for visualization and topological analysis. Genes with higher degree values occupy more central positions within the network, as reflected by progressively larger node sizes and intensified color saturation.

2.3. Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) Analysis

The candidate proteins were imported into the DAVID bioinformatics resource (<https://davidbioinformatics.nih.gov/home.jsp> (accessed on 5 November 2025)) [14,15] for functional annotation. GO enrichment was performed with Homo sapiens as the reference background and covered three independent domains: molecular function (MF), biological process (BP) and cellular component (CC). Concurrently, KEGG pathway mapping was executed to delineate putative signaling cascades through which HIG may exert effects on RHF. Enrichment outputs were ranked by modified Fisher’s exact p-value, and the top 20 significantly over-represented GO terms and pathways were graphically rendered via an in-house bioinformatics pipeline.

2.4. Phenotype-Genotype Association Profiling via Varelect

The Varelect web server (<http://varelect.genecards.org> (accessed on 11 November 2025)) implements a phenotype-driven algorithm that quantifies both direct and transitive gene–phenotype relationships. To strengthen the clinical relevance of the candidate targets, we employed Varelect to evaluate their direct phenotypic link to RHF. Varelect discriminates between direct and indirect gene–phenotype associations based on curated knowledge. The core intersection gene list was submitted to Varelect, and the subset of genes annotated as having a “direct” association with the “Right Heart Failure” phenotype was retained for subsequent analysis.

2.5. Molecular Docking

Molecular docking was conducted to explore the binding mode of HIG to key target proteins at an atomic level. The 2D and 3D structures of HIG were obtained from PubChem. The crystal structures of priority target proteins including ESR1, PPARG and TGFBR1, identified from prior network analysis, were downloaded from the RCSB PDB database (<http://www.rcsb.org> (accessed on 5 November 2025)). Protein structures were prepared using Discovery Studio 2019 Client: crystallographic water molecules, native ligands, and extraneous chains were removed, followed by hydrogen addition and charge assignment.

Semi-flexible docking was performed using the CDOCKER protocol within Discovery Studio 2019 Client software (BIOVIA, Dassault Systèmes, Vélizy-Villacoublay, France). The prepared proteins served as receptors, and BBB as the ligand. CDOCKER employs the CHARMM force field, generating multiple ligand conformations via high-temperature dynamics and docking them into the receptor’s active site, followed by refinement via simulated annealing.

2.6. MD Simulation and Binding Stability Assessment

Molecular docking was further validated by 100-ns NPT-MD simulations (GROMACS 2019.5 (The GROMACS Development Team, Stockholm, Sweden), CHARMM36m/TIP3P), a duration widely considered sufficient to evaluate the stability of protein–ligand complexes and capture essential conformational equilibration at the nanosecond timescale [16]. The docked pose was cleaned in PyMOL (Schrödinger, LLC, New York, NY, USA); ligand parameters were generated with SwissParam (University of Lausanne, Lausanne, Switzerland). The solute was centered in a dodecahedral box (1.2 nm padding), solvated, and neutralized with NaCl (≈ 150 mM). After energy minimization (steepest descent), the system was equilibrated (NVT 100 ps $\rightarrow$ NPT 100 ps, 300 K, 1 bar, 2 fs step) and subjected to production run (PME electrostatics, LINCS constraints); trajectories were post-processed to remove global translation/rotation.

In the absence of solvation effects, the van der Waals and electrostatic interactions between the small molecule and the protein within the complex were calculated to analyze the variations in binding forces throughout the simulation process. Considering the solvation energy, a comprehensive analysis was conducted by examining root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), the number of hydrogen bonds (HBond), Radius of gyration (Rg), solvent-accessible surface area (SASA). Trajectories of the complex in a stable conformational state were selected. The binding free energy and its associated components were then calculated using the Molecular Mechanics-Poisson Boltzmann Surface Area method.

2.7. Evaluation of Drug-Likeness Properties

An initial assessment of HIG’s drug-like properties was performed using the SwissADME (<http://www.swissadme.ch> (accessed on 11 November 2025)). The SMILES string of HIG was submitted to SwissADME, which generated a comprehensive profile including key physicochemical and pharmacokinetic parameters. This profile informs the compound’s potential as a drug development lead.

3. Result

3.1. Identification of Core Intersection Genes

A total of 359 targets retrieved from three independent databases were intersected with 3627 genes obtained from Genecards and OMIM, yielding a final set of 194 overlapping genes (Supplementary Materials Table S1). These genes were considered to be associated with the regulation of RHF by HIG (Figure 1A).

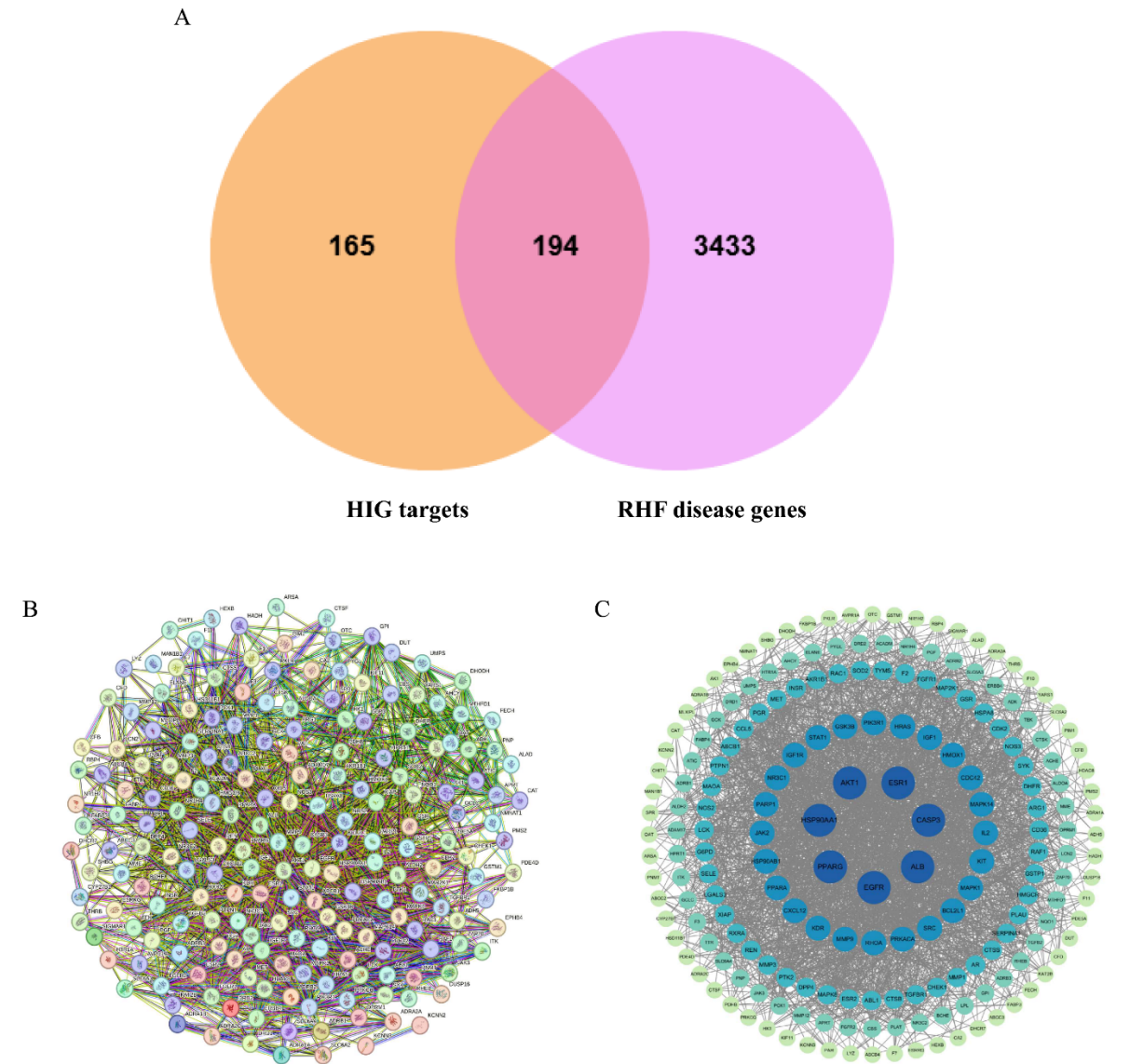


Figure 1. Network analysis reveals a highly interconnected PPI landscape underlying HIG-mediated regulation of RHF. (A) Venn analysis identifying 194 intersecting genes between HIG targets and RHF-related genes. (B,C) STRING and Cytoscape analyses demonstrating dense protein–protein interactions and suggesting the presence of potential central regulatory hubs such as ESR1.

3.2. PPI Network Construction

The 194 proteins were submitted to the STRING platform for PPI network analysis (Figure 1B) and visualized by Cytoscape 3.10 according to degree values (Figure 1C). They were ranked based on their degree values and the top 10 targets were shown in Table 1.

Table 1. The degree values of top 10 targets.

Gene	Full Name	Degree
AKT1	AKT Serine/Threonine Kinase 1	114
ALB	Albumin	108
EGFR	Epidermal Growth Factor Receptor	84
ESR1	Estrogen Receptor 1	84
CASP3	Caspase 3	82
HSP90AA1	Heat Shock Protein 90 Alpha Family Class A Member 1	80
SRC	SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase	80
PPARG	Peroxisome Proliferator Activated Receptor Gamma	80
MMP9	Matrix Metalloproteinase 9	76
IGF1	Insulin Like Growth Factor 1	70

3.3. GO and KEGG Enrichment

KEGG pathway mapping (Figure 2A), BP (Figure 2B), CC (Figure 2C), MF (Figure 2D) enrichment revealed that the candidate gene set was significantly enriched in “positive regulation of MAPK cascade”, “VEGF signaling pathway”, “PI3K–Akt signaling pathway” and “Endocrine resistance”, with substantial over-representation of membrane rafts, focal adhesions and extracellular exosomes, implying a multi-layered crosstalk among membrane receptors, nuclear receptors and the extracellular matrix. Among the high-degree nodes in the PPI network, ESR1, PPARG, and TGFBR1 were prioritized over other top-degree targets (e.g., AKT1) because these three targets were identified across various enrichment analyses of key targets and pathways. On the other hand, accumulating evidence has demonstrated the significant involvement of ESR1 and PPARG in pulmonary arterial hypertension, a primary etiology underlying right heart failure. TGFBR1 has been shown to attenuate myocardial hypertrophy and ameliorate ventricular remodeling. Collectively, these three targets are implicated in the pathogenesis of RHF. In contrast, pleiotropic targets such as AKT1, which are recurrently identified across diverse disease contexts and frequently emerge in network pharmacological analyses, fall outside the scope of our core investigative focus within this specific field. Within this interactome, ESR1 simultaneously occupied central nodes of “nuclear receptor activity”, “Estrogen signaling pathway” and “negative regulation of apoptosis”, thereby coupling hormonal responses to angiogenesis. PPARG linked lipid-microdomain remodeling to insulin sensitivity through the “Lipid and atherosclerosis” and “PI3K–Akt signaling pathway”, whereas TGFBR1 served as a molecular switch between the tumor-suppressive and pro-metastatic arms of TGF- β signaling by integrating “VEGF signaling”, “MAPK cascade” and “extracellular matrix” components. Converging on the FoxO–MAPK–VEGF axis, ESR1, PPARG and TGFBR1 collectively span transcriptional regulation by nuclear receptors, tyrosine-kinase-dependent membrane signaling and stromal microenvironment remodeling. In conjunction with the PPI network topology, they were prioritized as the core targets for subsequent mechanistic validation.

3.4. Phenotype-Genotype Direct Association Filtering

By the Varelect framework, 15 proteins whose documented associations with RHF are direct were retained. These proteins were subsequently rendered in a network plot in which central placement, larger diameter, and deeper hue jointly signify higher relevance scores (Figure 2E). Integrating evidence from GO, KEGG and Varelect analyses, ESR1, PPARG, TGFBR1 emerged as the consensus hub node and was therefore designated the key target through which HIG exerts its regulatory effect on RHF, serving as the entry point for all downstream investigations.

3.5. Molecular Docking

3D structures of the target proteins ESR1 (PDB ID: 9BQE), PPARG (PDB ID: 9F7W) and TGFBR1 (PDB ID: 5E8X) were downloaded and the PDB files were uploaded to the Discovery Studio 2019 Client software to generate 2D and 3D visualization maps of the docking results (Figure 3A–F). The -Cdocker interaction energy values (Table 2) showed that the HIG-ESR1 pair were the highest. Therefore, we propose that HIG affects RHF through ESR1.

3.6. MD Simulation and Binding Stability Assessment

The resulting trajectory was analyzed for key stability metrics: RMSD quantifies global structural drift, whereas RMSF reports per-residue mobility and the directional amplitude of thermal motion, thereby mapping protein flexibility. Rg monitors overall compaction, and HBond reflects the network of stabilizing interactions that lock a given conformation. SASA quantifies the area of a molecular surface that can be contacted by a spherical solvent probe. Together, these metrics provide a consensus stability fingerprint for the receptor–ligand complex. RMSD profile exhibits an initial ascent, followed by convergence to a stable plateau, indicating that the system progressively approaches equilibrium (Figure 4A). There are some fluctuations between 0.1 and 0.6 in RMSF, where regions with higher RMSF values are more flexible and lower RMSF values indicate more stable ones (Figure 4B). The number of hydrogen bonds between the small molecule and the protein is mainly distributed between 1 and 5 (Figure 4C) and in Figure 4D, the overall SASA exhibits a sustained decline, indicative of enhanced folding or progressive sequestration of hydrophobic residues. Over the last 50,000 ps, the Rg trajectory remains essentially flat, signifying the absence of appreciable global expansion or collapse of the macromolecule (Figure 4E). The specific numerical values related to the binding free energy are shown in Table 3.

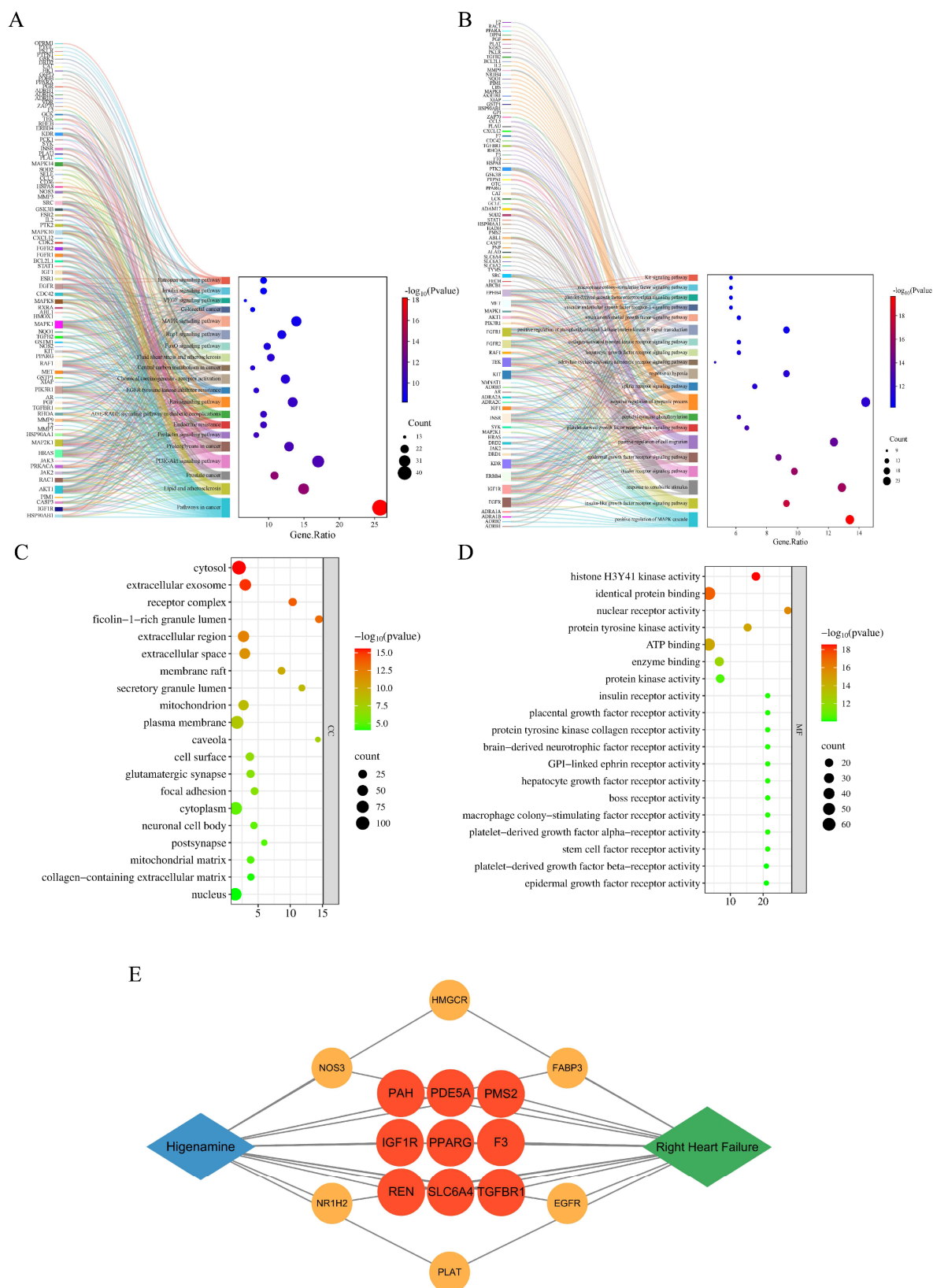


Figure 2. Identification of HIG’s core regulatory targets influencing RHF and functional enrichment analysis. **(A)** KEGG sankey diagram illustrating the major enriched signaling cascade like “VEGF signaling pathway” and “PI3K–Akt signaling pathway”. **(B)** BP sankey diagram highlighting dominant functional modules associated with cardiovascular regulation and cellular stress responses. **(C,D)** Bubble plots of CC and MF enrichment analyses demonstrating the subcellular localization and functional characteristics of the shared targets. **(E)** Varelect screening identifies 15 direct targets linking HIG to RHF, suggesting potential core regulatory mediators underlying its therapeutic actions.

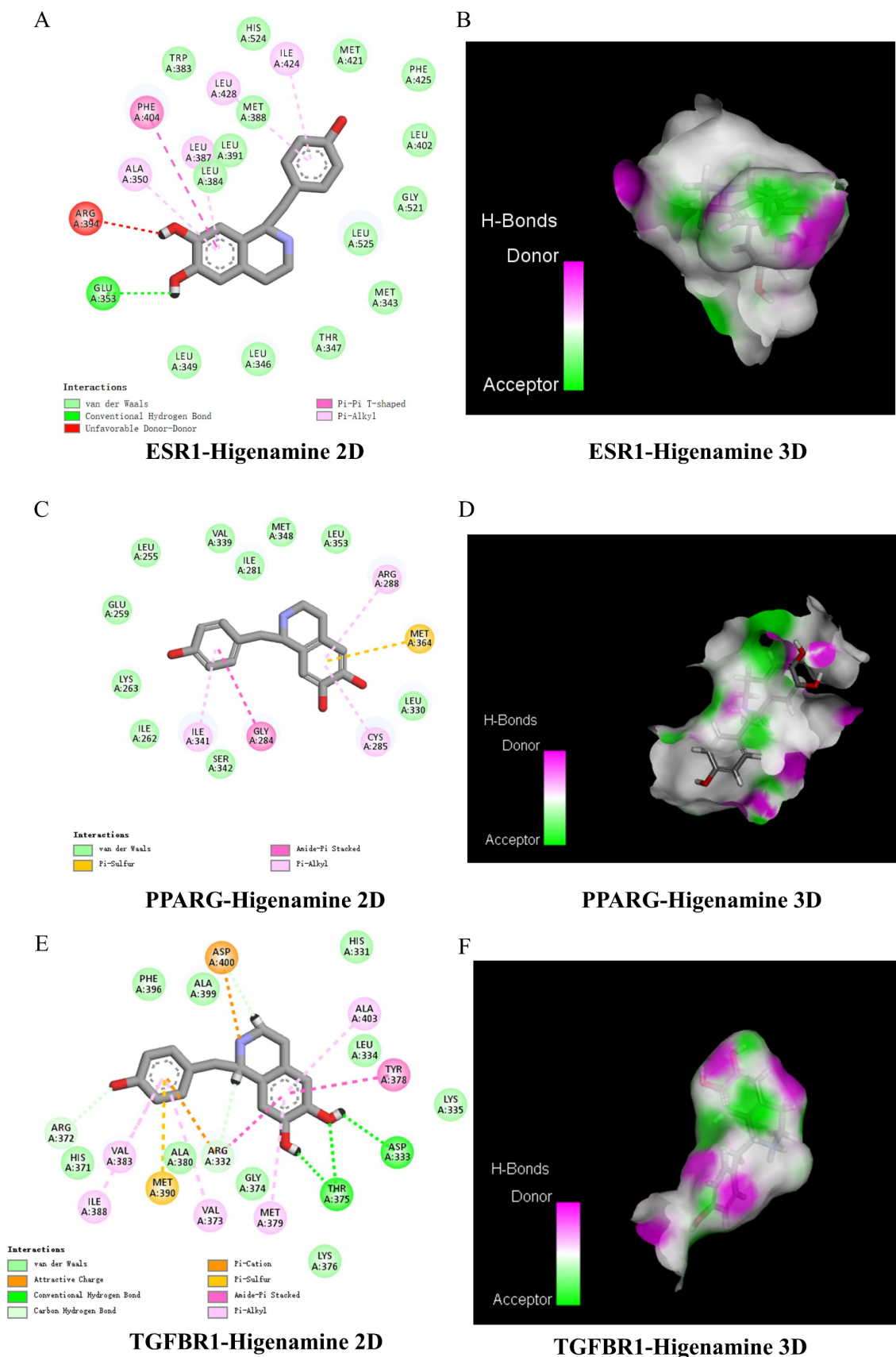


Figure 3. Molecular docking demonstrates stable binding interactions between HIG and the core targets ESR1, PPARG, and TGFBR1. (A,B) The 2D and 3D interaction models between HIG and ESR1. (C,D) The 2D and 3D docking conformations between HIG and PPARG. (E,F) The 2D and 3D docking analysis between HIG and TGFBR1.

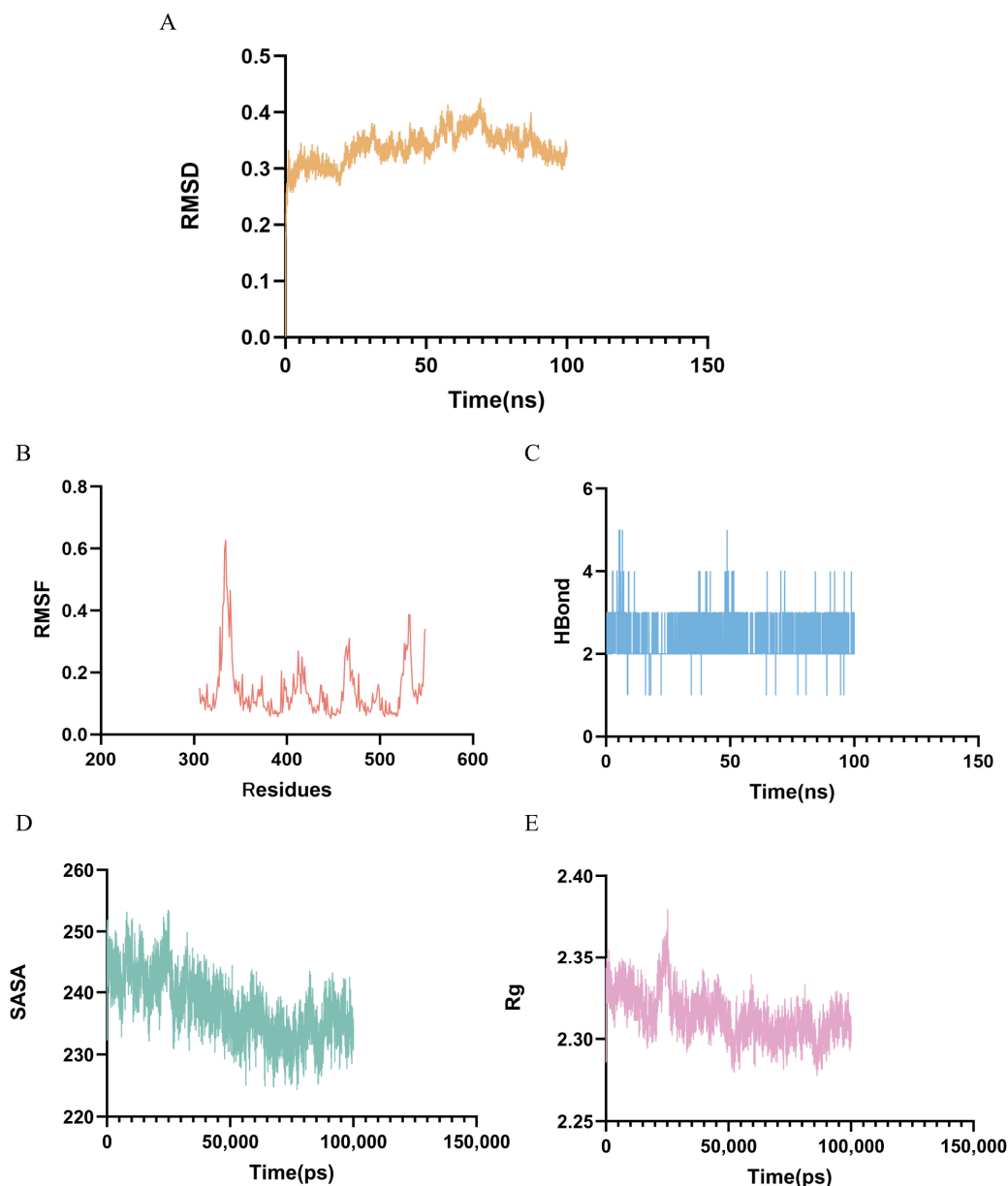


Figure 4. 100-ns MD simulation confirms the dynamic stability of the HIG–ESR1 complex. (A) Root Mean Square Deviation (RMSD) analysis demonstrating system equilibration and stable trajectory convergence over 100-ns. (B) Root Mean Square Fluctuation (RMSF) profile indicating limited residue-level fluctuations within the binding region. (C) Hydrogen Bond (HBond) analysis showing persistent intermolecular interactions throughout the simulation. (D) Solvent-Accessible Surface Area (SASA) analysis suggesting structural compactness. (E) Radius of Gyration (Rg) confirming overall conformational stability of the complex.

Table 2. The -Cdocker interaction energy values.

Target-Metabolite	-Cdocker Interaction Energy
HIG-ESR1	40.3707
HIG-PPARG	30.8511
HIG-TGFBR1	22.0612

Table 3. Numerical values of ESR1 (PDB ID:9BQE) and HIG related to the binding energy.

Van der Waal Energy	Electrostatic Energy	Polar Solvation Energy	SASA Energy	Binding Free Energy
-131.501 ± 1.329 kJ/mol	-81.184 ± 1.050 kJ/mol	152.394 ± 1.483 kJ/mol	-16.475 ± 0.069 kJ/mol	-76.829 ± 1.205 kJ/mol

3.7. Drug-Likeness Properties of HIG

SwissADME profiling indicates that HIG possesses a favorable drug-like signature within an acceptable developability window (Figure 5A,B). The specific indicators are shown in Table 4. The molecule exhibits a molecular weight of 271.31 g mol⁻¹, a topological polar surface area (TPSA) of 72.72 Å² and only two rotatable bonds, fully satisfying Lipinski's rule (zero violation) and passing additional filters (Ghose, Veber, Egan, Muegge). A consensus log P_{o/w} of 1.93 places it in the moderate lipophilicity range, adequate for passive membrane permeation while minimizing liabilities related to excessive lipophilicity. Pharmacokinetic predictions classify gastrointestinal absorption as “High” and assign an oral bioavailability score of 0.55, suggesting moderate first-pass loss. P-gp substrate positivity and a negative BBB penetration flag predict limited brain exposure, implying a low risk of central adverse effects. Among cytochrome P450 isoenzymes, only CYP2D6 is predicted to be inhibited, whereas CYP1A2, 2C9, 2C19 and 3A4 are not, indicating a restricted potential for metabolic drug–drug interactions. Aqueous solubility estimates (log S –4.25 to –3.25 across ESOL, Ali and SILICOS-IT models) correspond to 0.015–0.15 mg mL⁻¹, classifying the compound as slightly to moderately soluble; conventional salt formation or particle-size reduction is expected to achieve sufficient oral exposure. Structural alerts from PAINS and Brenk analyses flag the catechol motif; however, embedded within the natural benzyloquinoline scaffold and coupled with a synthetic accessibility score of 2.62, this liability can be mitigated by pro-drug or soft-drug strategies. Collectively, HIG balances physicochemical compatibility, oral exposure and metabolic safety, warranting its consideration as either a direct lead or an optimization starting point.

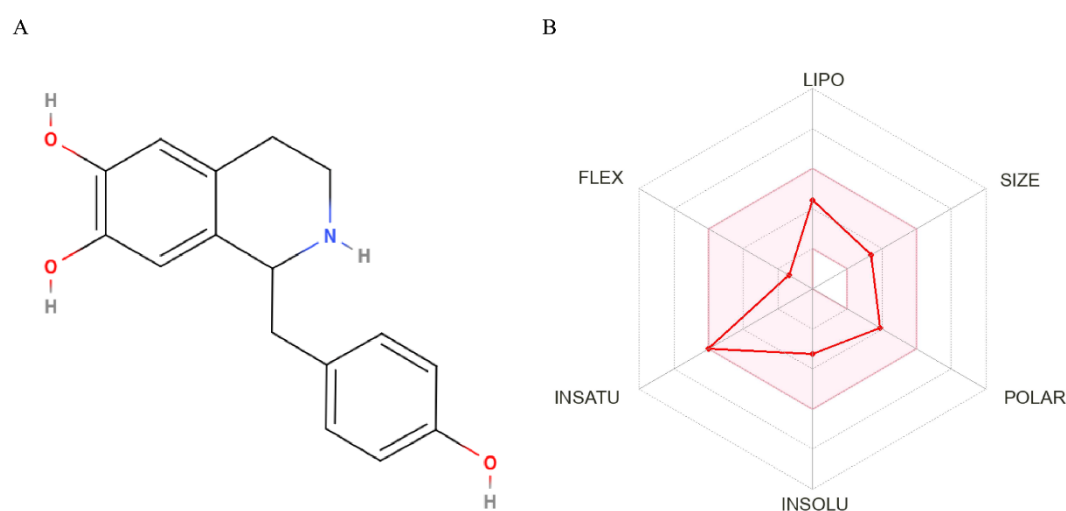


Figure 5. Drug-likeness and pharmacokinetic profiling suggest favorable drug development potential of HIG. **(A)** Chemical structure of HIG. **(B)** SwissADME bioavailability radar indicating compliance with key drug-likeness parameters including lipophilicity, size, polarity, solubility, flexibility and saturation. These findings support the pharmacokinetic feasibility of HIG as a candidate therapeutic agent.

Table 4. Evaluation of HIG's drug-likeness, lipophilicity, pharmacokinetics.

Drug-Likeness Parameters	Value
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
GI absorption	High

4. Discussion

In the landscape of integrative cardiovascular medicine, *Aconitum carmichaelii* Debx. (Fuzi) and its derived formulations, most notably Shenfu injection, have long served as a cornerstone for managing chronic heart failure. Extensive clinical evidence and meta-analyses have substantiated their efficacy not only in ameliorating left ventricular dysfunction but also in improving hemodynamic parameters in heart failure patients [17,18]. HIG,

chemically identified as 1-(4-hydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, is widely recognized as the principal bioactive alkaloid responsible for these cardiotoxic effects [19]. Extensive investigations have demonstrated that it exerts multifaceted pharmacological activities including β -adrenergic receptor agonism, anti-inflammation and antioxidation effects. While these mechanisms are established in left ventricular dysfunction and general cardiovascular disease [20], their precise role in modulating right ventricular remodeling, pulmonary vascular resistance, and RHF-specific pathophysiology remains largely unexplored. This gap highlights a critical need to elucidate the precise molecular and physiological pathways underlying its efficacy in RHF. Unlike prior work that primarily describes HIG as a general cardiotoxic agent, our analysis provides an RHF-oriented, systems-level mechanistic framework by aligning HIG's predicted target landscape with RHF-relevant vascular remodeling and right-ventricular maladaptation pathways. By integrating network topology, pathway convergence, and structure-dynamics validation, we identify a coherent “nuclear receptor–metabolism–fibrosis” triad (ESR1–PPARG–TGFB1) that links pulmonary vascular dysfunction to right-ventricular remodeling, thereby generating testable, RHF-specific mechanistic hypotheses rather than a descriptive list of targets.

By coupling GO enrichment with KEGG-pathway cartography, we identified ESR1, PPARG and TGFB1 as core nodes that collectively mediate HIG's multi-target effects on RHF, encompassing vascular protection, metabolic regulation, and tissue remodeling. Growing evidence positions ESR1, PPARG and TGFB1 as nodal regulators of RHF pathophysiology. ESR1 exerts its effects through both genomic and non-genomic pathways that modulate vascular tone, preserve endothelial integrity and curtail cardiomyocyte apoptosis and fibrosis. When RV confronts pressure overload, as occurs in pulmonary arterial hypertension (PAH), down-regulation of Estrogen-receptor signaling, particularly reduced ESR1 expression or activity, blunts the ventricle's adaptive response. Ligand-activated ESR1 enhances nitric-oxide generation, improves pulmonary endothelial function and lowers pulmonary vascular resistance, suggesting that HIG's activation of ESR1 may directly attenuate pulmonary hypertension-induced RV overload [21–23]. Mapping how ESR1 expression and function evolve during RHF progression therefore offers a rational basis for sex-hormone-centered therapeutics. PPARG, a nuclear receptor transcription factor, governs cardiac performance chiefly by re-programming fatty-acid metabolism, maintaining glucose homeostasis and restraining inflammation. Although best known for enhancing insulin sensitivity, PPARG within the myocardium orchestrates the balance between fatty-acid oxidation and glucose utilization. Beyond metabolic control, PPARG exerts anti-inflammatory and anti-fibrotic actions; in experimental PAH, PPARG agonists attenuate pulmonary vascular remodeling and reduce RV fibrosis. Pharmacological enhancement of PPARG signaling thus represents a feasible strategy to correct metabolic derangement and dampen inflammation in RHF [24]. TGFB1, the principal receptor for transforming growth factor- β (TGF- β), drives myocardial and vascular fibrosis. Pressure overload triggers excessive extracellular-matrix deposition that stiffens the RV and compromises its function. Ligand binding to TGFB1 phosphorylates SMAD2/3, promoting their nuclear translocation, fibroblast-to-myofibroblast conversion and collagen synthesis. Consequently, TGFB1 operates as a master regulator of maladaptive remodeling. Through modulation of TGFB1 signaling, HIG may limit maladaptive RV fibrosis and pulmonary vascular stiffening, key contributors to RHF progression [25,26].

The identified ESR1–PPARG–TGFB1 axis suggests that HIG may confer clinical benefit in RHF phenotypes driven by pulmonary hypertension-related remodeling, where right-ventricular afterload, endothelial dysfunction, metabolic derangement, and fibrosis jointly determine outcome [27]. Mechanistically, simultaneous modulation of endothelial NO/VEGF signaling (ESR1-associated) [21], myocardial metabolic flexibility and inflammation (PPARG-associated) [28], and profibrotic TGF- β /SMAD activation (TGFB1-associated) [29] could translate into improved pulmonary vascular resistance, preserved RV–pulmonary artery coupling [30], and attenuation of maladaptive RV fibrosis [31]. Moreover, these pathways nominate measurable biomarkers (e.g., ESR1/PPARG/TGFB1 expression signatures and downstream p-SMAD2/3, PI3K–Akt, VEGF/NO-related readouts) [32] that may support patient stratification and response monitoring in future translational studies [33].

Collectively, ESR1, PPARG and TGFB1 span the principal mechanistic axes of RHF, namely vascular protection and endothelial function, myocardial metabolism and inflammation, and tissue fibrosis and remodeling, particularly in the context of pulmonary hypertension-driven right ventricular overload. These intersecting networks illustrate how HIG's multi-target pharmacology can be leveraged to mitigate RHF-specific pathophysiology, providing a rational framework for integrated therapeutic intervention.

This study is primarily computational and thus subject to biases inherent to target databases, enrichment background selection, and parameter thresholds. While docking and 100-ns MD simulations support the structural plausibility and dynamic stability of the predicted interactions, they do not substitute for experimental binding affinity measurements or in vivo pharmacodynamics. In addition, the current analysis does not directly quantify RHF phenotypic outcomes, and the predicted pathways require validation in disease-relevant models of pulmonary hypertension-associated RHF.

While our bioinformatics analysis provides a comprehensive framework for understanding the potential mechanisms linking HIG to RHF, we acknowledge that these findings are inherently limited by the lack of direct experimental validation. The predicted interactions between ESR1, PPAR γ , TGFBR1, and downstream signaling pathways remain to be confirmed through functional studies. Additionally, the translational relevance of the identified axis from molecular modulation to physiological outcomes requires further verification. These limitations underscore the need for cautious interpretation and highlight opportunities for future investigations to validate the proposed mechanisms.

5. Conclusions

Beginning with a systems-pharmacology scan, we linked docking to extended MD to build a full-cycle pipeline that moves from target fishing to binding validation and stability assessment. The trajectory converged on a single, druggable node: ESR1. Moreover, HIG exhibits favorable oral bioavailability, low predicted toxicity, and physicochemical parameters residing within the accepted drug-like space. Collectively, these data ascribe a previously unrecognized role to this small molecule, namely, the modulation of estrogen receptor signaling, while furnishing a departure point for therapeutic intervention against RHF. However, the predictions of this study still need further experimental verification. At present, the results are mainly based on computer simulations and have not been validated by cell or animal experiments. Next, in vitro experiments and animal models are required to confirm its efficacy and safety.

Supplementary Materials: The following supporting information can be downloaded at: <https://media.sciltp.com/articles/others/2608130847480154/IJDDP-2025-000032-SM.pdf>. Table S1. 194 overlapping genes between HIG targets and RHF disease genes.

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