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Network Pharmacology and Molecular Docking Analysis of the Therapeutic Mechanisms of Qishen Yiqi Dropping Pills in Chronic Heart Failure

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ABSTRACT

Chronic heart failure (CHF) is a life-threatening disorder affecting millions worldwide, characterized by recurring symptoms such as shortness of breath, fluid retention, and fatigue, which significantly compromise daily functioning and contribute to elevated mortality and hospital readmissions. Qishen Yiqi Dropping Pills (QYDP), a formulation in Traditional Chinese Medicine (TCM) containing Danshen, Huangqi, Jiangxiang, and Sanqi, has shown promise in improving cardiac function by enhancing circulation and supporting Qi. Despite evidence from clinical studies suggesting symptom relief in CHF patients, the molecular mechanisms behind QYDP's effects remain largely undefined. This study applied network pharmacology alongside molecular docking analyses to uncover potential therapeutic targets of QYDP in CHF. Four pivotal genes—AKT1, HIF1A, STAT3, and MYC—were identified, and their interactions with bioactive compounds in QYDP, including kaempferol, luteolin, quercetin, tanshinone IIa, and cryptotanshinone, were confirmed. The findings indicate that QYDP may act through multiple molecular pathways to exert cardioprotective effects, providing a foundation for deeper mechanistic research and potential clinical application.

Keywords: Traditional Chinese medicine, CHF, QYDP, Cardiovascular disease

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Introduction

Chronic heart failure (CHF) represents a complex cardiac syndrome in which the heart gradually loses its ability to pump effectively, often triggered by multiple underlying conditions [1]. By 2019, global reports estimated over 56 million individuals living with heart failure, underscoring its widespread impact [2]. Alarmingly, CHF patients exhibit 5-year survival rates similar to those observed in certain cancers, reflecting the disease's severity [3]. Contemporary clinical management relies heavily on the so-called "fantastic four" medications, including beta-blockers, angiotensin receptor-neprilysin inhibitors, sodium-glucose cotransporter-2 inhibitors, ACE inhibitors, and mineralocorticoid receptor antagonists [4–6]. While effective, prolonged therapy may provoke adverse effects such as electrolyte disturbances, hypotension, and volume depletion, highlighting the need for complementary treatments, especially in patients sensitive to low blood pressure [6–9].

Qishen Yiqi Dropping Pills (QYDP), a traditional Chinese medicine (TCM) formulation, has gained recognition for managing CHF by alleviating symptoms related to Qi and blood deficiencies, with minimal side effects and sustained therapeutic benefits [10]. Randomized clinical trials support QYDP's efficacy and safety in treating persistent cardiovascular disorders [11]. Its main components—Danshen (Radix Salviae), Huangqi (Hedysarum multijugum Maxim), Jiangxiang (Dalbergia odorifera [Lignum]), and Sanqi (Panax notoginseng)—have demonstrated cardioprotective effects. For instance, Salvia miltiorrhiza modulates inflammatory signaling through the MD2/TLR4-MyD88 and TLR4-TRAF6-NF-κB pathways to mitigate myocardial damage [12], whereas Astragalus mongholicus enhances cardiac function by activating AMPKα2-mediated mitophagy via

extracellular vesicle miR-27a-3p derived from pericardial adipose tissue [13]. Panax notoginseng saponins also contribute to myocardial protection post-infarction by promoting autophagy [14].

Experimental studies further demonstrate that QYDP improves cardiac outcomes in CHF models by stimulating angiogenesis, reducing fibrosis, preventing hypertrophy, and suppressing apoptosis [15–17]. Despite these observations, the precise molecular mechanisms remain largely undefined. Network pharmacology has emerged as a valuable tool to systematically dissect the complex interactions of TCM at a molecular level [18, 19]. In this study, we applied a combined approach of network pharmacology and molecular docking to identify core target genes and elucidate the mechanistic pathways through which QYDP exerts its therapeutic effects in CHF.

Materials and Methods

Target identification

Active ingredients in QYDP were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) [20], with corresponding gene targets mapped using UniProt [21]. Genes associated with CHF were compiled from GeneCards [22], OMIM [23], TTD [24], and PharmGKB databases. Overlapping and duplicate entries were removed using the Venn package, yielding a refined set of CHF-related candidate genes.

Network construction and enrichment analysis

The intersection between QYDP targets and CHF-associated genes was determined using the Venn package [25]. Protein-protein interaction networks were constructed via STRING (species: Homo sapiens; combined score >0.95) [26]. Functional characterization was performed through Gene Ontology (GO) enrichment and KEGG pathway analysis, with significance defined as $q < 0.05$ [27–29].

Network analysis and core gene selection

To identify critical nodes within the PPI network, Cytoscape 3.8.0 with the CytoNCA plugin was used [30]. Key genes were selected based on six network topology measures: betweenness centrality, closeness centrality, degree centrality, eigenvector centrality, local average connectivity-based centrality, and overall network centrality, retaining genes with scores above the median.

Molecular docking

Core active compounds and key target proteins were prepared for docking. 2D structures were obtained from PubChem [31] and converted to 3D using ChemOffice software. Protein 3D structures were retrieved from the Protein Data Bank (PDB) [32], with water molecules and ligands removed in PyMol [33]. Both ligands and proteins were converted into pdbqt format, and docking simulations were conducted with AutoDock Vina and AutoDockTools 1.5.6. Binding interactions were visualized in PyMol, with known compound-protein interactions used as positive controls.

Results and Discussion

Target genes of QYDP

A total of 108 bioactive constituents were identified across the four herbs in QYDP: 65 from Danshen, 20 from Huangqi, 15 from Jiangxiang, and eight from Sanqi. These compounds corresponded to 2390 putative target genes: 932 for Danshen, 953 for Huangqi, 252 for Jiangxiang, and 253 for Sanqi. After removing redundancies, 1631 unique genes were obtained, with 218 retained as candidate targets relevant to CHF **(Figure 1)**.

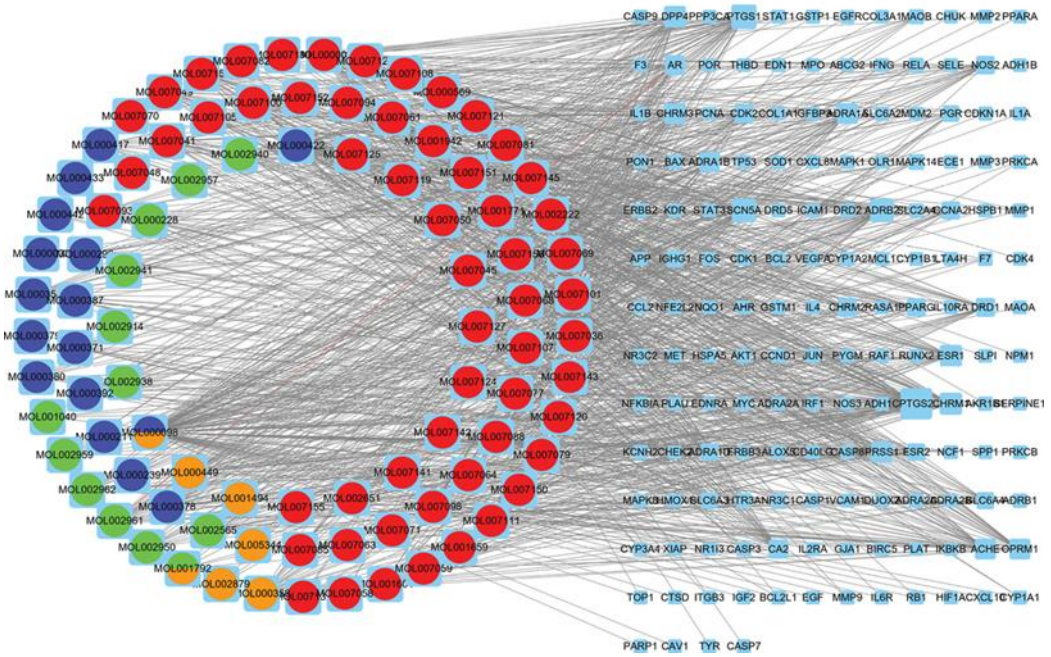


Figure 1. Gene targets for QYDP compounds.

Genes associated with CHF

Following the elimination of duplicate entries, a total of 2,915 genes were identified as associated with CHF. This included 2,818 genes from the GeneCards database (filtered with a relevance score >10), 152 genes from DrugBank, 268 genes from OMIM, 16 genes from PharmGKB, and 13 genes from TTD **(Figure 2)**.

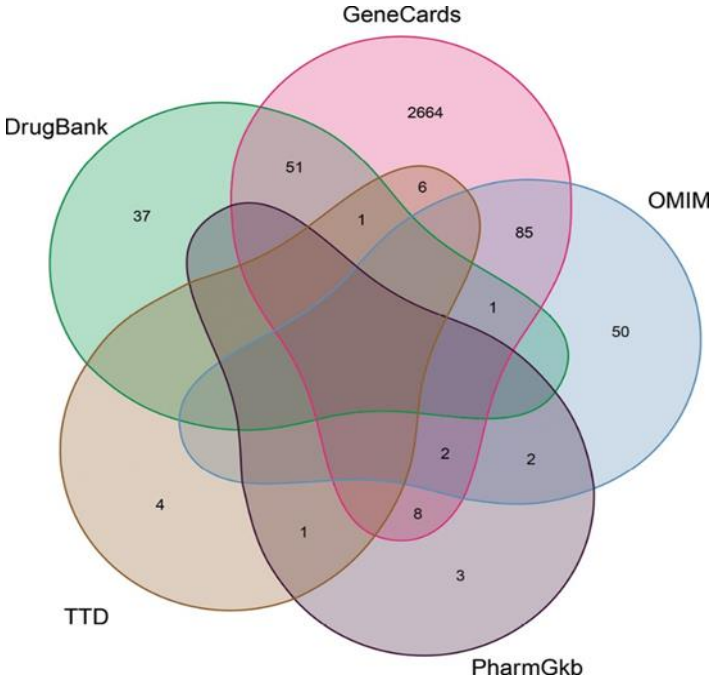


Figure 2. Gene targets of CHF identified from various databases.

Network construction

Overlap between CHF-related genes and QYDP targets

After removing duplicate entries with the Venn package in R, 218 potential therapeutic targets of QYDP and 2,915 CHF-associated genes were obtained. As shown in **Figure 3**, 157 genes were found at the intersection, representing targets of QYDP's active compounds that are also implicated in CHF.

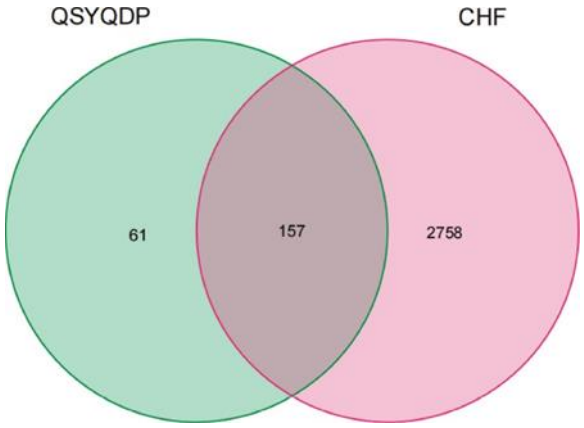


Figure 3. 157 genes shared between QYDP targets and CHF-related genes.

PPI network of disease and drug targets

Protein-protein interaction analysis of the 157 overlapping genes revealed that 117 of these genes engage in interactions with other proteins, as depicted in **Figure 4**.

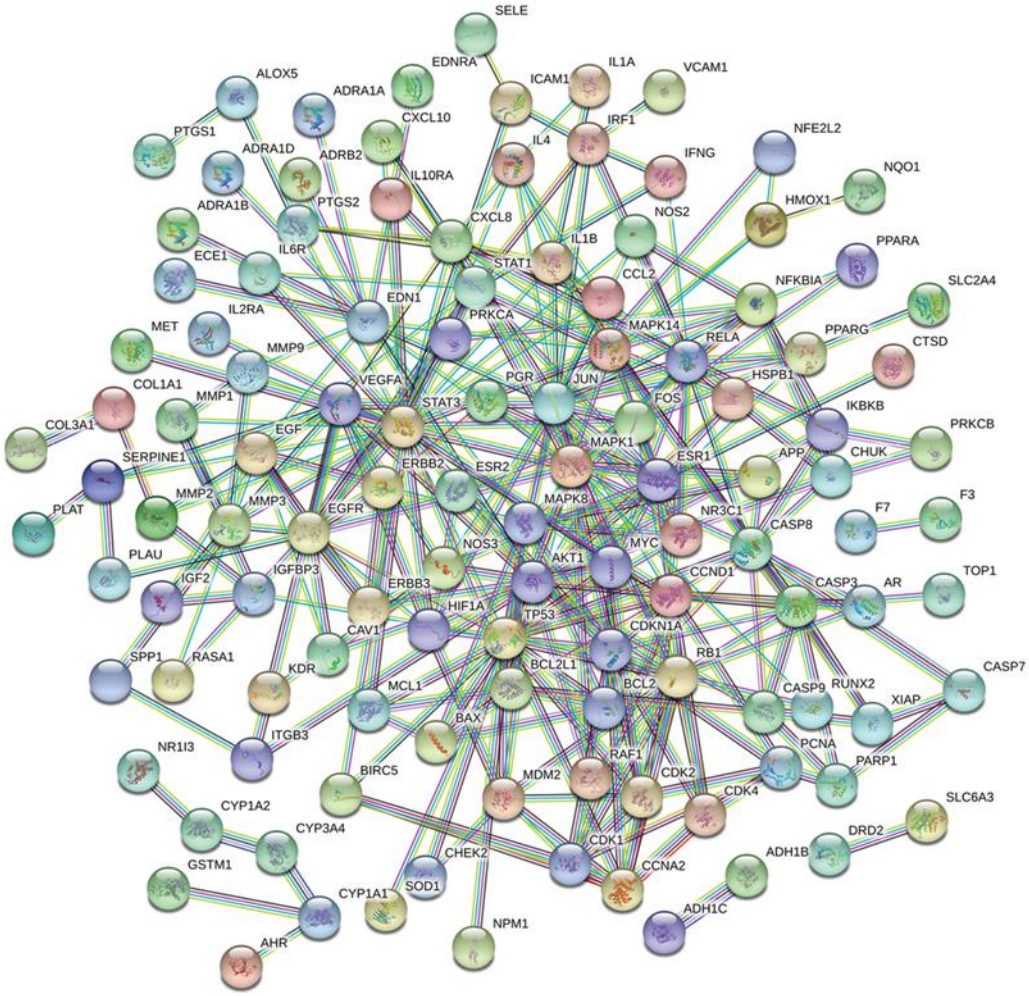


Figure 4. 117 genes interacting with other proteins from the results of the PPI network.

GO enrichment analysis

Analysis of the 157 overlapping genes using Gene Ontology revealed a total of 2,283 biological processes, 218 molecular functions, and 77 cellular components, applying a cutoff of $q < 0.05$. The ten most significantly enriched terms, ranked by q value, are illustrated in **Figure 5**, highlighting the key functional categories linked to QYDP's potential effects in CHF.

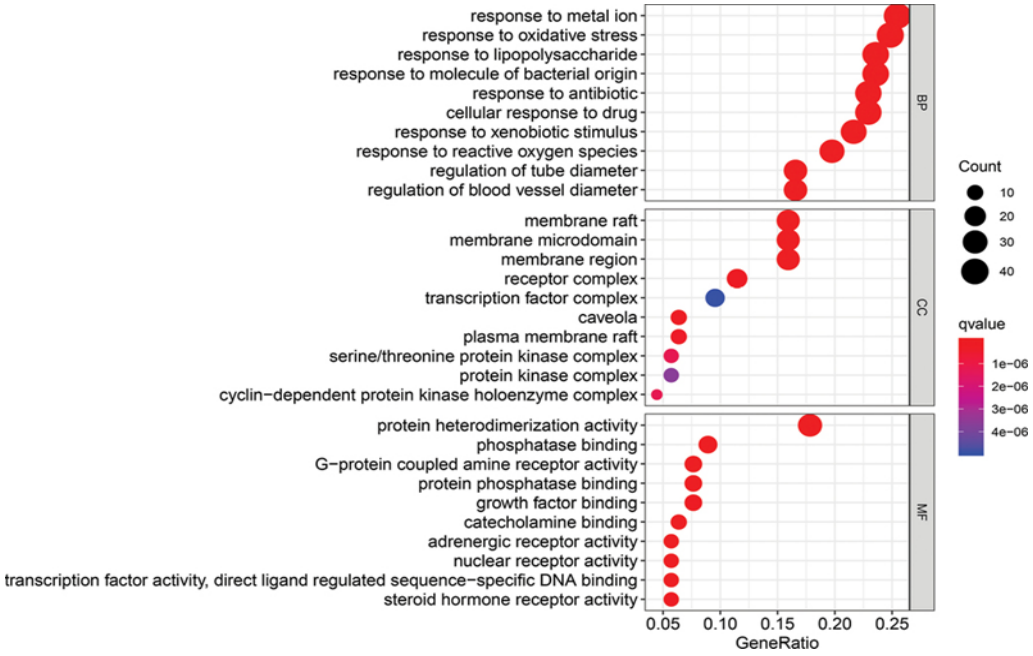


Figure 5. Top 10 enriched GO terms from the analysis.

KEGG pathway enrichment analysis

KEGG pathway enrichment identified 162 pathways that met the significance threshold of $q < 0.05$. The 30 most significantly enriched pathways, ranked by q value, are presented in **Figure 6**.

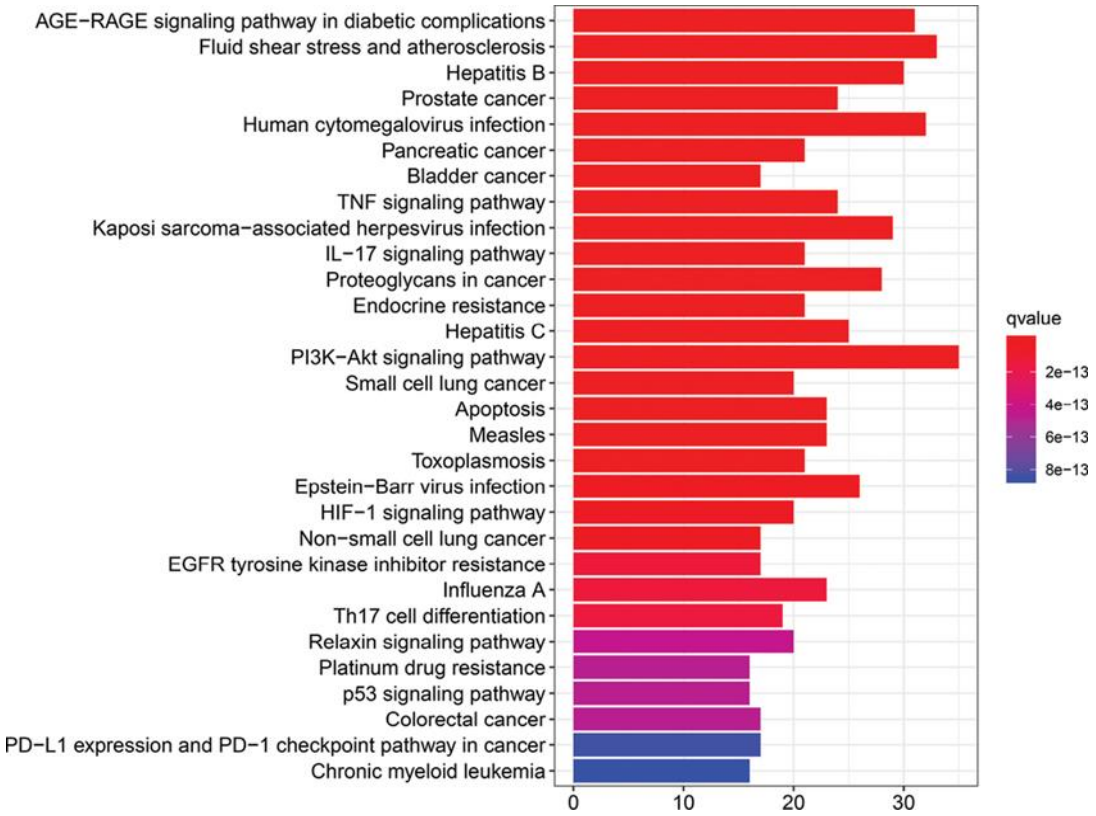
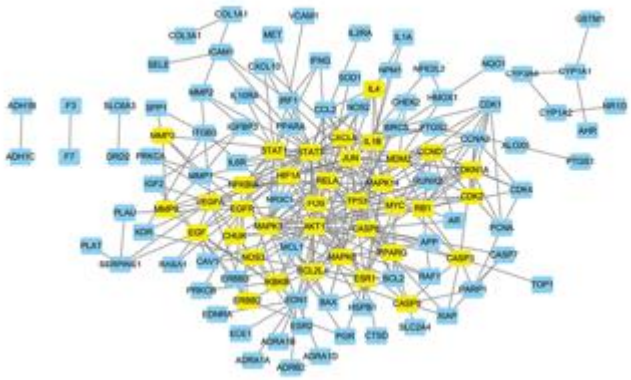


Figure 6. The top 30 KEGG pathways enriched in the analysis.

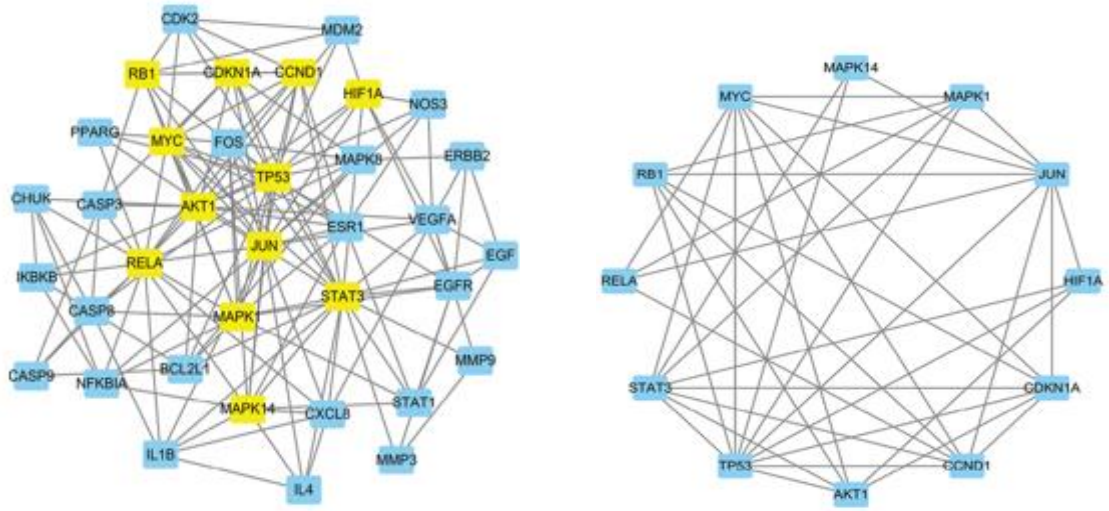
Identification of key genes through network topology analysis

Using the CytoNCA plugin, the PPI network of 117 overlapping genes was analyzed across six topological parameters with two sequential filters. The first filter yielded a network comprising 36 nodes (genes) and 151

edges **(Figure 7a)**. After applying the second, more stringent filter, 12 core genes were identified: CDKN1A, STAT3, JUN, AKT1, HIF1A, MAPK1, RB1, TP53, MAPK14, CCND1, MYC, and RELA **(Figures 7b and 7c)**.



a)



b) c)

Figure 7. PPI network of overlapping genes. Key genes are highlighted in yellow squares. Panel (a) shows the full PPI network of 117 overlapping genes; panel (b) displays 36 genes retained after applying the first CytoNCA filter; panel (c) presents the final 12 core genes identified using the second, more stringent filter.

Molecular docking

For docking simulations, five major bioactive compounds of QYDP—kaempferol, luteolin, quercetin, Tanshinone IIa, and cryptotanshinone—were tested against four central target proteins: HIF1A, MYC, STAT3, and AKT1. These targets were selected based on the combined results from network topology and enrichment analyses **(Table 1 and Figure 8)**. Trimetazidine, a compound known to bind these proteins experimentally, served as a positive control. Validation of the docking procedure confirmed strong and favorable interactions between Trimetazidine and each of the four targets, as detailed in **Table 2** and visualized in **Figure 9**.

Table 1. The molecular docking results in the compounds of QYDP and four core genes.

Number	Core targets	Compounds	Docking affinity (kcal/mol)
1	AKT1	kaempferol	-8.1
		Luteolin	-8.2
		Quercetin	-8.2
2	Myc	Quercetin	-6.2
		tanshinone IIa	-7.4

3	HIF1A	Quercetin	-8.0
4	STAT3	cryptotanshinone	-7.6

Table 2. The molecular docking results in the trimetazidine and four core genes.

Number	Core genes	Compound	Docking affinity (kcal/mol)
1	AKT1	trimetazidine	-6.6
2	Myc	trimetazidine	-5.1
3	HIF1A	trimetazidine	-5.4
4	STAT3	trimetazidine	-4.8

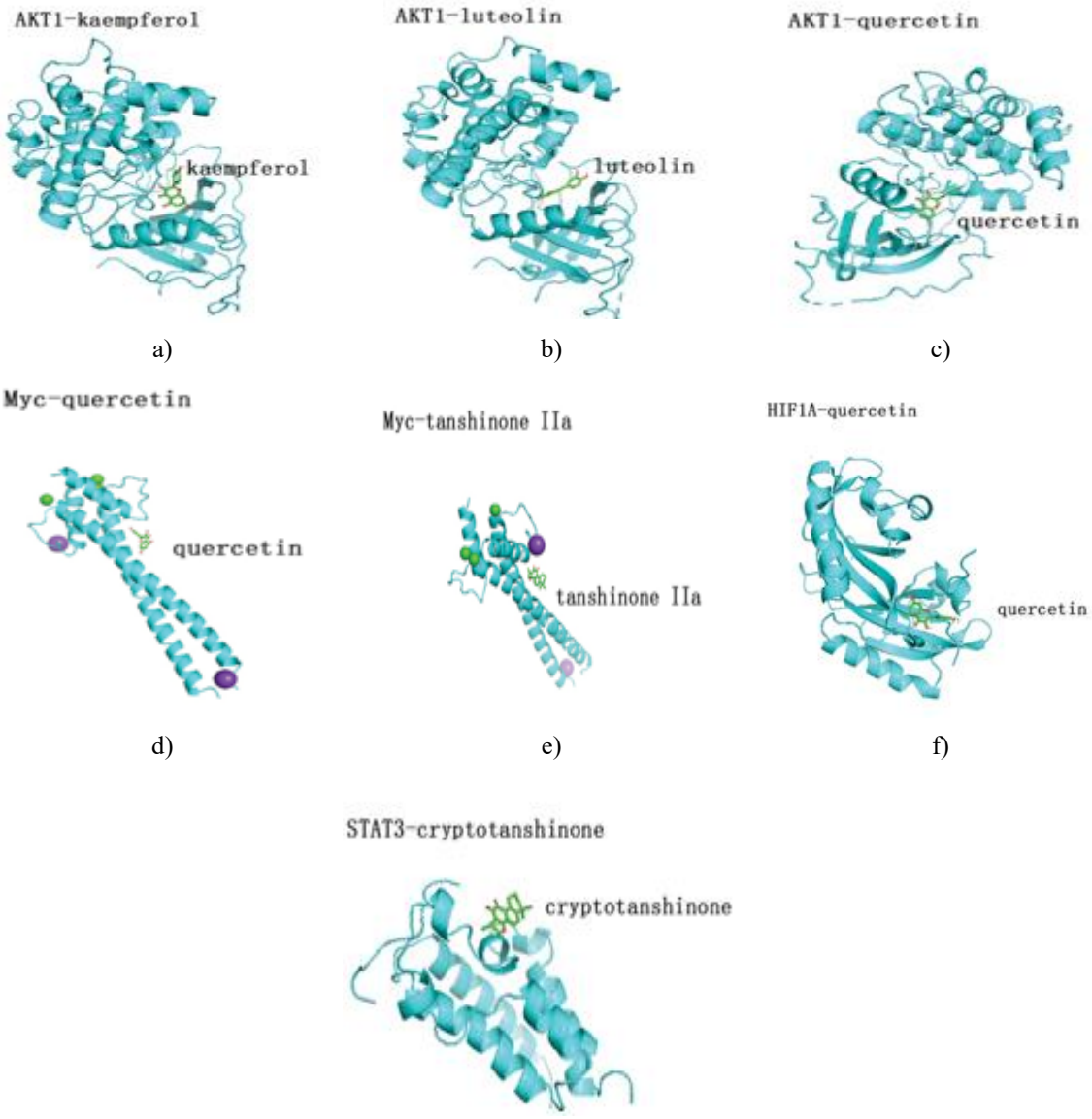


Figure 8. Molecular docking results showing interactions between active compounds and predicted target proteins.

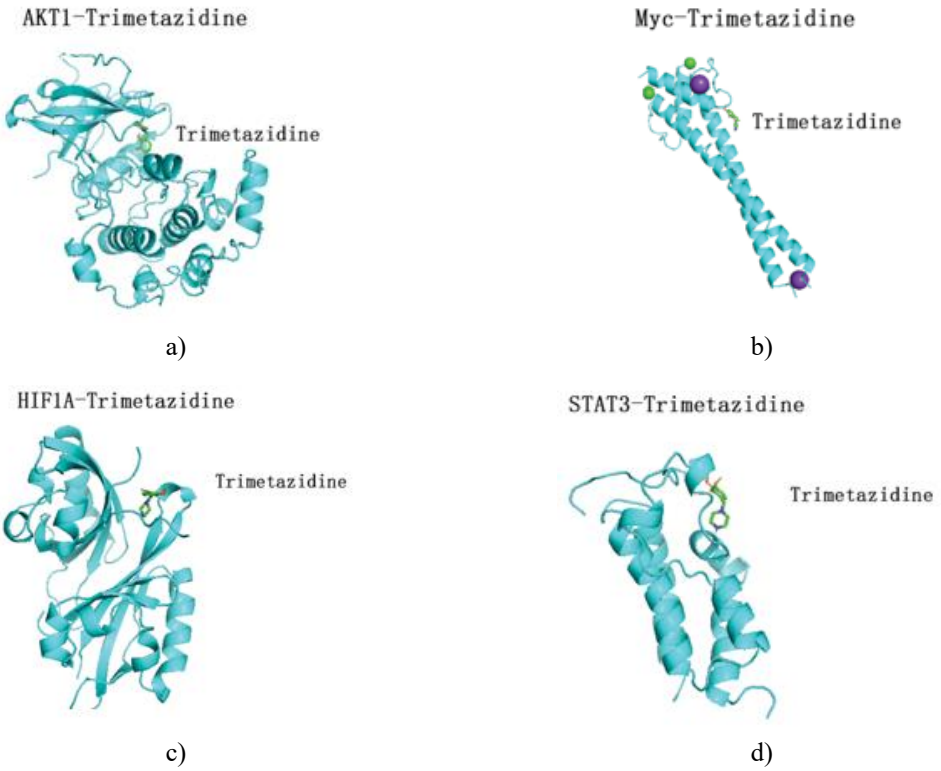


Figure 9. Molecular docking of the positive control, trimetazidine, with predicted target proteins.

Chronic heart failure remains a major contributor to global mortality, emphasizing the importance of refining therapeutic strategies to enhance patient outcomes [34–36]. Evidence from clinical studies indicates that Qishen Yiqi Dropping Pills (QYDP) can effectively improve cardiac performance in patients with CHF [11, 37–41]. Mechanistic investigations have linked QYDP's effects to regulation of noncoding RNAs such as TINCR and XIST [17, 42], while other studies have highlighted modulation of protein targets including Bax, VEGF, caspase-3, α-SMA, and TGF-β1 [15, 16]. Despite these findings, many of the molecular pathways through which QYDP exerts cardioprotective effects remain uncharted. Network pharmacology provides a systematic approach for mapping these pathways and uncovering additional therapeutic targets.

Our analysis suggests that QYDP may exert its beneficial effects on CHF through multiple interacting genes and signaling pathways. Notably, while some well-characterized targets like Bax, VEGF, and caspase-3 were not among the key genes identified after stringent filtering, their known roles in cardiac protection support the relevance of our findings. GO enrichment highlighted that the intersecting genes are mainly involved in phosphatase binding and oxidative stress-related processes. KEGG pathway analysis further indicated that these genes participate in critical signaling cascades, including TNF, IL-17, PI3K-Akt, atherosclerosis-related pathways, and responses to fluid shear stress. Across these analyses, 12 hub genes were pinpointed, including CDKN1A, JUN, MAPK1, RB1, TP53, MAPK14, CCND1, and RELA, with four core targets—STAT3, HIF1A, MYC, and AKT1—emerging as central regulators.

Each of these four core genes plays a distinct role in cardiac physiology and CHF progression. STAT3 is a key mediator of cellular proliferation and apoptosis, and prior research shows that activating the JAK-STAT3 pathway via astragaloside IV can improve heart failure outcomes [43]. MYC regulates cell cycle progression and transformation, and evidence from microarray data (GSE1145) links its expression to heart failure, while the Wnt/β-catenin/MYC axis is implicated in maladaptive cardiac remodeling [44–46]. AKT1 orchestrates processes including angiogenesis, metabolism, and cell survival, and its activation in endothelial cells has been shown to enhance cardiac function, partly through modulation of angiogenic networks [47, 48]. HIF1A, a critical subunit of HIF-1, regulates apoptosis, energy metabolism, and vascular growth; its upregulation, as observed with muscone-induced VEGFA expression, promotes angiogenesis and improves cardiac function [49], while HIF1A also protects the heart from chronic pressure overload [50].

In this research, five bioactive constituents of QYDP—quercetin, kaempferol, luteolin, tanshinone IIA, and cryptotanshinone—were prioritized from the TCMSP database based on their favorable oral bioavailability and

drug-likeness properties. These compounds have been widely reported to possess cardioprotective effects, including inhibition of apoptosis, reduction of oxidative stress, and anti-inflammatory activity. Quercetin has been shown to influence cardiovascular disease through the TNF and PI3K-Akt signaling pathways [51–53]. Kaempferol, a flavonoid known for its antioxidant and anti-inflammatory effects, protects cardiomyocytes in heart failure models by regulating NF-κB/MAPK and AMPK/Nrf2 pathways [54]. Luteolin has been found to improve cardiac performance by modulating sarcoplasmic reticulum Ca^{2+}-ATPase 2a activity in failing hearts [55]. Tanshinone IIA contributes to cardiac repair by promoting angiogenesis, reducing inflammation, preventing oxidative damage, and suppressing apoptosis [56–58]. Although evidence for cryptotanshinone in heart failure is limited, it has been reported to inhibit STAT3 and subsequently block the NF-κB pathway [40].

Trimetazidine, known for its ability to enhance myocardial energy metabolism in both clinical and experimental contexts [59], was employed as a positive control to assess the reliability of molecular docking for QYDP's active compounds. Docking results indicated that kaempferol, luteolin, tanshinone IIA, quercetin, and cryptotanshinone exhibited binding affinities to the core targets comparable to trimetazidine. These findings suggest that AKT1, MYC, HIF1A, and STAT3 may act as pivotal molecular targets mediating QYDP's cardioprotective effects. However, since this study relies on computational network pharmacology methods, further experimental and clinical investigations are required to validate these targets and clarify the mechanisms by which QYDP exerts therapeutic effects in CHF.

Conclusion

This study provides a network pharmacology-based framework supporting the use of QYDP in CHF management by identifying key molecular targets and potential mechanisms. The core targets—AKT1, MYC, HIF1A, and STAT3—underscore QYDP's potential as an adjunct or alternative therapy for CHF. Future studies are essential to experimentally confirm these targets and to elucidate the specific pathways through which QYDP improves cardiac function.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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