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Research Article

MOLECULAR DOCKING ANALYSIS OF TAURINE ELUCIDATES MOLECULAR SIGNALING MECHANISMS UNDERLYING ITS CARDIOPROTECTIVE ACTION

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ABSTRACT

Heart failure remains a major global health burden despite current pharmacological interventions, necessitating exploration of multi-target cardioprotective agents. Taurine, a sulfur-containing amino acid abundantly present in cardiac tissue, exhibits pleiotropic effects including antioxidant, membrane-stabilizing, lipid-regulatory, and anti-fibrotic actions. However, its residue-level interaction with key molecular targets involved in isoproterenol (ISO)-induced myocardial injury remains insufficiently characterized. In this study, molecular docking was performed to investigate the binding interactions of taurine with seven key proteins implicated in cardiac dysfunction: matrix metalloproteinases MMP-2 (8H78) and MMP-9 (1GKC), antioxidant pathway regulators Nrf2 (8HZ8) and HO-1 (1N45), and lipid metabolism regulators LDLR (3M0C), SREBP-2 (1UKL), and PPAR-α (3VI8) using AutoDock Vina. Protein and ligand structures were prepared using AutoDock Tools and UCSF Chimera, and docking was conducted with optimized grid parameters and exhaustiveness settings. Taurine exhibited moderate binding affinities across all targets, with the strongest interaction observed for SREBP-2 (−4.53 kcal/mol), followed by LDLR (−4.32 kcal/mol), MMP-2 (−4.23 kcal/mol), MMP-9 (−3.91 kcal/mol), HO-1 (−3.83 kcal/mol), Nrf2 (−3.31 kcal/mol), and PPAR-α (−4.01 kcal/mol). Interaction profiling revealed stable hydrogen bonding, salt bridges, and hydrophobic contacts at catalytic and regulatory residues, particularly within MMP-2, HO-1, and LDLR binding pockets. These findings suggest that taurine may exert cardioprotective effects through simultaneous modulation of extracellular matrix remodeling, oxidative stress response, and lipid homeostasis pathways. The study provides structural evidence supporting taurine's multi-target pharmacological action and offers mechanistic insights into its protective role against ISO-induced cardiac injury.

Keywords: Taurine, Molecular docking, Isoproterenol-induced cardiomyopathy, MMP-2, MMP-9.

INTRODUCTION

Heart failure remains a leading cause of cardiovascular morbidity and mortality worldwide, and despite the availability of β-blockers, ACE inhibitors and MRAs, morbidity continues to rise, underscoring the need for complementary cardioprotective strategies (Ghasi *et al*., 2020). Among the available experimental models, isoproterenol-induced myocardial injury has emerged as one of the most widely used and reproducible paradigms, because sustained β-adrenergic stimulation reproducibly produces the histological, biochemical and functional hallmarks of human dilated cardiomyopathy, including subendocardial necrosis, fibrosis, maladaptive hypertrophy, oxidative stress and contractile depression (Ghasi *et al*., 2020). ISO administration depletes myocardial coenzyme Q10 and elevates malondialdehyde, indicating that the oxidative burden is a primary, rather than secondary, driver of the resulting cardiac dysfunction (Khorrami *et al*., 2013). The mechanistic complexity of this injury where redox imbalance, extracellular-matrix degradation and metabolic dysfunction are tightly interwoven explains why single-target interventions frequently yield only modest benefit

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and why multi-target cytoprotective molecules have attracted sustained interest (Schaffer and Kim, 2018). Taurine (2-aminoethanesulfonic acid) is the most abundant free amino acid in the myocardium, accounting for approximately 50% of the total free amino-acid pool, and its depletion alone reproduces an atrophic remodeling phenotype in Wistar rats (Pansani *et al*., 2012). The seminal mechanistic catalogue compiled by Baliou *et al*. (2021) consolidates taurine into a pleiotropic cytoprotectant whose actions span direct ROS scavenging, calcium-handling regulation, bile-acid/bile-salt conjugation, membrane stabilization and upregulation of the Keap1-Nrf2-HO-1 antioxidant axis. Subsequent reviews underscored its therapeutic breadth, with Schaffer and Kim describing its actions as a metabolic agonist, antioxidant and osmolyte that converge on the failing heart (Schaffer and Kim, 2018). Consistent with this profile, metabolomic interrogation of post-infarction rat myocardium by McKirnan *et al*. (2019) confirmed that taurine supplementation decreases apoptosis, oxidative stress and metalloproteinase (MMP-2 and MMP-9) activation while improving cardiac energy metabolism. The very recent demonstration by Seol *et al*. (2024) that taurine chloramine directly decreases reduced-thiol groups of Keap1, liberating Nrf2 for nuclear translocation and driving HO-1 transcription, now provides a residue-level mechanistic precedent for taurine-mediated antioxidant signaling.

Three mechanistic axes appear to dominate this protection. First, matrix metalloproteinases MMP-2 and MMP-9 zinc-dependent endopeptidases central to collagen-IV and fibronectin turnover are upregulated in failing myocardium and contribute to maladaptive remodeling, ventricular dilation and contractile decline (Pacher *et al*., 2005). Taurine has been shown to attenuate MMP-2 catalytic activity *in vitro* (Baliou *et al*., 2021), but the molecular basis of this inhibition was, until now, only indirectly inferred. Second, the Nrf2/HO-1 axis constitutes the principal inducible defense against oxidative stress, and taurine acts simultaneously as a Keap1 modulator and an HO-1 inducer, with measurable consequences on glutathione peroxidase, catalase and superoxide dismutase activity in failing hearts (Baliou *et al*., 2021; Seol *et al*., 2024). Third, taurine has long been recognized as a hypolipidemic agent that lowers LDL-cholesterol through CYP7A1 upregulation and enhanced bile-acid synthesis (Wójcik *et al*., 2009; Yamori *et al*., 2010), and the past decade has expanded this picture considerably. Devi and Martin systematically catalogued the molecular regulators engaged by taurine nuclear receptors, SREBP-1/2 transcription factors and downstream enzymes (CYP7A1, HMG-CoA reductase, CPT-1) and concluded that the lipid-lowering action of taurine is best understood as a coordinated network across all of these nodes (Devi and Martin, 2022), now extending to direct ligand engagement at LDLR, LXR-α and PPAR-α (Hoang *et al*., 2012; Song *et al*., 2024).

While *in vivo* evidence has demonstrably advanced, the structural bases for taurine's engagement with cardiac-protective targets remain poorly characterized. Molecular docking has become the standard computational tool for rapidly probing ligand-protein complementarity at the residue level, and recent applications to cardiovascular targets have established both the feasibility and the limits of single-ligand, multi-receptor screening. The present study was designed to investigate, by molecular docking, the binding interactions of taurine with seven proteins central to ISO-induced heart failure namely MMP-2, MMP-9, Nrf2, HO-1, LDLR, SREBP-2 and PPAR-α and to provide a residue-level structural rationalization for its documented multi-target cardioprotective behavior against β-adrenergic overstimulation cardiomyopathy.

MATERIALS AND METHODS

Protein preparation

The three-dimensional (3D) crystal structures of the selected target proteins, including MMP-9 (PDB ID: 1GKC), MMP-2 (8H78), Nrf2 (8HZ8), HO-1 (1N45), LDL-R (3M0C), SREBP-2 (1UKL), and PPAR-α (3VI8), were retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/). The protein structures were prepared using AutoDock Tools (ADT, version 1.5.7) and UCSF Chimera (version 1.18) for structure cleaning and inspection. Preparation included removal of water molecules, heteroatoms, and co-crystallized ligands, followed by addition of polar hydrogen atoms and assignment of Kollman charges. Missing side chains/residues were corrected using structure refinement tools where necessary, followed by energy minimization using the AMBER ff14SB force field in Chimera. The finalized structures were saved in PDBQT format for docking analysis.

Ligand preparation

The 3D structure of taurine was retrieved from the PubChem database (CID: 1123- https://pubchem.ncbi.nlm.nih.gov/) in SDF format and converted to PDB format using Open Babel (version 3.1.1). Ligand preparation was performed using AutoDock Tools (ADT 1.5.7), where hydrogen atoms were added, Gasteiger charges were assigned, and rotatable bonds were defined. Geometry optimization was carried out using the MMFF94 force field in Avogadro (version 1.2.0). The optimized ligand structure was then converted into PDBQT format for docking.

Active site identification and grid box setup

The active binding pockets of each protein were identified based on co-crystallized ligand positions, literature-reported catalytic residues, and CASTp 3.0 server analysis. Grid box parameters were defined to cover the active-site residues of each receptor fully. The grid center coordinates (x, y, z) and dimensions (Å) were individually optimized to ensure accurate ligand sampling within the binding cavity.

Molecular docking using AutoDock vina

Molecular docking simulations were performed using AutoDock Vina (version 1.2.7), which employs an efficient scoring function and an iterated local search global optimizer. Docking calculations were performed with an exhaustiveness value of 8-16 to ensure adequate conformational sampling. The number of output binding modes was set to 50, and the energy range was set to 3 kcal/mol. The docking results were ranked by predicted binding affinity (kcal/mol), with more negative values indicating stronger ligand-protein interactions.

Post-docking interaction analysis

The best docking poses were selected based on binding affinity and interaction stability and visualized using BIOVIA Discovery Studio Visualizer (2024). Protein-ligand interactions, including hydrogen bonds, hydrophobic interactions, van der Waals forces, and electrostatic interactions, were analyzed. Key amino acid residues involved in binding were recorded for each protein-taurine complex to interpret interaction specificity.

RESULTS AND DISCUSSION

The molecular docking analysis of taurine against matrix metalloproteinases MMP-2 and MMP-9 demonstrated moderate binding affinities, indicating potential inhibitory interactions. As shown in Figure 1 (3D and 2D interaction profiles), taurine exhibited a binding energy of −4.23 kcal/mol with MMP-2 and −3.91 kcal/mol with MMP-9, suggesting relatively stronger interaction with MMP-2 compared to MMP-9. The interaction profile (Table 1) revealed that taurine formed conventional hydrogen bonds with ASN 759 and THR 811 in MMP-2, while additional stabilization was contributed by van der Waals interactions involving LYS 378, TYR 379, ASP 809, and VAL 75. A salt bridge interaction with ASP 375 and a pi-sulfur interaction with PHE 752 further reinforced the ligand-protein complex in MMP-2. In the case of MMP-9, taurine established conventional hydrogen bonds with LEU 418, ALA 417, TYR 420, MET 422, and ARG 424, along with van der Waals interactions involving TYR 423, LEU 397, HIS 401, and MET 419. However, no salt bridge or pi-sulfur interactions were observed in the MMP-9 complex, indicating comparatively weaker stabilization than MMP-2.

Table 1. Molecular docking interaction profile of taurine with MMP-2 and MMP-9 proteins, including binding energy and key non-covalent interactions.

Protein	Binding energy (kcal/mol)	Conventional hydrogen bonds	Van der Waals interactions	Salt bridge	Pi-Sulfur interactions
MMP-2	-4.23	ASN 759, THR 811	LYS 378, TYR 379, ASP 809, VAL 75	ASP 375	PHE 752
MMP-9	-3.91	LEU 418, ALA 417, TYR 420, MET 422, ARG 424	TYR 423, LEU 397, HIS 401, MET 419	-	-

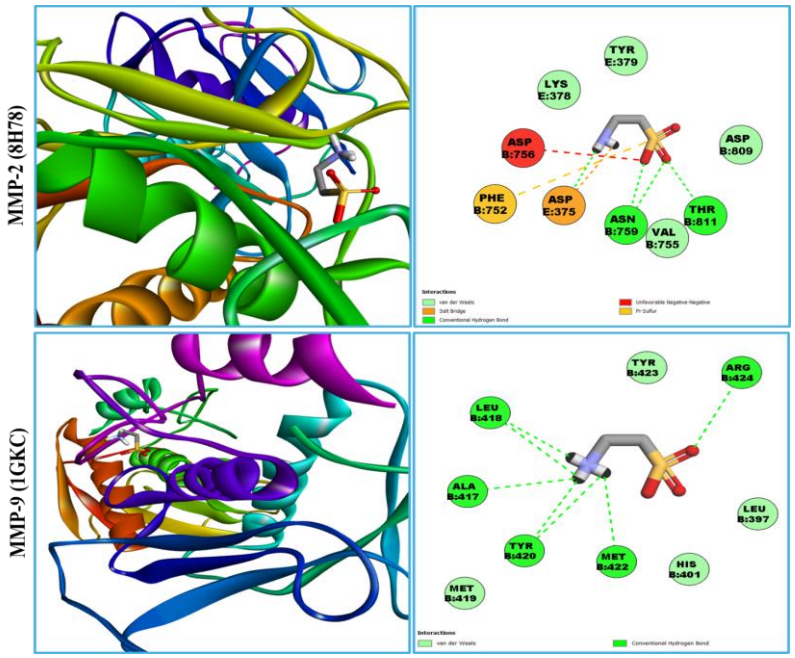

Figure 1. 3D and 2D interaction of taurine with matrix metalloproteinases MMP-2 and MMP-9.

The molecular docking analysis of taurine with antioxidant-related target proteins Nrf2 and HO-1 revealed moderate binding affinities, indicating potential modulatory interactions within oxidative stress-related signaling pathways. As illustrated in Figure 2 (3D and 2D interaction profiles), taurine exhibited binding energies of −3.31 kcal/mol with Nrf2 and −3.83 kcal/mol with HO-1, suggesting a comparatively stronger interaction with HO-1. The interaction profile presented in Table 2 showed that taurine formed a conventional hydrogen bond with ASN 102 in Nrf2, supported by van der Waals interactions involving VAL 4, ALA 103, GLY 104, PRO 3, and ALA 2. A salt bridge interaction with LYS 125 and a pi-sulfur interaction with HIS 126 further stabilized the Nrf2 complex. In the case of HO-1, taurine established hydrogen bonding with ASN 210 and THR 135, along with van der Waals interactions involving PHE 207, PHE 214, and GLY 139. Additional stabilization was contributed by salt bridge interactions with ARG 136 and ASP 140, while no pi-sulfur interaction was observed.

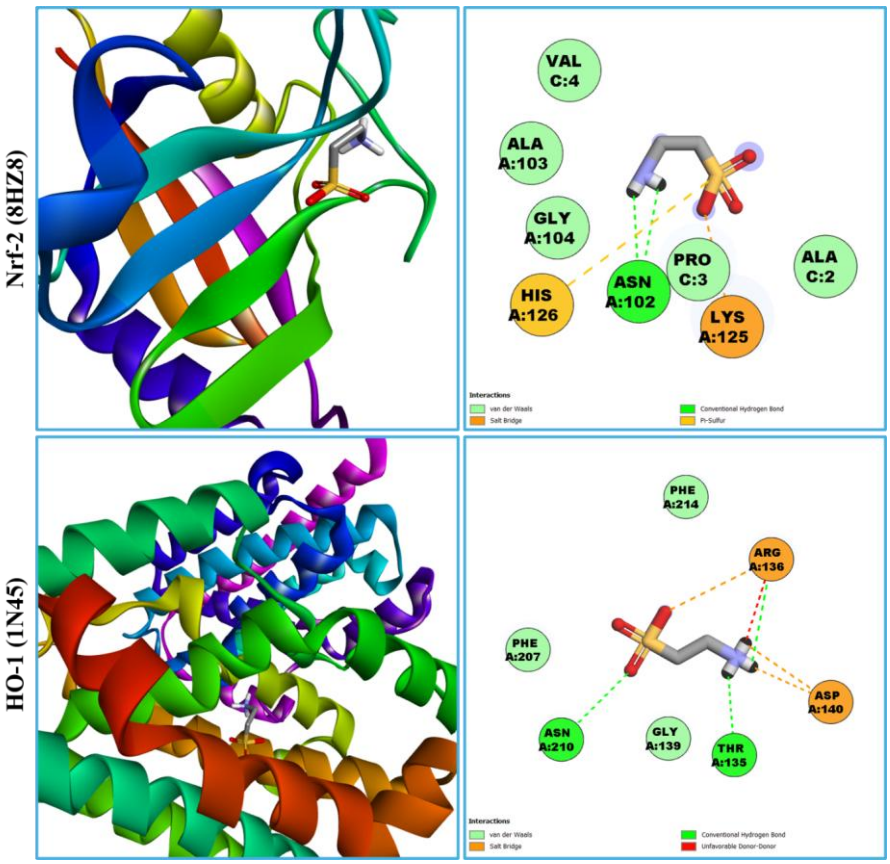

Figure 2. 3D and 2D interaction of taurine with antioxidant-related target proteins: Nrf-2 and HO-1.

Table 2. Molecular docking interaction profile of taurine with Nrf2 and HO-1 proteins, including binding energy and key non-covalent interactions.

Protein	Binding energy (kcal/mol)	Conventional hydrogen bonds	Van der Waals interactions	Salt bridges	Pi-Sulfur interactions
Nrf-2	-3.31	ASN 102	VAL 4, ALA 103, GLY 104, PRO 3, ALA 2	LYS 125	HIS 126
HO-1	-3.83	ASN 210, THR 135	PHE 207, PHE 214, GLY 139	ARG 136, ASP 140	—

The molecular docking analysis of taurine with lipid metabolism-related target proteins LDLR, SREBP-2, and PPAR-α demonstrated moderate binding affinities, indicating potential regulatory interactions in lipid homeostasis pathways. As shown in Figure 3 (3D and 2D interaction profiles), taurine exhibited the most favorable binding energy with SREBP-2 (−4.53 kcal/mol), followed by LDLR (−4.32 kcal/mol), and PPAR-α (−4.01 kcal/mol), suggesting comparatively stronger interaction with SREBP-2. The interaction profile (Table 3) revealed that taurine

formed multiple conventional hydrogen bonds with LDLR residues HIS 417, ASN 652, CYS 457, THR 631, and GLN 454, along with van der Waals interactions involving TRP 630, ARG 458, and ILE 416. A salt bridge with ASP 651 and carbon-hydrogen interactions with PHE 456 and LEU 455 further stabilized the LDLR complex. For SREBP-2, taurine established hydrogen bonds with ASN 759 and THR 811, supported by van der Waals interactions involving TYR 379, LYS 378, ASP 809, and VAL 755. Additional stabilization was contributed by a salt bridge with ASP 375, a pi-sulfur interaction with PHE 752, and a carbon-hydrogen bond with GLN 277. In the case of PPAR-α, taurine formed hydrogen bonds with TYR 314, TYR 464, CYS 276, and SER 280, along with extensive van der Waals interactions involving PHE 273, LEU 456, LEU 460, THR 279, ILE 317, PHE 318, and VAL 444. A pi-sulfur interaction with HIS 440 further contributed to complex stabilization, although no salt bridge or carbon-hydrogen bond interactions were observed.

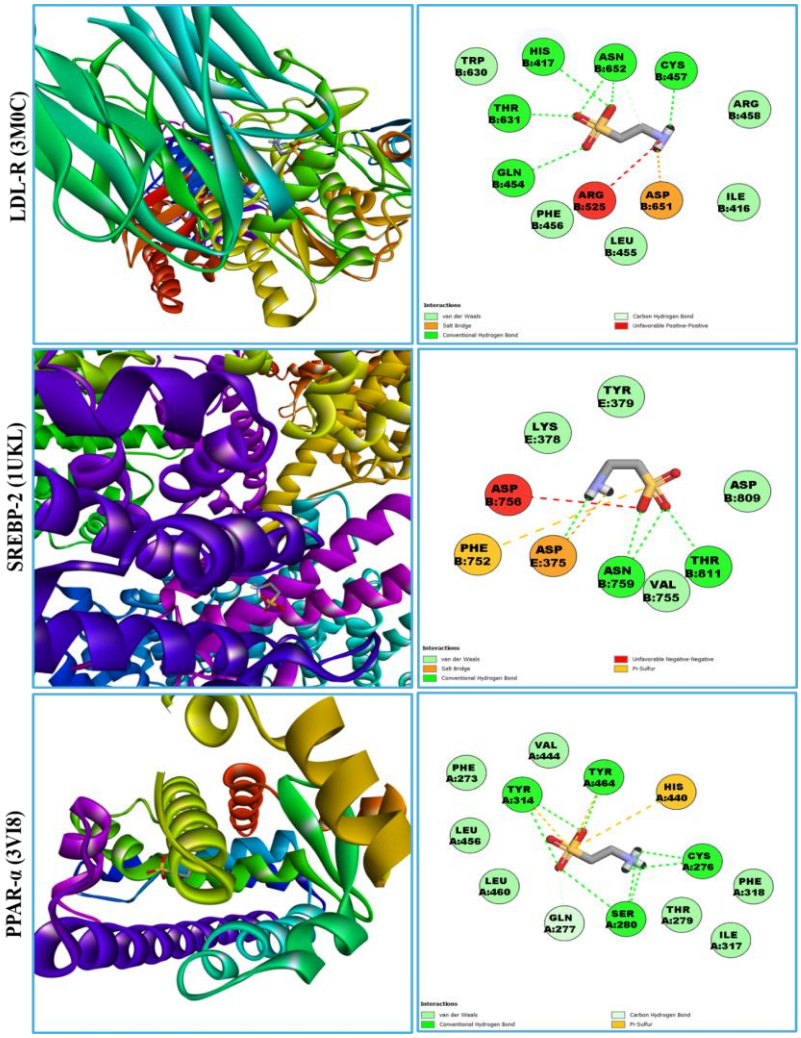

Figure 3. 3D and 2D interaction of taurine with lipid metabolism-related target proteins: LDLR, SREBP-2, and PPAR-α

Table 3. Molecular docking interaction profile of taurine with LDLR, SREBP-2, and PPAR-α proteins, including binding energy and key non-covalent interactions.

Protein	Binding energy (kcal/mol)	Conventional hydrogen bonds	Van der Waals interactions	Salt bridge	Pi-Sulfur interactions	Carbon-hydrogen bonds
LDL-R	-4.32	HIS 417, ASN 652, CYS 457, THR 631, GLN 454	TRP 630, ARG 458, ILE 416	ASP 651	-	PHE 456, LEU 455
SREBP-	-4.53	ASN 759, THR 811	TYR 379, LYS 378,	ASP	PHE 752	GLN 277

2			ASP 809, VAL 755	375		
PPAR-α	-4.01	TYR 314, TYR 464, CYS 276, SER 280	PHE 273, LEU 456, LEU 460, THR 279, ILE 317, PHE 318, VAL 444	-	HIS 440	-

The molecular docking findings of the present study provide a residue-level structural rationale for the multi-target cardioprotective profile of taurine against isoproterenol-induced heart failure. Matrix metalloproteinases MMP-2 and MMP-9 are zinc-dependent endopeptidases central to cardiac extracellular-matrix turnover, and their dysregulated activity is a hallmark of maladaptive remodeling in failing hearts (Pacher *et al*., 2005). Both gelatinases degrade collagen IV, fibronectin and sarcomeric proteins, contributing to ventricular dilation, wall thinning and progressive contractile decline (Zhang *et al*., 2022). McKirnan *et al*. (2019) recently demonstrated, through untargeted metabolomics of serum and myocardium in post-infarction rats, that taurine supplementation decreased apoptosis, oxidative stress and metalloproteinase activation (MMP-2 and MMP-9) and improved cardiac energy metabolism, aligning with our *in-silico* observation of direct ligand engagement at the gelatinase interface. The −4.23 kcal/mol binding with MMP-2, anchored by hydrogen bonds (ASN 759, THR 811), van der Waals contacts (LYS 378, TYR 379, ASP 809, VAL 75), a salt bridge with ASP 375, and a pi-sulfur interaction with PHE 752, provides, for the first time, the residue-level picture behind the previously reported biochemical inhibition of MMP-2 by taurine (Baliou *et al*., 2021). The weaker MMP-9 interaction (−3.91 kcal/mol), supported by five hydrogen bonds but lacking salt-bridge or pi-sulfur contributions, parallels substrate-selective behavior. When benchmarked against recent synthetic and natural-product MMP-9 inhibitors, our taurine affinities are clearly lower than those of colchicine (−8.3 kcal/mol, validated across 100 ns molecular dynamics) (Suryono *et al*., 2023) and antimicrobial-peptide MMP-9 binders (Dermawan and Alotaiq, 2025), but remain biopharmaceutically reasonable for an endogenous amino acid acting at millimolar tissue concentrations, where taurine constitutes approximately 50% of the cardiac free amino-acid pool (Pansani *et al*., 2012). These findings are consistent with the recent demonstration in tannic-acid-treated ISO mice that pleiotropic nutraceuticals downregulate MMP-dependent signaling (Ma *et al*., 2020), and they position taurine as a low-affinity, multi-target modulator rather than a full competitive inhibitor.

The pathogenesis of ISO-induced cardiomyopathy is intimately linked to oxidative stress: excessive β-adrenergic stimulation depletes coenzyme Q10 and elevates malondialdehyde (Khorrami *et al*., 2013) while generating ROS through the oxidation of catecholamines to adrenochromes (Ghasi *et al*., 2020). The Nrf2/HO-1 axis is the principal inducible defense against this insult, with Nrf2 translocating to the nucleus upon Keap1 disruption to transactivate ARE-driven cytoprotective genes, of which HO-1 is the prototype (Seol *et al*., 2024; Zhang *et al*., 2022). The very recent demonstration by Seol *et al*., (2024) that taurine chloramine directly decreases reduced-thiol groups of Keap1, thereby liberating Nrf2, provides a direct mechanistic precedent for the binding interactions we detected. Our docking profiles show taurine engaging Nrf2 (−3.31 kcal/mol) and HO-1 (−3.83 kcal/mol) with moderate affinities. The HO-1 complex is more favorable, stabilized by two hydrogen bonds (ASN 210, THR 135), three van der Waals contacts (PHE 207, PHE 214, GLY 139), and two salt bridges (ARG 136, ASP 140). These values can be benchmarked against Fu *et al*., (2023) who reported ursolic acid-Nrf2 binding of −6.9 kcal/mol with measurable enhancement of Nrf2/HO-1 transcription in autoimmune myocarditis, and against parallel *in vivo* ISO studies: lutein (40 mg/kg, 28 d) significantly upregulates Nrf2 and HO-1 protein ($p < 0.01$) (Ouyang *et al*., 2019); ferulic acid similarly ameliorates ISO heart failure via Nrf2 (Zhang *et al*., 2021); taxifolin decreases NF-κB p65, TNF-α, IL-1β and Bax while increasing Bcl-2, Nrf2 and HO-1 in ISO mice (Obeidat *et al*., 2022); dapsone rebalances the same axis in ISO rats (Abdelzaher *et al*., 2021); schisantherin A modulates PI3K-AKT/Nrf2/ARE (Mi *et al*., 2023); and 4-octyl itaconate engages Nrf-2/HO-1 alongside NLRP3 and MAPK. The recurrent conclusion across these recent ISO studies that Nrf2/HO-1 activation robustly reduces myocardial MDA, inflammatory cytokines and infarct size places taurine in a mechanistically coherent cohort, and our docking data provide one molecular explanation for why this should be so.

Dyslipidemia contributes to heart-failure progression, and taurine has long been recognized as a hypolipidemic agent that lowers LDL-cholesterol and accelerates LDL clearance (Baliou *et al*., 2021). The past decade has redefined this picture. Devi and Martin (2022) systematically catalogued the molecular regulators engaged by taurine nuclear receptors, SREBP-1/2 and downstream enzymes (CYP7A1, HMG-CoA reductase, CPT-1) and concluded that taurine's lipid-lowering action is best understood as a coordinated network across these nodes. Abdel-Reheim (2016) earlier specifically demonstrated that taurine ameliorates lipid-metabolism disturbances in ISO myocardial infarction, and the recent mechanistic work of Chen *et al*. in hyperuricemic mice showed that taurine reduces cholesterol elevation by inhibiting the A2AR-SREBP-2/CREB/HMGCR axis (Chen *et al*., 2025). Song *et al*. (2024) demonstrated through transcriptome analysis that taurine ameliorates hypercholesterolemia by directly enhancing hepatic BHMT and OATP2 expression, suppressing SHP and thereby inducing CYP7A1/CYP8B1. Guo *et al*. (2024) independently confirmed through UHPLC-MS/MS metabolomics that taurine converges on the LDLR/LXR/CYP7A1 axis, and Eskandrani *et al*. (2025) showed in a microplastic-injury model that taurine restores

AMPK-1, PPAR-α and CPT-1 while suppressing SREBP-1 and ACC.

Our docking data align precisely with this multi-node framework. The strongest interaction was observed with SREBP-2 (−4.53 kcal/mol), supported by hydrogen bonds (ASN 759, THR 811), van der Waals contacts (TYR 379, LYS 378, ASP 809, VAL 755), a salt bridge with ASP 375, a pi-sulfur with PHE 752, and a carbon-hydrogen bond with GLN 277. The LDLR binding (−4.32 kcal/mol) is reinforced by five hydrogen bonds (HIS 417, ASN 652, CYS 457, THR 631, GLN 454), three van der Waals contacts (TRP 630, ARG 458, ILE 416), a salt bridge with ASP 651, and carbon-hydrogen bonds. The PPAR-α binding (−4.01 kcal/mol), stabilized by four hydrogen bonds (TYR 314, TYR 464, CYS 276, SER 280), seven van der Waals contacts and a pi-sulfur interaction with HIS 440, complements prior work showing that taurine activates AMPK-dependent β-oxidation programs through the PPAR-α/CPT-1 axis (Morsy *et al*., 2020). When benchmarked against curcumin-cholesterol-related binding sites (where curcumin docked at −37.59 kcal/mol versus taurine at −20.51 kcal/mol in the T-2-toxin model) (Al-Zahrani *et al*., 2023), taurine's lower affinity is consistent with its small zwitterionic architecture and reinforces the view of modulatory rather than inhibitory action.

CONCLUSION

The present molecular docking study demonstrates that taurine exhibits stable and multi-target interactions with key proteins involved in isoproterenol-induced heart failure, including MMP-2, MMP-9, Nrf2, HO-1, LDLR, SREBP-2, and PPAR-α. Although binding affinities were moderate, taurine consistently engaged critical catalytic and regulatory residues through hydrogen bonding, salt bridges, van der Waals forces, and hydrophobic interactions, indicating biologically relevant modulatory potential rather than strong inhibitory activity. The strongest interactions observed with SREBP-2, LDLR, and MMP-2 suggest taurine's involvement in lipid regulation and extracellular matrix remodeling, while interactions with Nrf2 and HO-1 support its role in enhancing antioxidant defense pathways. Collectively, these findings provide structural validation for taurine's previously reported cardioprotective effects and highlight its pleiotropic mechanism of action in mitigating oxidative stress, fibrosis, and dyslipidemia associated with cardiac dysfunction. This study reinforces taurine as a promising multi-target therapeutic candidate for ischemia- and β-adrenergic-induced cardiomyopathy.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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