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Research Article

MOLECULAR DOCKING ANALYSIS OF PROTOCATECHUIC ACID TARGETING MMPs, STRESS-RELATED AND APOPTOTIC PROTEINS ASSOCIATED WITH HEART FAILURE

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ABSTRACT

Heart failure (HF) remains a significant global health challenge, characterised by adverse ventricular remodelling, cardiomyocyte apoptosis, and elevated biomarkers such as B-type natriuretic peptide (BNP). Protocatechuic acid, a naturally occurring polyphenol, exhibits antioxidant and anti-apoptotic properties; however, its mechanistic effects in HF are not fully elucidated. Molecular docking analyses revealed strong binding affinities of protocatechuic acid with key apoptotic and stress-related proteins, including Bax, Bcl-2, Bcl-xL, Caspase-3, Caspase-9, Cytochrome c, and BNP, suggesting modulation of mitochondrial apoptosis and ventricular stress pathways. Protocatechuic acid also showed significant binding interactions with MMP-2 and MMP-9, indicating attenuation of extracellular matrix degradation and fibrotic remodelling. These findings demonstrate that protocatechuic acid exerts multi-target cardioprotective effects by modulating apoptotic signalling, reducing matrix metalloproteinase activity, and mitigating myocardial fibrosis, highlighting its therapeutic potential in HF management.

Keywords: Heart failure, Protocatechuic acid, Molecular docking, Apoptosis, MMP-2, MMP-9.

INTRODUCTION

Heart failure (HF) has emerged as a global pandemic and represents a major public health concern, currently affecting an estimated 64 million individuals worldwide (Savarese and Lund, 2017; Shahim *et al*., 2023). Despite substantial advances in therapeutic interventions, HF remains associated with high mortality rates, diminished quality of life, and considerable healthcare costs (Savarese and Lund, 2017; Savarese *et al*., 2022). Epidemiological studies report that the lifetime risk of developing HF is approximately one in five, highlighting its widespread impact, particularly among ageing populations (Bui *et al*., 2011). The clinical course of HF typically progresses from compensated cardiac stress to overt pump failure, driven by a complex interplay of hemodynamic overload, cardiomyocyte loss, and maladaptive structural remodelling (Shahim *et al*., 2023; Van Empel *et al*., 2005). A defining feature of HF progression is adverse ventricular remodelling, characterised by pathological alterations in the extracellular matrix. This process is primarily mediated by matrix metalloproteinases (MMPs), notably the gelatinases MMP-2 and MMP-9 (Nishikawa, 2003; Radosinska *et al*., 2017). Upregulation and enhanced activity of these enzymes contribute to the degradation of the myocardial basement membrane and collagen fibers, culminating in progressive ventricular dilation and wall thinning (Spinale, 2000; Ducharme *et al., 2000)*. Given their central role in chamber enlargement, therapeutic modulation of the myocardial MMP system is considered critical for controlling matrix remodelling and preserving cardiac function (Nishikawa, 2003; Spinale,2000).

Concomitantly, the persistent loss of functional cardiomyocytes through apoptosis significantly contributes to cardiac dysfunction (Van Empel *et al*., 2005; Foo *et al*., 2005). The intrinsic apoptotic pathway in HF is often initiated by mitochondrial impairment, leading to cytosolic release of cytochrome c and subsequent activation of caspase-3 (Zhou *et al*., 2021; Narula *et al*., 1999). This

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process is tightly regulated by the balance of Bcl-2 family proteins, wherein pro-apoptotic Bax promotes mitochondrial outer membrane permeabilization, and anti-apoptotic Bcl-2 maintains membrane integrity (Zhou *et al*., 2021; Saraste *et al*.,1999) Targeted inhibition of this apoptotic cascade is therefore pivotal in preventing irreversible myocardial damage (Van Empel *et al*., 2005; Narula *et al*., 1999).

Clinically, the severity of cardiac stress and risk of adverse outcomes are frequently assessed via plasma biomarkers, with B-type natriuretic peptide (BNP) being the most widely employed (Mueller *et al*.,2019). BNP is synthesized and secreted predominantly by the ventricles in response to increased wall stretch and volume overload (Maeder *et al*.,2010; Nyawo *et al*.,2022). Elevated BNP levels serve as sensitive indicators for HF diagnosis and prognostication (Mueller *et al*., 2019; Ruskoaho, 2003), making the reduction of mechanical and molecular stimuli that drive BNP expression a key therapeutic objective (Mueller *et al*., 2019).

In recent years, natural polyphenols have attracted attention as multi-target cardioprotective agents. Protocatechuic acid, a principal metabolite of anthocyanins and procyanidins, exhibits potent antioxidant, anti-inflammatory, and cardioprotective effects (Pozgajova *et al*., 2024; Masella *et al*., 2012). Evidence indicates that protocatechuic acid can attenuate cardiac hypertrophy and suppress Nppb gene expression, thereby mitigating HF development (Pozgajova *et al*., 2024; Bai *et al*., 2021). While its antioxidant and anti-apoptotic effects are established, the specific interactions of protocatechuic acid with stress-related proteins and its influence on MMP-mediated remodeling remain underexplored. Accordingly, the present study aims to investigate the cardioprotective potential of protocatechuic acid through molecular docking analysis to elucidate its mechanistic actions.

MATERIALS AND METHODS

Molecular Docking Analysis

Molecular docking studies were performed to evaluate the binding interactions of protocatechuic acid with selected apoptosis, and remodeling proteins, including Bax (PDB ID: 6EB6), Bcl-2 (8HTS), Bcl-xL (1R2D), Caspase-3 (2CJX), Caspase-9 (1JXQ), Cytochrome c (1HRC), BNP (1BND), MMP-2 (1RTG), and MMP-9 (1L6J). The three-dimensional structures of target proteins were retrieved from the Protein Data Bank, while the structure of protocatechuic acid was obtained from the PubChem database. Protein structures were prepared by removing water molecules, adding polar hydrogens, and assigning Kollman charges. The ligand was energy-minimized and optimized for protonation states prior to docking. Docking was performed using AutoDock Vina, with grid boxes defined to encompass the active sites of each protein. The binding energies, hydrogen bonding, van der Waals, and pi-based interactions were analyzed using Discovery Studio Visualizer.

RESULTS AND DISCUSSION

The molecular docking analysis of protocatechuic acid with selected target proteins demonstrated significant binding affinities and diverse interaction patterns, as presented in Table 1. The binding energies varied from −5.02 kcal/mol for Caspase-3 (2CJX) to −6.98 kcal/mol for BNP (1BND), indicating moderate to strong interactions. Protocatechuic acid formed van der Waals interactions with key residues in all proteins, such as GLY157, GLN18, ILE19, and LEU59 in Bax (6EB6); ASP34 and SER20 in Bcl-2 (8HTS); and ARG102, ARG103, GLY148, LYS16, LYS20, PHE105, SER145, TYR101, and VAL152 in Bcl-xL (1R2D). Conventional hydrogen bonding also contributed to the stability of these complexes, exemplified by interactions with ASP53, ASP159, THR56, and TRP158 in Bax, ARG98, LYS17, and SER24 in Bcl-2, and ALA104 in Bcl-xL. Additionally, certain residues participated in pi interactions, such as ALA104 (pi-sigma) and ALA149 (pi-alkyl) in Bcl-xL, highlighting the multifaceted nature of these molecular contacts. Caspase-3 and Caspase-9 displayed both hydrogen bonding and van der Waals contacts, with ARG147, SER104, ALA150, and ARG149 in Caspase-3, and ARG177, ASP505, and GLY238 in Caspase-9, indicating stable binding within the active sites. Cytochrome c (1HRC) and BNP (1BND) showed the strongest binding affinities, with −6.64 and −6.98 kcal/mol, respectively. Protocatechuic acid interacted with LYS8 and GLU90 via van der Waals forces and formed hydrogen bonds with ASP93, LYS5, and THR89 in Cytochrome c, while ILE9 and LYS5 contributed to pi-sigma and pi-alkyl interactions. Similarly, BNP established van der Waals contacts with ILE41, LYS42, and VAL97, hydrogen bonds with SER45 and THR43, and pi interactions with LEU89 and VAL44. Figures 1 and 2 represent the 3D and 2D interaction of protocatechuic acid with apoptosis and stress-related target proteins, respectively.

Table 1. Binding energy and amino acid interaction of target proteins with protocatechuic acid.

S. No	Protein (PDB ID)	Binding Energy	Van der Waals	Conventional Hydrogen Bond	Pi-sigma	Pi-Alkyl
1.	Bax (6EB6)	-5.51	GLY157, GLN18, ILE19, LEU59	ASP53, ASP159, THR56, TRP158	-	-
2.	Bcl-2 (8HTS)	-5.26	ASP34, SER20	ARG98, LYS17, SER24	-	-
3.	Bcl-xL (1R2D)	-5.73	ARG102, ARG103, GLY148, LYS16,	ALA104	ALA104	ALA149

			LYS20, PHE105, SER145, TYR101, VAL152			
4.	Caspase-3 (2CJX)	-5.02	GLU106, HIS108, LYS105	ARG147, SER104		ALA150, ARG149
5.	Caspase-9 (1JXQ)	-6.28	CYS239, CYS285, GLU288, GLY175C, TYR244	ARG177, ASP505, GLY238	LEU176	-
6.	Cytochrome c (1HRC)	-6.64	LYS8, GLU90	ASP93, LYS5, THR89	ILE9	LYS5
7.	BNP (1BND)	-6.98	ILE41, LYS42, VAL97	SER45, THR43	LEU89	VAL44

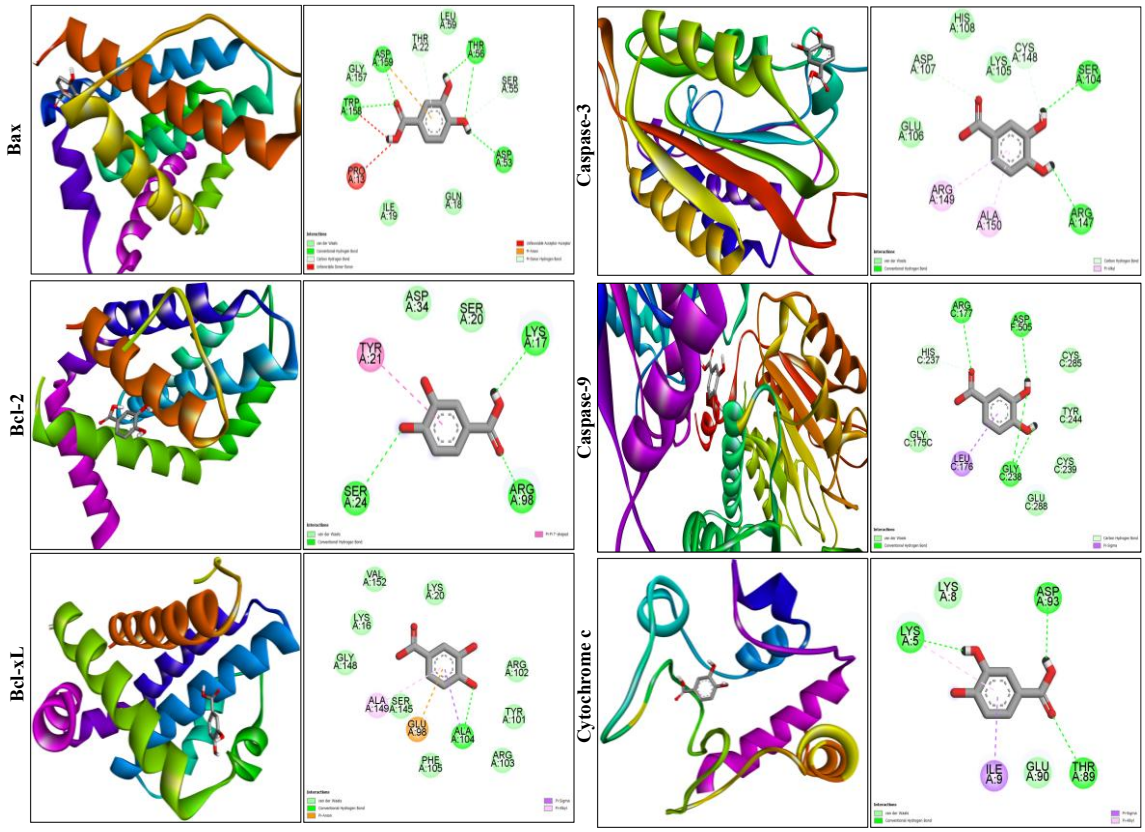

Figure 1. 3D and 2D interactions of apoptotic proteins with protocatechuic acid.

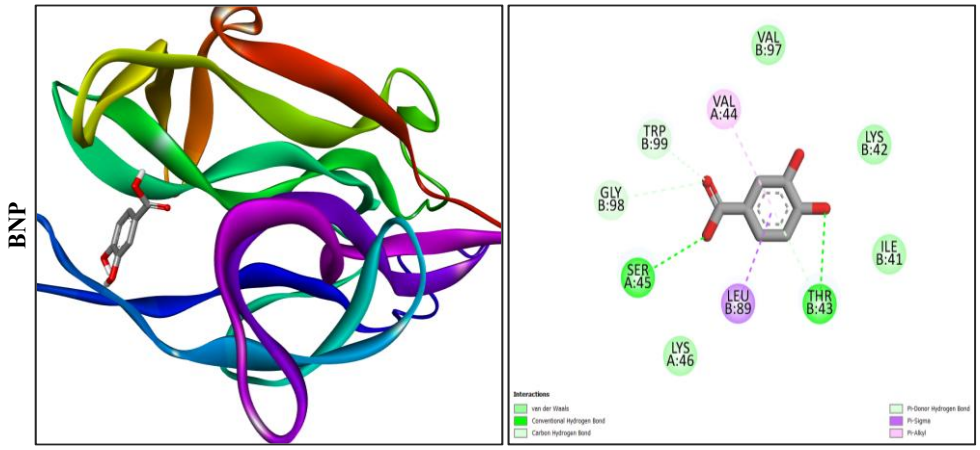

Figure 2. 3D and 2D interaction of BNP protein with protocatechuic acid.

The molecular docking analysis of protocatechuic acid with matrix metalloproteinases demonstrated strong binding affinities and stable interaction profiles, as presented in Table 2. Protocatechuic acid exhibited a binding energy of −6.38 kcal/mol with MMP-2 (1RTG) and −7.14 kcal/mol with MMP-9 (1L6J), indicating favorable molecular interactions with both remodeling-associated proteins. In MMP-2, protocatechuic acid formed van der Waals interactions with key residues including ILE481, ARG482, PHE486, and TRP513, while conventional hydrogen bonds were observed with SER546, ALA545, and GLU484, contributing to the stability of the protein–ligand complex. Additionally, an unfavorable donor–donor interaction was noted with ARG495, along with pi–pi stacked interaction involving PHE512, suggesting further stabilization within the active binding pocket. Similarly, MMP9 displayed the strongest binding affinity among all proteins analyzed. Protocatechuic acid established van der Waals interactions with GLN391, PHE425, SER394, PRO97, and ASP390, while conventional hydrogen bonding interactions were formed with GLY213, GLY392, TYR393, and TYR423. Pi–pi stacked interactions with TYR423 further enhanced ligand stabilization within the catalytic region of the protein. These interaction patterns indicate that protocatechuic acid may effectively modulate extracellular matrix remodeling by inhibiting MMP-mediated degradation processes associated with heart failure progression. Figure 3 represents the 3D and 2D interaction of protocatechuic acid with MMP-2 and MMP-9 proteins.

Table 2. Binding energy and amino acid interaction of MMP-2 and MMP-9 proteins with protocatechuic acid.

S.No	Protein (PDB ID)	Binding Energy	Van der Waals	Conventional Hydrogen Bond
1.	MMP-2 (1RTG)	-6.38	ILE481, ARG482, PHE486, TRP513	SER546, ALA545, GLU484
2.	MMP-9 (1L6J)	-7.14	GLN391, PHE425, SER394, PRO97, ASP390	GLY213, GLY392, TYR393, TYR423

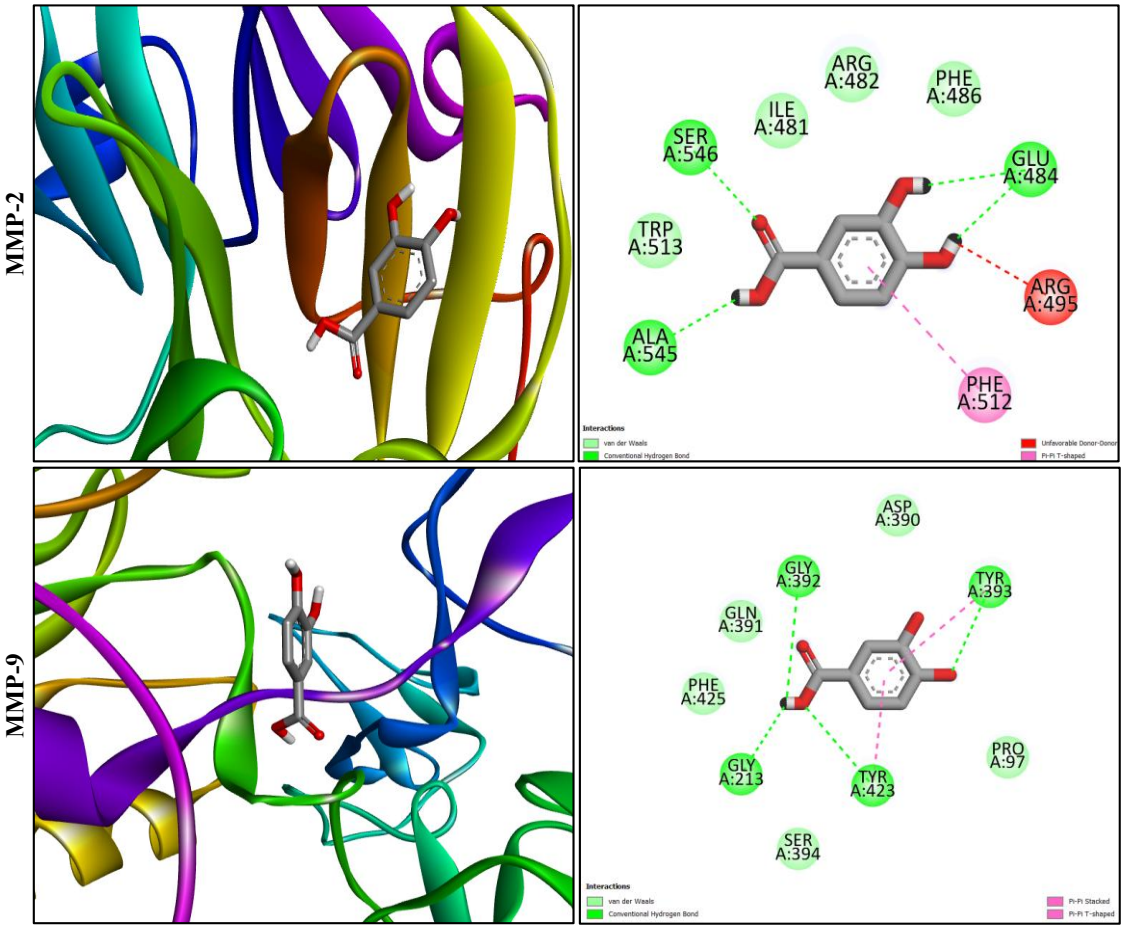

Figure 3. 3D and 2D interaction of MMP-2 and MMP-9 proteins with protocatechuic acid.

The present molecular docking study highlights the potential binding interactions of protocatechuic acid with several proteins implicated in heart failure progression. The observed binding affinities suggest that protocatechuic acid may modulate proteins associated with apoptotic signaling, stress responses, and maladaptive cardiac remodeling. Molecular docking analyses revealed that protocatechuic acid exhibits strong binding affinities toward several proteins central to the pathophysiology of heart failure. Notably, B-type Natriuretic Peptide (BNP; PDB ID: 1BND) demonstrated the highest affinity with protocatechuic acid (−6.98 kcal/mol). Clinically, BNP serves as a reliable biomarker of ventricular wall stress and pressure overload. The observed high binding energy suggests that protocatechuic acid may directly modulate pathways governing the heart's response to mechanical strain.

Similarly, protocatechuic acid displayed significant interaction with Cytochrome c (PDB ID: 1HRC; binding affinity −6.64 kcal/mol), a key regulator of mitochondrial-mediated apoptosis. The release of Cytochrome c into the cytosol initiates apoptosome assembly, promoting programmed cell death (Praveen *et al*., 2025). By potentially stabilizing mitochondrial Cytochrome c, protocatechuic acid contributes to the preservation of functional cardiomyocytes, which is essential for maintaining systolic performance (Tang *et al*., 2014). Heart failure progression is marked by cardiomyocyte loss via apoptosis. Protocatechuic acid exhibited stable interactions with members of the Bcl-2 family and executioner caspases, which act as critical regulators of cell survival. Specifically, Bax, Bcl-2, and Bcl-xL control mitochondrial membrane permeability, with Bax promoting pore formation and Bcl-2/Bcl-xL maintaining membrane integrity. Protocatechuic acid formed stable complexes with these proteins, notably through hydrogen bonding with ASP53 in Bax and ARG98 in Bcl-2. Previous investigations corroborate that protocatechuic acid attenuates myocardial injury by decreasing Bax expression while enhancing Bcl-2 levels, thereby inhibiting progression toward heart failure (Tang *et al*., 2014; Li *et al*., 2023). Furthermore, protocatechuic acid interacts with Caspase-3 and Caspase-9, the executioner and initiator caspases of the apoptotic cascade, respectively. By binding to active sites such as ARG147 in Caspase-3, protocatechuic acid aligns with its documented ability to reduce caspase activity in failing hearts, preventing excessive cardiomyocyte loss (Li *et al*., 2023). Adverse ventricular remodeling, a hallmark of heart failure progression, is largely mediated by MMPs. Protocatechuic acid showed strong binding interactions with MMP-2 and MMP-9, gelatinases responsible for extracellular matrix degradation. Inhibition of these enzymes has been shown to decrease left ventricular end-diastolic pressure and enhance the maximal rate of pressure rise (+dP/dt_max), thus improving cardiac contractility (Li *et al*., 2023; Song *et al*., 2008). Excessive collagen accumulation contributes to myocardial stiffness and impaired diastolic filling. The anti-fibrotic effect of protocatechuic acid is associated with the downregulation of fibrotic genes such as Col1a1 and Col1a2, likely mediated through inhibition of the NOX4/ROS/p38 signaling pathway a key driver of fibroblast-to-myofibroblast transformation and collagen synthesis (Bai *et al*., 2023; Song and Ren, 2019). By preserving myocardial architecture, protocatechuic acid effectively slows the progression of cardiac dysfunction in heart failure.

CONCLUSION

Protocatechuic acid demonstrated favorable binding interactions with key apoptotic, stress-related, and remodeling proteins associated with heart failure, including Bax, Bcl-2, Caspase-3, Caspase-9, BNP, MMP-2, and MMP-9. The observed molecular docking results suggest the potential of protocatechuic acid to interact with pathways involved in apoptosis, mitochondrial stress responses, and extracellular matrix remodeling. These molecular docking findings suggest the potential of protocatechuic acid as a promising multi-target molecule associated with proteins involved in heart failure-related pathways.

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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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