

ORIGINAL ARTICLE

Mechanisms of Myocardial Damage and Structural Remodeling Caused by Doxorubicin-Triggered NF- κ B Modulation

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ABSTRACT

Myocardial ischaemia reperfusion (I/R) injury remains a critical challenge in cardiovascular therapy, particularly in patients receiving anthracycline chemotherapy. Doxorubicin, though highly effective as an anticancer agent, is limited by its cardiotoxic effects that are exacerbated during I/R events. Nuclear factor-kappa B (NF- κ B), a key transcription factor regulating inflammation and apoptosis, is strongly implicated in this dual-insult mechanism. In this *in-silico* study, molecular docking and structural analyses were performed to evaluate the interaction between doxorubicin and NF- κ B, and to assess the resulting conformational and physicochemical changes. Docking simulations revealed nine binding modes, with Mode-1 showing the strongest affinity (-8.5 kcal/mol), stabilized by hydrogen bonds, van der Waals forces, and hydrophobic interactions. Hydrophobicity and isotropic displacement analyses demonstrated that doxorubicin binding introduced marked fluctuations and enhanced protein flexibility, leading to structural destabilization. Ramachandran plot evaluation further confirmed significant loss of residues in favorable conformational regions,

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suggesting impaired folding. Visualization of NF- κ B under drug exposure revealed increased intensity and altered spatial distribution, indicative of enhanced activation. Collectively, these findings suggest that doxorubicin modulates NF- κ B through strong binding and structural perturbation, thereby amplifying myocardial injury mechanisms. The study provides molecular insights into cardiotoxicity and identifies NF- κ B as a potential target for cardioprotective interventions.

KEYWORDS

- NF- κ B • Doxorubicin • Ischaemia-reperfusion injury • Hydrophobicity
- Myocardial injury

INTRODUCTION

Acute ischaemia-reperfusion (I/R) injury in the myocardium remains a major challenge in the treatment of cardiovascular diseases, particularly during interventions such as thrombolysis or coronary angioplasty.¹ While restoring blood flow to the heart is essential for limiting infarct size and preserving cardiac function, the sudden reintroduction of oxygen and nutrients can paradoxically lead to additional tissue damage.² This injury is driven by complex cellular and molecular processes, among which inflammation plays a critical role.³

Doxorubicin, a widely used chemotherapeutic agent, has proven effective in treating various malignancies, yet its clinical application is often limited by its cardiotoxic effects.⁴⁻⁶ One of the major concerns associated with doxorubicin therapy is the increased risk of myocardial injury, which may be further aggravated during episodes of ischaemia followed by reperfusion.^{7,8} The interplay between drug-induced cardiotoxicity and acute I/R injury represents a significant area of interest in cardiovascular research, as it involves both direct cellular damage and complex inflammatory responses.

Among the key molecular regulators implicated in this process, nuclear factor-kappa B (NF- κ B) stands out as a central player. NF- κ B is a transcription factor that becomes activated in response to cellular stress, oxidative damage, and pro-inflammatory signals all of which are elevated in the setting of doxorubicin exposure and I/R injury.⁹⁻¹¹ Once activated, NF- κ B modulates the expression of numerous genes involved in inflammation, apoptosis, and immune signaling, potentially

amplifying myocardial damage and impairing recovery.¹² In recent years, there has been growing interest in the use of antioxidants, vitamins, and plant-derived compounds for their potential to protect different organs and tissues including heart from different injuries and complications by preserving redox balance.¹³⁻¹⁹ Several naturally occurring substances, such as folic acid, vitamins B12, C, and E, along with trace elements like selenium, have been widely studied for their strong antioxidant properties.²⁰⁻²⁵ These compounds function as effective scavengers of free radicals, helping to shield cellular structures particularly membranes from oxidative stress and related damage.

So, understanding how NF- κ B is activated in the context of doxorubicin-induced I/R injury could shed light on critical pathways involved in cardiotoxicity and reveal targets for therapeutic intervention. This *in-silico* study aims to explore the mechanisms by which NF- κ B contributes to myocardial injury in this dual-insult model and to assess its potential as a target for cardioprotective strategies.

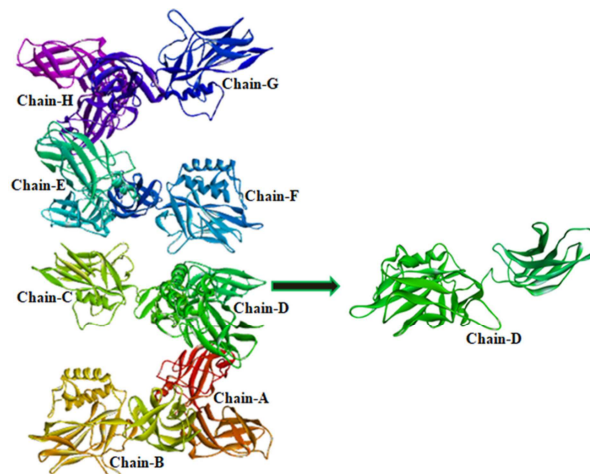


Figure 1: Nuclear factor-kappa B (NF- κ B) protein

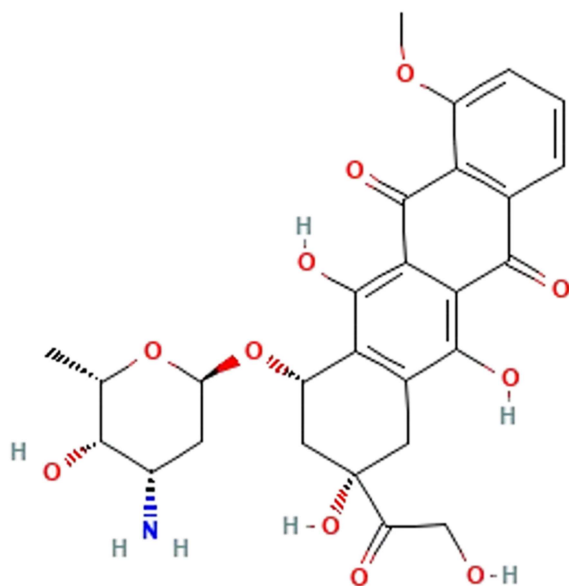


Figure 2: Doxorubicin (PubChem CID 31703)

MATERIALS AND METHODS

Materials

Both the receptor and ligand files are used in this study for the analysis of molecular docking outcomes. The three-dimensional crystal structure of NF-κB (PDB ID: 3GUT) was obtained from the Protein Data Bank (<https://www.rcsb.org>). As a stress producing ligand, doxorubicin (CID: 31703) was achieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov>).

Methods

Selection of Target Protein and Ligand

Nuclear factor-kappa B (NF-κB) was chosen as the target protein in this study because of its well-recognized role in regulating inflammatory processes. Doxorubicin was selected as the ligand, as it is commonly associated with the induction of myocardial injury.

Protein and ligand Preparation

For the process of molecular docking simulations, both the receptor (protein) and the ligand were carefully arranged in advance. The NF-κB receptor protein structure was retrieved from the RCSB Protein Data Bank in PDB format. Its native ligand and the A, B, C, E, F, G and H chains were detached from the receptor by using BIOVIA Discovery Studio, and then the receptor structure was

saved for more one time in PDB format for the analysis process. The doxorubicin ligand, was downloaded from the PubChem in 3D SDF file format and consequently transformed into PDB format utilization of Open Babel software.

Before the starting of molecular docking, all molecules were processed in AutoDock Tools. In this step of analysis, all water molecules were removed, polar hydrogen atoms and charges were added to make sure the exact depiction of molecular interactions. Then the preprocessed structures were saved in PDBQT format, which is essential for utilize in AutoDock. This methodical preparation of both the receptor and ligand is very critical to maintain the accuracy, reliability, and consistency during the docking simulations.

Software and Tools Used

The computational workflow was carried out using Discovery Studio, OpenBabel, and PyRx. Discovery Studio facilitated protein preparation and visualization of molecular interactions, OpenBabel was used for ligand format conversion, and PyRx (integrating AutoDock Vina) was employed for docking simulations and binding affinity estimation.

Docking Procedure and Interaction Analysis

Molecular docking was performed with the ligand-free NF-κB structure. Among the 8 (eight) chains namely A, B, C, D, E, F, G and H, only chain D is selected for the study and the rest chains are removed. Then the water molecule of the protein is removed and then polar hydrogen is added to the chain and finally the NF-κB protein is prepared for docking. Before the onset of molecular docking the protein is selected as macromolecule and doxorubicin is selected as ligand in PyRx, where the energy of the ligand is minimized.

Then, a grid box of dimensions 51.996 Å × 100.274 Å × 47.084 Å was defined around the active site, with a cluster radius of 1 Å was created in the PyRx display. The docking simulations were executed using the default parameters of AutoDock Vina.²⁶

The binding free energy (ΔG) was calculated as a combination of several interaction terms:

$$\Delta G = \Delta G_{\text{vdW}} + \Delta G_{\text{Hbond}} + \Delta G_{\text{elec}} + \Delta G_{\text{tor}} + \Delta G_{\text{desolv}}$$

ΔG_{vdW} denotes the Van der Waals contribution to the docking energy, while ΔG_{Hbond} reflects

the energy derived from hydrogen bonding. Similarly, ΔG_{elec} represents the electrostatic interaction energy. The parameter ΔG_{tor} accounts for the torsional free energy, which arises from the conformational transition of the ligand between its unbound and bound states. In addition, ΔG_{desolv} corresponds to the desolvation energy.²⁷ To further investigate receptor-ligand binding, Discovery Studio Visualizer 2021 was employed to identify and analyze non-covalent interactions such as π -lone pair, π -alkyl, π - π stacking, and π - π T-shaped stacking interactions between doxorubicin and the amino acid residues of the NF- κ B active site.

RESULTS AND DISCUSSION

Table 1: Docking Analysis of Doxorubicin with NF- κ B

Modes of Binding	Binding Affinity	rmsd/ub	rmsd/lb
Mode-1	-8.5	0	0
Mode-2	-8.2	5.521	4.013
Mode-3	-7.9	7.477	4.287

Modes of Binding	Binding Affinity	rmsd/ub	rmsd/lb
Mode-4	-7.9	16.478	12.271
Mode-5	-7.4	8.834	2.848
Mode-6	-7.1	14.388	10.134
Mode-7	-7.1	30.144	26.46
Mode-8	-7.1	17.08	13.401
Mode-9	-7.0	5.839	3.113

The molecular docking of doxorubicin with NF- κ B produced nine distinct binding modes with varying affinities (Table 1). Among these, Mode-1 exhibited the strongest binding affinity (-8.5 kcal/mol) with an RMSD value of 0, indicating it as the most reliable and stable pose. Mode-2 and Mode-3 also showed relatively high affinities (-8.2 and -7.9 kcal/mol, respectively) but with higher RMSD values compared to Mode-1. The remaining modes demonstrated lower binding affinities, ranging from -7.9 to -7.0 kcal/mol, along with increasing RMSD values, suggesting less stable and less favorable conformations.

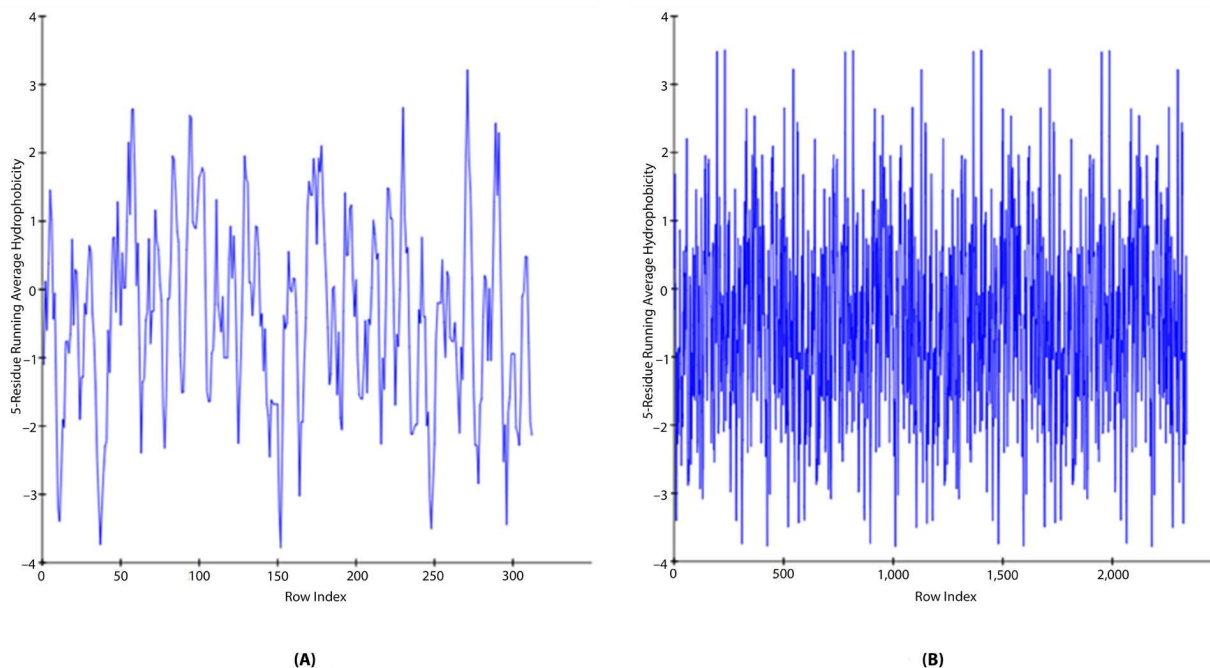


Figure 3: Comparative hydrophobicity profiles of (A) Native NF- κ B protein and (B) Doxorubicin-induced NF- κ B protein

In the native state (Figure 3A), the protein exhibited moderate fluctuations in hydrophobicity with values ranging

approximately between -4.0 and $+3.5$, showing relatively balanced hydrophobic and hydrophilic regions. In contrast, the

doxorubicin-induced NF- κ B (Figure 3B) demonstrated markedly higher fluctuations, with an increased density of peaks and troughs

across the sequence, suggesting a shift in the overall hydrophobicity distribution.

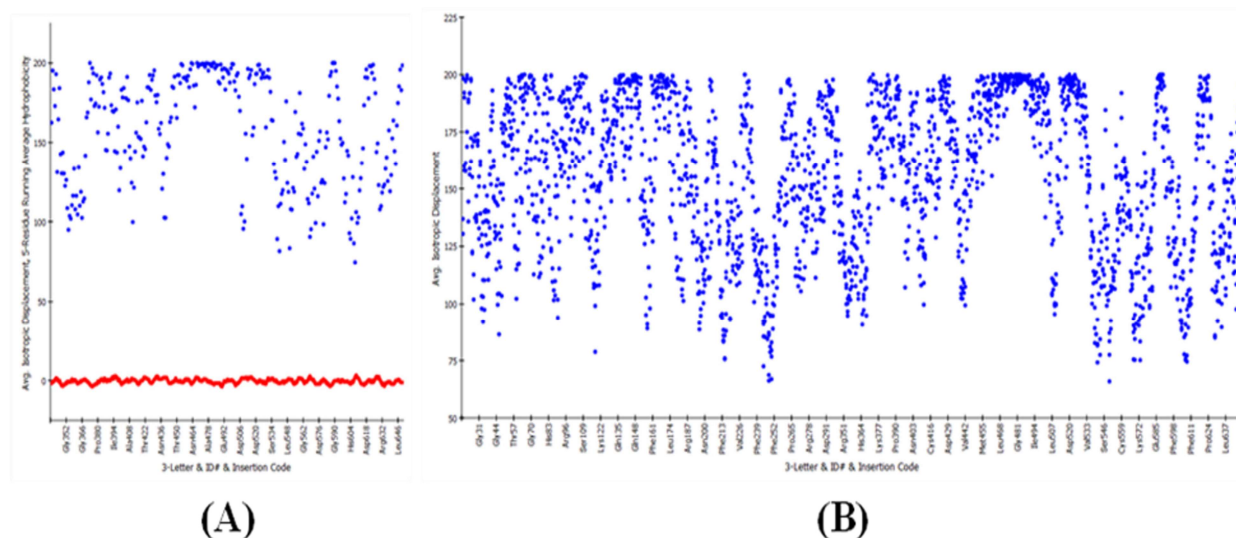


Figure 4: Comparative isotropic displacement and hydrophobicity profiles of (A) NF- κ B protein and (B) Doxorubicin-induced NF- κ B protein

Figure 4A shows the native protein, isotropic displacement values remained relatively low and consistent, with minimal fluctuations across the residues, accompanied by stable hydrophobicity distribution. In contrast, the doxorubicin-induced NF- κ B protein exhibited

markedly elevated isotropic displacement values, ranging between ~ 75 and 200, with frequent fluctuations across residues (Figure 4B). The altered profile highlights structural variations and increased dynamic behavior induced by doxorubicin binding.

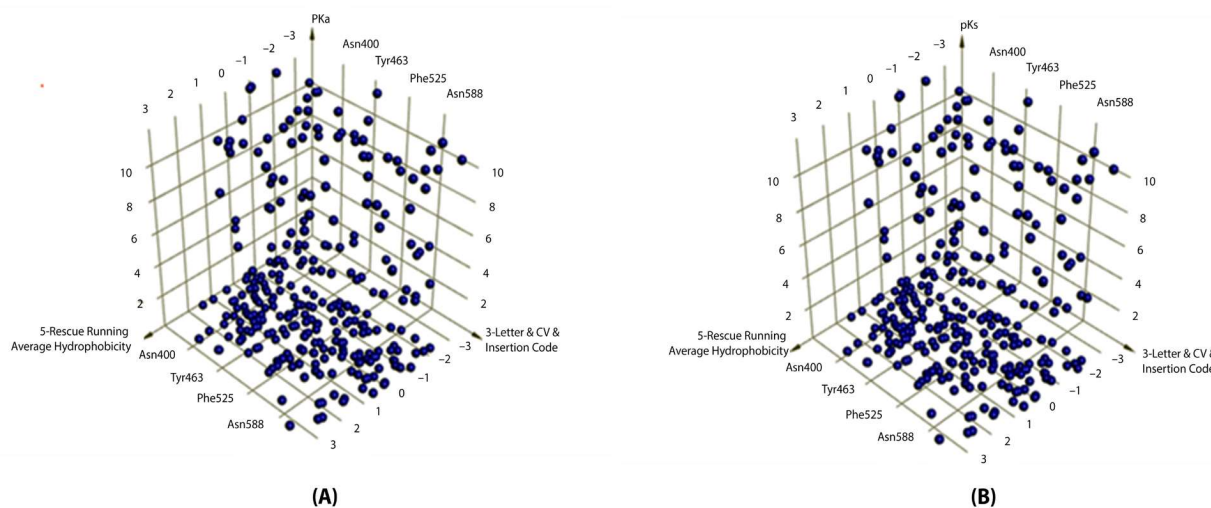


Figure 5: Three-dimensional hydrophobicity and pKa distribution of (A) NF- κ B protein and (B) Doxorubicin-induced NF- κ B protein

In the native NF- κ B, the hydrophobicity distribution appears moderately scattered, with residues such as Asn400, Tyr463, Phe525, and Asn588 showing distinct clustering patterns (figure 5A). Upon doxorubicin

binding, the protein exhibits a broader spread of data points, with increased variability in both hydrophobicity and pKa, indicating altered physicochemical properties of key residues (figure 5B).

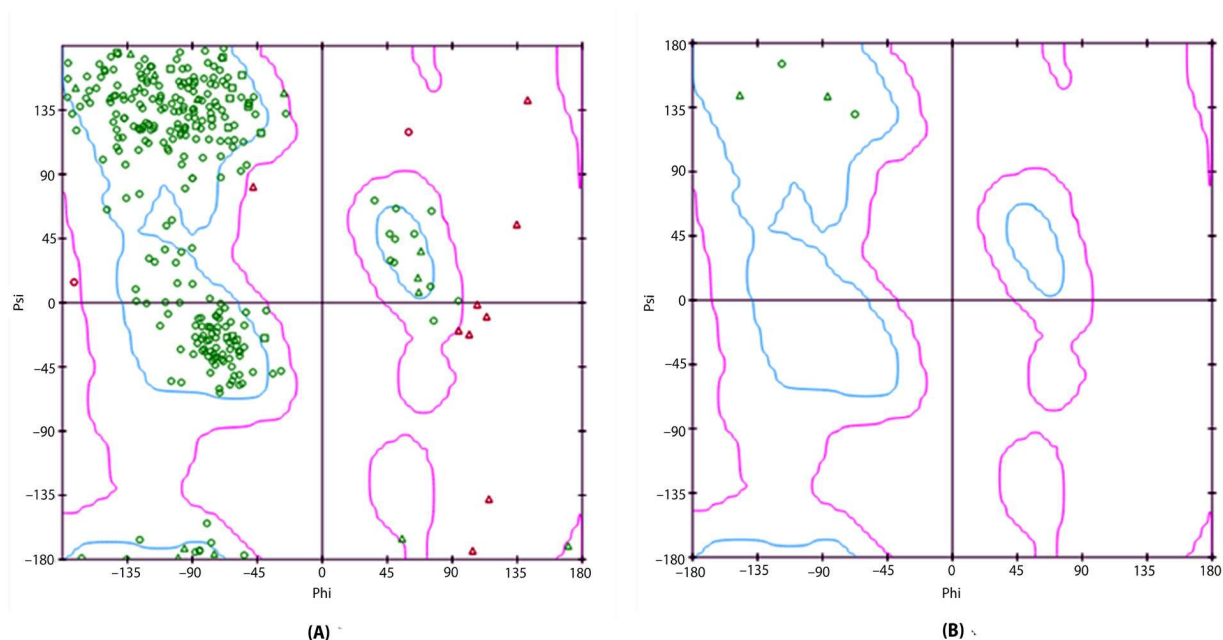


Figure 6: Ramachandran Plot of (A) NF- κ B protein and (B) doxorubicin-induced NF- κ B protein

In the native NF- κ B structure (Figure 6A), the majority of residues are distributed within the favored and allowed regions, reflecting a stable and well-folded conformation. A substantial clustering is observed in the β -sheet and right-handed α -helix regions, with only a few residues lying in the disallowed zones. In contrast, the doxorubicin-bound NF- κ B structure shows a drastic reduction in

the number of residues present in the favored regions (figure 6B). Only a small cluster of residues remains within the acceptable conformational space, while most of the structural features are lost. This suggests that ligand binding has induced significant conformational distortion, reducing the overall structural integrity of the protein.

Graphical Abstract

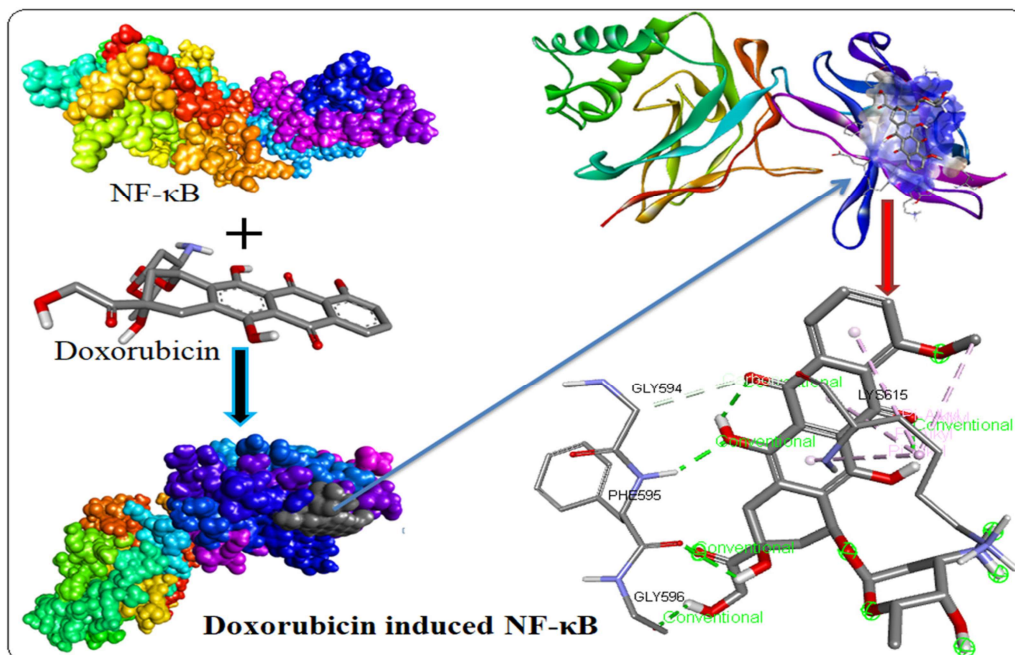


Figure 7: Interaction profile of doxorubicin with NF- κ B protein

Figure 7 shows that, doxorubicin forms multiple conventional hydrogen bonds with residues such as PHE D:595, GLY D:596, and ASP D:597, which play a central role in stabilizing the complex. Additionally, carbon hydrogen bonds are observed with residues including GLY D:563, LYS D:612, and GLY

D:594, contributing further to binding stability. Hydrophobic interactions, such as alkyl and π -alkyl interactions, are noted with LYS D:615 and aromatic residues like PHE D:595. These non-covalent interactions collectively suggest a strong and stable binding mode between doxorubicin and NF- κ B, which is essential for its inhibitory potential.

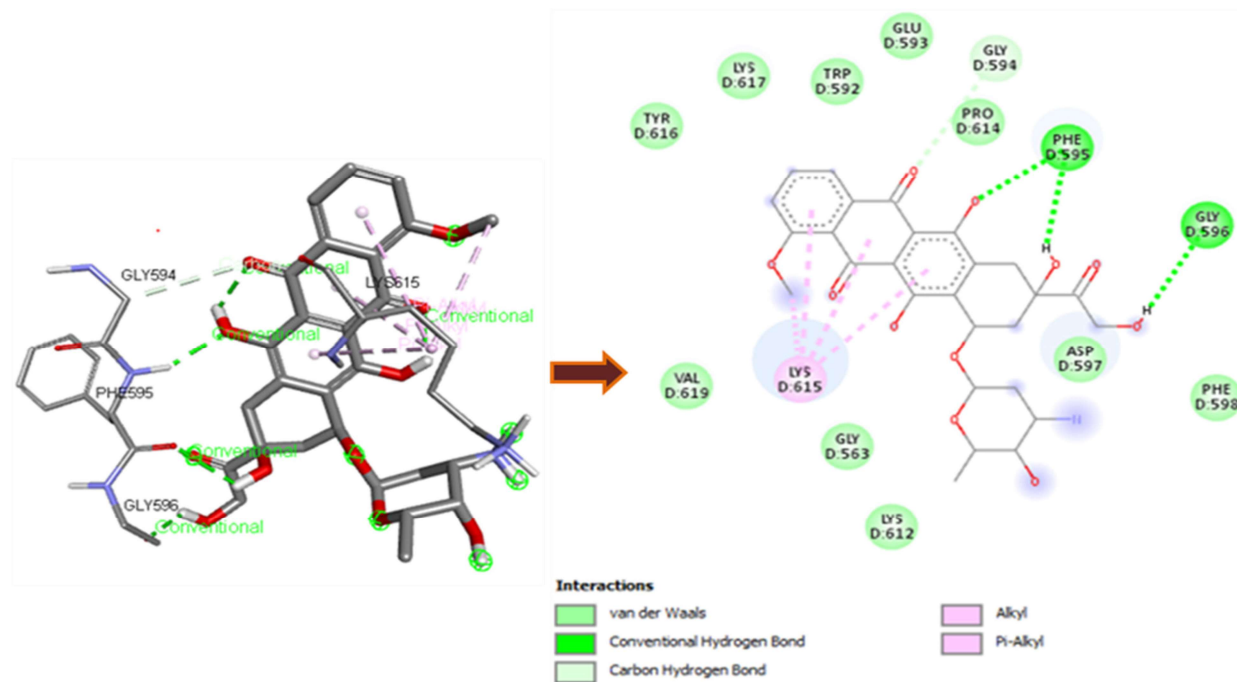


Figure 8: Spatial distribution and relative intensity of NF- κ B protein (A) under control conditions and (B) after doxorubicin treatment

Panel A (NF- κ B, control) of figure 8A: The untreated/control sample shows a heterogeneous, low-to-moderate intensity signal for NF- κ B across the field. Color mapping indicates many regions with lower intensity values (cooler colors) interspersed with occasional localized higher-intensity zones (warmer colors). The overall pattern is diffuse rather than forming distinct bands or tightly clustered hotspots. Panel B (Doxorubicin-induced NF- κ B) of figure 8B: After doxorubicin exposure, NF- κ B signal intensity is markedly increased and displays a banded/stripped pattern across the imaged region. The color scale for panel B shows higher maximum values compared with panel A, and many regions shift into the warmer colors, indicating upregulation of NF- κ B signal. The distribution also appears more regular and periodic in the treated sample compared with the control.

Comparative observation: Doxorubicin treatment produces a clear increase in NF-

κ B signal intensity and a change in spatial organization from diffuse and heterogeneous (A) to more intense and periodically patterned (B). This suggests both an elevation in NF- κ B levels and an alteration in its localization pattern upon drug exposure.

The docking analysis (Table 1) revealed that Mode-1 represents the most favorable binding conformation of doxorubicin with NF- κ B, characterized by the lowest RMSD value and highest accuracy. This suggests that doxorubicin interacts efficiently with critical residues of NF- κ B, potentially suppressing its functional role as a transcription factor.²⁸ The strong affinity in Mode-1 highlights the importance of this pose in the inhibitory mechanism. Although Modes 2 and 3 showed relatively high binding affinity, their increasing RMSD values imply reduced stability and reliability compared to Mode-1. These may represent alternate conformations of the drug-protein complex but are unlikely to be the

dominant inhibitory form. Modes 4 through 9, with weaker affinities and higher structural deviations, appear to be less significant for NF- κ B inhibition.²⁹ The findings suggest that doxorubicin targets NF- κ B by stabilizing within its binding pocket through non-covalent interactions such as hydrogen bonds, π - π stacking, and van der Waals forces.³⁰ This supports its proposed inhibitory role, particularly relevant given NF- κ B's established involvement in inflammation and doxorubicin-induced cardiotoxicity.⁸ Furthermore, the analysis indicates that plant-derived molecules with binding affinities weaker than -8.5 kcal/mol could serve as potential cardioprotective agents by attenuating NF- κ B activation during doxorubicin treatment.³¹

Hydrophobicity analysis (Figure 3) showed that doxorubicin binding introduced greater fluctuations compared to the relatively stable profile of native NF- κ B. This variability suggests ligand induced conformational changes that expose residues otherwise shielded in the native state. Hydrophobicity plays a central role in protein-ligand interactions, influencing affinity, specificity, and stability.³² These findings highlight that doxorubicin's interactions likely alter NF- κ B's functional conformation. The isotropic displacement results (Figure 4) further supported this by showing enhanced residue mobility in the doxorubicin-bound form. Unlike the native protein, which maintained structural rigidity, the drug-bound NF- κ B displayed increased flexibility, consistent with destabilization of protein folding. Such enhanced dynamics may expose hydrophobic regions and impair NF- κ B's DNA-binding and regulatory functions.³³ This observation is aligned with reports that small-molecule inhibitors destabilize NF- κ B by inducing conformational flexibility.³⁰ Additional insights from Figure 5 indicate that doxorubicin binding perturbs hydrophobicity and pKa distribution, particularly around residues Asn400, Tyr463, Phe525, and Asn588. These changes may alter residue ionization states and microenvironment interactions, weakening protein stability and reducing DNA-binding efficiency. Since both hydrophobicity and pKa shifts play crucial roles in protein folding and intermolecular interactions, the observed perturbations may directly disrupt NF- κ B's signaling capacity.³⁴

Ramachandran plot analysis (Figure 6) revealed a reduction of residues in favorable regions upon drug binding, indicating structural destabilization. The disruption of α -helical and β -sheet conformations suggests impaired protein folding, consistent with the loss of NF- κ B's functional conformation and transcriptional activity.³⁵ The interaction map (Figure 7) demonstrated that doxorubicin interacts with NF- κ B through hydrogen bonding, van der Waals forces, hydrophobic contacts, and π -alkyl interactions. Key residues such as Phe, Asp, Gly, and Lys contributed to stabilizing these interactions, underscoring their role in protein flexibility and regulatory functions.³⁶ Image-based analysis (Figure 8) further confirmed NF- κ B modulation. In the untreated sample (Panel A), NF- κ B showed a diffuse, low-to-moderate signal intensity with heterogeneous distribution. In contrast, the doxorubicin-treated sample (Panel B) displayed markedly increased NF- κ B intensity, with a more regular, band-like spatial organization. This shift indicates not only upregulation but also altered localization of NF- κ B upon drug exposure, consistent with its activation under stress conditions.²⁸ While these qualitative findings strongly suggest NF- κ B upregulation, definitive confirmation would require quantitative validation through biochemical assays such as protein fractionation, target gene expression analysis, or functional inhibition studies.

CONCLUSION

This study highlights the molecular basis of doxorubicin-induced myocardial injury through NF- κ B modulation. Docking analyses confirmed strong and stable interactions between doxorubicin and NF- κ B, driven by multiple non-covalent forces. These interactions disrupted the protein's structural integrity, altered hydrophobicity and pKa distributions, and reduced conformational stability, collectively impairing NF- κ B's functional state. The resulting upregulation and spatial reorganization of NF- κ B support its involvement in promoting inflammation and apoptosis during drug-induced cardiotoxicity. While the *in-silico* findings provide important mechanistic insights, further experimental validation is essential to confirm these effects in biological systems. Future research should explore natural antioxidants, vitamins, and

small molecules with competitive binding potential to mitigate NF- κ B activation and protect against doxorubicin-associated cardiac damage. By targeting this pathway, novel cardioprotective strategies may be developed to improve the therapeutic index of doxorubicin in cancer treatment.

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Methodology: Surajit Bhattacharjee

Project administration: Surajit Bhattacharjee

Resources:

Software: Surajit Bhattacharjee

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Validation: Sangita Roy, Reena Kulshrestha, Pooja Sitholay

Visualization:

Writing - original draft: Aditi Das, Samarpita Debbarma

Writing - review & editing: Surajit Bhattacharjee, Sudipta Pal, Samarpita Debbarma

Data Availability: None.

Conflict of Interest

The authors do not have any conflicts of interest associated to this research study.

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