

Doxorubicin Disrupts the Calcium Homeostasis through its Antagonistic Activity on PINK1—An *In-silico* Approach

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Abstract: Doxorubicin (DOX) is an anthracycline antitumor drug, and though it is a widely used chemotherapeutic agent to treat various types of cancers, it induces irreversible dilated cardiomyopathy. In the face of many attempts, the molecular mechanism of doxorubicin-induced cardiotoxicity has not been entirely determined. On this note, we hypothesize that doxorubicin might dysregulate the calcium homeostasis through the electron transport chain (ETC). Therefore, we analyzed doxorubicin interaction with proteins involved in calcium homeostasis and electron transport chain by molecular docking. From our observation, we suggest that the doxorubicin strongly interacted with the protein of cardiolipin at their active binding site of Tyr63 with higher binding energies, while Tyr63 amino acid residue act as C3H1-type. and doxorubicin also interact with PINK1 and RYR2 at their active site. Thus, the significant binding of cardiolipin and PINK1 leads to the formation of oxidative stress, which increases ROS generation. An increased level of ROS activates RYR2 to release Ca^{2+} ions in mitochondria. Therefore, the interaction of doxorubicin with PINK1 is directly related to the accumulation of Ca^{2+} ions in the mitochondria by activating RYR2. Changes in the Ca^{2+} level of the mitochondria negatively affect the membrane potential ($\Delta\psi$), leading to dysfunction in cardiac contraction.

Keywords: Doxorubicin; calcium receptor channel; IP3R; RYR; SEIPIN; SERCA; Ubiquitin; Cardiolipin; PINK 1; cardiomyopathy.

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1. Introduction

Doxorubicin is also referred to as Adriamycin® and Rubex®, an anthracycline anticancer drug isolated from *Streptomyces peucetius*, a mutant strain. It has a potent anticancer activity to treat various cancers, such as solid tumors, leukemia, breast cancer, lymphoma cancer, etc. But the clinical application of the drug is hampered due to its toxic nature [1]. They also cause side effects such as nausea, extravasation, vomiting, alopecia, suppression of hematopoietic cells, and cardiotoxicity [2–5]. Irreversible cardiomyopathy is one of doxorubicin's major life-threatening side effects [6–8]. Doxorubicin-induced cardiotoxicity is due to short- or long-term toxic effects that alter the myocardial structure leading to

cardiomyopathy due to cardiac cell death [9,10]. In the face of many attempts, the molecular mechanism of DOX-induced cardiotoxicity has not been entirely determined [11–13]. Even though various kinds of mechanisms were proposed from previous literature that DNA damage, modification in protein synthesis, free radical formation, lipid peroxidation, cell membrane lesions, mitochondrial dysfunction, the release of catecholamines and histamine, immunogenic reaction induction, and dysregulation of calcium homeostasis, combination of all these factors causes the myocardial lesions [14–18]. Modification in the cellular process might affect cardiac muscle contraction, which leads to cardiomyopathy [19–21].

Cardiac muscle contraction is based on its excitation-contraction coupling process connected with sarcolemma surface membrane depolarization to muscle fiber contraction. Notably, calcium plays a crucial role in myocardial contraction through the excitation-contraction (EC) coupling process [22,23]. The entry of Ca^{2+} activates the ligand-gated cardiac ryanodine receptor (RyR2) in the sarcoplasmic reticulum (SR), which acts as a Ca^{2+} store membrane. RyR2 released Ca^{2+} rises the cytoplasmic Ca^{2+} concentration to stimulate contractile proteins due to muscle contraction (systole). During relaxation (diastole) the level of cytoplasmic Ca^{2+} was reduced while the SR Ca^{2+} was normal. The returning of Ca^{2+} to the SR is by SR Ca^{2+} ATPase (SERCA2A) and extrusion from the cytosol by $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX). If there are any modifications in these processes, they lead to various pathological functions in cardiac cells [24].

Previously, *In vitro* experiments show that Dox can stimulate and inhibit RYR-mediated Ca^{2+} release in cardiac muscle [25] and reduce the Ca^{2+} -binding capacity of Calsequestrin 2 (CSQ 2) [26]. They are believed to compromise the SERCA2A function [27] in skeletal muscle. In addition, binding directly to RyR2 and CSQ 2, doxorubicin is also thought to decrease the number of reactive thiol groups on RyR2 directly or indirectly via increased ROS production [28,29]. There have been limited studies exploring the interactions between the metabolites and specific cardiac targets involved in calcium homeostasis and doxorubicin. For analyzing the binding efficiency and orientation of doxorubicin with the Ca^{2+} receptor channel, we used the *in-silico* study of molecular docking by autodock.

Molecular docking is a tool to determine the structure orientation between two molecules while bound to each other and form a complex structure [30–32]. The binding affinity of those complexes was determined by a scoring function based on the preferred orientation [33,34]. In endorsing the fundamental biomolecular process, proceedings include enzyme-substrate, drug-nucleic acid, and drug-protein, wherein the recognition of molecular interaction plays an impact role. It suggested that modification in the binding or orientation causes the defect in signal transduction. Thus, docking is a novel tool to predict the binding strength and signal produced [33]. In this study, we docked the proteins such as IP3R, RYR, SEIPIN, SERCA, Ubiquitin, Cardiolipin, PINK with doxorubicin for analyzing the upsetting of calcium homeostasis, causing cardiomyopathy.

2. Materials and Methods

2.1. Protein searching.

The crystal structure of the calcium channel receptor and respiratory chain enzymes were retrieved from the Protein Data Bank (www.pdb.org) [35]. To identify the protein structure and amino acid position from active locations, we used Discovery Studio (version: 2017 R2 client), which was later used for docking.

2.2. Ligand searching.

In our experiment, the relationship between doxorubicin with calcium channel receptor and respiratory chain enzymes was to be analyzed. So, we selected doxorubicin as a ligand, and its composition was extracted from existing ligand databases: PubChem (<http://pubchem.ncbi.nlm.nih.gov>).

2.3. Molecular docking.

The molecular docking method was developed using the AutoDock Vina [36]. Doxorubicin was used as a ligand, and other proteins were used as receptors. They were prepared in PDB using the Discovery Studio 2017 R2 Client. Ligands and receptors with hydrogen atoms to protonate the input structure. The configuration file was developed as the size of the box and the coordinates on the receptor. For each ligand, we used both hydrogen and potential molecular torsions [36]. Receptor and ligand files have been saved in pdbqt format to calculate docking energy affinities (Kcal / Mol). AutoDock Vina created energy affinity values of up to 10 separate docking poses for each ligand.

For analysis, Autodock vina effects were evaluated to obtain each complex affinity energy according to the ligand conformation at the active gene site, taking into account the RMSD between the original and subsequent structures. The Discovery Studio 2017 R2 Client [37] was used to calculate the number of hydrogen bonds and non-covalent interactions for each complex and produce details, compounds, and interaction images [37].

2.4. Molecular properties prediction.

Molecular formulation, molecular weight, isoelectric stage, log P, H-bond acceptor sites, H-bond donor sites, Atom count, bond numbers, polar region, Vander Waals surface area, polarizability, and Lipinski's rule were used in the prediction of the molecular properties of bioactive compounds using Discovery Studio 2017 R2 Client software [38].

3. Results and Discussion

Our studies indicate the relationship between doxorubicin and alterations in the release of calcium and the function of calcium handling proteins associated with myocardial dysfunction. In general, Ca^{2+} released from the sarcoplasmic reticulum (SR) is amplified during excitation-contraction coupling in cardiac cells via the sarcolemmal L-type Ca^{2+} channels. Mitochondrial calcium is mainly obtained from the ER through the IP3R channel [39]. Calcium enters from the endoplasmic reticulum through one of the 4 receptors, namely IP3R, RYR, SERCA, and SEIPIN. The SERCA and SEIPIN complex is useful in maintaining calcium homeostasis. We identified the interaction between the Dox and calcium receptors in the current work by molecular docking.

3.1. IP3R.

Inositol triphosphate receptor (IP3R), a ligand-gated channel, transfers calcium ions from ER stores to the mitochondria [40]. In between the IP3R and mitochondria, the calcium ions are transferred across mitochondrial intermembrane space via voltage-dependent anion channels (VDACs), a class of mitochondrial porins [41]. Indeed, any changes in the expression level of IP3R ultimately lead to cell death [42]. Molecular docking of IP3R with doxorubicin

revealed the interacting residues (Asp 444, Asn 447, Leu 30, Asp 448, Asn 203, Ala 43, ser 28, Lys 42) (Figure 1). The amino acid residues involved in H-bond are Asn 203, Asp 444, Asn 447, Leu 30. None of the interacting residues reside in the active site. Therefore, the interaction between IP3R and doxorubicin is unlikely to affect calcium entry from the ER to mitochondria.

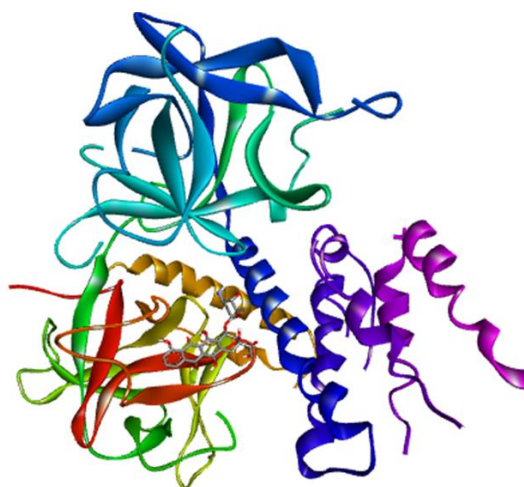


Figure 1. Interaction between IP3R and DOX.

3.2. RYR.

RYR is a receptor for Ca^{2+} ions. Ca^{2+} entry is facilitated via voltage-sensitive L-type Ca^{2+} channels, which trigger the SR to release Ca^{2+} through RyR. RyR increases the level of Ca^{2+} in the cytoplasm, which makes the heart contract, which is known as calcium-induced calcium release [43]. RYR molecular docking with doxorubicin revealed that RYR interactive residues are Pro 2671, Ala 2672, Tyr 2743, Leu 2787, Tyr 2621, Lys 2783, Ser 2625, Lys 2628, His 2626, Asp 2786, Leu 2723. Among the mentioned residues, Tyr 2668, Tyr 2621, Ser 2625, and Asp 2786 are involved in H-bonding (Figure 2; Table 1 and 2). These residues interact with each other hydrophobically but not at the active site. Thus, RyR-doxorubicin interactions might not affect the calcium intake into the cardiac cell.



Figure 2. Interaction between DOX and RYR.

3.3. RYR2.

RYR2 is the key SR calcium release channel in excitation-contraction coupling. The level of calcium ion release from SR via RYR2 determines the Ca^{2+} transient amplitude, which is related to the strength of the systolic contraction [44]. Moreover, the RYR2 channel has many phosphorylation sites. The phosphorylation sites depend on the dynamic equilibrium between multiple protein kinases and phosphatases that allows the control of RYR2 phosphorylation and, consequently, channel function [45,46]. RYR2 molecular docking with doxorubicin showed Phe 12, Ala 15, Glu 11, Glu 84, Leu 18, Met 145, Phe 92, Ala 88, Leu 112, Glu 91, Glu 108, and Glu 87 were interactive. Among the residues Glu11, Glu 84, and Glu 14 interact with doxorubicin through H-bonding (Figure 3; Table 1 and 2). Interestingly, the Glu84 resides within the active site of RYR2. Our molecular docking between RYR2 and doxorubicin revealed that the RYR2 might be rendered dysfunctional and, therefore, affect the controlled release of Ca^{2+} into ER in mitochondria. However, RYR2 gating is maintained by various factors during systole. Modification in the RYR2 phosphorylation causes several cardiac diseases such as heart failure (HF), atrial and ventricular arrhythmias. Previous research reports suggest that RYR2 is vulnerable to doxorubicin, potentially altering cardiac Ca^{2+} homeostasis [47].



Figure 3. Interaction between DOX and RYR2.

3.4. SERCA.

Sarco/Endoplasmic reticulum calcium ATPase (SERCA) plays a major role in transferring calcium ions from the cytosol to the SR. The release of Ca^{2+} from SERCA enables muscular relaxation in both skeletal and cardiac muscle. The dysregulation in SERCA activity is reported in several pathological conditions like cardiac diseases [48]. The molecular docking analysis revealed that SERCA interacts with doxorubicin at Asn111, Ser 731, Ser335, Arg 334, Glu 732, Glu 732, Thr 247, Asp 245, Lys 712, and Thr 242, and their H-bonding is Ser 731, Glu 732, Lys 712, Thr 242 (Figure 4; Table 1 and 2). Even though it makes hydrophilic interaction with doxorubicin, there is no involvement in their active sites. Thus, the doxorubicin has no apparent effect on SERCA function.

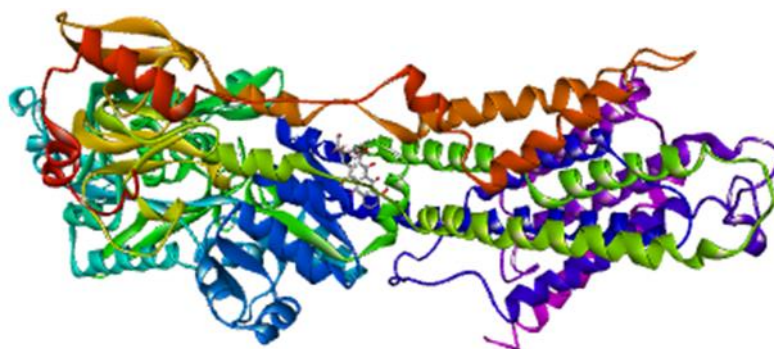


Figure 4. Interaction between DOX and SERCA.

3.5. SEIPIN.

SEIPIN is an intrinsic ER protein with two transmembrane proteins. It promotes ER calcium homeostasis along with Ca^{2+} -ATPase SERCA. SEIPIN promotes adipose tissue lipid storage via calcium-dependent mitochondrial metabolism [49]. Mutation or deletion in the SEIPIN leads to ER stress [50]. As a result of ER stress, cardiac diseases are developed [51]. Molecular docking shows that SEIPIN interacts with doxorubicin at Leu 90, Phe 66, Phe 59, Leu 412, Thr 63, Leu 124, Met 89, Met 89, Ile 398, Ser 67, Phe 297, and Ala 64 (Figure 5; Table 1 and 2). There is a hydrogen bond with doxorubicin at the amino acid residue Ala 64. However, it is not at their active site. It clarifies that the binding of doxorubicin might not alter the function of SEIPIN.



Figure 5. Interaction between DOX and SEIPIN.

3.6. Cardiolipin.

Cardiolipin is essential for the activation of certain enzymes involved in the electron transport chain, which are complex IV (cytochrome oxidase), complex I (NADH–ubiquinone oxidoreductase), and Complex III (ubiquinone–cytochrome oxidoreductase) [52,53]. Doxorubicin significantly binds with cardiolipin, and its binding energy is -6.07 KJmol^{-1} . Doxorubicin makes hydrophobic interaction with cardiolipin at the Lys 216, Asp 236, Gln 29, Tyr 63. Tyr 63 falls within the domain C3H1-type, a zinc finger factor site (Figure 6 and Table 1 and 2). It indicates that cardiolipin is a direct target of doxorubicin, and it inhibits the transcription process. The binding of doxorubicin with cardiolipin causes the inactivation of complex I-III [54]. Previous studies also revealed that the doxorubicin has a high affinity with

cardiolipin, which renders the oxidative phosphorylation mechanism [55]. Moreover, cardiolipin deficiency releases a higher level of cytochrome in IMM and triggers apoptosis [56]. Modification in the cardiolipin profile could be responsible for the changes in the bioenergetics, such as reduced level of O₂ consumption dysfunction of complexes I, III, and IV [57]. Defects in cardiolipin can be correlated with alteration of ETC complexes resulting in energy deficit [58].

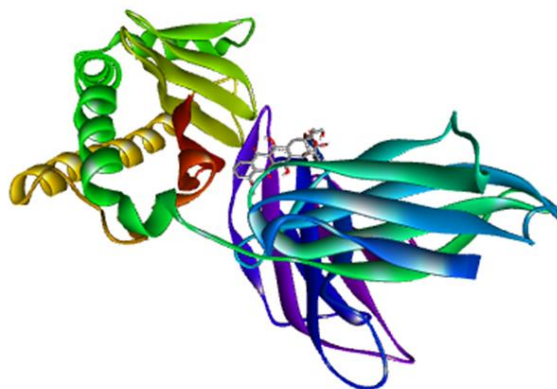


Figure 6. Interaction between DOX and Cardiolipin.

3.7. *PINK1*.

PINK1 is a mitochondrial serine/threonine kinase that has been demonstrated to protect cells against apoptosis induced by oxidative stress [59]. PINK1 deficiency results in bioenergetic deficiencies such as calcium buffering, loss of membrane potential, ATP synthesis rate, and respiration [60–62]. Doxorubicin makes a hydrophobic interaction with PINK 1 at the amino acid residues Asp 229, Cys 362, Lys 339, Asn 231, Asn 227 where Cys 362 is a proton acceptor with a binding energy of -6.36 KJmol^{-1} (Figure 7, Table 1 and 2). Mutations/knockout of PINK1 results in impaired mitochondrial function, including reduced membrane potential ($\Delta\Psi_m$) and impaired oxidative phosphorylation, excessive vulnerability to raised mitochondrial calcium, and reduced mtDNA copy number increased free radical generation [62–64]. The impairment/loss of PINK1 increases the heart's risk of ischemia-reperfusion injury, which may be partly due to impaired mitochondrial activity [65].

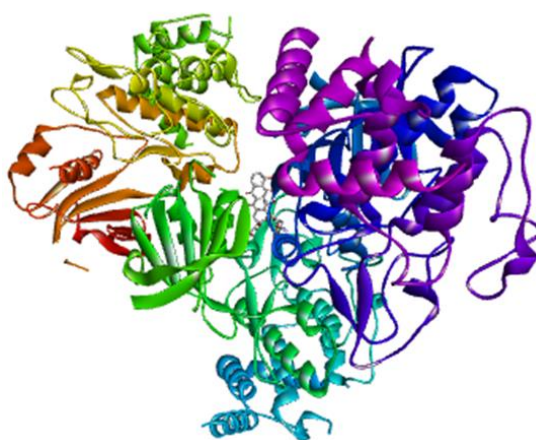


Figure 7. Interaction between DOX and PINK1.

3.8. *CoQ enzyme*.

Coenzyme Q (ubiquinone) is a lipid-soluble electron carrier located in the inner mitochondrial membrane [66]. They play a vital role in the production of ATP since it is an

electron acceptor in the electron transport chain [67]. CoQ enzyme has a molecular connexion to doxorubicin at the amino acid residues Lys 577, Gln 534, Arg 542, Gln 443, Gln 575, His 446, and Leu 538 Thr 571, Gln 570, Arg 549, Gly 567, Leu 541, Gln 574 and Pro 539. Gln 443, Arg 442 make a hydrogen bonding with doxorubicin (Figure 8; Table 1 and 2) but not at their active site. This makes a clear note that the interaction of doxorubicin does not directly affect the function of ubiquitin. Complex I enzymes in ETC oxidizes the NADH and transfer an electron to ubiquinone. The function of PINK1 directly affects complex I [68]. As already shown, the activity of PINK1 is affected due to its binding with doxorubicin (Section 3.8). Whereas any dysfunction in the PINK1 negatively affects the complex, I function might lead to inactivation of ubiquinone [68]. Subsequently, this process causes the increased production of ROS due to impaired ATP synthesis and cell apoptosis. The increased ROS level activates the Ca^{2+} /calmodulin-dependent protein kinase II, a critical regulator of several proteins that contributes to contractile dysfunction, HF, and arrhythmias, including RyR2s, phospholamban, L type Ca^{2+} , and late Na^+ current [69,70]. Doxorubicin, therefore directly affects the calcium channels leading to cardiac arrest.

Table 1. Comparison of Molecular Docking result of Adriamycin with Calcium channel and Respiratory chain enzymes.

S.No	Gene Name	Binding Energy	Ligand Efficiency	Inhibit Constant	internal energy	vdw hb dissolve energy	Electrostatic Energy	Total Internal	Torsional Energy	Unbound Energy
1	IP3R	-6.41	-0.16	19.95	-9.69	-8.43	-1.26	-4.15	3.28	-4.15
2	RyR	-9.38	-0.24	132.43	-12.66	-9.8	-2.86	-3.84	3.28	-3.84
3	SERCA	-9.28	-0.24	162.16	-12.54	-10.64	-1.9	-2.87	3.28	-2.87
4	SEIPIN	429.66	11.02	-	426.38	426.66	-0.27	14.17	3.28	14.17
5	RyR2	-6.39	-0.16	20.54	-9.68	-6.31	-3.37	-3.82	3.28	-3.82
6	Cardiolipin	-6.07	-0.16	35.44	-9.35	-8.52	-0.83	-5.99	3.28	-5.99
7	PINK1	-6.36	-0.16	21.69	-9.64	-8.38	-1.26	-4.61	3.28	-4.61
8	CoQ enzyme	54.95	1.41	--	51.67	52.28	-0.61	-1.91	3.28	-1.91

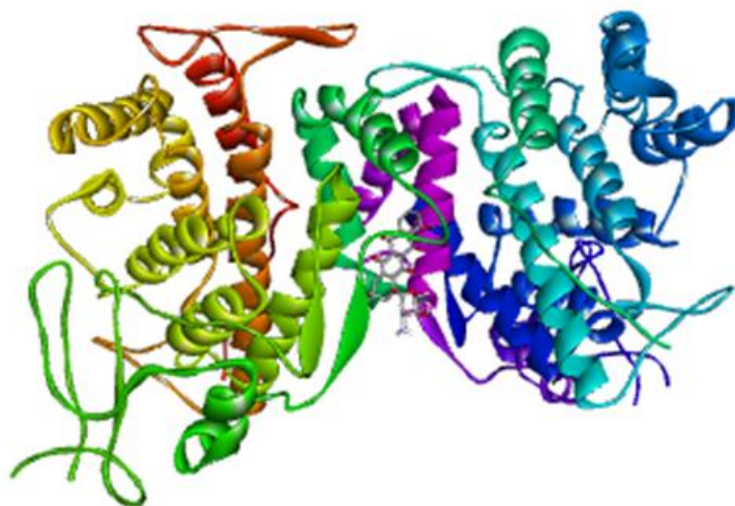


Figure 8. Interaction between DOX and ubiquitin.

Table 2. Docking calculation depicting interacting residues, binding site residues, and atoms involved in H-bonding along with interacting residues common to reported active binding site residues.

S.NO	Protein	Interacted Residues	Ligand and Protein atom involved in H-bonding	Interacting residues common with reported active binding sites
1	IP3R	Asp 444, Asn 447, Leu 30, Asp 448, Asn 203, Ala 43, ser 28, Lys 42	Asn 203, Asp 444, Asn 447, Leu 30	Nil
2	RyR	Pro 2671, Ala 2672, Tyr 2743, Leu 2787, Tyr 2621, Lys 2783, Ser 2625, Lys 2628,	Tyr 2668, Tyr 2621, Ser 2625, Asp 2786	Nil

S.NO	Protein	Interacted Residues	Ligand and Protein atom involved in H-bonding	Interacting residues common with reported active binding sites
		His 2626, Asp 2786, Leu 2723, his 2624, Trp 2629, Ile 2667, Tyr 2668		
3	SERCA	Asn 111, Ser 731, Ser335, Arg 334, Glu 732, Thr 247, Asp 245, Lys 712, Thr 242	Ser 731, Glu 732, Lys 712, Thr 242	Nil
4	SEIPIN	Leu 90, Phe 66, Phe 59, Leu 412, Thr 63, Leu 124, Met 89, Ile 298, Met 39, Ser 67, Phe 297, Ala 64, Gly 294, Ile 68, Asp 65, Pro 413, Ser 97, Ser 84, Phe 415, Leu 139, Ala 377, Val 214, Ile 141, Leu 131, Ile 414, Leu 86, Tyr 127, Asp 407,	Ala 64	Nil
5	Cardiolipin	Lys 216, Asp 236, Gln 29, Thr 28, Tyr 26, Phe 237, Pro 239, Tyr 63, Trp 31, Gly 33, Asp 34, Trp 245,	Lys 216, Asp 236, Gln 29,	C3H1-type; atypical Tyr 63
6	PINK1	Glu 217, Ala 213, Gly 361, Asp 359, Cys 362, Asp 337, Lys 339, Thr 386, Asp 229, Asn 231, His 228, Leu 230, Asn 227, Asn 173, Ile 210	Asp 229, Cys 362, Lys 339, Asn 231, Asn 227	Cys 362 (Proton acceptor)
7	Ubiquitin	Lys 577, Leu 534, Arg 442, Ile 578, Gln 443, Gln 575, His 446, Leu 538, Thr 571, Gln 570, Arg 549, Gly 567, Leu 541, His 574, Pro 539	Gln 443, Arg 442	Nil
8	RYSR2	Phe 12, Ala 15, Glu 11, Glu 84, Glu 14, Leu 18, Met 145, Phe 92, Ala 88, Leu 112, Val 91, Val 108, Glu 87	Glu11, Glu 84, Glu 14	Nil

Our analysis shows that doxorubicin affects the receptor indirectly as it inhibits PINK 1. The dysfunction of PINK1 alters the function of Complex I in ETC, which ultimately leads to the increased production of ROS. The increased ROS activates the RYSR2 to release increased Ca^{2+} ions and cause accumulation. Mitochondrial calcium, a vital intracellular calcium pool, is derived from connexions between ER and mitochondria. Mitochondrial calcium is necessary for the TCA cycle since the enzymes, mitochondrial matrix dehydrogenases (Pyruvate Dehydrogenase complex (PDH), isocitrate dehydrogenase, and α -ketoglutarate dehydrogenase) require calcium to function properly [71]. Mitochondrial calcium regulates ATP synthesis, respiration, and ROS substrate-dependent. Furthermore, calcium regulates the membrane potential ($\Delta\psi$) for ATP synthesis [72].

Our results are in agreement with earlier studies. Kim et al. (2006) and Arai et al. (1998) also had reported that there is an altered expression of calcium regulator genes in rabbits administered with doxorubicin [73,74]. The binding target of doxorubicin is RyR2, and by targeting this molecule, it is possible to restore calcium homeostasis [75,76]. CAMK II signaling changes have been observed during pathological conditions, including doxorubicin-induced cardiomyopathy [77].

4. Conclusions

In conclusion, the interaction of doxorubicin with PINK1 negatively impacts the calcium homeostasis in mitochondria. Our docking result implicit that the interaction of doxorubicin with cardiolipin leads to the release of cytochrome b6 resulting in increased ROS production. In parallel, the dysfunction of PINK also affects the function of complex I in ETC and in CoQ. But doxorubicin binds with PINK1 at its active site and makes it lose its control on CoQ, which further increases the ROS. An increased level of ROS activates the RYSR2 to release Ca^{2+} into the mitochondria in an abnormal way leading to calcium accumulation. On the other hand, doxorubicin also makes significant binding with RYSR2 at their binding site.

Overall, we conclude that the interaction of doxorubicin with PINK1, RYR2, and cardiolipin alters the mitochondrial calcium homeostasis and leads to dysfunction in cardiac contraction.

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Conflicts of Interest

The authors declare no conflict of interest.

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