Chapter

# Overview on the Side Effects of Doxorubicin

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## Abstract

Doxorubicin is an anthracycline antibiotic extracted from the bacterium Streptomyces peucetius. Its cytotoxic effect produced by intercalating with DNA causing breakdown of DNA strand which causes cancer cell apoptosis. Despite being an effective anticancer agent it causes several crucial side effects like carditoxicity, neuropathy, hepatotoxicity, nephrotoxicity, alopecia, typhlitis, myelosuppression, neutropenia, anaemia, thrombocytopenia, nausea, and diarrhoea were caused mainly due to the inability to distinguish between cancer cells and normal cells. This chapter mainly focuses on doxorubicin's side effects, current understanding of the molecular mechanisms, and management and preventive strategies of doxorubicin's cardiotoxicity during the treatment of various type of cancer.

**Keywords:** doxorubicin, nephrotoxicity, neurotoxicity, hepatotoxicity, cardiotoxicity

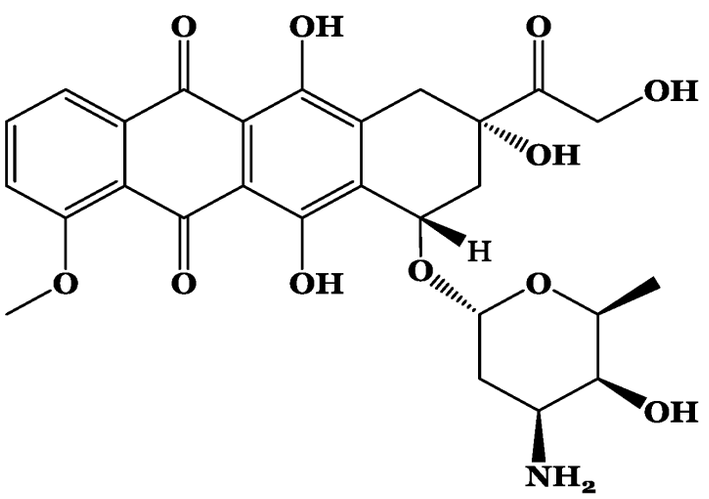
## 1. Introduction

### 1.1 Historical background

In the 1950s Italian based company; Farmitalia research laboratory began a research program in finding the anticancer compounds from soil-based microbes. In the process of research collected a soil sample from the castle named as castle Del monte, which was built in the 13th century. The collected soil sample contains new strains of bacterial species and isolated from it. The separated microbe recognised with the name Streptomyces peucetius which is typically produces a significant red pigment. The antibiotic produced from this bacterium discovered to be efficient in treating the tumours especially solid tumours while researching on mice. Since a group of French scientists found the same compound about at the same time, they agreed to call the antibiotic daunorubicin, referring to the two nations. In which, Dauni refers to the pre-Roman tribe who inhabited the position in Italy where the species of bacteria were isolated and ruby represents the colour in Italy. The clinical trials of daunorubicin were began in 1960s and confirmed as successful in treating the lymphoma and acute leukaemia [1, 2]. After a short note of the time, in 1967 daunorubicin was discovered to be cause fatal cardiotoxicity. Then, by using nitroso-N-methyl urethane, the Italian research company mutated the strains of Streptomyces peucetius and developed a new strain of bacterial species that produces 14-hydroxylated daunorubicin, also known as Adriamycin (named after the Adriatic Sea), then changed its name to doxorubicin, which has a strong therapeutic index, but cardiac toxicity remains [3].

### 1.2 Doxorubicin chemical structure and properties

Doxorubicin (DOX) is an anthracycline antibiotic structurally similar to Daunorubicin as natural anti-cancer antibiotic used in cancer treatment. Its anti-cancer effect produced intercalating with DNA and this will inhibit DNA transcription and replication; and by binding to the topoisomerase II enzyme and inhibit the resealing of the DNA fragments. The presence of sugar moiety attached to the anthracycline ring further enhances the binding to phosphate and sugar moieties in to DNA. This led to stops the proliferation of cancer cells in the host [4]. Besides, the presence of quinone moiety apart from contributing the cytolytic ability by generating the intermediate radicals, which further react with the oxygen and forms superoxide ions and these ions also shows a high tendency towards the damaging the cell membranes causes a dose-dependent the cardiac myopathy [5, 6].




The Doxorubicin is mainly used in case of patients suffering from Breast cancer, ovarian cancers, lung cancers, bladder cancers, leukaemia (acute lymphoblastic leukaemia, acute myeloid leukaemia) and AIDS-related Kaposi's sarcoma and various solid tumours. DOX also used in combination with other agents in case of bone sarcomas, soft tissue sarcomas, uterus cancer, endoblastoma cancer, cervix cancer, pancreatic cancer, Ewing's sarcoma, mesothelioma, multiple myeloma, Wilms tumour and in neuroblastoma [7, 8].

## 2. Doxorubicin side effects

### 2.1 Hepatotoxicity

Liver is one of the essential organs of the body; it plays a major role in metabolism and detoxification of several drugs. This can explains why liver is the primary body organ affected by chemotherapy. Despite being cytostatic and cytotoxic effects on cancer cells DOX documented to accumulate in the various tissues include liver cells. In humans, it is estimated as 50% of DOX eliminated in un-exchanged form, the remainder dose metabolised through hydroxylation, semiquinone formation [9]. The major pathway for biotransformation of DOX is catalysed by the NADPH-dependent carbonyl reductase, Nitric oxide synthase, cytochrome P-450 reductase, aldo-keto reductase enzymes. The hydroxylation occurs at C-13 carbon in group commonly reaction referred as electron reduction forms the secondary alcohol metabolites [10–13].

The metabolized intermediates in the presence of oxygen converted to carbonyl moieties resulting in generation of Superoxide anions and hydrogen peroxides causes peroxidation of lipids in membranes of cell, aggregation of proteins (**Figure 1**) [13–15].

The regenerative capacity of liver is more can cure the damage caused by various agents such as DOX, which causes damage and decreases the regeneration of liver cells by increasing the oxidative stress due to the radical generation by oxidation in hepatocytes. The generated radical causes decrease in GSH levels, damages in DNA and also act as secondary metabolites in in many metabolic pathways which includes in cell proliferation and cell death [16–18]. To overcome such situations liver employs the efflux mechanisms, the efflux of DOX is achieved through from liver by ATP dependent ABC proteins (P-glycoprotein) which increase the efflux of the intracellular DOX and maintain the homeostasis. The mechanism uses large quantity of energy but with the presence of the DOX in liver cells decreases the ATP production and increases the ADP and Pi within the cells [19–21]. Due to this effect sometimes liver cells can't able to regenerate from DOX induced effects and causes hepatotoxicity.

## 2.2 Nephropathy

Besides maintaining the homeostasis by regulating the body fluids, kidneys work to reabsorb the low concentrations general constituents in the body and also remove the foreign substances like drugs or other kinds of agents. For this kind of reasons kidneys considered as metastatic organs of human beings [22]. The regenerative capacity of the kidneys is low when compared to the liver and highly susceptible to

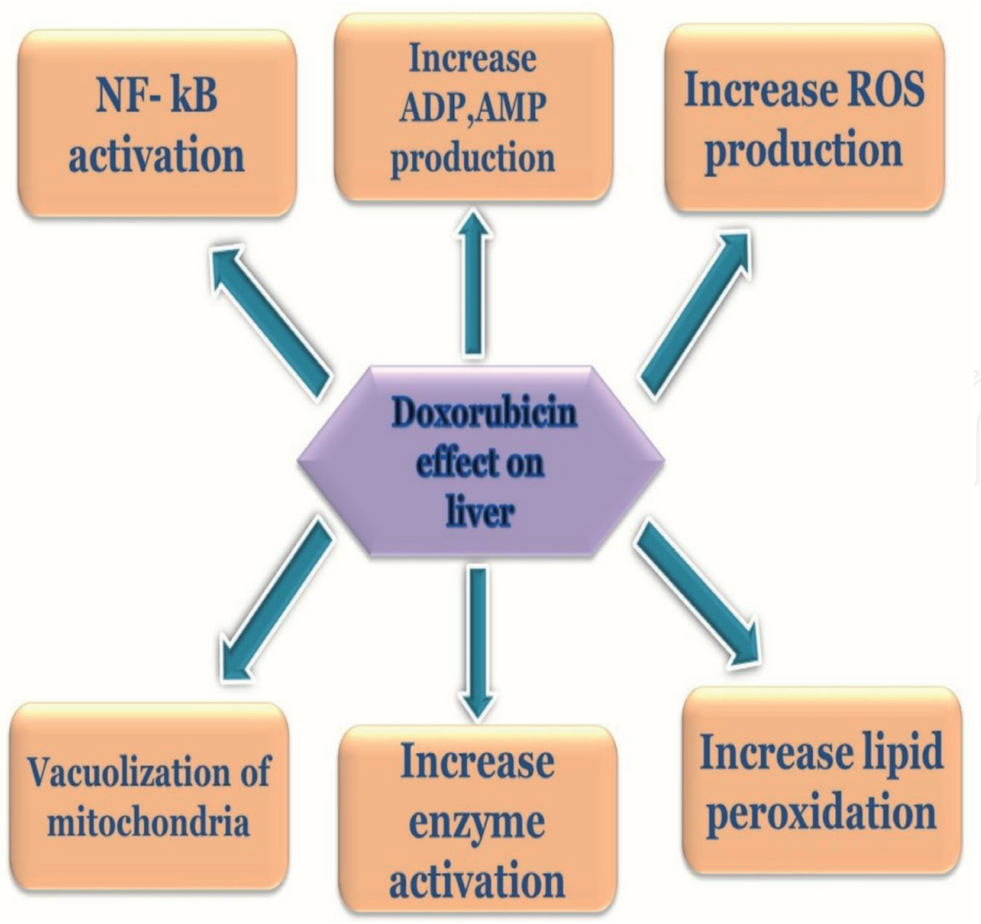



**Figure 1.**
*DOX mediated effects on the liver.*

epithelial degeneration occurs at renal glomerulus where the filtration occurs may lead to the glomerulosclerosis [23].

DOX interferes with the glandular podocytes of the kidney and cause nephropathy the most accepted mechanism behind the nephropathy is an accumulation of proteinuria in the kidney by the local passage of leaked proteins [23]. Increase in the structural changes in nephrons causes hypertension, steroid resistance, high incidents of renal failure and glomerular vacuolization, inflammation, tubular dilation, intestinal fibrosis, permeability differences in the glomerulus, and certain conditions like hypoalbuminemia, dyslipidemia, hypercoagulation, size differences in kidney most likely observed [24]. A study conducted on the DOX effect on the mitochondria by the Lebrecht suggested that DOX interfere the mitochondrial mtDNA in the kidney with ROS produced from it and accelerating the damaging of the nephron. Another study reports suggesting that DOX forming an iron-mediated anthracycline complex, which produces the ROS led to an increase in the oxidative lesions in the cells causing damage to the critical cellular components [25, 26].

The decreasing the levels of the GSH (Glutathione), vitamin E levels and other natural oxidant levels production from the liver cells enhances the nephropathic conditions which may initially affect the Bowman's capsule thickness and the glomerular tuft of the nephron. The study conducted by Rook et al. [26] Reported as Angiotensin-converting enzyme is said to be one of the responsible factors for tissue damage triggered by the DOX therapy. The ACE is causing the pro-inflammatory, pro-fibrotic effects which make interference in the kidney and nephrons to maintain the glomerular pressure and filtration rate of blood [27, 28]. The cases of nephropathy and proteinuria are rare in humans susceptibility towards such condition based on the genetic makeup of the individual.

### 2.3 Neurotoxicity

The brain is the largest and most complex organ in the human body contains about 100 billion neurons with 1 trillion established connections throughout the body. DOX is not able to transfer through the blood–brain barrier (BBB), therefore DOX effects against the brain via indirect way [29, 30]. These effects include: depression, anxiety, decrease in motor functions, haemoglobin levels, perception skills affected, and menopausal status, visuospatial skills are affected through cancer chemotherapy. The recovery of the cognitive functions may take up to a year [31]. The DOX mediate increase TNF-α level (inflammatory cytokines produced by the macrophages/monocytes during the acute inflammation involved in many signalling pathways) in the brain at cortex and hippocampus of mice [32–34]. The mitochondrial activity, glutathione-S-transferase, GSH levels, and MnSOD levels in the brain are decreased and increase in levels of 4-hydroxynoneal (HNA), thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA) and increase in levels of protein carbonyl groups [35–38], which causes increase the oxidative stress in the brain cells and further led to cause cell damage.

The MnSOD levels in the brain generally detoxify the oxygen free radicals, inactivated by the Nitric oxide (NO). The DOX indirectly increased the concentration of NO by overexpressing the Nitric oxide synthase enzyme [37]. A study conducted on the NOS dependent brain injury with DOC reinforcing the nitric oxide tissue damage [38]. The mitochondrial activity is very important in the brain because it is a powerhouse of cells (energy production) brain uses 20% of body glucose for energy production to conduct and maintain the regular activities [39]. The DOX induces generation of MDA, TBARS, and HNA which cause the decrease the mitochondrial activities. A study conducted on the DOX-induced toxicity on rats with 10 mg/kg dose, the rats died between 10 and 50 days with observed

light microscopic studies reveals that specific changes in the ganglionic cells of the peripheral nervous system [40].

### 2.4 Cardiomyopathy

This side effect found to be a dose-dependent on DOX. The DOX-induced cardiotoxicity occurs acutely and chronically. The acute effects occur within one week period the patient may experience arrhythmia, hypotension, and super ventricular tachycardia. These abnormalities are generally reversible in a noticeable period [41]. The chronic effects are shown in only 1.7% of patients with a 50% mortality rate [42, 43]. The chronic effect of DOX such as congestive heart failure reported in a study, when the patients are treated with dose 500–550 mg/m$^2$ in more than 4% of patients when treated with the dose is 551–600 mg/m$^2$ 18% of patients cause the CHF, and almost 35% of patients observed with CHF when treated with >601 mg/m$^2$ [44, 45].

A study conducted by the Zordosky and EI-kadi on DOX-induced toxicity reported as the induction of Brain natriuretic peptides, atrial natriuretic peptides genes, monooxygenases, cytochrome P genes and hypertrophy markers responsible for the xenobiotics and certain endogenous substances [46]. The inductions of these genes are cause cardiac hypertrophy leading to heart failure and altered the arachidonic acid mechanisms. A study reported the DOX effects based on the concentrations, at low concentrations DOX dose (o.5–1 μM) causes the alterations in structural proteins (includes sarcomeric myosin, nuclear lamina), plasma membrane blebbing (causes change in cell shape), and mitochondrial depolarization and fragmentation. At high concentration causes (5–50 μM) causes the cytoplasm vacuolization, swelling of mitochondrial cells, promote the cellular alterations (**Figure 2**) at the cellular and nuclear membranes [47]. The DOX reportedly binds

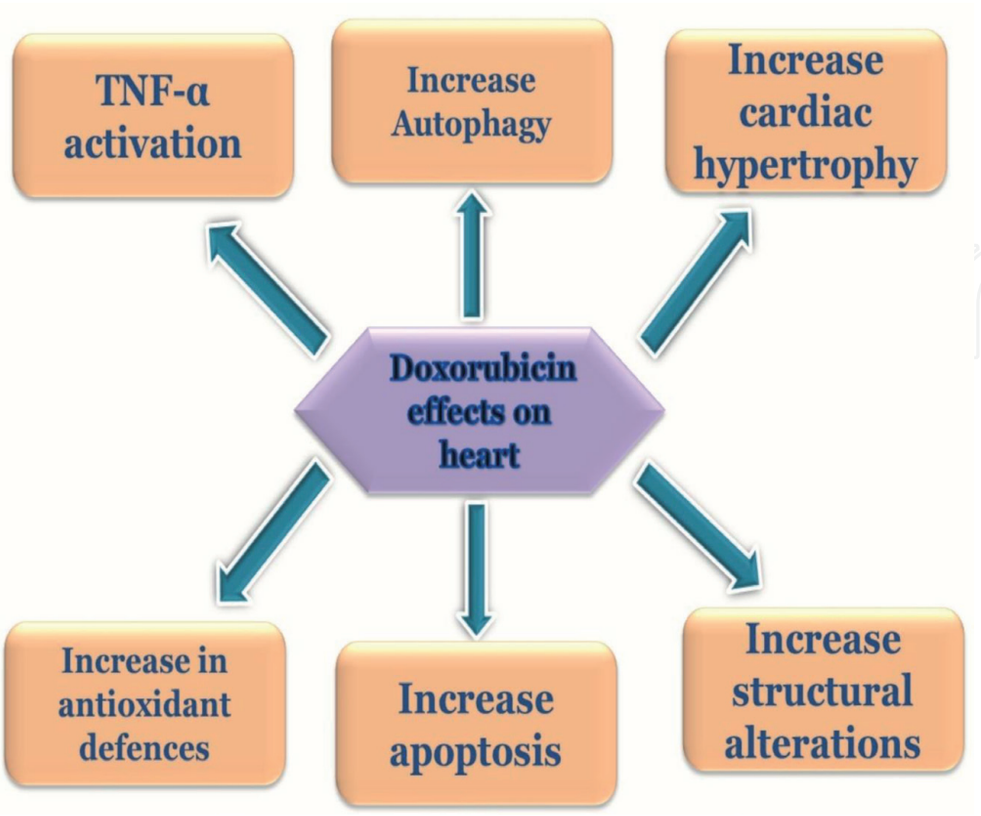



**Figure 2.**
*DOX-mediated effects on the Heart.*

to the cardiolipin (a mitochondrial inner membrane component), which raises the accumulation of the DOX inside the mycoplasma when compared to the other body cells. The high concentration existence of the NADPH dehydrogenase inside the mitochondria initiates the redox reaction in the complex and promotes the production of the Reactive oxygen species. Myocytes are generally having low levels of anti-oxidants when compared to the other tissue cells, considerably DOX shows enhanced effects on the heart and cause toxicity [48–50].

The antioxidant level differences were observed in rats under DOX treatment based on the age differences, younger Fischer rats contain more levels of antioxidants when compared to old Fischer rats. A recent study stated the involvement of the Toll-like receptor TLR-4 (a specific receptor in the immune system generally recognise the multiple bacterial antigens and plays a major role in the maturation of the phagosomes) [51]. The increase in TLR-4 expression in the DOX-induced Cardiomyocytes, when studied the cardiomyopathic cells in humans and animals. The deficiency of TLR shows decreased in lipid peroxidation and nitrotyrosine levels in cardiomyopathic cells. The other study on the glutathione peroxidase 1 (GPx) enzyme is present in both cytosol and mitochondria play a major role in the detoxification. The study conducted with the insertion of DOX on non-GPx and wild type mice, the results showed based on the study on myocytes of the non-GPx mice having the high concentration of the DOX deposits in cells, when compared to wild type mice [52–54].

The oxidative stress is a major cause for the exhibiting the cardiotoxicity, involved the generation of higher amounts of ROS cause the cellar alterations and damage are referred to as oxidative stress. The ROS is countered by the anti-oxidant system in the body, in cancer patients under the DOX chemotherapy observed the decreased the levels of GSH, TRAP levels in the body. The ROS is generation is catalysed by NADPH oxidase enzyme [55, 56].

$$\begin{gathered} O_2 + e^- \rightarrow \dot{O}_2^- \\ 2O_2 + NADPH \rightarrow 2O_2^{\bullet -} + NADP^+ + H^+ \end{gathered} \tag{1}$$

In mitochondrial cells, the same reaction is mediated by NADH –ubiquinone oxidoreductase enzyme.

$$2O_2 + NADH + H^+ \rightarrow O_2^{\cdot -} + NAD^+ + 2H^+ \tag{2}$$

The generated oxygen radical undergo dimutation with hydrohen molecules and forms hydrogen peroxide reaction is mediated by the SOD enzyme [55].

$$2O_2^{\cdot -} + 2H \xrightarrow{SOD} H2O2 + O_2 \tag{3}$$

The generated less active hydrogen peroxide is removed by the enzymes like catalase, glutathione peroxidase.

$$\begin{gathered} H2O2 \xrightarrow{Catalase} 2H2O + O2 \\ 2GSH + H2O2 \xrightarrow{GPx} GSSG + 2H2O \end{gathered} \tag{4}$$

The generated oxygen radicals combine with the H2O2 and form the highly active hydroxyl radicals. The H2O2 also reacted with the ferrous ions resulting in the formation of ferric ions and reactive hydroxyl radicals [55].

$$\begin{gathered} O_2^{\cdot -} + \mathbf{H2O2} \rightarrow OH^- + OH^{\cdot} + O_2 \\ Fe^{2+} + H2O2 \rightarrow Fe^{3+} + OH^- + OH^{\cdot} \\ Fe^{3+} + O_2^{\cdot -} \rightarrow Fe^{2+} + O_2 \end{gathered} \tag{5}$$

Under stress conditions, oxygen radical facilitates the ferrous iron from the ferric ion. The iron, under normal conditions sequestered within the ferritin (a globular protein and forms the nanocage with the metal-protein complexes) but with regards to DOX when converted to its semi-quinone form complexes with iron-free radical and converted to DOX forms while generating the oxygen free radical. The generated complexes block the iron-free regulating proteins (IRP), and then these IRPs bound to the iron-responsive elements in mRNA ferritin. The tremendous amounts of free iron releases and gain complexes with the DOX. This specific condition magnifies the production of ROS in cells [57–59].

The ROS acts as secondary signalling molecules shows direct effects on the lipids, proteins, DNA, and RNA in various pathways involved in cell proliferation, cell death and maintain the homeostasis. It is domineering to maintain the levels of ROS in the body, in case of the heart the effect is maximum by ROS due to lack of efficient levels of anti-oxidants in myocytes. The conditions such as cellular hypertrophy, alterations in the gene expressions, ventricular remodelling, the extracellular matrix of the mitochondria transformation, calcium transient perturbation and cell death activation such kinds of pathological changes may be observed in myocytes lead the death of cells.

## 2.5 Mechanisms involved at different levels of cardio toxicity

### *2.5.1 Cellular hypertrophy*

A particular disorder marked by an increase in cell size and volume. The abnormality shows an improvement in the degree of protein synthesis, increased in the organisation of sarcomere (contractile muscle fibre unit). At molecular level induction of hypertrophy associated genes are triggered by the DOX treatment which are alpha myosin heavy chain, ventricular myosin light chain-2, and atrial natriuretic peptide genes [60]. The main signalling cascades of the hypertrophy are tyrosine kinases, PI3K/Akt [61], and NF-$\kappa$B [62, 63], protein kinase C (PKC), mitogen-activated protein kinases (AMPK [64]; ERK1/2 [65], p38 [66], and JNK) which are increased in DOX therapy induce cellular hypertrophic conditions [67].

### *2.5.2 ECM remodelling*

Extra cellular matrix is a molecular network consisting of glycol conjugates, proteins, glycosaminoglycans and adhesive receptors that associate with each other and forms frame network, where cells reside on them [68]. The ECM frame work is present in all tissues it continuously shifts in quantitative and qualitative terms on a daily basis. In case of myocytes ECM is essential for attachment, alignment and orientation facilities the cellular contractions in myocytes. Changes in the ECM of the heart found in DOX treatments, the symptoms of DOX are related to the activation of the Membrane Metalloproteinase enzymes MMP-2 & 9 in 4 weeks of treatment [69]. Changes in MMP-2 activate the Akt channels; suppress the superoxide dismutase enzyme, which raises the amount of superoxide levels, and induce caspase-3 and all other agents together promote remodelling and apoptosis [70].

### *2.5.3 Impaired cardiac contraction*

The heart cells (cardiomyocytes) composed of myofibrils with typical contraction and relaxation. Pump and propel the blood to systemic circulation. Myofibrils contain multiple contractile units called sarcomere, which have actin and myosin filaments. In a calm state, actin is coated in tropomyosin and protects

the myosin-binding sites. The troponin and tropomyosin are attached when the calcium enters into the cytosol from the sarcoplasmic reticulum; calcium binds to the troponin and the position of the tropomyosin and troponin changes resulting in shortening of the sarcomere. That specific condition termed as cardiac contraction controlled by calcium influx and myofilaments. DOX could affect the transcription and expression of the specific proteins [71]. Transcription factor-like GATA4 for the regulation of sarcomeric synthesis and cardiac differentiation and survival of myocytes. DOX-induced ROS decreases binding function, disrupts sarcomere structure, contractile reduction and myofibrillar deterioration [72]. DOX is believed to interact with calcium homeostasis by modifying the ion pump and modifying the ion channel movement, resulting in lipid peroxidation. ROS quickly targets the fatty acids of the membrane lipids and disrupts the mitochondrial calcium channels by increasing the activity of the voltage-sensitive L-type calcium channels on the cell membrane resulting in accumulation of calcium [73]. Calcium overload throughout cytosol, Causes the disruption in the contraction and relaxing of cardiomyocytes.

### *2.5.4 Cell death*

The general apoptosis is a process where a cell commits to suicide, damage to genetic material, protein, cellular organelles that beyond the repair would trigger the suicide to save the energy and resources. Apoptosis firmly regulated process involves intrinsic mitochondrial apoptosis, extrinsic death receptor pathways [74]. The mitochondrial pathway relays on the Trans membrane potential is a key indicator of membrane permeability. It is assumed that permeability can be either permeability-dependent or independent of the pore transition [PT]. The PT pore consists of the adenine nucleotide translocator, matrix protein cyclophilin D, and voltage-dependent anion channel. The opening of the PT pore activates the dissipation of the proton gradient produced by electron transport, resulting in the uncoupling of oxidative phosphorylation. The opening of the PT pore also allows water to penetrate the mitochondrial matrix, resulting in the swelling of the intermembrane space and the rupturing of the outer membrane allowing the release of apoptogenic proteins. Released proteins include cytochrome c, apoptosis-inducing factor and endonuclease G. Cytochrome c in conjunction with apoptosis protease activating factor (APAF-1) and pro-caspase 9 forms an apoptosome, which in turn activates effector caspases that collectively facilitate the execution of apoptosis. Due to decrease in the number of normal cardiomyocytes is significantly reduced, the heart failed to pump the blood sequentially ventricular remodelling and death of myocytes [75].

The death receptor pathway involves the binding of death ligands such as FasL, TNF-α to their respective membrane-bound receptors. The bonded ligands signals to various proteins mediate the cascade, which leads to apoptosis of the cell [76]. In cancer therapy, DOX-induced ROS activates the $p^{38}$, $p^{53}$ and NF-kB pathways resulting in the differences in pro- and anti-apaptonic signalling imbalance, such imbalance cause release of cytochrome C from mitochondrial membrane proteins, subsequently lead to apoptosis of cell [77, 78].

### *2.5.5 Autophagy*

Autophagy is a method of restoring or repairing the destroyed cells. It is a self-degrading mechanism (survival mechanism) to maintain a balance of life in response to dietary stress, energy depletion. Autophagy destroys malformed proteins, weakened organelles, and other cell infections, which can be unique or non-specific, but processes are not completely thought out. Under diseased

environments, autophagy either facilitates cell death or induces cell death depending on the demands of different people [79, 80]. In DOX-based therapy toxicity mediated autophagy by suppressing GTAT4 expression and activating S6K1, this plays a direct and indirect role in autophagy control. Autophagy varies due to species differences; autophagy dependent on DOX is increased in mice but decreased in autophagy has been seen in mouse cases [81–84]. The autophagy achieved in DOX therapy via several mechanisms, such as ATG 5 & 12 is the inhibitors of the Bcl-2 family, which regulate the cytochrome release from the mitochondria. Cytochrome C releases the caspase-9 lead to the autophagosome, can regulate the apoptosis. In some other studies, autophagy reduces the DOX-induced cardiotoxicity by decreasing mitochondrial ROS formation.

### 2.6 Diagnosis

The DOX-induced cardiomyopathy consists of a complete examination of the cardiovascular system for detecting the symptoms, such as S3 gallop and elevated jugular vapour pressure, T wave impairments; low voltage QRS complexes are measured.

- Electrocardiography combined with Doopler studies used to study early diagnostic symptoms of the cardiac myopathy through the measure of latero-ventricular dysfunction.

- Radionuclide ventriculography used to access the latero-ventricular systolic and diastolic function. Observes the cardiac adrenergic denervation occurs in case of doxorubicin induced cardiomyopathy.

- Metaiodobenzylguanidine based nuclear imaging can be employed to assess cardiac adrenergic denervation occurred trough the DOX based cardiomyopathy.

- The DOX treated patients are sensitive to the indium labelled monoclonal antimyosin antibodies (myosin an ATP dependent superfamily of motor proteins major role in muscle contraction and motility) used to detect the cardiac myopathy, myocarditis, chagas heart disease ischemic myocardium, and kawasaki heart disease [85].

- The measurement of the cardiac enzymes and neurohormones are used for detecting the heart failure but not a characteristic feature of the DOX-induced cardiomyopathy [86].

- The presence of endomyocardial biopsy is the best route for detecting the DOX-induced diseases, according to the grade of biopsy severity of the disease is measured [87, 88]. It is invasive and requires experience for recognising the results become a disadvantage for this technique.

## 3. Management & preventive strategies for doxorubicin cardiotoxicity

The DOX has an extreme side effect like cardiotoxicity, but is still in use because of its efficacy in the treatment of cancers. Toxicity can be avoided in several ways. Many studies have shown that cardioprotective agents can achieve a reduction in cardiotoxicity. A recent research on HSP-20 (heat-shock protein) has shown that the

protection of Akt activity prevents the cardiotoxic effect caused by DOX [89–92]. Different kind of agents is used to control the DOX effects such as Dexrazoxane (DZR); it contains bisdioxopiperazine rings falling under alpha-amino acid and the derivative compound also known as cardioxane or Totect or Zincard. A promising compound that activates after hydrolysis and resembles the EDTA structure after conversion makes complexes with Iron and reduces the incidence of anthracycline-iron complexes, thus preventing ROS generation in myocytes. Dexrazoxane has also been known to contain the Topoisomerase II enzyme function and inhibit the tumour cell growth. Used mainly for the activities of iron-chelating agent, cardiac protection, anti-neoplastic activities, and chemo protection. Indirectly active in chromatin remodelling complexes by activating vitamin D receptors. DZR is often known to provide up-regulation of the ERK and Akt pathways to guard against cardiomyopathy [93–96] but DZR is not approved for routine use in patients with metastatic cancer and other forms of cancer, as stated by the American Clinical Oncology Society [97, 98]. DOX was analysed in association with DZR for 10 years in women with breast cancer [99]. No, people suffer from heart disease over the time and there are no records of adverse effects with respect to the heart.

Diuretics are used to avoid signs of systemic and pulmonary ventricular obstruction, and medications dependent on β-adrenergic receptors are used depending on the type of systolic heart problem [100]. Metoprolol is safe and effective in the treatment of cardiac myopathy [97], angiotensin II is also recommended for advanced heart disease cases, and low-dose isosorbide dinitrate substituted angiotensin inhibitor medication is favoured and hydralazine is favoured for cardiomyopathic myopathy.

The successful release of DOX at a particular site of operation is another form of preventive step. Like liposomal dosage formulations, the specified delivery mechanism passively decreases the impact caused by non-cancerous cells. For liposomes drug interaction with blood and cancer cells, structural characteristics such as vesicle size, pharmacokinetic characteristics such as stability and pharmacodynamic characteristics such as plasma clearance are important. Tumour cells have conditions that favour high-level depositions, because newly developed cells have microvasculature-permeable vessels, which contain poor lymphatic drainage, low levels of lipase enzymes and other oxidising agents. Due to these features of cancer cells shows aggregation. Once liposomes enter the tumour cells the differences in the intestinal pH favours the release of drugs constituents. The pH of cancer cells is differ from other normal cells because of this the drug is preferentially released in tumour cells and avoid the toxicity in non-cancer cells. The recently reported formulation of polyethylene glycol-coated liposomal doxorubicin (PLD) shows better pharmacokinetics relative to general formulations and has fewer side effects [101]. A phase clinical trial of 50 mg/m2 PLD administration in patients with carcinoma with a demonstrated history of platinum-based chemotherapy at intervals of 4 weeks reported low toxicity. The other formulation like poly (ethylene oxide)-b-poly (e-caprolactone-DOX) [PEO-b- P(CL-DOX)] prevents the premature release outside of the tumor cells [102].

The development of analogues is another possible strategy for reducing the toxicity [96], in the case of anthracyclines nuclear targeted and Non-nuclear targeted are two kinds of strategies concerned in the development of non-toxic chemotherapeutic agents. Analogues such as Methoxymorpholinyl doxorubicin (MMDX), sabarubicin and *N*-Benzyladriamycin-14-valerate now under development to reduce the toxicity caused by DOX. In which, MMDX is nuclear-targeted analogue activated by the liver enzyme cytochrome P450 3A and metabolize into a cytotoxic metabolite and degrades slowly [103]. Based on gene therapy expression of cytochrome enzyme activity increased, cytochrome increases the therapeutic

potency of the DOX. The sabarubicin (disaccharide analogue) is also another nuclear targeted molecule that has improved efficiency especially used in case of lung and gynaecological cancer [104]. This stimulates the NF-kB transcription factor, which happens earlier as DNA is involved with multiple tumorogenesis, regulating the expressions of differentiation, variations, cell adhesion and apoptosis [105]. N-Benzyladriamycin-14-valerate is a non-nuclear target molecule obtained by modification of the C-3 amino group and the C-14 position [106]. The compound has comparable activity to DOX but is theoretically more effective than DOX by activating the protein kinase enzyme resulting in cardio-protective activity.

## 4. Conclusion

Even DOX used for treating several types of cancers as a result of its wide range of pharmacological activities, but at the same time it causes a wide range of side effects. The major side effects caused by DOX are: carditoxicity, neuropathy, hepatotoxicity, nephrotoxicity, alopecia, typhlitis, myelosuppression, neutropenia, anaemia, and thrombocytopenia. DOX increasing the oxidative stress, decrease the GSH, vitamin E levels, and activates the NF-kB levels causes' hepatotoxicity. Besides, it interferes with the glandular podocytes of the kidney and cause nephropathy. Also, it induces generation of MDA, TBARS, and HNA which decrease the mitochondrial activities and increase in ROS generation causes cell necrosis. Moreover, it causes induction of brain natriuretic peptides, atrial natriuretic peptides genes, mono oxygenases, cytochrome P genes; binds to the cardiolipin, the increase in TLR-4 expression, generation of ROS led to several pathological changes in myocytes causes cardiomyopathy. Several strategies are made to manage and decrease DOX's cardiotoxicity effects, includes a change in the dosage forms for efficacious delivery systems, administration along with anti-oxidants, DZR, diuretics and β-adrenergic agents, and development of different analogues for increasing the efficiency of DOX.

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## Conflict of interest

The author declares no conflict of interest.

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