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Different Drugs are Tried to Counteract the Cardio Toxicity of Doxorubicin and their Suggested Mechanisms: A Review Article

Ibrahim El-Sayed*

Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo, Egypt

***Corresponding author:** Ibrahim El-Sayed, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo, Egypt, Tel: +201009384801; E-mail: ibrahimelsayed_hassen@yahoo.com

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Abstract

Doxorubicin remains an important drug of chemotherapeutic agents. Unfortunately, its efficacy in treating in different types of cancer cancer is limited by a cumulative dose-dependent cardiotoxicity, which can cause irreversible heart problems and cardiomyopathy. It is very critical to understand the mechanism of doxorubicin induced cardiotoxicity to counteract this problem. Oxidative stress, apoptosis, autophagy and senescence are the most important causes for its cardiotoxicity, therefore, different drugs like melatonin, metformine, captopril, rosuvasatatin and omega-3 can be considered feasible candidates to protect against its cardiotoxicity. Therefore, the mechanisms of its cardiotoxicity as well as different drugs used to counteract it are discussed in this review.

Keywords: Doxorubicin; Cardiotoxicity; Oxidative stress; Melatonin; Metformin; Captopril; Rosuvastatin; Omega-3

Introduction

Doxorubicin, also known as hydroxydaunorubicin, is an anthracycline antibiotic, its structure is closely related to the natural product daunomycin, and like all anthracyclines, works by inhibiting DNA replication [1,2]. Its effectiveness is marvelous as it is commonly used to treat some types of leukemia and Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma, and others [3,4]. Unfortunately, it has well known dose dependent cardiotoxicity effects [5]. The mechanism underlying the severe cardiotoxicity of doxorubicin and other anthracyclines is not fully cleared ,however, there is evidence that drug toxicity may be produced due to free radical formation and subsequent redox cycle with O_2 resulting in the generation of reactive oxygen species such as superoxide anion, hydroxyl radicals and hydrogen peroxide[6,7]. The heart is particularly susceptible to injury by doxorubicin induced oxygen radicals because of its less developed antioxidant defenses, like Glutathione in reduced form (GSH) and Superoxide Dismutase (SOD) [8,9]. There are different trials to counteract the cardiotoxicity of doxorubicin in an attempt to increase its safety without reducing its antitumoral effect.

Mechanism of Cardio toxicity

Doxorubicin-induced heart damage may be due to different mechanisms such as an increase in cardiac oxidative stress, as indicated by Reactive Oxygen Species (ROS) induced damage such as lipid peroxidation, along with reduced levels of antioxidants and mercapto groups (SH) [6,7]. It was found that irregularities in myofibrillar and intracellular calcium are also important mechanisms for doxorubicin-induced cardiac toxicity [10,11]. There are at least two targets for doxorubicin-induced apoptosis, it was found that cardiac cells and endothelial cells are affected by doxorubicin-induced apoptosis, as evidenced by caspase activation and internucleosomal DNA damage [12,13]. Additionally, the changes in the high-energy phosphate pool, endothelin-1 levels, and disturbances of myocardial adrenergic signaling are the most suggested causing factors of cardiac toxicity associated with doxorubicin administration [14,15]. All of these molecular mechanisms of cardiotoxicity are discussed in greater detail below.

Oxidative stress

The induction of free radicals production is the best described mechanism through which doxorubicin injures the myocardium [6,7]. The heart's unique sensitivity to oxidative stress, has given this aspect of doxorubicin-induced cardiomyopathy an overwhelming interest in the old and recent researches [6-9]. Through the past thirty years, it was focused on that the understanding of how free radicals are produced and how they destroy the heart. It was found that the enzymes such as Nitric Oxide Synthases (NOS) and NAD(P)H oxidase have a pivotal role in inducing oxidative stress when interacted with doxorubicin [16].

Mitochondrial dependent ROS: The mitochondria are the most importantly and aggressively damaged subcellular organelles of doxorubicin-induced cardiomyopathy [17]. This may be due to the fact that the cationic drug doxorubicin is

enclosed in the mitochondrial inner membrane by forming a nearly-irreversible bond with cardiolipin [18]. The electron-transport chain requires cardiolipin binding to function properly, and it has been discussed that since doxorubicin disrupts the binding between cardiolipin and protein, more superoxide (O^{2-}) formation occurs [6]. Other membrane proteins, such as those responsible for carnitine transfer, can also be adversely affected by doxorubicin, contributing to the decline in mitochondrial function [19]. It is quite understood that these events disrupt mitochondrial and therefore cellular metabolism, because more than 90% of the ATP utilized by cardiomyocytes is produced by mitochondria [20,21]. This functional disruption causes ultrastructural pathologic changes such as mitochondrial swelling and myelin figures within the mitochondria [22].

However, experiments showing doxorubicin-induced myocardial dysfunction were often done with supraclinical doses of doxorubicin [23]. Yet clinical doses of doxorubicin can also directly produce mitochondrial disruption, but the effects are less severe [24]. In a model of chronic doxorubicin-induced cardiomyopathy, it was found that the oxidation of long chain fatty acids in cardiac mitochondria is significantly reduced, while glucose metabolism is increased, expressing an overall shift from aerobic to anaerobic metabolic state [25].

Manganese Superoxide Dismutase (MnSOD) overexpression has been shown to enhance cell survival in case of doxorubicin through its role as a free radical scavenger in mitochondria [26]. In addition, upregulation of glutathione peroxidase (Gpx1), a cytosolic and mitochondrial enzyme that decreases hydrogen peroxide (H_2O_2) and fatty acid hydroperoxides, protects cardiac cells against acute doxorubicin-induced cardiomyopathy and prevents deterioration of mitochondrial respiration and inhibition of complex I activity [27,28]. It is well-known that mitochondria play a pivotal role in the pathogenesis of doxorubicin-induced cardiomyopathy [29]. Prevention of mitochondria dysfunction will protect from myocardial alteration and subsequently make better cardiac outcomes [30].

NAD(P)H-dependent ROS: Doxorubicin and NAD(P)H can produce O^{2-} in the absence of any enzymatic activity, although this is a minor source of O^{2-} radicals at best [31]. Recently, the importance of the NAD(P)H complex in the development of doxorubicin-induced cardiomyopathy has been confirmed pharmacologically *in vitro* using NAD(P)H inhibitors on cultured cell lines and in experiments where inhibitors of NAD(P)H activity were found to enhance cell survival [32]. Furthermore, NAD(P)H is such a large polypeptide chain, it was suggested that Single Nucleotide Polymorphisms (SNP) in any one of the subunits might make the NAD(P)H complex more vulnerable to doxorubicin induced cardiomyopathy as it can produce more free radical [33].

Fe–DOX complex: It was demonstrated that doxorubicin had a strong affinity for iron, and that the iron complex could cause defects in lipid metabolism through its interactions with the negatively-charged membranes [34]. It was noted that doxorubicin reduction in the presence of free iron also sets up a cycle for free radical generation (redox recycling) and the metabolite doxorubicinol is known to interact with mercapto groups on proteins, producing the damages to the cell [35].

However, the free iron content of most cells is very low including cardiomyocytes [36]. In physiological conditions, there is no enough free iron to couple with doxorubicin to the extent necessary to cause cardiomyopathy [37]. It was suggested that the effects of doxorubicin on iron metabolism are not mediated by doxorubicin-iron interactions, but rather *via* the proteins that sequester and bind intracellular iron [38]. One such mechanism involves the doxorubicinol metabolite forming complexes with the Fe–S group the cytoplasmic aconitase/IRP-1 (iron regulatory protein), thereby enhancing the stability of transferrin mRNA and preventing translation of iron sequestration proteins [39]. The subsequent decrease in IRP-1 leads to a decrease in the iron sequestering protein and an increase in free iron, which could continue the cycle of free radical generation [39]. It is concluded that a critical component of doxorubicin-induced cardiotoxicity is interference with iron sequestration.

Noteworthy, there is a wide variability in body iron stores in patients complaining of cancer chemotherapy due to abnormal blood losses, blood transfusions, iron supplementation, and nutritional status in these patients. Adult and pediatric patients undergoing treatment for leukemia, thalassemia, sickle cell anemia and other malignancies can develop a significant level of iron overload during, and as a result of chemotherapy, bone marrow transplantation and blood transfusion [40].

Cellular death

The most probable second mechanism of doxorubicin induced cardiotoxicity is cellular death. There are different types of cell death as apoptosis, necrosis, autophagy and senescence.

Apoptosis: Apoptosis is a programmed cell death which is critical for cell homeostasis. The steps of apoptosis include cell membrane shrinkage, DNA destruction, chromatin concentration, and form what is called "*apoptotic body*" that allows for its removal by phagocytosis. There are two pathways of apoptosis including extrinsic and intrinsic pathways. In the extrinsic pathway, death ligands (FasL, TNFα, TRAIL) bind with their receptors leads to activation of caspase 8 and then activation of caspase 3 [41]. Mitochondrial cytochrome C release leads to activation of the intrinsic pathway. The Bcl-2 family has a pivotal role in case of this pathway , the Bcl-2 family includes three groups: anti-apoptotic members Bcl-2, Bcl-XL, and Mcl-1, pro-apoptotic members Bax and Bak, and BH3 only proteins such as Bad, Bid, Nix and BNip3 that increase apoptosis via inhibition of anti-apoptotic Bcl-2 proteins or activation of pro-apoptotic Bax and Bak [41]. In the cytosol, cytochrome c forms a complex with the adaptor protein apoptosis protease activator protein-1 (Apaf-1), dATP, and caspase 9. The result is the formation of a structure known as the apoptosome, which in turn activates caspase 9 [42]. Both extrinsic and intrinsic apoptotic pathways converge on the activation of downstream executioners, caspases 3, 6, and 7 [43]. The mechanism of DOX-induced cardiomyocyte apoptosis has been extensively studied in both acute and chronic cardiotoxicity and it was suggested that the caspase 3 has a pivotal role in doxorubicin induced cardiotoxicity [44]. Additionally, it was reported that Death Receptors (DRs), including TNF receptor 1 (TNFR1), Fas, DR4 and DR5, are critical mediators of apoptosis through which

doxorubicin may cause cardiomyocytes apoptosis as Fas and FasL expressions were increased in rat cardiomyocytes following doxorubicin treatment [44].

Necrosis: On the other hand, necrosis is a different form of cell death which is typically described as early rupture of the plasma membrane and swelling of cytoplasmic organelles, in particular the mitochondria [45]. Necrosis is different from apoptosis as necrosis is swelling then rupture of cell membrane but apoptosis is shrinkage of cell contents [45]. However, it was shown that necrotic cell death can be well controlled and programmed [45]. Additionally, it was shown that DOX treated mice hearts have a cardiac expression of proinflammatory cytokine, inflammatory cell infiltration, and necrosis [46]. Oxidative stress is implicated in necrotic cardiomyocyte death. The use of free radical scavengers protected cardiomyocytes from anthracycline induced necrosis due to a strong relation between necrosis and oxidative stress [47]. The rationale is that increased ROS leads to mitochondrial calcium overloading, promotes Mitochondrial Permeability Transition (MPT) pore opening, causes mitochondrial swelling and ATP depletion, and hence triggers necrotic cell death [48].Therefore, it was assumed that the mitochondrial calcium homeostasis may exert a critical factor in the accumulative and irreversible cardiomyopathy associated with long-term DOX treatment.

Autophagy: Additionally, when cytosolic proteins and organelle are degraded through engulfment into double-membraned vesicles known as "*autophagosomes*", which then fuse with lysosomes and subsequently degrade the contents, this process is called autophagy [49]. It normally occurs in the myocardium, represents the most prevalent renewal mechanism of cellular constituents. Additionally, autophagy is substantially enhanced in pathological conditions, including cardiac hypertrophy, cardiomyopathy, and heart failure [50]. It was indicate that autophagy has an advantage and a disadvantage in the heart under stress. The advantage is the removal of protein aggregates and damaged organelles as a pro-survival pathway maintaining energy homeostasis, while the disadvantage is cell death occurred by intense enhancement of autophagy [50]. There is a strong correlation between calcium, ROS and autophagy. Reactive oxygen species-induced increase in intracellular calcium induces autophagy by activation of calmodulin dependent kinase and AMP-activated protein kinase [51].

Mitochondria play a pivotal role for autophagic, apoptotic, and necrotic pathways. Autophagy is induced to degrade and recycle cytoplasmic components in condition of mild stress. With increasing stresses, apoptosis begins to occur because of cytochrome c release from mitochondria. Under extreme stress, mitochondrial permeability transition occurs in all mitochondria, the intracellular supply of ATP is exhausted, and necrosis occurs because of ATP depletion in case of extreme stress [52]. Doxorubicin induced cardiotoxicity may be due to apoptosis, necrosis and autophagy. These three types of cell death may be occurred due to free radicals production due to oxidative stress and alteration in calcium hemostasis.

Aging (senescence): Moreover, progressive accumulation of macromolecular damage, growth arrest of normal somatic cells, and reduction in function, mainly affects long-lived postmitotic cells such as neurons and cardiac myocytes is called aging. Telomere shortening, accumulation of DNA and chromosomal damage, as well as the expression of cell cycle inhibitors p16INK4a and p53 lead to controlling senescence. Oxidative stress, altered gene expression/mutations, inflammation, reduced cellular protection and repair, altered cellular metabolism, altered protein degradation machinery and autophagy machinery are the known factors involved in senescence [53]. Cardiomyocyte senescence may play a role in DOX-induced latent myocardial toxicity many years after the last treatment.

Approaches to reduce the cardiotoxicity of doxorubicin

There are different trials were done to reduce the cardiotoxicity of doxorubicin and increase its antitumoral effect aiming to use a lower dose of doxorubicin and we here want to demonstrate different drugs or herbal components used to achieve this goal.

Melatonin: Melatonin is a hormone secreted from the pineal gland at night. It has different pleiotropic actions such as direct and indirect anti-apoptotic effects and most prominently the antioxidant activities which include expression of genes relevant to redox metabolism, including modulation of mitochondrial electron flux [54]. These aforementioned data supported different researchers to suppose that melatonin might reduce the cardiotoxicity of doxorubicin.

For example, Govender et al. aimed to investigate the effects of melatonin on cardiac function and tumor growth in an acute model of doxorubicin-induced cardiotoxicity *in vivo* and *in vitro*. For the *in vitro* study, H9c2 rat cardiomyoblasts were pre-treated with melatonin (10 μM, 24 h) followed by doxorubicin exposure (3 μM, 24 h). It was observed that melatonin increased the level of ATP in rat cardiomyocytes which was attenuated by doxorubicin treatment. In the in vivo study, female rats were inoculated with a LA7 rat mammary tumor cell line and tumors were measured daily. Animals were injected with doxorubicin (3 × 4 mg/kg) and/or received melatonin (6 mg/kg) for 14 days in their drinking water. It was found that doxorubicin treatment increased cardiac cell death which was reduced with melatonin treatment as melatonin might inhibit the level of caspase -3 in cardiomyocytes and different pathways of apoptosis were inhibited after melatonin treatment. Additionally, it was observed that melatonin when used with doxorubicin increased cardiac output in rats compared to doxorubicin-treated rats. Furthermore, melatonin reduced the tumor growth when combined with doxorubicin. These results indicated that the melatonin treatment has a dual cardio-protective and antitumoral effects by improving cardiac function whilst simultaneously reducing tumor growth during doxorubicin-induced cardiotoxicity [55].

Additionally, Liu et al. designed a study to explore the protective effects of melatonin and its analogs 6-hydroxymelatonin on the survival of doxorubicin-treated mice and on doxorubicin-induced cardiac dysfunction. It was found

that melatonin protected against doxorubicin-induced cardiotoxicity and increased the survival rate of mice treated with 25 mg/kg doxorubicin without interference with its antitumor effect [56]. Furthermore, Fan et al. found that there is a synergism between melatonin and doxorubicin by inhibiting hepatoma cell growth and induces cell apoptosis in cancer cells [57].

Metformin: Metformin (dimethyl-biguanide) is an effective oral antidiabetic drug which decreases hepatic glucose production. It also increases the peripheral glucose uptake in skeletal muscles. It is a drug of choice for the treatment of overweight and obese type 2 diabetic patients. It increases insulin sensitivity and reduces the glycated hemoglobin A1C. Additionally, it has multiple biological benefits including platelet antiaggregating effect. There is also a demonstrable anti-oxidant action of the drug explaining its vascular protective effect. Additionally, it has a cardioprotective effect as it improves cardiac remodeling in heart failure. There is evidence that activation of adenosine monophosphate-activated protein kinase and endothelial nitric oxide synthase, and a reduced collagen expression are crucial for this effect [58]. Therefore, metformin is one of different drugs used to reduce cardiotoxicity of doxorubicin.

For example, Zilinyi et al. aimed to examine the protective role of metformin and its effect on autophagy in doxorubicin-induced cardiotoxicity. Rats were used and divided into four groups at random. The doxorubicin-treated group received doxorubicin (3 mg/kg every second day) intraperitoneally. The metformin-treated group received 250 mg/kg/day metformin *via* gavage. The doxorubicin + metformin-treated group were given both at the above-mentioned doses. Serum levels of Lactate Dehydrogenase (LDH), creatine phospho kinase iso-enzyme MB (CK-MB) enzyme, troponin T, and cardiac Malondialdehyde (MDA) were evaluated. Histopathological examination by Masson's trichrome staining and Western blot analysis were conducted for heart tissue samples for evaluating the expression level of AMP-activated protein kinase (AMPK) and autophagy-associated proteins. It was revealed that the treatment with metformin caused a significant decline in serum troponin T and cardiac MDA levels, and remarkable improvement in heart function confirmed by histopathological features [59].

Angiotensin converting enzyme inhibitors (ACEIs): ACE inhibitors (ACEIs) are drugs that are routinely administered in the clinic and have clearly shown positive therapeutic profiles for the treatment of heart failure caused by a number of cardiovascular diseases. ACEIs have free radicals scavenger and antioxidant properties. The protective effects of ACEIs against hypertension and oxidative damage may in part be related to the increase of specific activities of antioxidant enzymes such as the superoxide dismutase, glutathione peroxidase, and catalase [60]. Moreover, ACEIs have a cardioprotective effect due to inhibition of the formation of angiotensin II and aldosterone. Angiotensin II has a bad effect on the heart due to its mitogenic and vasoconstrictor effects [60]. It was reported that the sulfhydryl group in captopril is responsible for its free radicals scavenger effect [61]. The scavenging action of captopril was examined against superoxide anion, hydroxyl radical, or hypohalite radical [61]. Bagchi et al. reported that captopril is an extremely potent free radical scavenger, scavenging power being as effective as superoxide dismutase against superoxide anion [61]. Additionally, Andreoli demonstrated that captopril is able to scavenge hydrogen peroxide and prevent oxidant-induced cell injury [62]. Finally, Zieden et al. showed that captopril has antioxidant effect against copper-induced oxidation of low-density lipoprotein [63]. It was reported that the concurrent administration of ACEI with doxorubicin treatment not only ameliorated cardiotoxic effects of doxorubicin, but also prevented doxorubicin-induced free radical formation [64, 65]. Noteworthy, it was reported that doxorubicin-induced cardiac dysfunction was attenuated by administration of enalapril in the drinking water through preservation of mitochondrial respiratory efficiency and reduction in free radicals formation [64].

Recently, El-Sayed et al. showed that captopril (25 mg/kg) administration produced a significant increase in the survival rate of mice which markedly declined after doxorubicin (12 mg/kg) treatment. It was found that captopril increased the ratio of heart weight to body weight in mice. Additionally, captopril decreased the levels of MDA and TNFα in mice hearts. Additionally, they found captopril might increase the antitumoral effect of doxorubicin in hepatocellular carcinoma [66].

Statins: Statins are competitive reversible inhibitor of 3-Hydroxy-3-methylglutaryl coenzyme (HMG-CoA-reductase). They are very effective in treating patients with lipid disorders and atherosclerosis [67]. However, in addition, it is their anti-inflammatory and antioxidative pleiotropic effects which, independent of their lipid lowering potential, are relevant beneficial mechanisms of this drug class [68]. It was shown that a chronic treatment with statins using a dose too low to alter the lipid profile, led to attenuation of vascular damage, which was contributed by a reduction of inflammation and oxidative stress [69]. Because doxorubicin-induced cardiotoxicity has been shown to be sufficiently triggered by cardiac oxidative stress and inflammation, different statins for example atorvastatin, fluvastatin, simvastatin, and rosuvastatin were used in different trials aiming to reduce the cardiotoxicity of doxorubicin [66,70,71]. Riad et al. aimed to know whether or not statin pretreatment can produce cardioprotective effects in a mouse model of doxorubicin-induced cardiomyopathy and they found that fluvastatin (100 mg/kg p.o.) improved left ventricular function which was declined after doxorubicin treatment in mice [70]. Fluvastatin treatment was associated with reduced cardiac expression of nitrotyrosine, enhanced expression of the mitochondrial located antioxidative SOD 2, attenuated mitochondrial apoptotic pathways, and reduced cardiac inflammatory response [70].

Additionally, it has been reported that simvastatin can exert significant cardioprotective effects against doxorubicin-related cardiotoxicity through suppression of endoplasmic reticulum stress and activation of Akt signaling and its administration has been suggested as an encouraging approach to manage doxorubicin cardiotoxicity [71]. Furthermore, El-Sayed et al.

showed that rosuvastatin (20mg/kg p.o. for three weeks) might increase the antitumaoral effect of doxorubicin and reduce its cardiotoxicity in experimentally induced hepatocellular carcinoma in mice [66].

Fermented *Cordyceps sinensis*: *Cordyceps sinensis* (CS) is one of the rare traditional Chinese herbs, only a very limited amount of natural CS is produced. Fermented CS, as a substitute for natural CS, is widely used in the field of supplementary medical treatment and health products. CS has long been used to improve quality of life and promote longevity. It has a wide range of pharmacological effects, such as immune regulation, antitumor, anti-senescence, and hypoglycemic and hypolipidemic actions [72]. Wu et al. demonstrated that the activities of glutathione peroxidase and catalase and the scavenging activity of O^{2-} in serum, and the total superoxide dismutase activity in cardiac tissue compared to doxorubicin treated mice (7.5 mg/kg) were significantly elevated after CS treatment. Additionally, CS declined the malondialdehyde content in liver and cardiac tissues [72]. Therefore, fermented CS may be considered as good trial used for the prevention against various cardiac diseases induced by doxorubicin.

Omega-3: Omega 3 fatty acids are fats commonly found in marine and plant oils. They are Polyunsaturated Fatty Acids (PUFA) have a double bond (C=C) starting after the third carbon atom from the end of the carbon chain when counting is started from the methyl group. The fatty acids have two ends—the acid (COOH) end and the methyl (CH_3) end. It was found that the certain n−3 fatty acids are converted into eicosanoids, but at a much slower rate. Eicosanoids made from n−3 fatty acids are often referred to as anti-inflammatory [73].

Additionally, omega-3 fatty acids have important properties as membrane stabilizers and can alter cell membrane fluidity. Fatty acids are an essential constituent of the cell membrane, where they modulate the action of membrane-bound transporters and enzymes. Noteworthy, El-Sayed et al. designed an experiment using omega-3 (1 gm/ kg p.o.) with doxorubicin (12 mg/kg i.p.) in an attempt to reduce the cardiotoxicity of doxorubicin, in this study also, captopril and rosuvasatatin were used with doxorubicin and a comparison was made between these three drugs. They showed that omega-3 increased the level of anti-oxidant power as glutathione in reduced form (GSH) and Superoxide Dismutase (SOD). Paradoxically, the level of malondialdehyde as a parameter of oxidative stress was increased after omega-3 treatment. It was found that omega 3 might reduce the cardiotoxicity but to a lesser extent than captopril or rosuvastatin did [66].

Additionally, Uygur et al. demonstrated the cardioprotective effects of fish omega-3 fatty acids on doxorubicin-induced cardiotoxicity in rats. Omega-3 (400 mg/kg/day) was given for 30 days by intragastric intubation. Doxorubicin (30 mg/kg) was injected intraperitoneally by a single dose to induce acute cardiotoxicity. The doxorubicin-treated group with fish n-3 fatty acids therapy caused a significant reduction in the activity of terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling in cardiomyocytes. Furthermore, in contrast to the results of El-Sayed et al., the doxorubicin-treated with fish n-3 fatty acids group showed a significant decline in malondialdehyde level, and an increase in superoxide dismutase and glutathione peroxidase activities when compared to the doxorubicin-treated group [74]. It was concluded that the both studies examined the cardioprotective effects of omega-3 as anti-oxidant or anti-apoptotic drug.

Beta blockers: Beta blockers such as carvedilol and nebivolol have cardioprotective effects especially in case of heart failure. Carvedilol has anti-oxidant properties, anti-ischemic and vasodilator effects [75,76]. There are different animal studies reported that the anti-oxidant properties of carvedilol lead to the reduction of acute cardiotoxicity and nephrotoxicity from doxorubicin [77,78]. However, Kim et al. reported that myocardial injury and LV systolic/diastolic dysfunction caused by doxorubicin was alleviated by co-administered rosuvastatin, but not by carvedilol [79]. Nebivolol is vasodilator and cardioselective beta blocker through the releasing of nitric oxide; it has anti-oxidant and anti-apoptotic effects [80]. Additionally, Shafik et al. showed a significant reduction of Doxorubicin induced cardiotoxicity and nephrotoxicity in nebivolol-treated animals more than carvedilol treated animals [80]. Therefore, they can be considered a good combination to protect against cardiotoxicity commonly encountered with doxorubicin treatment.

Calcium channel blockers: The mechanism of doxorubicin induced cardiotoxicity may be attributed to calcium overload in mitochondria which leads to activation of ROS and consequently causes mitochondrial swelling and ATP depletion, and therefore triggers necrotic cell death [47,48]. Felodipine is one of dihydropyridine and vaso-selective calcium channel blockers and it was assessed against doxorubicin-induced cardiotoxicity. The results were marvelous as felodipine improved cardiac marker enzymes, additionally; it prevented damage to myocardial tissue through inhibition of myocardial caspase-3 activity. Felodipine was able to maintain normal histopathological examination of heart without causing any harmful effects on the myocardium [81]. Additionally, nicardipine and amlodipine have a cardioprotective effect against doxorubicin induced cardiotoxicity and this effect is not only due to calcium channel blocking activity but also due to their antioxidant effects that act by direct scavenging effect, conservation of glutathione peroxidase enzymes activity, and inhibition of lipidperoxidation [81].

Conclusion

Doxorubicin is very effective drug in treatment of different types of cancer but it has a problematic issue inducing severe dose dependent cardiotoxicity. It is very critical to understand the mechanism of doxorubicin induced cardiotoxicity to counteract this problem. Oxidative stress and cellular death are the most important causes for its cardiotoxicity, hence, different drugs like melatonin, metformine, captopril, rosuvasatatin, beta blockers, calcium channel blockers and omega-3 can be considered feasible candidates to protect against its cardiotoxicity. These drugs may have anti-oxidant, anti-apoptotic effects or reduce the calcium overload in cardiomyocytes. Therefore, it is recommended that more researches and clinical studies are needed to demonstrate the actual mechanism of

doxorubicin induced cardiotoxicity and to decelerate this effect aiming to increase the effect of doxorubicin without causing serious side effects.

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