



Review Article

Doxorubicin-Induced Cardiotoxicity: Mechanisms and Management

Karmand Salih Hamaamin¹ , Tavga Ahmed Aziz^{1*} ¹ Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Kurdistan Region, Iraq

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Abstract

Unfortunately, anticancer medications are extremely harmful to normal cells. Doxorubicin (DOX) is a highly cardiotoxic medication that can result in cardiomyopathy. The most significant mechanism for DOX-induced cardiotoxicity is oxidative stress, while other pathways have also been put forth. This review aims to highlight the mechanisms of DOX-induced cardiotoxicity and the most updated managements. Trustworthy sites such as Google Scholar, PubMed, and Research Gate were used to find the most updated articles. Many titles have been used for searching, such as "doxorubicin and cardiotoxicity," "cardioprotection," and "cardio-protective effects of phytochemicals." Preprints, review articles, and research with meta-analyses were disregarded. Three pathways, including oxidative stress, mitochondrial damage, and calcium excess, were responsible for DOX-induced cardiotoxicity. Cardiotoxicity may be partially caused by cell death, activation of the ubiquitin-ligase-proteasome system, and changes in its gene expression brought on by DOX. In the instance of DOX cardiotoxicity, medications and nutraceuticals with antioxidants and iron chelating properties have been found to have cardio-protective benefits. In conclusion, doxorubicin-treated cancer patients have been linked to cardiotoxicity, making cardioprotection extremely important in these patients. All of the mechanisms included in this review's discussion might provide light on fresh approaches to the treatment and/or prevention of DOX-induced cardiotoxicity.

Keywords: Doxorubicin, Cardiotoxicity, Mechanisms, Management.

السمية القلبية التي يسببها دوكسوروبيسين: الآليات والوقاية

الخلاصة

لسوء الحظ، الأدوية المضادة للسرطان ضارة للغاية بالخلايا الطبيعية. دوكسوروبيسين (DOX) هو دواء شديد السمية للقلب يمكن أن يؤدي إلى اعتلال عضلة القلب. الآلية الأكثر أهمية للسمية القلبية التي يسببها DOX هي الإجهاد التأكسدي، وهناك أيضا مسارات أخرى. تهدف هذه المراجعة إلى تسليط الضوء على آليات السمية القلبية التي يسببها DOX والوقاية منها. تم استخدام مواقع جديرة بالثقة مثل الباحث العلمي من Google و PubMed و Research Gate للعثور على أحدث المقالات. تم استخدام العديد من العناوين للبحث، مثل "دوكسوروبيسين والسمية القلبية" و "حماية القلب" و "التأثيرات الوقائية للقلب للمواد الكيميائية النباتية". تم تجاهل المطبوعات المسبقة ومقالات المراجعة والتحليلات التلوية. هناك ثلاثة مسارات، بما في ذلك الإجهاد التأكسدي، وتلف الميتوكوندريا، وزيادة الكالسيوم، مسؤولة عن السمية القلبية التي يسببها DOX. قد تكون السمية القلبية ناتجة جزئيا عن موت الخلايا، وتنشيط نظام ubiquitin-ligase-proteasome، والتغيرات في التعبير الجيني الناتج عن DOX. في حالة السمية القلبية، تم العثور على الأدوية والمغذيات مع مضادات الأكسدة وخصائص مخلب الحديد لها فوائد وقائية للقلب. في الختام، تم ربط مرضى السرطان المعالجين بالدوكسوروبيسين بالسمية القلبية، مما يجعل حماية القلب مهمة للغاية في هؤلاء المرضى. قد توفر جميع الآليات المدرجة في مناقشة هذه المراجعة الضوء على مناهج جديدة لعلاج و/أو الوقاية من السمية القلبية التي يسببها DOX.

* Corresponding author: Tavga A. Aziz, Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Kurdistan Region, Iraq, Iraq; Email: tavga.aziz@univsul.edu.iq

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INTRODUCTION

Patients with cancer may live longer thanks to chemotherapy. The slight positive impact, nevertheless, might be explained by a poor quality of life. Cardiovascular damage appears in the majority of cancer patients who survive as a result of the use of cytotoxic medications and [1-3]. The long-term cardiotoxic effects of doxorubicin (DOX) are particularly dangerous for cardiac muscle cells because of their high degree of specialization and minimal potential for regeneration [4]. Doxorubicin, a cytotoxic medicine from the antibiotic antitumor family, is used alone or in combination with other therapeutic approaches such surgery, radiation therapy, and chemotherapy to treat a variety of malignancies. It is recognized that certain types of cardiac illness, such as cardiomyopathy and heart failure, are brought on by high cardiotoxicities of DOX. It could take some time for this harmful effect to become latent and may not immediately manifest [5,6]. Cardiotoxicity brought on by DOX is categorized as either acute or chronic [7]. Cardiotoxicity can be indicated by heart electrical abnormalities such as ST-segment and T-wave abnormalities, sinus tachycardia, attenuated QRS values, prolonged QT intervals, and ventricular and atrial arrhythmias. Acute toxicity affects 40% of patients [6]. Cardiotoxicity that persists over time is a symptom of fatal cardiac cell damage [8]. The loss of left ventricular ejection fraction is typically the most severe side effect of chemotherapy-induced cardiotoxicity in clinical settings [9]. Cardiomyopathy affects 8–26% of DOX patients, according to one study [10]. The three main processes behind DOX-induced cardiotoxicity are assumed to be the development of oxidative stress, mitochondrial damage, and calcium overload [11].

Risk Factor Associated with DOX-Induced Cardiotoxicity

Several risk factors are related to the development of cardiovascular problems associated with DOX, among those risk factors that are pre-claimed to be linked to cardiotoxicity are the following:

1. The total dose of DOX is more than 500-550 mg/m². The dosage regimen is considered to be the most critical and serious risk factor related to cardiomyopathy [12].
2. Concomitant use of DOX with radiation enhances cardiac cell damage [13]. Allen and Ace [14] documented that children are more likely to develop cardiotoxicity because of such a combination.
3. Other pre-existing cardiovascular morbidities, such as low left ventricular ejection fraction and high blood pressure, increase the risk of cardiotoxicity following DOX treatment [15].
4. DOX-induced cardiotoxicity is more common in children (15 years) and the elderly (> 65 years) [14]. It has been emphasized that the suppressive effect of DOX on the development of cardiac cells accounts for this effect in children [16], while in geriatrics, DOX increases the severity of other cardio-degenerative morbidities [14].

Monitoring DOX-Induced Cardiotoxicity

The early detection of DOX cardiotoxicity requires therapeutic drug monitoring (TDM). TDM entails measuring DOX's plasma levels in order to evaluate its pharmacokinetics for a suitable dosage regimen [17]. TDM can be treated using a variety of methods, such as measuring DOX and its metabolite or obtaining a sample of cardiac cells. In addition, cutting-edge methods like 111-antimyosin imaging with 123-labeled meta-iodobenzylguanidine are promising monitoring tools in the event of DOX-induced cardiotoxicity. Additionally, the electrocardiogram (ECG) is regarded as another method for assessing cardiotoxicity prior to the start of DOX medication since changes to the ECG, such as the lengthening of the QRS and an increase in heart rate, have been linked to DOX treatment [18].

Biomarkers of DOX-induced Cardiotoxicity

Alterations in heart rhythm, radionuclide angiography, and physical examinations can all be utilized to detect DOX-induced cardiotoxicity [19]. Ischemia is the condition that causes heart damage the most frequently. In cases of heart failure, stressful conditions including inflammation and oxidative stress can potentially injure cardiac cells. Troponin T and I are the most common markers for myocyte damage [20]. Not long after doxorubicin therapy, the serum level of troponin starts to increase. This result has been linked to left ventricular dysfunction [21]. Two other biomarkers, brain natriuretic peptide and N-terminal pro-brain natriuretic peptide, are also elevated during left ventricular failure. These two markers are particularly useful for detecting cardiotoxicity brought on by DOX [22]. Since it is generally established that oxidative stress is a key factor in DOX-induced cardiotoxicity, many biomarkers have been created to measure the level of oxidative stress. These biomarkers include indirect indicators of oxidative stress including heat shock protein, malondialdehyde (MDA), myeloperoxidase, and plasma-oxidized low-density lipoproteins. Cardiotoxicity can also be identified using other biomarkers such chromogranin A, galectin-3, and osteoprotegerin [23]. This study will go through all the molecular theories put forth for DOX-induced cardiotoxicity as well as all the drugs and nutraceuticals used in the past 12 years, either as preventative measures or as treatments.

METHODS

The following databases were searched: PubMed, Research Gate, and Google Scholar. At first, the research was studied, and then the results were gathered for scientific evaluation. Out of the 120 articles searched for the current study, 76 were eligible and included in the review. Several different titles were applied to search for DOX induced cardiotoxicity, such as "DOX and cardiac problems," "cardiotoxic effect of DOX," "molecular mechanisms of DOX-induced toxicity," "cardioprotective

effect of different drugs in DOX-induced cardiotoxicity," "treatment of DOX-induced heart problems," etc.

RESULTS AND DISCUSSION

Molecular Mechanisms of Doxorubicin-Induced Cardiotoxicity

DOX-induced cardiotoxicity is caused by a variety of varied routes, including increased amounts of intracellular iron, increased formation of free radicals, and decreased levels of glutathione and antioxidant enzymes such as glutathione peroxidase [24].

Interaction with topoisomerase II β

Induction of double-strand DNA damage and apoptosis via inhibition of topoisomerase 2 β (TOP2 β) and 2 α in the cardiac cells partly accounts for DOX-induced cardiotoxicity. In fact, the heart only expresses TOP2 β while TOP2 α is specifically generated in cancerous cells. In this respect, Zhang *et al.* [25] conducted a study on mice to emphasize the role of TOP2 β in DOX-induced cardiotoxicity. The result elucidated that knocking out TOP2 β protected cardiac cells from cardiotoxicity, which could be due to the downregulation of DNA damage and cardiac cell death together with the protection of mitochondria against reactive oxygen species generated by DOX.

Mitochondrial reactive oxygen species generation

Doxorubicin activates the calcium/calcineurin signaling pathway. The stimulation of nuclear factor-activated T cell type 4 (NFAT4) is to blame for this. The level of Fas and Fas ligand (Fas/FasL) will consequently rise [26]. The nuclear factor kappa β (NF- κ B) signaling pathway, which functions as an apoptotic stimulator and mediates this via stimulating apoptotic regulators including Fas, Fas ligand (FasL), and the C-Myelocytomatosis oncogene (c-Myc), is likewise activated by reactive oxygen species (ROS) [27].

Reduction of FLICE-like inhibitory protein's appearance

The production of ROS, which has a number of additional mechanisms to mediate cardiotoxicity, is a result of the action of DOX. Reduced FLICE-like Inhibitory Protein (Flip), a FLICE/caspase-8 inhibitory protein, appearance is one of these ways. It consequently quickens Fas-mediated programmed cell death. The innate immune system has also been connected to the regulation of apoptotic pathways. Toll-like receptor-2 (TLR-2) is a "death receptor" that also makes use of caspase-8 and Fas Associated Via Death Domain (FADD) as apoptotic inhibitors without the traditional cytoplasmic death domain (Figure 1) [28].

Doxorubicin-induced cardiotoxicity

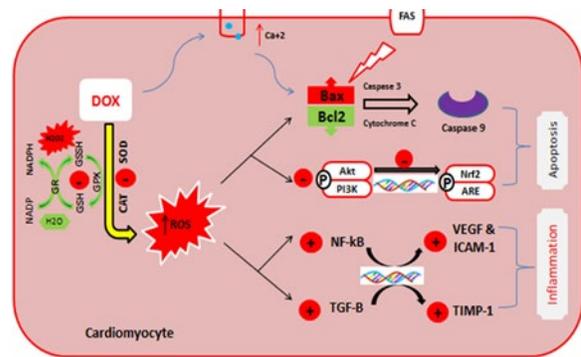


Figure 1: Schematic representation of molecular mechanism of DOX induced cardiotoxicity [75].

Change in calcium homeostasis

A shift in calcium homeostasis will result from the oxidative stress brought on by DOX. It causes ryanodine receptors in the sarcoplasmic reticulum to release calcium, increasing intracellular calcium concentrations by obstructing cardiomyocyte calcium clearance systems. When intracellular calcium levels are increased, an enzyme that generates calcium-sensitive ROS is triggered. More ROS will be produced as a result of the unequal calcium homeostasis [29]. The release of cytochrome c and apoptosis-stimulating substances from the mitochondria is encouraged by reactive oxygen species and increased intracellular calcium levels. In addition, DOX damages the heart by increasing the production of genes such as p53 that prevent tumor formation [30]. Therefore, extracellular signal-regulated kinase 1/2 (ERK1/2) activity is directly increased by DOX or ROS, which both encourage DNA damage. The downstream BCL2-associated X protein (Bax) is therefore suppressed, and p53 is then phosphorylated [28]. A mechanism other than cardiomyocyte death that can produce cardiotoxicity—p53-mediated rapamycin signaling suppression—has been connected to the cardiac defects observed in acute doxorubicin cardiotoxicity [31].

Regulation of zinc finger transcription factor GATA-4

It has been established that the zinc finger transcription factor GATA-4, which is well recognized to be a transcriptional factor, has a role in the regulation of apoptosis. It protects the usefulness and dependability of the mitochondria by turning on the anti-apoptotic gene B-cell lymphoma extra-large (Bcl/XL). This finding suggests that during DOX-induced cardiotoxicity, an inhibitor of GATA-4 known as glycogen synthase kinase-3 beta (GSK3 β) is elevated during DOX-induced programmed cell death of cardiac cells [31]. Recent studies have demonstrated that DOX increases ceramide synthesis, which promotes cardiac cell death [32]. Finally, endoplasmic and sarcoplasmic pathways are also involved in DOX-induced cardiotoxicity. Cardiomyocyte apoptosis depends on caspase-12, which is found in the sarcoplasmic reticulum. Doxorubicin (DOX) activated caspase 12 in the

rat heart when heme oxygenase-1 expression was downregulated in H9c2 cells exposed to the drug in a study [33]. Furthermore, doxorubicin's down-regulation of HO-1, which promotes intrinsic apoptosis and cardiac mitochondrial biogenesis, is mediated by the HO-1/Akt/Nrf2 pathway. The up-regulation of the lectin-like oxidized LDL receptor-1 (LOX-1) and the deregulation of a phosphodiesterase-3A/inducible cyclic adenosine monophosphate (cAMP) early repressor feedback loop were both influenced by the activation of the endocannabinoid system, activation of volume-sensitive chloride channels, and oxidative stress [34].

Role of Immunity in DOX-Induced Cardiotoxicity

The breakdown of the cardiac cell membrane brought on by doxorubicin can be brought on by immune system activation. In a rat model of high blood pressure, for instance, data analysis showed that DOX therapy increased the expression of dendritic cell antigen. This data implies that the immunological responses that follow oxidative stress have an impact on the cardiotoxicity caused by DOX [35].

Oxidative Stress in DOX-Induced Cardiotoxicity

Based on a number of in vitro studies, researchers have proposed that the main mechanism of DOX-induced cardiotoxicity is the production of free radicals such as superoxide anion [36]. Because DOX is a quinone-containing anthracycline, several enzymes, including cytochrome 450, xanthine oxidase, and nicotinamide adenine dinucleotide (NADH) dehydrogenase, can reduce DOX by one-electron reduction [4]. Through a redox-cycling process, this reaction generates a semi-quinone intermediate that can replenish doxorubicin and create a superoxide anion by reducing oxygen. After that, oxygen and hydrogen peroxide are produced by the dismutated superoxide anion. As a result, superoxide anion formation will rise while nitric oxide synthesis declines [4,36]. When active transition metals like iron are present, the Fenton reaction results in free radicals like hydroxyl radicals (OH[•]). Because of this characteristic, it has been suggested that the mechanism behind DOX toxicity may involve the creation of superoxide anion from DOX itself as well as the generation of hydrogen peroxide and hydroxyl radicals by the action of redox-active metals like iron (Figure 2) [4]. Because cardiac cells lack adequate antioxidant systems, oxidative stress brought on by DOX is extremely harmful to the heart [37,38]. Typically, mitochondrial damage occurs in conjunction with oxidative stress. As a result, DOX concentrates heavily in the mitochondria of cardiac cells, which are the cells that DOX targets [39]. An experimental study using a rat model to determine the chronic toxic effects of DOX revealed that cardiotoxicity is not caused by ROS generated by the redox cycle, despite the fact that many evidence-based studies support the role of the redox cycle and ROS generation in DOX-induced cardiotoxicity. The usage of the mitochondrial targeting

co-enzyme Q, on the other hand, was discovered to have cardio-protective benefits by promoting the redox cycle in other mitochondria [40].

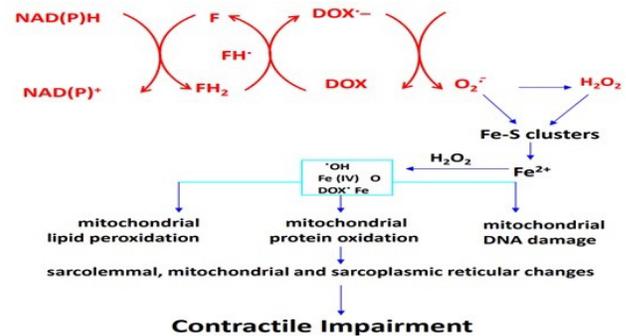


Figure 2: Schematic representation of DOX induced mitochondrial damage via generation of ROS from redox cycle [4].

Role of Calcium Level in DOX-induced Cardiotoxicity

The mitochondrial membrane is severely harmed by oxidative stress. As a result, DOX's production of free radicals will result in the permeability of the mitochondrial membrane and a variety of mitochondrial calcium carriers. Interestingly, oxidative stress alters calcium transport, which results in tissue damage, cell death, and cardiac cell excitation. When they conducted an experimental investigation to determine its impact on calcium, they discovered that DOX irreversibly reduced the capacity of mitochondria to fill with calcium [29].

Metabolic Disturbance in DOX-induced Cardiotoxicity

Unexpectedly, DOX prevents lipid peroxidation, which frequently happens in cancer patients. In actuality, lipid peroxidation results from the partial oxidation of iron to ferric iron. By altering the Fe (II)-Fe (III) balance of iron-oxygen complexes, hydrogen peroxide and DOX decrease lipid peroxidation in cardiac cells. This finding implies that cardiotoxicity may be caused by the parent DOX and other semiquinone-related metabolites. This idea is supported by the findings of a study on DOX that sought to discover its metabolites. Data analysis revealed that the function of iron-regulating proteins decreased as DOX metabolites enhanced iron release [41].

Alteration of Sarcomeric Structure

Sarcomere myofilaments that are disorganized or absent have been connected to DOX. The heart muscle sarcomere's titin, a large protein that extends from M-line to Z-disk, is an essential component. This protein has a big impact on how sarcomeres are regulated and function structurally. According to recent study, changes in titin function are the root cause of cardiomyopathy [42]. It has been demonstrated that DOX activates the proteolytic pathway, causing titin to be swiftly degraded. The energetics of the cardiac muscle become out of balance as a result. Titin can also be broken down by the calcium-

dependent protease calpain, which is activated by DOX. It's interesting to note that the reduction of this protein has been associated with the maintenance of cardiac function after DOX treatment [43]. Sarcomeric disarray may result from a decrease in cardiac ankyrin repeat protein (CARP) [44].

Role of Modulating Gene Expression

DOX may block a wide range of essential cardiac proteins, including sarcoplasmic reticulum proteins, mitochondrial proteins, contractile proteins, and others. Due to downregulation of the cardiac muscle gene, patients receiving DOX have impaired heart function [45]. In studies, GATA-4 depletion with DOX has been seen. As a result, the sarcoplasmic reticulum's expression of troponin and myosin heavy chain has been altered [46]. Numerous scientific research has shown that DOX's suppression of mitochondrial proteins causes a reduction in the energy generated by heart muscle, which ultimately results in cardiac dysfunction [47]. Another thing to keep in mind is that DOX stimulates endothelin-1 and its receptor expression [48]. Data analysis revealed that bosentan, an endothelin antagonist, effectively reduced DOX in a study by Bien *et al.* [49] to ascertain the effects of an endothelin A/B antagonist on DOX-induced cardiotoxicity. Furthermore, the author claimed that the cardioprotective benefits seen in this study were caused by lower TNF α and Bax expression, lower lipid peroxidation, and higher GATA4 expression.

Role of Apoptosis

Numerous potential routes are thought to contribute to the apoptosis brought on by DOX. Two of the most important and well-studied mechanisms are the production of reactive oxygen species and oxidative stress. Apoptosis-signaling kinase-1 (ASK1), which is also upregulated in response to oxidative stress, activates c-jun N-terminal kinase and p38 mitogen-activated protein kinase, two pathways through which ROS typically drive apoptosis [50]. In actuality, NF- κ B causes the rat's heart muscle to proliferate. As a result, the activation of NF- κ B by DOX directly stimulates apoptotic genes such as FasL, Fas, c-Myc, and p53, as has been demonstrated [51]. The activation of p53 by superoxide anions and hydrogen peroxide leads to the stimulation of the Bax gene and finally to apoptosis [52]. Furthermore, evidence suggests that the activation of the heat shock factor 1 (HSF-1), which is brought on by DOX-dependent oxidative stress, leads to an increase in heat shock protein-25 (Hsp-25), which in turn promotes the production of proapoptotic proteins. The mitigation of DOX-induced cardiac dysfunction and apoptosis, however, appears to be mediated by Hsp proteins, including Hsp27, Hsp10, Hsp20, and Hsp60, according to a number of studies [53]. Dox substantially increases the expression of death receptors at both the mRNA and protein levels, according to an *in vitro* investigation on cardiomyocytes made from

human pluripotent stem cells. According to this study, activation of the death receptor may be another way that DOX induces cardiotoxicity [54]. There is proof that DOX affects the activation of caspase. DOX activation was the root cause of cardiotoxicity, according to the findings of an animal investigation and an *in vitro* experiment employing cultured cardiomyocytes and rat hearts [55].

Role of Micro-RNA

MicroRNAs are involved in all cardiac functions, including heart electrical activity and cardiac cell expansion and contraction (miRNA). Numerous studies have demonstrated that microRNA is changed by DOX-induced cardiotoxicity. When the amount of DOX was increased, it was found that a number of microRNAs, including miR-34a, miR-34c, miR-208b, miR-215, miR-216b, and miR-367, were elevated dose-dependently in rats. It has been demonstrated that increasing the DOX dose increased the levels of multiple other microRNAs in the mouse cardiac muscle, including miR-21, miR-34a, miR-208a, miR-208b, miR-221, miR-222, and miR-320a. The downregulation of several additional microRNAs, such as miR-30a, miR-30c, and miR-30e, was seen in rats administered DOX, on the other hand. These results imply that microRNA is successfully modified by DOX [56]. The results of an excellent study performed on rat H9C9 cardiomyocytes demonstrated that upregulating miR-21 expression can minimize DOX cardiotoxicity. On the other side, downregulating miR-21 will enhance DIC. Additionally, the author discovered that miR-21 modifies the proliferation-inhibiting B cell translocation gene 2 (BTG2) to have cardioprotective effects [57].

Management of DOX Induced Cardiotoxicity

To lessen DOX-induced cardiotoxicity, a large number of pharmaceuticals and nutraceuticals have been used as a treatment approach (Table 1) and a preventive approach (Table 2).

Conclusions

In order to extend the life expectancy of cancer patients while simultaneously enhancing their quality of life, DOX-induced cardiotoxicity is a crucial issue that requires careful management. Numerous pathways, such as oxidative stress, mitochondrial damage, and disruption of calcium homeostasis, have been identified as the cause of DOX-induced cardiotoxicity. Additionally, the cardiotoxicity brought on by DOX is also influenced by changes in gene expression and stimulation of the ubiquitin-ligase-proteasome. The two main ways by which medications and phytochemicals exert cardio-protective properties are: first, their antioxidant capacity, which is amplified by increasing antioxidant enzymes and reducing lipid peroxidation; and second, their anti-apoptotic effects. All of the aforementioned pathways might provide light on fresh approaches to the treatment and/or prevention of DOX-induced cardiotoxicity.

Table 1: Medications used in the management of DOX-induced cardiotoxicity

Reference	Treatment	Type of study	Method	Mechanism	Outcomes
Alanazi <i>et al.</i> , 2020 [55]	Carvedilol Resveratrol and Liposomal resveratrol	Animal study	Five groups of animals: 1 st , Negative control group; 2 nd , Positive control group treated with DOX; 3 rd , Carvedilol+DOX; 4 th , Carvedilol+ Resveratrol+DOX; 5 th , Carvedilol+Liposomal resveratrol+ DOX	- Reduced degeneration of myocardium - Decrease inflammatory cell infiltration - Reduce oxidative stress and calcium dysregulation induced by DOX.	Beta blocker such as CAR alone possess moderate cardio-protective effect against DOX induced cardiotoxicity. The combination of CAR with RES and LIPO-RES provided better cardioprotection
Sikandar <i>et al.</i> , 2020 [56]	Trimetazidine	Animal study	Five groups of animals: 1 st , Negative control. 2 nd , positive control group treated with DOX. 3 rd , TMZ (10 mg/kg) for 5 days; 4 th , TMZ for 5 days and 10 mg/kg DOX at day-3; 5 th , TMZ for 10 days and 10 mg/kg DOX at day-8.	Trimetazidine pre-treatment for 5 days very effectively prevent elevation of biomarker enzyme of cardiac injury such as CK-MB. Pretreatment for 3 days prohibited elevation of LDH by 27%.	Pretreatment with TMZ significantly reduce cardiac and hepatic damage produced by DOX.
Ahmed <i>et al.</i> , 2018 [57]	Rosuvastatin and Telmisartan	Animal study	Eight groups of animals: 1 st , Control; 2 nd , received 15 mg/kg DOX only at day eight; 3 rd and 6 th , received 2 & 10 mg/kg rosuvastatin for 9 days and 15 mg/kg DOX one hour before administration of rosuvastatin; 4 th & 7 th received 2 or 4 mg/kg/day telmisartan for 9 days, and at day-8 15 mg/kg DOX.	Decrease oxidative stress via elevation of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, it also alleviates lipid peroxidation	The antioxidant effect of statins mainly responsible for reducing DOX induced cardiotoxicity
Jačević <i>et al.</i> , 2018 [58]	Amifostine	Animal study	Four groups of animals: 1 st , Control group; 2 nd , received amifostine only; 3 rd , received 20 mg/kg DOX only; 4 th , received 20 mg/kg DOX + 75 mg/kg amifostine 30 min before DOX.	Antioxidation via scavenging of free radicals, encourage DNA repair and inhibit programmed cell death.	Amifostine was effective protection against DOX induced cardiotoxicity
Lai <i>et al.</i> , 2017 [59]	Recombinant ACE2 agonist	Animal study	The animals were allocated into 3 groups: 1 st , control; 2 nd , received DOX; 3 rd , treated with recombinant ACE2 for 4 weeks.	Improvement of cardiac contractility, inhibition of DOX-induced autophagy, and increasing mi-R30e level and reduces beclin-1/LCII/I ratio.	Recombinant ACE2 mitigate DOX induced cardiotoxicity via its action on micro-RNA and autophagy.
Guo <i>et al.</i> , 2014 [60]	metallothionein	Animal study	Mice with deficit metallothionein I and II and mice with intact metallothionein. After 9 weeks each mouse was injected with 15 mg/kg/day doxorubicin.	Prevents disruption of mitochondrial biogenesis involving PGC-1 α pathway	Mice with deficit metallothionein are more prone to develop DOX induced cardiotoxicity. Basal MT protects against DOX-induced mitochondrial biogenesis disruption.
Ghandi <i>et al.</i> , 2013 [61]	Calcium channel blocker, felodipine	Animal study	Four animal groups: 1 st , control group; 2 nd , received 5 mg/kg/day felodipine for 2 wks; 3 rd , received 10 mg/kg/day DOX; 4 th , pretreated with 5 mg/kg/day felodipine for 2 wks then injected with DOX (10mg/kg/day).	Prevents ST elongation by DOX, normalize LDH level, prevent CK-MB elevation, inhibits apoptosis pathways and increase activity of GSH-Px together with attenuation of lipid peroxidation.	Felodipine possess cardio-protective effect against DOX induced cardiotoxicity via antioxidant effect
Choi <i>et al.</i> , 2010 [62]	Dextrazoxane	Case-control study	47 patients received dextrazoxane in a ratio of 10:1 to doxorubicin. 42 patients were received doxorubicin only.	Chelation and reduction of DOX iron conjugates.	Dextrazoxane reduces the incidence and severity of late and early cardiotoxicity associated with DOX.

Table 2: List of Phytochemicals that reduce DOX induced cardio-toxicity.

Reference	Treatment	Type of study	Method	Mechanism of action	Outcomes
Ahmed <i>et al.</i> , 2021 [63]	Chia seed oil	Animal study	4 groups of female rats: 1 st , control; 2 nd received DOX; 3 rd DOX+chia seed oil (2.5 ml/kg/d); 4 th , DOX+ chia seed oil (5 ml/kg/d).	Prevent QT prolongation, QRS and ST disturbance, mitigates CK-MB and LDH and increase GSH with reduction of MDA level	It protects against DOX cardiotoxicity via decreasing ROS and inhibits QT prolongation and QRS changes.
Zhang <i>et al.</i> , 2020 [64]	Luteolin	Animal study	4 groups of male rats: 1 st , control; 2 nd , DOX treated group; 3 rd , received 50mg/kg luteolin + DOX; 4 th , received 100 mg/kg luteolin + DOX. Heart tissue evaluated after H & E staining.	100 mg luteolin prevents histological changes, averted ECG changes, decreased CK-MB, LDH, BNP levels, attenuates ROS generation, inhibits apoptosis, elevates bcl2/bax ratio, decreases caspases, and increases p-AKT and phlpp1 expression.	Luteolin is a very strong cardioprotective phytochemical via inhibition of ROS generation, ECG changes improvement, and blocking the expression of p-AKT and Phlpp1.
Sun <i>et al.</i> , 2019 [65]	Blueberry	In vitro study	Rat cardiac cell line (H9c2) treated with four types of blueberry (Vn, Vm, Va and Vc). 1 st is control group; 2 nd , treated with 15 g blueberry extract for 4 h; 3 rd , treated with DOX only; 4 th ; treated with blueberry + DOX.	The three types of wild blueberry (Vn, Vm, Va) significantly attenuated caspas 3/7 activity and mitigate the generation of free radical (ROS) by DOX, but Vc showed no significant effect.	Blueberry possess cardioprotective effect via modulation of caspase 3/7 activity together with attenuation of ROS generation by DOX.
He <i>et al.</i> , 2018 [66]	Curcumin	Animal study	Six mice groups: 1 st , received 50 mg/kg curcumin for 6 wks; 2 nd , received 2.5 mg/kg DOX for 3 wks; 3 rd , received curcumin + DOX; 4 th ; received Curcumin + Dox + pAD/14-3-3 γ -shRNA; 5 th ; received Curcumin + Dox + pAD/scrRNAi for 4 wks, then myocardium was injected with negative control adenovirus (pAD/scrRNAi); 6 th , Control group.	It reduces LDH and CK-MB levels, mitigates ECG changes associated with DOX, increases 14-3-3 γ synthesis, enhances the anti-oxidant enzymes such as SOD, GSH-Px and decreases MDA. Curcumin maintains normal function of mitochondria.	It exerts cardioprotective effects via protecting myocardium against Dox-induced injury. It promotes translocation of Bcl-2 to mitochondria, and improves mitochondrial function.
Ma <i>et al.</i> , 2017 [67]	Rutin	Animal study	Four mice groups: 1 st , control group; 2 nd , received 3 mg/kg DOX for 2 wks; 3 rd , received 100 mg/kg rutin for 11 wks; 4 th , received rutin + DOX for 11 wks with DOX.	Rutin alleviated body and heart weight reduction mediated by DOX. It attenuates morphological changes and fibrosis by DOX, and improves cardiac function via reduction of apoptosis and autophagy.	The cardioprotective activity of rutin is mainly mediated via suppression of autophagy and apoptosis in DOX-induced cardiac injury.
Gao <i>et al.</i> , 2016 [68]	Ginkgolide B	In vitro & in vivo study	Rat heart cell line (H9c2), and rats randomly divided into 4 groups: 1 st , treated with saline and 20 mg/kg DOX group, received saline and 20 mg/kg DOX; 2 nd , received 100 mg/kg/day Ginkgolide B 4 days before DOX; 3 rd , received 20 mg/kg DOX then saline for 5 days; 4 th , received 20 mg/kg DOX and ginkgolide B (100 mg/kg/day) for 5 days.	Ginkgolide B prevents myocardial cell death and alleviates apoptosis induced by DOX. It attenuates ROS generation, prevents elevation of intracellular calcium together with mitigation of CaMKII and Akt phosphorylation by DOX.	Ginkgolide B has cardioprotective effects via regulation of the ROS, Akt and calcium pathways. Suggesting the combination of GB with DOX a promising therapy to avoid cardiotoxicity
Agustini <i>et al.</i> , 2016 [69]	Mangiferin	Animal study	Four groups of rats: 1 st , control group; 2 nd , received 15 mg/kg DOX; 3 rd , received DOX + 30 mg/kg/day mangiferin; 4 th , received DOX + 60 mg/kg/day mangiferin.	Attenuates TNF- α mRNA expression and reduces cytosol Ca level specifically at dose of 60 mg/kg, and elevates the expression of SERCA2a.	Protects against DOX-induced cardiotoxicity, down-regulates expression of proinflammatory, proapoptotic genes, increases SERCA2a gene expression, and maintains Ca homeostasis.
Hao <i>et al.</i> , 2015 [70]	Cannabidiol	Animal study	Male C57BL/6J mice. A single 20 mg/kg DOX was injected IP. Then the mice were treated with cannabidiol (10 mg/kg) either IP or via PO 1.5 hr before DOX once daily.	CBD reduces GSH level, GSH-Px activity and limits mit. complex I and II damage. It reduces iNOS, PPAR α activity and co-activator of PPAR, medium-chain Acyl-CoA dehydrogenase, estrogen-related receptor α , uncoupling protein 2 and 3, and Inhibits MMP2 and MMP9 activation.	CBD attenuates DOX-induced cardiac dysfunction, oxidative stress and cell death. CBD also enhanced the DOX-induced impaired mitochondrial function and biogenesis.
Chen <i>et al.</i> , 2013 [71]	Quercetin	In vivo study	Rat heart cell line (H9C2) was used for conducting this study.	Quercetin blocks apoptosis and changes the level of chaperone protein in myocardium.	Quercetin protects against DOX cardiotoxicity via modulating protein levels.

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Conflict of interests

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