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A review on: Doxorubicin induced cardiotoxicity and its mechanism

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Abstract

A member of the anthracycline family, doxorubicin (Dox) is a secondary metabolite of the mutant strain of *Streptomyces peucetius* var. Caesius. Dox primarily inhibits the topoisomerase II enzyme in rapidly growing tumors and intercalates DNA to exert its anti-cancer effect. Dox, however, has limited practical applicability due to dose-dependent and cumulative cardiotoxicity, which raises cancer patients' death chances. The most often described pathways for doxorubicin-induced cardiotoxicity and oxidative stress are free radical production and apoptosis.

In addition, there are additional mechanisms that contribute to Dox-induced cardiotoxicity, including decreased mitochondrial function, altered gene and protein expression linked to apoptosis, disruption of Ca2+ homeostasis, autophagy, release of nitric oxide and inflammatory mediators, and perturbation of iron regulatory protein.

As a result, we have given a thorough update on our current understanding of the pathogenic mechanisms underlying the well-known Dox-induced cardiotoxicity in this review. Additionally, we have included a few of the most likely herbal drugs can that have been tried and tested to prevent Dox-induced cardiotoxicity.

Keywords
Cardiotoxicity, Doxorubicin, Oxidative stress, free radicals

Introduction

In the early 1960s, the bacterium *Streptomyces peucetius* was the source of doxorubicin (DOX), an anthracycline antibiotic that was initially utilized as a cytotoxic medication in 1969(1, 2). Solid tumors, soft-tissue sarcoma, breast cancer, Hodgkin's disease, Kaposi's sarcoma, acute lymphoblastic leukemia, pediatric leukemia, lung cancer, lymphomas, and different metastatic malignancies can all benefit from this extremely effective chemotherapeutic drug (3, 4, and 5). Due to the drug's numerous adverse effects, which include baldness, gastrointestinal issues, and hematopoietic system suppression—with heart damage being the most serious—its usefulness is restricted (6, 7, 8).

With a prevalence rate of over 30%, patients with advanced cancer who received repeated doses of doxorubicin for longer than a month experienced severe symptoms of myocardial toxicity. Ventricular failure, a reduction in the QRS segment, cardiac dilatation, tachycardia (150 beats per minute), and hypotension (blood pressure of 70/50 mmHg) were among the many symptoms that were present (9).

Doxorubicin-induced cardiotoxicity is caused by a variety of processes and has been associated with decreased levels of antioxidants and sulfhydryl groups, as well as an increase in myocardial damage from oxidative free radicals. Apart from myofibrillar deterioration and intracellular calcium dysregulation, myofibrillar deterioration is also known to be caused by doxorubicin-induced cardiac toxicity (10, 11).

Because mi tochondrial biogenesis can activate the cell death pathway while inhibiting topoisomerase 2β, it is also thought to play a significant role in doxorubicin-mediated cardiac damage (12, 13).

In acute doxorubicin cardiotoxicity, it has been demonstrated that changes in the expression of genes specific to the heart, such as muscle-specific genes (myosin light chain, cardiac actin, and muscle creatine kinase), decrease in response to doxorubicin exposure (14, 15).

Doxorubicin-induced cardiotoxicity is caused by a number of factors, including endothelial dysfunction, an activated ubiquitin protease system, autophagy, and cell death, as well as NO release, reduced adenosine triphosphate (ATP) levels, iron regulatory protein (IRP) production, and increased inflammatory mediator release(16,17).

Mechanism of Doxorubicin-Induced Cardiotoxicity

Doxorubicin-induced DNA damage

Doxorubicin's anticancer effects may be largely attributed to the irreversible destruction of tumor cell DNA. Intercalation into DNA, which prevented the manufacture of micromolecules, the production of reactive oxygen

species (ROS), DNA binding and cross-linkage, DNA damage induced by the suppression of topoisomerase 2b (TOP2b), and the triggering of apoptosis were among the hypothesized mechanisms for its anticancer actions [18,19,20].

In a rat model, TOP2b was recently found to be a mediator of doxorubicin-induced cardiotoxicity [21]. All quiescent cells, including cardiomyocytes, contain TOP2b, which unwinds DNA strands during transcription, replication, and recombination [22,23].

Doxorubicin was once thought to be a TOP2b toxin that intercalated into DNA strands to stop DNA synthesis from occurring. DNA topology is altered by TOP2b, which can cause DNA supercoil dysregulation and temporary breakage of double-strand DNA, both of which can cause cardiomyocyte mortality. [24]

In doxorubicin-induced cardiotoxicity, P53 and activation of the apoptotic pathway have been demonstrated [25]. In cardiomyocytes exposed to doxorubicin-induced DNA damage, TOP2b is necessary for P53 activation; however, ROS generation from doxorubicin was caused by a decrease in the expression of genes encoding antioxidant enzymes, which was also TOP2b dependent [26].

On the other hand, once DNA damage occurs in a cell, DNA repair pathways are triggered. Certain enzymes eliminate oxidized bases from the nucleotidic pool, cleave oxidized bases prior to replication, or remove oxidized bases from DNA following replication (27, 28).

It has been demonstrated that these oxidized adducts are mutagenic substances, which increase DNA polymerase proofreading error and inhibit DNA replication [29].

Furthermore, doxorubicin caused damage to mitochondrial DNA (mtDNA) through the creation of adducts with its circular genome, which disrupted the mitochondrial machinery and resulted in mtDNA changes such as rearrangements, deletions, and copy number reductions. These effects were seen in the heart of doxorubicin-treated patients and animal models, but not in the skeletal muscle. This implied that mtDNA alterations might gradually accumulate, even in the absence of therapy, leading to a respiratory chain deficiency that increased ROS production and mtDNA damage. Doxorubicin has been shown to be toxic to both cancer and normal cells, however the mechanisms underlying the death of individual cells may differ [30]

Oxidative Stress

The primary cause of the degeneration of cardiac cells is the massive amount of oxidative stress produced by DOX. Oxidative stress arises from an imbalance between reactive oxygen species, reactive nitrogen species, and the intrinsic antioxidant systems. The development of this oxidative stress is caused by a number of significant cellular mechanisms, some of which are listed below [31,32].

A.Modified activities of mitochondria

The enormous oxygen requirement of cardiomyocytes is supplied by the mitochondria. The depletion of energy production in the form of ATP is caused by structural changes in the mitochondria that result from DOX treatment [33,34].

A vital component found in mitochondrial inner membranes is cardiolipin. One of the main processes causing the cardiotoxicity linked to DOX is the interaction between cardiolipin and DOX. Because cardiolipin has an anionic charge and DOX has a cationic charge, they bind irreversibly, causing DOX to build up in mitochondria. Cardiolipin plays a significant role in electron transport, but when it forms a complex with DOX, it inhibits the activation of multiple enzymes, which modifies the electron transport chain. Aside from this, myocardial toxicity events are significantly influenced by DOX-mediated oxidative phosphorylation(35,36)

B. Complex Fe–Dox

In response to interactions with the ferric ion (Fe3+), the hydroxy and ketone groups of DOX form a complex. Through its interactions with the cell membrane, this complex produces free radicals and lipid peroxidation. DOX is in charge of the buildup of iron in mitochondria and starts the myocardial cell's apoptotic process. Iron regulatory protein IRP1 is rendered inactive by DOX treatment, and transport protein Mitoferrin-2 carries iron into mitochondria along with IRP2. DOX results in alterations to IRP1's post-translational modification, loss of iron-responsive element recognition, and altered iron homeostasis [37,38].

C. NADPH's function in the production of ROS

Free radicals are produced by the catalytic actions of the enzymes mitochondrial NADH dehydrogenase and nicotinamide adenosine dinucleotide phosphate (NADPH). Angiotensin II is in charge of raising NADPH oxidase and plays a crucial part in the production of free radicals. Nitric oxide synthase is gradually produced in response to DOX treatment; P450 reductase and nitric oxide reductase enzymes help produce reactive oxygen species, which leads to the development of oxidative stress in the cardiac cell [39,40].

D. Nitric oxide produces reactive oxygen species

The enzymes neuronal NO synthase, inducible NO synthase, and endothelial NO synthase are responsible for the increased synthesis of nitric oxide that occurs during DOX treatment. Damaged cardiac tissues have elevated levels of nitric oxide. Oxidative stress in mitochondria is caused by nitric oxide produced by lipid peroxidation from peroxynitrite, which leads to necrosis and apoptosis [41,42].

E. Nrf2's production of oxidative stress

The related cardiac toxicities during DOX treatment are caused by Nrf2 protein depletion. Autophagy is induced by Nrf2 expression, which also preserves the balance between autophagy and oxidative stress [43].

Apoptosis

Cardiomyocyte apoptosis is stimulated by DOX via both intrinsic and extrinsic pathways. When DOX toxicity occurs, a number of factors become unbalanced. For example, oxidative stress increases and activates HSF-1 (heat shock factor 1), which in turn causes HSP-25 (heat shock protein). This causes p53 to become equalized, which in turn produces proapoptotic factors like Fas, FasL, and c-Myc, which is what causes cardiac muscle cell death [44,45].

DOX-induced cardiotoxicity, which results in the depletion of transcriptional factor GATA-4, is another factor accountable for the cardiotoxicity linked to DOX. GATA-4 regulates the apoptotic pathway by activating the anti-apoptotic gene Bcl-XL. Furthermore, it has been discovered that DOX-induced cardiotoxicity raises active glycogen synthase kinase 3β (GSK3β), a nucleus-based negative regulator of GATA-4 [46].

Similarly, it has been noted that DOX-induced cardiotoxicity involves a role for TLR-2 (Toll-like receptor-2)-mediated cytokine production, cardiac dysfunction, and apoptosis through the activation of the pro-inflammatory nuclear factor-κB (NF-κB) pathway [5].

According to certain research, Protein Kinase B (PKB/AKT), which is involved in the control of cell survival, proliferation, and metabolism, is inhibited in the murine hearts treated with DOX. Additionally, it is discovered that AKT is essential in reducing oxidative stress by deactivating GSK3β, which in turn reduces the nuclear export and degradation of NF-E2-related factor 2 (Nrf2) mediated by FYN nuclear translocation [47,48].

Necrosis

Various factors related to cytoplasmic and mitochondrial swelling, rupture of the plasma membrane, and coagulated sarcomere have been identified as contributing to the cellular necrosis in cardiomyocytes. The disruption of mitochondrial function may have resulted from dysregulated lipid metabolism, elevated calcium levels in the mitochondria, and stimulated mPTP opening, which causes mitochondria to swell and use less ATP, ultimately inducing necrotic cell death. Because DOX can degrade titin, a component of the cardiac sarcomere, by activating the proteolytic pathway, it has also been observed that DOX-induced cardiotoxicity is accompanied by disarray and a loss of sarcomere myofilaments [49,50].

Pyroptosis

It has been discovered that the Bnip3–caspase-3–GSDME pathway-regulated DOX-induced cardiotoxicity involves pyroptosis, a novel form of programmed cell death characterized by cell lysis, swelling, and large bubbles blowing from the plasma, which further results in the release of cell contents and pro-inflammatory molecules [51].

Increased inflammation and the activation of caspases (caspase-1, caspase-3, caspase-4, and caspase-11) are common outcomes of pyroptosis. Additionally, it is linked to the activation of the NLR family pyrin domain

containing 3 (NLRP3), which cleaves Gasdermin D (GSDMD) or GSDME and ruptures the plasma membrane, releasing interleukin-1beta (IL-1β) and IL-18, which damages cardiac cells [52,53]

Autophagy

The administration of DOX is essential for autophagy. Autophagy reactions have been observed to be both induced and inhibited by DOX treatment. AMPK and unc-51-like kinase 1 pathways mediate the reduction in the autophagy reaction [54, 55].

Additionally, DOX has been linked to a reduction in the expression of the GATA4 and Bcl-2 genes, while a rise in the expression of S6 kinase beta-1 has been linked to an increase in the expression of the autophagy gene. The up-regulation of Atg12, Atg4, Atg5, and Bad genes is caused by DOX treatment. The overexpression of the autophagy marker LC3B is linked to DOX-induced cardiomyopathy. In doxorubicin-induced cardiomyopathy, the processes of autophagy induction and inhibition are crucial [56,57].

Fibrosis

Similar to fibrosis, the pathological process is also frequently observed in doxorubicin-induced cardiotoxicity. The development of perivascular and interstitial fibrosis is caused by DOX treatment [58,59].

It is clear that the effects of DOX treatment on the MMP-1 and MMP-2 genes in cell culture and animal models are linked to the fibrosis of cardiac tissues. By blocking the transcription and translation processes that cause myocardial cells to die, DOX is the cause of the inhibition of collagen synthesis. The activation of the fibrosis signal pathway is caused by the modulating effects of DOX treatment on phosphor-SMAD3 and transforming growth factor-beta (TGF-β) [60,61,62].

Role of Herbs as Antioxidants in the Drug-Induced Cardiac Toxicity

Due to its apparent safety and potency, the use of herbs and herbal-based therapy is becoming more and more popular worldwide for treating a variety of medical ailments. Plant-based therapy has been used by traditional healers since ancient times to treat a variety of clinical symptoms. Strong antioxidant properties can be found in the powerful phytoconstituents found in various plant sections. Natural antioxidants derived from plant sources are proven to be highly helpful in treating severe drug-induced toxicities, such as organ toxicities caused by drugs . Significant preventive efficacy against organ toxicities caused by anticancer drugs was observed in many preclinical studies [63].

Animals Used	Method and Intervention	Major Findings	References

Wistar rats	Rats were exposed to cisplatin toxicity with the dose (2 mg/kg/day) for 1 week. The animals were treated with ginger (500 mg/kg) for 12 days.	Ginger treatment reported significant restoration of cardiac histology ultrastructure and a decrease in P53 and TNF-α immune expressions and creatinine kinase and lactate dehydrogenase levels against cisplatin-induced cardiotoxicity.	[**64**]
Wistar rats	Rats were intoxicated with a dose of (6 mg/kg, i.p.) with doxorubicin on alternate days (cumulative dose 30 mg/kg). The rats were treated with aloin as aqueous solution (1, 5, 25 and 125 mg/kg, p.o., once a day)	Aloin treatment restored ECG tracings and tissue antioxidant levels and reduced the levels of proinflammatory cytokines TNF-α, IL-1β, and IL-6 against doxorubicin-induced cardiotoxicity.	[**65**]
C57BL/6 mice	Mice were administered with doxorubicin with a dose of (15 mg/kg, i.p.). Mice were treated with asiatic acid (10 mg/kg and 30 mg/kg) two weeks before doxorubicin treatment	Asiatic acid treatment restored echocardiographic and tissue antioxidant level. Asiatic acid reduced oxidative stress and apoptosis induced by doxorubicin by AKT signaling pathway.	[**66**]

Conclusion

Doxorubicin (DOX), an anthracycline anticancer medication, is frequently recommended to treat malignant tumors in both adults and children, including those of the breast, ovary, leukemia, lymphoma, and other organs. Unfortunately, the administration of Dox causes cardiac toxicity, which raises the risk of mortality and restricts its broad clinical use in cancer patients. Dox-induced cardiotoxicity is caused by a variety of pathways, including as oxidative stress, reduced mitochondrial function, Necrosis , Fibrosis , Pyroptosis ,dysregulated Ca2+ homeostasis with compromised apoptosis. Targeting these changes with new phytochemicals included in herbel drugs such as ginger, Aloin, mangiferin , Asiatic acid has therefore demonstrated protective effects against Dox-induced cardiotoxicity and may lower the death rate among cancer patients.

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