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Review Article:

A Comprehensive View on Drugs-Induced Cardiotoxicity and Its Prevention

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Abstract

Background: The prevention of drug-induced cardiotoxicity is a complicated challenge facing healthcare providers during the last few decades. This challenge is raised from the unclear definition of the term "cardiotoxicity", the overlapping of the symptoms of heart dysfunction due to the underlying diseases and the used drugs or using a combination of drugs which makes it difficult to distinguish between the side effects of each drug. **Objective:** This review discusses the most causative agents of cardiotoxicity, and their mechanisms to induce cardiac muscle damage, and finally focuses on the most applicable methods to deal with these dangerous heart problems. **Methods:** The search method involved electronic databases, including PubMed, Web of Science, Springer, Google Scholar, and others to resume relevant trials of heart disease published in the period between 2010-2023. **Conclusion:** Cardiotoxicity is a common substantial adverse effect of many drugs including anticancer drugs and others. The prevention methods may include medications, such as (Enalapril or carvedilol), supplementation with antioxidants, or cardioprotective natural products.

1. Introduction

The National Cancer Institute defines cardiotoxicity as any form of toxicity that influences the heart, including direct effects on the organ and changes in hemodynamic flow or any form of thrombosis associated with disease treatment. Shockingly, research information from the National Health and Nutrition Examination reveals that 33% of long-term cancer survivors have developed heart disease (1). About 10% of drugs entered the clinical market worldwide over the past 40 years have been withdrawn due to heart-related safety problems, e.g., rofecoxib, tegaserod, and sibutramine (2). Even though massive efforts to detect cardiotoxicity during the preclinical phase of drug inventory, remain a top safety concern, primarily due to an inadequate understanding of the underlying mechanisms for cardiotoxicity development (3).

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There are multiple ways and methods for detecting cardiotoxicity. One of these methods is by measuring the left ventricular ejection fraction (LVEF) which gives an idea about variations in the left ventricular systolic work, and this is considered an important diagnostic approach for cardiotoxicity. Drug-induced cardiac tissue injury is a gradual process that causes an increase in cardiac biomarkers and structural myocardial deformation, leading to a decrease in left ventricular ejection fraction (LVEF) (4). A significant decrease in LVEF below a certain level (<50) indicates the early stages of cardiotoxicity. However, the threshold for clinical decisions may vary depending on the guidelines in place (5). Clinical data suggests that the cardiomyocytes death occurs instantaneously with the progression of cardiotoxicity (6).

People's health and even their lives are immediately at risk when drug-induced cardiotoxicity occurs. Cardiotoxicity is usually linked to anti-cancer drugs, but in fact, it's not limited to this type of drugs, as many kinds of drug groups can have unexpected cardiotoxic effects. The term 'cardiotoxicity' was first used in 1946 to describe the negative effects on the heart caused by local anesthetics, mercurial diuretics, and digitalis. In the 1970s, the term was expanded to include the heart problems resulting from cancer-treating drugs such as anthracyclines mainly

(daunorubicin and doxorubicin (DOX) (7), combined therapy (DOX and radiation), and 5-fluorouracil (5FU). In 2022, a recent study showed that the anticancer drugs that mainly have the potential to cause cardiotoxicity other than anthracyclines include, vascular endothelial growth factor inhibitors, human epidermal growth factor-2 inhibitors, proteasome inhibitors, tyrosine kinase inhibitors, and ibrutinib. In addition to these drugs, radiotherapy and hormonal therapy can also have negative effects on the heart (8).

Problems correlated to cancer-treating drugs often include dilated cardiomyopathy caused by myocardial necrosis, arrhythmias, and angina or myocardial infarction due to occluded blood vessels or vasospasm. The prevalence of both malignant and heart diseases increases with age and the existence of an underlying cardiovascular disease increases the risk of cardiotoxicity of any type making old-aged individuals more prone to develop cardiotoxicity (9). Over the years, the use of new immune, biological, and small molecule medications in addition to existing chemotherapies has led to a rise in the number of persons who survive cancer but experience cardiovascular disease which has now become a great challenge. As a result, collaborative efforts between oncology and cardiology disciplines are crucial, as patients diagnosed with cancer today may become cardiac patients in the future (10).

In addition, cardiotoxicity can be induced by other drugs prescribed for a long time, such as psychiatric or neurologic medications (11). This poses a significant challenge as the toxicity may not become apparent until after the drug or its metabolites have accumulated over a long time of usage (12). Thus, monitoring and preventing cardiotoxicity is important to avoid long-lasting and dangerous cardiac complications (13). Some researchers have studied different methods of prevention of cardiotoxicity such as using cardioprotective drugs, natural products, antioxidants and other measures (14–16). This review aimed at highlighting the mechanisms of drugs-induced cardiotoxicity and exploring the most effective approaches to treat or prevent it.

2. Method

A systematic search was conducted from August 2023 to December 2023 on the databases of PubMed, Web of Science, SpringerLink, Google Scholar, and others. The following keywords were used alone or in combination: "cardiotoxicity", "drugs-induced cardiotoxicity", "cardioprotectants", and "prevention of cardiotoxicity". We conducted a manual search of the reference lists of the included studies to identify manuscripts that were not retrieved by the electronic search engines mentioned above. The most important inclusion criteria for entering research in this review is to be published in the period from 2010 to 2023. Additionally, the research should be related to cardiac toxicity which is resulted from the use of drugs, and it is characterized by scientific rigor and reliability of the references. Whereas the exclusion criteria were any study published by other than the English language or published before 2010. In addition, studies that don't provide a sufficient detail about the drug, the dose, duration, and frequency of administration were excluded.

3. Mechanisms of drug- induced-cardiotoxicity

Drug-induced cardiotoxicity can be classified into two types. The first type, known as type 1, is irreversible and caused by anthracyclines anticancer drugs. It causes microstructural lesions in cardiomyocytes resulting in necrosis and apoptosis. On the other hand, cardiotoxicity of the second type (type II) is reversible and associated with biological drugs that target specific proteins responsible for controlling the proliferation of cancerous cells, these proteins are also essential for maintaining cardiovascular homeostasis. This type of cardiotoxicity could resolve either after the end of the treatment course or even during it (17,18).

The precise way of the cardiotoxicity induced by the drugs is still not fully understood, though it is likely to be multifactorial (19). It is essential to understand the mechanisms of anthracycline-induced cardiotoxicity to understand drug-induced cardiotoxicity in general. This comprehension is crucial for developing effective cardioprotective measures. The most common mechanisms of anthracyclines cardiotoxicity are iron complexes formation, increases in the synthesis of reactive oxygen and reactive nitrogen species, peroxidation of the lipids, inflammation, induced cardiac cells apoptosis, interstitial fibrosis, and atypical signaling of epidermal growth factor as well as beta-Arestin inhibition of nuclear topoisomerase II beta (17–20). These consequences eventually will lead to an increase in oxidative stress, which is thought to be the main cause of anthracyclines cardiotoxicity, hence the cardiac muscle lacks adequate antioxidant mechanisms (21).

There is a significant variation in the susceptibility to cardiotoxicity caused by Anthracyclines among individuals, and genetic predisposition may play a role in the presence of drug-induced cardiotoxicity. Polymorphisms in many genes involved in anthracyclines metabolism, free radical detoxification, or differences in body Fe levels may contribute to Anthracyclines-induced cardiotoxicity, Therefore, it is recommended to undergo gen examination to decrease the probability of anthracyclines-induced cardiotoxicity (22).

Antiretroviral drugs like zidovudine can cause dysfunction of the cardiac cell's mitochondria by inhibiting DNA polymerase-gamma and inducing mitochondrial DNA mutations, this can lead to cardiomyopathy (23). Mitochondria are particularly important for maintaining myocardial tissue homeostasis, so any alteration in mitochondrial function can ultimately cause cardiovascular dysfunction, and many factors can contribute to it, such as DNA damage, growth factor signaling inhibition, defective mitochondrial biogenesis, and calcium overloading (2). **Figure 1** summarizes the mechanisms of drug-induced cardiotoxicity.

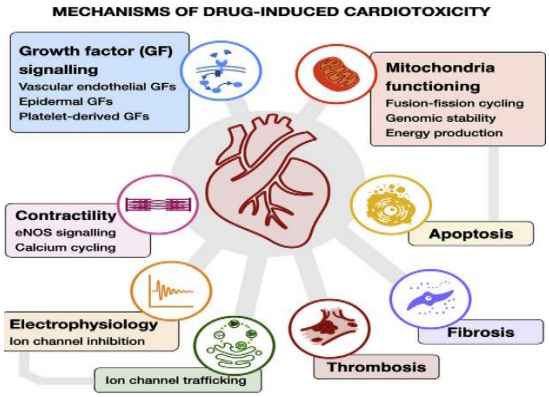

Figure 1. Mechanisms of drug-induced cardiotoxicity (3)

4. Risk factors for cardiotoxicity

Patients who are receiving chemotherapy are at a higher risk of developing cardiovascular complications, especially if they have an underlying heart disease or have also undergone radiotherapy. The time frame for cardiotoxicity varies depending on several factors such as the age of the patient during treatment and the type of chemotherapeutic drug used (12). Individuals who were treated with DOX therapy for lymphoblastic leukemia during their childhood are nearly eight times more likely to experience cardiac complications during adulthood compared to those who did not undergo such treatment (24).

Other risk factors are gender (females are more susceptible), black people, total cumulative dose, and administration of radiotherapy/cardiac irradiation with the chemotherapeutic drug (19). In addition, some researchers mentioned other potential risk factors such as abnormal echocardiogram and/or increase in cardiac biomarkers level, hypertension, obesity, diabetes, dyslipidemia, sedentary lifestyle, cigarette smoking, and genetic predisposition (24, 18, 25).

5. Drugs having the potential to cause cardiotoxicity

Many drugs have a great potential to exert a harmful effect on the heart. **Table 1** summarizes some cytotoxic drugs and their cardiotoxic effects. The most important cardiotoxic drugs will be discussed in the next section.

5.1 Anthracyclines anticancer drugs

Anthracyclines are the backbone chemotherapeutic agent of breast cancer, sarcoma, and blood cancerous diseases (26). These drugs can severely cause cardiotoxicity that can occur quickly after starting the drug regimen or as a chronic adverse effect. Cardiovascular complications within 2 weeks of dosing include electrocardiographic abnormalities, arrhythmias, and pericarditis or myocarditis (27).

revealing that acrolein triggers oxidative and nitrite stress by inhibiting intracellular Glutathione GSH and SOD while increasing Malondialdehyde (MDA) levels causing cell wall

Anthracyclines are thought to inhibit topoisomerase IIa in cancer cells that divide rapidly, while also impeding topoisomerase IIb in cardiomyocytes. This results in the formation of DNA breaks and the accumulation of reactive oxygen species (ROS), which activate apoptotic pathways, ultimately leading to cell death. Cardiomyopathy symptoms may develop in as many as 9% of patients treated with anthracyclines (28). Accordingly, the harmful effects of anthracyclines on the heart often belong to the formation of ROS, mitochondrial dysfunction, and heart muscle cell apoptosis. In addition, DOX also has been found to increase the expression of cell death receptors triggered by tumor necrosis factor (TNF), which can lead to cardiomyocyte apoptosis (29). While anthracyclines are known to cause cumulative heart damage, some manufacturers claim that their products do not cause cardiotoxicity. One such example is amrubicin, which was approved by the FDA in 2011 for the treatment of lung cancer (3).

5.2 Alkylating agents

One of the earliest platinum-based antineoplastic agents is Cisplatin, which can be used to treat several malignant diseases (30). The occurrence rate of cisplatin-induced cardiotoxicity is not well established yet. However, according to a certain study the cardiotoxicity incidence was found to be 6% in patients receiving cisplatin and 5-FU, and 1.6% in patients receiving 5-FU alone (31). Cisplatin has been shown to have both acute and cumulative cardiotoxic effects (32). These abnormalities eventually lead to the activation of caspase-3 and induce apoptosis. Recently, several studies demonstrated a strong link between production of ROS and cisplatin-derived cardiomyocyte apoptosis. It has been found that cisplatin can induce lipid peroxidation, decrease the level of glutathione (GSH), and impede the activity of superoxide dismutase (SOD), indicating the presence of oxidative stress. In addition, there were some studies indicated that cisplatin can induces nuclear DNA and mitochondrial DNA damage (4,33–35). Cisplatin is thought to enhance thromboxane A2 (TXA2) synthesis and aggregation of platelets, which can ultimately lead to serious heart diseases such as ischemic heart disease. Cisplatin also can induce electrolyte disturbances, that have a crucial role in gastrointestinal toxicity and are thought to be implicated in cisplatin cardiotoxicity (3).

Cyclophosphamide (CP) is commonly used to treat leukemia and lymphoma, as well as autoimmune diseases (4). Because of the dose-dependent manner, CP-induced cardiotoxicity can occur if administered in large doses. The percentage of patients suffering from CP cardiotoxicity ranges from 7 to 28% of the total patients using CP, Acute heart failure (HF) is also common and recognized in 7 to 33% of cases (38). These manifestations usually become clear within one week of administering a dose of more than 150 mg/kg (47). Acrolein, the active metabolite of CP, is mainly in charge of cardiomyocyte death (48). Additional studies have linked these harmful effects to oxidative stress,

lipid peroxidation. This eventually triggers damage to mitochondrial function, which ultimately leads to a decline in ATP synthesis and the activation of caspase-3, ultimately resulting in apoptosis (49–51).

Table 1. Overview of some anticancer drugs and their cardiotoxic effects

drugs		Cancer uses	Effect on the heart	Reference
Anthracyclines	Doxorubicin	Breast, sarcoma, lung, bladder, gastric, prostate, leukemia, lymphoma,	LVD, HF, arrhythmia	(36)
Alkylating agents	isofosfomide	Testicular, sarcoma, lymphoma	HF, LVD, Myopericarditis Arrhythmia	(37)
	Cisplatin	Leukemia, lymphoma	HF	(38)
	cyclophosphamide	Lung, bladder, testicular, breast, esophageal, head and neck	Arrhythmia, Ischemia, VTE HTN	(4)(38)
Antimetabolites	Capecitabine	Colon, pancreatic, breast, head, and neck	Coronary vasospasm Ischemia Arrhythmia LVD Myocarditis	(39)
	5-Fluorouracil	Breast, colon, gastric, pancreatic	Coronary vasospasm Ischemia Arrhythmia LVD	(40)
Antimicrotubular Agents	Vinblastine	Breast, ovarian, lung, sarcoma, bladder, cervical, gastric, esophageal, head and neck	HF LVD Arrhythmia Ischemia Bradyarrhythmia	(41)
	Paclitaxel	Hodgkin's lymphoma, choriocarcinoma, and testicular tumors	myocardial ischemia and infarction	(42)
HER2-Targeted Therapies (Monoclonal Antibodies)	trastuzumab	Breast, gastric, gastroesophageal	HF LVD	(43)
Tyrosine kinase inhibitors	Lapatinib	Renal, thyroid, sarcoma, GIT stromal tumor, pancreatic neuroendocrine tumor	HTN HF LVD VTE ATE	(44)
	Imatinib	Breast	HF LVD	(45)
	Sunitinib	leukemia	systolic heart failure, heart failure, left ventricular dysfunction	(46)
Hormonal therapy	Anastrozole	breast	HTN, ischemia, thromboembolism	(13)

LVD (left ventricular dysfunction), HF (heart failure), HTN (hypertension), VTE (venous thromboembolism), ATE (aortic thromboembolism).

Cyclophosphamide (CP) is commonly used to treat leukemia and lymphoma, as well as autoimmune diseases (4). Because of the dose-dependent manner, CP-induced cardiotoxicity can occur if administered in large doses. The percentage of patients suffering from CP cardiotoxicity ranges from 7 to 28% of the total patients using CP, Acute heart failure (HF) is also common and recognized in 7 to 33% of cases (38). These manifestations usually become clear within one week of administering a dose of more than 150 mg/kg (47). Acrolein, the active metabolite of CP, is mainly in charge of cardiomyocyte death (48). Additional studies have linked these harmful effects to oxidative stress, revealing that acrolein triggers oxidative and nitrite stress by inhibiting intracellular Glutathione GSH and SOD while increasing Malondialdehyde (MDA) levels causing cell wall lipid peroxidation. This eventually triggers damage to mitochondrial function, which ultimately leads to a decline in ATP synthesis and the activation of caspase-3, ultimately resulting in apoptosis (49–51).

5.3 Microtubule inhibitors

Vinca alkaloids are alkaloids derived from Periwinkle plant, including vinblastine, vinorelbine, and vincristine as the most used agents derived from this plant (52). These drugs exhibit anti-microtubule and anti-mitotic properties which are used for the treatment of Hodgkin's lymphoma, choriocarcinoma, and testicular tumors. Vinblastine acts via binding to tubulin, arresting of dividing cells at the metaphase stage and causing tumorous cell death. However, use of vinca alkaloids has been linked with cardiotoxicity (53). For instance, vinblastine is associated with myocardial ischemia and infarction (41). Vincristine causes coronary spasm and cardiac arrest (54). However, the toxoids, paclitaxel and docetaxel, which act by promotion of microtubule assembly and inhibition of microtubule depolymerization can cause bradycardia, ischemia, and heart failure (1).

5.4 Antimetabolites

Fluoropyrimidines such as 5-FU and capecitabine are integral components of various chemotherapeutic schedules. 5-FU ranks in the third position as the most frequently utilized chemotherapeutic agent for treating solid malignancies worldwide. However, it is important to note that 5-FU also utilizes the second position of the drugs that cause cardiotoxicity, following Anthracyclines (55). The most

typical manifestation of fluoropyrimidine-associated cardiotoxicity is chest pain, as well as acute coronary syndromes, including myocardial infarction (56). Other less common symptoms of 5- FU cardiotoxicity include arrhythmias (57), myocarditis, pericarditis (58), and HF (40). The administration of 5-FU triggers oxidative stress by generating O2−, which activates the caspase cascade reactions, ultimately leading to apoptosis. Researchers have observed that the increase in ROS formation induced by 5-FU is accompanied by a decrease in GSH, which acts as a ROS scavenger. This will trigger lipid peroxidation, decreasing Matrix metalloproteinase (MMP) levels, and causing mitochondrial dysfunction and caspase3 activation (59). Fluoroacetate, a metabolite of 5-FU, as illustrated in Figure (2), can inhibit aconitase and disrupt the tricarboxylic acid cycle, leading to a mitochondrial energy metabolism crisis (60). Additionally, the accumulation of autophagosomes and lysosomal membrane permeabilization was observed in 5-FU-treated human cardiomyocytes, indicating the involvement of autophagic cell death in the development of 5-FU-induced cardiotoxicity (61).

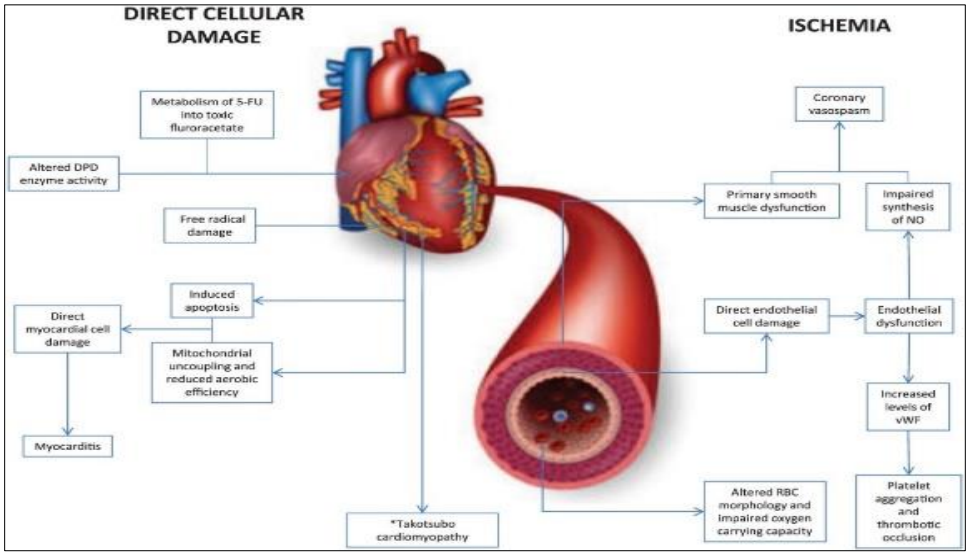

Figure 2. Mechanism of 5FU-induced cardiotoxicities (61)

DPD (dihydropyrimidine dehydrogenase), NO (nitric oxide), RBC (red blood cell), vWF (von Willebrand factor).

5.5 Monoclonal antibodies

A new and widely used monoclonal antibody medicine, also known as Herceptin®, it is a humanized monoclonal antibody. This antibody specifically binds to the extracellular domain of the human epidermal growth factor receptor-2 (EGFR-2, HER2) (62). Although this therapy has many benefits, TZP has been associated with many cardiotoxic side effects, which can exert a substantial danger to patients. As the other medications used to treat cancer, trastuzumab usage is associated with many adverse effects on the heart, including LVEF, CHF, arrhythmias, acute coronary syndrome, increased blood pressure, pericardial diseases, vasospasm and dilated cardiomyopathy (63). Anticipated that the cardiotoxicity caused by TZP may result from its negative regulation of murine double minute 2 (MDM2) and Tumor protein (p53). In addition, TZP-induced cardiac cell apoptosis was found to be related to inflammatory infiltration, and the Toll-Like receptor (TLR4) - mediated chemokine expressions of TNFα, Monocyte chemoattractant protein-1 (MCP-1) contributed to its inflammatory response. Currently, combined drug regimens including TZP are very widely used for treating cancerous diseases. The use of combination therapies is associated with an increased risk of cardiotoxicity as compared to single-drug regimens. The combination of TZP and DOX results in worsened depletion of antioxidant enzymes and damage to the structure of mitochondria (64).

5.6 Tyrosine-Kinase Inhibitors

Different mechanisms have been suspected to understand the cardiotoxicities imposed by tyrosine kinase inhibitors. Imatinib cardiotoxicity is essentially linked to the mitochondrial damage caused by B cell lymphoma 2 release (65). Furthermore, imatinib and sunitinib can promote high

ROS production which will lead to reduced cardiac cell viability (66). Dasatinib and nilotinib also have the potential to induce cardiotoxicity, probably by inhibition of vascular endothelial factor (VEGF) signaling (67).

5.7 Antidiabetic Drugs (Rosiglitazone and Pioglitazone)

Thiazolidinedione is a group of drugs to treat type II diabetes mellitus, previously regarded as a cardio protectant (68). However, as their usage expanded, rosiglitazone and pioglitazone were observed to have dangerous side effects on the heart such as myocardial hypertrophy and HF (69). A study by Baranowski et al. reported that pioglitazone up-regulates the levels of sphingomyelinase and ceramidase (70), which are mediators of cardiac cell apoptosis (71).

5.8 Antiviral Drug (Zidovudine)

Zidovudine is a member of the nucleoside reverse transcriptase inhibitors, which is commonly used in the treatment of human immunodeficiency virus type 1 (HIV-1) infection (72). However, its unwanted adverse reactions such as increased blood pressure and cardiac diseases limit its chronic use. Zidovudine causes ROS accumulation and peroxynitrite, which will cause single-strand DNA breaks, and finally results in the depletion of mitochondrial energy in a NAD+-dependent manner (73).

6. Protective strategies against drug-induced cardiotoxicities

Several strategies can help to alleviate or treat drug-induced cardiotoxicity. The most used and acceptable approach is to minimize the total dose of the cytotoxic drug (74), and to extend infusion time (75). Another way to reduce the risk of cardiotoxicity is to integrate it into the initial phases of medication creation, Substantial attempts have been made to decrease the cardiotoxic effects of the drugs during the drug design stages. For instance, epirubicin, a semisynthetic epimer of DOX, has a low cardiotoxic tendency due to its liposomal structure which decreases its distribution into the heart (7).

It is common to underestimate cardiovascular risk factors in cancer patients. According to some studies, a significant number of patients have at least one cardiovascular risk factor. A published observational data indicated that 48.8% of patients had hypertension, 26% had hypercholesterolemia, 22% had type II diabetes, and 12.8% were hypertriglyceridemic (76).

As previously described, it is essential to adequately control reversible risk factors and electrolyte disturbances to reduce and manage cardiotoxicity (77). Other risk factors, such as chronic renal failure, elderly patient, gender (female), and postmenopausal status, have also been suspected as contributing to cardiotoxicity. It is necessary to actively manage the modifiable risk factors following current guidelines. Additionally, many primary preventive approaches are recommended such as cessation of smoking, exercise in regular manner, balanced and healthy food intake (78).

Encouraging the early involvement of cardiologists is crucial in managing patients with preexisting heart conditions or those taking QT-prolonging drugs (79). In some situations, it may be necessary to stop or hold off on systemic treatment, such as when the left ventricular ejection fraction (LVEF) drops below 40% (80). To reduce the risk of prolonging the QT interval, various strategies can be adopted, such as limiting the use of other drugs that have the same effect, such as 5-hydroxytryptamine (5-HT3) antagonists and antihistamines, which are often used to prevent chemotherapy-induced nausea and vomiting.

Additionally, managing and treating comorbidities and correcting any electrolyte imbalances can also help to minimize the risk (80). It is believed that certain cardiotoxic effects associated with tyrosine kinase inhibitors might be caused by the drug's inhibition of a different kinase that is not related to its anticancer properties. To improve the drug's cardiotoxic profile, it may be necessary to reformulate it to reduce its affinity for these off-target kinases. The successful redesign of imatinib for gastrointestinal stromal tumors (GIST) is a prime example of this approach (77).

7. Most commonly used approaches in the management of cardiotoxicity

7.1 Drugs

7.1.1 ACE inhibitors and Beta-blockers

According to a clinical study, treating patients who have a LVEF of less than 45% with enalapril and carvedilol within six months after finishing anthracycline treatment can improve their LVEF (38). Additionally, studies have shown that using enalapril as a preventative measure in childhood cancer survivors with asymptomatic cardiac dysfunction can be effective in reducing cardiotoxicity (81,82). These standard heart failure medications can also function as

cardioprotectants. Some clinical studies indicate that angiotensin-converting enzyme inhibitors (ACE) and beta-blockers decrease the incidence of cardiac events when administered as prophylactic therapy (81).

It is evident that in the majority of the cases, enalapril and carvedilol usage is associated with better surrogate endpoints, such as LVEF, troponin, and natriuretic peptide levels, in addition to lower incidence of cardiac adverse events, hospitalization, and death (62). Beta blockers has been shown to enhance prosurvival signaling via the EGFR pathway and reduce the effects of free radicals (83). Carvedilol and nebivolol have shown the most promising results. Carvedilol, a third-generation nonselective beta-blocker has been found to effectively decrease free radicals, prevent mitochondrial dysfunction, and inhibit lipid peroxidation (82). Nebivolol is a third-generation beta-blocker with antioxidant properties and vasorelaxant that reduces ROS and increases NO. Like other beta-blockers in its beneficial effects on the myocardium, 5 mg of Nebivolol daily has been shown to protect from impairment in LVEF.
ACEI can act as a cardioprotective agent by mitigating ROS production and myocardial fibrosis whereas enhancing intracellular calcium signaling, mitochondrial function and metabolism of cardiac cell (84). Clinical studies have demonstrated that Lisinopril provides LVEF protection and significantly reduces long-term cardiovascular disorders in comparison with the placebo group (85). As a protective measure in patients receiving chemotherapeutic agents, Enalapril has been administered daily at the beginning of chemotherapy, there was a significantly lower increase in troponin levels and fewer incidents of cardiotoxicity compared to the group that didn't receive enalapril therapy (86).

Further studies revealed that anthracyclines-related cardiotoxicity suffering patients who were started with HF therapy for six months according to Guideline-directed medical therapy (GDMT) for HF had an improved LVEF (87). Carvedilol and lisinopril administered together have been proven effective in the (OVERCOME) trial to prevent the decline in LVEF. The PRADA trial discovered that breast cancer patients who received candesartan while undergoing anthracycline chemotherapy experienced less LVEF decline, in contrast to metoprolol which did not yield the same results. Combining metoprolol with candesartan did not produce any additional benefits. (88). **Table 2** summarizes some clinical studies that show some of the most used drugs to alleviate the effects of some cardiotoxic drugs.

Table 2. Summary of cardio-protectants used as prophylactic/treatment against cardiotoxic drugs

Cardiotoxic drug	Cardio-protectant	Conclusion	Ref.
TZP	Candesartan Metoprolol	Administration of cardioprotectants is very necessary for patients with preexisting heart problems. These drugs offered this protection	(89)
DOX	Enalapril	Enalapril is important in the treatment of cardiotoxicity after dox therapy	(90)
DOX or epirubicin	Carvedilol	When used prophylactically, carvedilol can prevent deterioration of LVEF	(91)
DOX, CP, 5FU and docetaxil	Nebivolol	Prophylactic use of nebivolol can prevent cardiotoxicity	(92)
epirubicin	Perindopril	Administration of perindopril can preserve the systolic function	(93)
Anthracyclines	ACEIs	Consumption of ACEIs can inhibit any troponin level increase	(94)
DOX	Eplerenone	Treatment with eplerenone for 6 months wasn't associated with high benefits with concern to systolic and diastolic function	(95)
epirubicin	Telmisartan	Telmisartan has a protective effect against anthracycline-induced cardiotoxicity	(96)
Anthracycline +TZP	Carvedilol	Concomitant giving of a maximum tolerable dose of carvedilol with TZP was associated with better cardiac function	(62)
DOX	Enalapril Metoprolol	There weren't any differences between metoprolol and enalapril, both drugs offered a significant cardioprotection	(97)
TZP	Carvedilol Lisinopril	Both drugs can prevent cardiotoxicity in breast cancer patients	(85)

7.1.2 Statins

Statins exhibit pleiotropic effects and may also be used to prevent anthracycline-induced cardiotoxicity. They are also able to reduce inflammatory cytokines and decrease oxidative stress (98). Statins can enhance endothelial function and NO production (99). In vivo studies demonstrated that statins were able to potentiate antiapoptotic and antioxidant functions and improve heart function (100). Some clinical studies revealed that using statins in different doses during or after Anthracyclines usage was associated with better outcomes on the hearts function especially improved LVEF (101).

7.1.3 Aldosterone

Aldosterone receptor blocker (spironolactone) is commonly used to treat heart failure and decrease cardiac remodeling, so it improves HF symptoms (81). Clinical research on 40 women suffering from breast cancer, who were treated with chemotherapy, those women also took 25 mg of spironolactone, those women were compared with another group on placebo, this study revealed that spironolactone provided significant cardio protection resembled by improving LVEF and small change in cardiac markers compared to control (102).

7.1.4 Metformin

For the treatment of type 2 diabetes mellitus, metformin is an anti-diabetic drug that has been in use for a long time. Some studies have indicated that metformin can help in preventing DOX-induced cardiotoxicity (103,104). Apart from its ability to lower blood glucose levels, metformin has been found to possess antioxidant properties in various tissues and can reduce lipid peroxidation. These effects are unrelated to its impact on insulin sensitivity (105). Its antioxidant properties, hindrance of the apoptotic pathway, and maintenance of mitochondrial function are the proposed mechanisms. Moreover, in the DOX model, metformin is capable of preserving cellular energy and activating the adenosine monophosphate-activated protein kinase (AMPK) pathway, which contributes to its cardioprotective effects (106).

7.1.5 Dexrazoxane

The prevention of Anthracyclines-induced cardiotoxicity has only been approved by the FDA with the use of dexrazoxane (8). Children and adolescents who are expected to receive high cumulative doses of anthracyclines, specifically more than 300 mg/m2 of doxorubicin, have been approved to receive this treatment (107). Reducing the formation of ROS is the primary mode of action of this drug, which is achieved by preventing the formation of the anthracyclines-iron complex. Dexrazoxane binds with iron before it enters cardiac cells so it prevents the production of free radicals and the resulting damage to cardiac cells (88). Reduction of DNA damage, one of the mechanisms of action of Anthracyclines, can also be achieved by using Dexrazoxane. This is done by inhibiting DNA topoisomerase II, which leads to the selective degeneration of topoisomerase IIb - a molecular target of Anthracyclines (108). Patients who have been treated with Anthracyclines have better cardiac outcomes in long-term survival thanks to dexrazoxane. The occurrence of cardiotoxicity is dose-dependent, which is why dexrazoxane was emphasized for its cardioprotective effects in cumulative doses up to 300 mg/m2. However, there was no statistical difference observed in doses of 400 mg/m2 or above (107).

7.2 Natural products

Natural products could have a potential cardioprotective effect and may have a role in the treatment of drug-induced cardiotoxicity. In the next section, a few examples of natural products which have proven cardioprotection will be discussed.

7.2.1 Silymarin (milk thistle)

Milk thistle has been utilized for hepatic and biliary disorders for centuries in Europe. It can be used as an antidote to Amanita mushroom poisoning as well as to guard the liver and kidneys against toxic drugs. Dyspeptic complaints, toxin-induced liver damage, hepatic cirrhosis, and supportive therapy for chronic inflammatory liver conditions are all recommended by the German Commission E (109). Silymarin adds antioxidant defenses in a variety of ways. It does this by directly scavenging radicals, inhibiting specific enzymes that produce free radicals, or maintaining mitochondrial electron transport chain integrity. It also contributes mainly to preserving the cell's optimal redox state by activating several antioxidant enzymes and non-enzymatic antioxidants, including Nrf2 and NF-SB. Finally, it activates various defensive molecular vintages responsible for synthesis, such as HSP, thioredoxin (Trx), sirtuins, and additional stress safety (110). Silymarin reacts with reactive oxygen species (ROS) and converts them into less reactive and toxic compounds. It enhances the effects of physiological antioxidants (glutathione, superoxide dismutase) and prevents the reduction of their concentrations and structural and functional consequences (111,112).

It was found that pre-treatment with silymarin had a positive effect on doxorubicin-induced cardiotoxicity. This can be seen in the significant decrease in serum CK and LDH activities. The administration of silymarin helped to prevent the increase in CK serum activity and myocardial excitability caused by doxorubicin in rats. Additionally, silymarin was observed to reduce doxorubicin-prooxidative activity and minimize histological changes in the liver and heart tissue of animals that were treated with doxorubicin. A clinical study on humans demonstrated that silymarin significantly increased the antioxidant capacity of human cardiac tissue, which may explain silymarin's cardioprotective effect (113). It has been discovered that when silymarin is administered alongside doxorubicin, it can help reduce the negative effects on the heart caused by the latter drug. The cardioprotective effects of silymarin are achieved through various mechanisms, including its antioxidant, anti-inflammatory, and anti-apoptotic activities. (114)

7.2.2 Flavonoids

Flavonoids are an important member of naturally occurring products, generally found in plants (115). Flavonoid's pharmacological action underwent very detailed studies applied to animals, cell lines, and humans (116). The main action of some of them is thought to be by nuclear factor (Nf-KB) inhibition (117), free radicals scavenging (118), anti-

thrombosis and inhibition of platelet aggregation (119), ACE inhibitors (120), anti-malignancy (121), calcium overload and lipoxygenase inhibitors (122). **Figure 3** shows the effect of flavonoids against DOX-induced cardiotoxicity.

Luteolin (3,4,5,7-tetrahydroxy flavone) is found in many natural products like fruits and vegetables which are consumed by humans every day (123). Moreover, its pharmacological action is studied in many researches and has been found to have a significant role as anti-cancer, hypocholesterolemic, and protects against DOX-induced cardiotoxicity (124–127). Moreover, luteolin can prevents the conversion of DOX to its toxic metabolite doxorubicinol by inhibition of carbonyl reductase3 (128). Various studies show that luteolin can protect against some heart disorders such as atherosclerosis, ischemia/reperfusion, and heart failure (129,130).

Another flavanol member is called Quercetin, it's present in many plant products such as onion, apples, and hot green peppers (131). This hopeful natural product has been commonly investigated for many therapeutic applications including use as a cardioprotective since it can encounter DOX-induced cardiotoxicity (132). Many upstream and downstream of the cell's signaling pathways are affected by Quercetin which are very important for the cell's longevity (133). When the cardiac cell undergoes an injury, these processes cause up-regulation of polycomb complex proteins (Bmi-1) which play an important role in ROS formation and mitochondrial damage. However, all the previous processes are downregulated by Quercetin by its action on type of extracellular regulated kinase ERK.

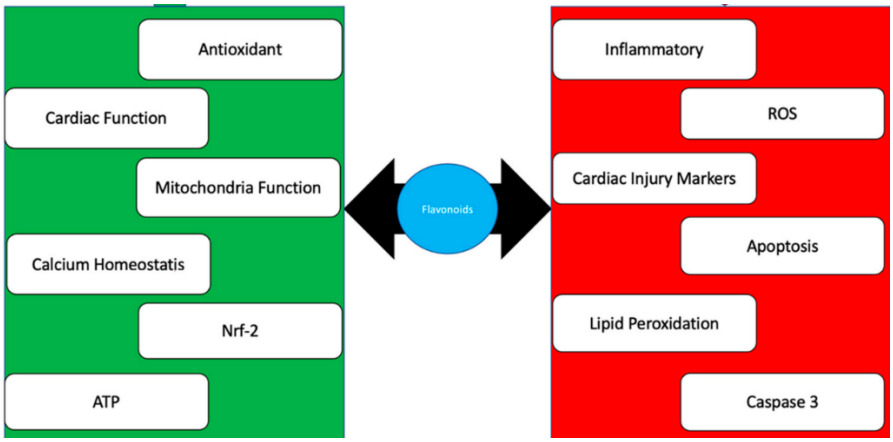

Figure 3. Summarization of flavonoids' effects against Dox. green color part indicates increasing antioxidant activity, ATP, mitochondria function, calcium homeostasis, Nrf-2 expressions, and heart function, whereas red color part indicates reducing ROS, inflammatory, lipid peroxidation, caspase 3 activity and apoptosis (63)

There is a significant reduction in the apoptosis in the cell line (H9c2) that has been treated with Quercetin, while those treated with DOX shows a significant increase in apoptotic activity. In addition, another in vivo study applied on rats revealed that there was a significant decrease in heart and heart/body weight ratio when the DOX only was used at a dose of 20mg/kg. The same study also found an elevation in serum creatine kinase (CK), and aldehyde dehydrogenase (LDH) levels, in contrast, the use of 100mg/kg of the Quercetin in the pretreatment study showed that there was a significant decrease in these biomarkers (134).

The other type of flavonoid is called cyanidin, which is mainly found in purple sweet potatoes and is named (anthocyanin) PSPA. It has been investigated in vitro on the H9c2 cell line and significantly decreased the concentration of NO and tumor necrosis factor TNF, also there was a significant decrease in CK, LDH, and trimethylamine-N-oxide in the cell line examined with DOX+PSPA (135). Moreover, an in vivo study in which a mouse model was used, the mice were treated with PSPA of doses 100 and 200 mg/kg. This study revealed that there was a great decrease in serum and cardiac tissue concentration of LDH,CK, and TNF when compared to DOX only (136).

Chrysin is a flavonoid found in honey, some types of mushrooms, and several plants (137). Its pharmacological action has been investigated in vitro and in vivo showing a cardioprotective potential due to its ability to deplete ROS formation which leads to a decrease in the expression of p38, p53 proteins, and Nf-kB in the cardiac cells (138). The stimulation of p53 protein leads to an increase in the activity of certain pro apoptotic protein and decreased the activity of anti – apoptotic protein. Some studies discovered that chrysin can reduce the pro inflammatory indicators such as inflammatory NO, cyclooxygenase 2, and TNF in the DOX treated rats (136).

7.3 Antioxidants

Generally, the antioxidant system consists of several mechanisms and molecules that have a vital role in maintaining cell viability (139). Because of its important role in keeping the oxidative state at a stable level, particularly when cells are exposed to an increase in the synthesis of free radicals. The antioxidant system consists of two parts, the first one is enzymatic which may be considered the first line of defense against oxidants. They include Catalase (CAT), Superoxide dismutase (SOD), Glutaredoxins, Thioredoxins, Glutathione peroxidase (GPX) and

Peroxiredoxins (140). The second part is the non-enzymatic antioxidants which include reduced glutathione (GSH), nicotinamide adenine dinucleotide phosphate (NADPH), and exogenous molecules including ascorbic acid, vitamin E, vitamin A, flavonoids, and polyphenols (141).

7.3.1 L-glutamine

It has the highest concentration among other essential amino acids in the bloodstream (142). Using this amino acid during the treatment course with DOX can greatly diminish the oxidative damage through its positive upregulation of glutathione so that it will offer a very necessary cardio protection (143). This amino acid is very necessary for NAD+ formation, glutamine can regulate the redox in the cell through its effect on NAD+ and its reduced form NADH because oxidative damage always occurs with a decrease in the redox potential (NADH/NAD+) (144). Glutathione synthesis is increased by the effect of L-glutamine which enhances NAD by being a substrate for glutaminase and NAD synthetase. Ammonia-derived from glutamine is used by L-glutamine through glutaminase activity. Supplementation with L-Glutamine can be very effective in the prevention of cardiomyocyte injury caused by cytotoxic drugs and radiation (145).

7.3.2 Coenzyme Q10

The use of coenzyme Q10 was demonstrated by a clinical study on fetal heart cells to be an important factor in maintaining cell viability and lowering inflammatory and oxidation biomarkers. When the coenzyme Q10 was used as an antioxidant with trastuzumab (TZP) in an in vivo study using a rate model, the study revealed a favorable effect on the cardiac cell's viability and a significant decrease in apoptosis (146). A recent research study found that administering CoQ10 to rats before ischemia reperfusion injury resulted in significant protection. The study concluded that CoQ10 may defend against cardiac apoptosis caused by ischemia reperfusion injury by reducing apoptosis, regulating the expression of the Bcl-2 gene in cardiac cells, and demonstrating a clear cardioprotective effect (147).

8. Conclusion

Cardiotoxicity is a severe side effect that can arise from many medications including mainly anticancer drugs. The most common mechanisms of cardiac cell death may include ROS formation, lipid peroxidation, and mitochondrial damage. Prevention is a multifaceted challenge that depends on various factors such as patient selection, using the lowest effective dose, avoiding combination regimens of potentially cardiotoxic drugs, and using cardioprotective agents. The most effective cardioprotectants are enalapril, carvedilol, antioxidants, and some of the natural products.

9. References

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نظرة شاملة على السُّمية القلبية الناتجة عن الادوية والوقاية منها

الخلاصة

المقدمة: الوقاية من السُّمية القلبية الناتجة عن استعمال الادوية هي مهمة معقدة تواجه القائمين على الرعاية الصحية خلال العقود الأخيرة. هذا التحدي قد ينبع من عدم الوضوح في تعريف السُّمية القلبية وتداخل أعراض تدهور وظيفة القلب الناتجة عن بعض الامراض الكامنة للقلب مع بعض اعراض الادوية المسببة للسُّمية القلبية او استخدام أكثر من دواء واحد في نفس الوقت ما يجعل التمييز بين الاعراض الجانبية لأي منهم امراً صعباً. **الهدف:** هذه المراجعة تناقش اهم مسببات السُّمية القلبية من الادوية والميكانيكية التي تتم من خلالها، كما تسلط الضوء على اهم الطرق العملية من اجل التعامل مع هذه المشكلة الخطيرة. **طريقة المراجعة:** تضمنت مراجعة البيانات الالكترونية المنشورة في اهم المواقع العلمية مثل PubMed، Web of Science، Springer، Google scholar وغيرها من اجل البحث عن البحوث المتعلقة بأمراض القلب والمنشورة في الفترة من 2010-2023. **الاستنتاج:** السُّمية القلبية هي من الاعراض الجانبية الخطيرة والشائعة لكثير من الادوية من ضمنها ادوية علاج السرطان وغيرها. طرق الوقاية منها تتضمن استعمال أنواع معينة من الادوية مثل (اينالابريل، كارفيدولول) واستخدام بعض المكملات الغذائية المضادة للأكسدة او استعمال بعض المنتجات الطبيعية.

كلمات مفتاحية :السُّمية القلبية، الادوية المضادة للسرطان، حماية القلب، مضادات الأكسدة