REVIEW

Cancer therapy-induced cardiotoxicity: mechanisms and mitigations

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Abstract
Cancer treatments like chemotherapy, radiotherapy, and combined immunotherapies have significantly increased patient survival. However, these treatments are frequently linked to cardiovascular toxicity, which has a significant impact on clinical outcomes and patient well-being. Chemotherapy, targeted therapy, and radiotherapy induce significant cellular stress in cardiomyocytes and endothelial cells, causing DNA damage, activating pro-inflammatory and pro-apoptotic signalling pathways. Cumulative damage causes cardiomyocyte loss, followed by fibrosis, resulting in pathological structural and functional remodelling of the myocardium. Endothelial cell damage disrupts vascular integrity, increasing the risk of atherosclerosis, coronary artery disease, and ischaemia. Over time, these changes can lead to clinical conditions like dilated and restrictive cardiomyopathy, which are frequently accompanied by arrhythmias and can result in heart failure and sudden cardiac death. To overcome this problem, the novel field of cardio-oncology aims to provide effective cancer treatments with a multifaceted cardioprotection approach involving pharmacological, diagnostic, natural compounds, and lifestyle interventions during and after cancer therapy. In this review, we cover the important cancer therapies, and their cardiotoxic mechanisms and detail different cardioprotective strategies aimed at mitigating these adverse effects and improve patient outcomes.

Introduction

Chemotherapy, immunotherapy, targeted therapy, and radiotherapy are the cornerstones of cancer treatment. Long-term cancer survivors are inevitably harmed by cancer therapy-related toxicity, which includes organ dysfunction, impaired cognitive function, and physiological disabilities that reduce the quality of life [1]. Long-term studies of childhood cancer survivors have shed light on the critical issue of cancer therapy-related cardiovascular toxicity (CTR-CVT) [2]. The childhood cancer survivors study revealed an 8.2 fold greater risk of mortality from cardiac issues when compared to

individuals of the same age and gender almost two decades after diagnosis [3]. Similarly, a 15 fold rise in cases of congestive heart failure and a 10 fold increase in other cardiovascular diseases (CVD) were observed among the 14,000 survivors [4]. Hence, to improve survival rates, it is crucial to understand and address these potential challenges associated with emerging cancer therapies.

Despite significant progress in understanding CTR-CVT, several challenges remain. First, there is no universally accepted definition of the condition; it is often clinically defined as a reduction in left ventricular ejection fraction (LVEF). Second, a widely referenced classification system proposed by Ewer et al. [5] distinguishes cancer treatment drugs into two major categories based on their mechanisms of inducing cardiotoxicity: Type I, characterised by irreversible myocardial damage, and Type II, typically causing transient myocardial dysfunction. However, there is a limitation in this classification system as several drugs, like trastuzumab (type II drug), can trigger irreversible myocardial damage, given the treatment is not terminated as and when cardiac complications arise. This highlights the need for simultaneously monitoring the patients for any evidence of cardiotoxic occurrence [6]. This overlap complicates clinical

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management and reveals gaps in our understanding of the cardiotoxic mechanisms of drugs generally used in cancer treatment [7, 8].

Finally, the pathological mechanisms underlying CTR-CVT remain incompletely understood, making this condition one of the most underappreciated sequelae of cancer treatment [2]. The CTR-CVT can arise due to several aetiologies. Although effective against tumour cells, anticancer therapies trigger a cascade of reactions that damage cardiomyocytes and neighbouring endothelial cells. This can be due to the increased oxidative stress and overproduction of pro-inflammatory and pro-apoptotic cytokines [9]. Cardiomyopathy is an extreme condition caused by the pathological remodelling of the myocardium due to the loss of cardiomyocytes, which leads to heart failure, arrhythmias, and sudden cardiac death [10]. In addition, the degree of toxicities also varies across treatment modalities; with radio therapy, outcomes are influenced by factors such as the mean heart dose and bifurcated radiotherapy schedules. Similarly, chemotherapy-induced toxicities are modulated by drug type, patient demographics, and comorbidities [11].

To address these challenges, the multidisciplinary field of cardio-oncology consisting of experts from disparate fields like cardiology, haematology, and oncology seeks to balance effective cancer treatment while minimising cardiovascular toxicity and avoiding unnecessary treatment interruptions [12, 13]. The 2022 European Society of Cardiology (ESC) guidelines on cardio-oncology emphasise the importance of tailoring cardiovascular care to the individual needs of cancer patients, demanding a multidisciplinary approach to develop personalised strategies for managing cardiovascular health throughout the treatment regimen [14]. Several

cardioprotective strategies, including pharmacological interventions, natural compounds and physical exercises during or after cancer therapy, show promise in mitigating late cardiac complications [10]. However, significant gaps remain in understanding the mechanisms driving therapy-induced cardiac damage and the development of universal cardioprotective guidelines. This review examines various cancer treatment modalities and their cardiotoxic mechanisms in cardiomyocytes and endothelial cells. We also discuss various cardioprotective strategies used for mitigating CTR-CVT.

Cancer therapy-induced cardiotoxicity

Conventional cancer therapy and recently introduced targeted therapies have tremendously improved the lives of cancer patients [15]. Several preclinical models have been considered to understand CTR-CVT because they allow for examining the complex interaction between treatment agents, their cardiotoxic response, and the underlying mechanisms. Once an appropriate model is established, defining a reliable or reproducible endpoint for evaluating cardiovascular toxicity is crucial. A summary of the occurrence and underlying mechanisms of cardiotoxicity associated with various cancer therapies is presented in Table 1.

In vitro models

HL-1 cardiomyocyte cell lines from mouse atria were used to study doxorubicin (DOX) induced reactive oxygen species (ROS) production, oxidative stress, and changes in myocardial

Table 1 The incidence and mechanisms of cardiotoxicity for various cancer therapies. (reactive oxygen species- ROS, chronic heart failure-CHF, tyrosine kinase inhibitors- TKIs, immune checkpoint inhibitors- ICIs)

Therapy type	Incidence	Mechanisms of Cardiotoxicity	References
Anthracycline	5–48% (dose-dependent)	ROS production, mitochondrial dysfunction, DNA damage, and activation of pro-apoptotic pathway leading to cardiomyocyte death	[16–20]
Fluoropyrimidines	1–19%	Coronary vasospasm, ischemic heart disease, and myocardial infarction; linked to *DYPD* genetic variants affecting drug metabolism	[21–24]
Taxanes	5–20%	Oxidative stress, arterial stiffness, and reduced ventricular function; higher risk when combined with anthracyclines	[25–27]
Alkylation Agents	Cisplatin: 6–30% Cyclophosphamide: 7–28%	Apoptosis, inflammation, mitochondrial damage, and impaired endothelial cell function	[28, 29]
Monoclonal antibodies	CHF: 2–7% (early stage BC); up to 28% with anthracyclines	NRG-1/ERBB2 pathway inhibition, oxidative stress, and disrupted cardiomyocyte survival signalling	[30–33]
TKIs	Hypertension: 43%; CHF: ~8%	Endothelial dysfunction, NO depletion, mitochondrial apoptosis, and microvascular rarefaction	[34–38]
ICIs	Myocarditis: 0.1–1.3%; Severe: 0.5%	T-cell mediated myocarditis, increased inflammatory cytokines, and immune system hyperactivation	[39–41]
Radiotherapy	Late toxicity > 10%	DNA damage, inflammation, oxidative stress, fibrosis, and microvascular injury; dose and site-dependent	[42–45]

energy metabolism [46, 47]. Long-term cultured adult rat cardiomyocytes revealed severe effects of DOX on protein degradation pathways. Higher doses of DOX triggered autophagy, apoptosis, and necrosis [48]. DOX-mediated dose-dependent cytotoxicity was studied in three-dimensional cardiac spheroids created by co-culturing stem cell-derived cardiomyocytes, endothelial cells, and fibroblasts [49]. Cardiac muscle tissue models were engineered from rats and humans to understand apoptosis, contractility, and mitochondrial dysfunction in sunitinib-induced cardiotoxicity [50].

Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) offer a promising in vitro model to study drug-induced cardiac dysfunction in arrhythmia modelling, CRISPR/Cas9 applications, and 3D cultures for advanced electrophysiological analysis [51, 52]. The hiPSCs can accurately replicate human cardiomyocytes and offer a more reliable and physiologically relevant tool [53–56]. The hiPSC-CMs were generated from patients undergoing chemotherapy and targeted therapy to understand cardiotoxic effects. Studies revealed severe cardiac dysfunction in patients treated with HER2-targeted drugs, while anthracyclines caused decreased antioxidant activity and increased ROS levels [57, 58].

Preclinical models

Echocardiographic monitoring of LVEF is commonly used to monitor cardiac function; however, a novel echocardiographic strain imaging technique was developed to detect early cardiac damage more effectively and precisely in mice [59]. ErbB2-deficient mice in ventricular cardiomyocytes developed dilated cardiomyopathy (DCM) [60]. Sunitinib-treated mice showed depletion in coronary microvascular pericytes, leading to cardiotoxicity [61]. Human-like variability in anthracycline cardiotoxicity can be effectively modelled using Collaborative Cross mouse strains [62]. Large animals like pigs were utilised to study early markers of anthracycline-induced cardiotoxicity through advanced imaging techniques such as cardiac magnetic resonance imaging [63]. Proteomic analysis in Zebrafish models has established that DOX induces small molecules, resulting in myocardial damage [64]. Some limitations of animal models are that genetic variability within the same species can influence the study results, and they fail to replicate specific human cardiac responses.

Chemotherapy

Anthracyclines

Anthracyclines are the foundation of chemotherapy regimens. Drugs such as DOX and daunorubicin have been successful in treating both solid and haematological cancer types for more than five decades. Although anthracycline treatment has shown better survival rates, one of the significant clinical limitations is the cardiac complications observed in exposed patients [65]. Maintaining a low incidence rate of cardiotoxicity is crucial to minimise the chances of mortality and maximise patient survival. At a cumulative dose of 550 mg/m^2, the incidence rate is estimated to be as low as 5%. However, for a higher dose of 700 mg/m2, the incidence rate ranges from 18 to 48% [16, 17]. Since anthracycline poses cardiotoxicity, 400–450 mg/m2 has been considered the highest clinical allowance [16]. Older patients receiving a cumulative dose of 400 mg/m2 are more vulnerable to chronic heart conditions post anthracycline treatment compared to their middle-aged counterparts [17]. A cohort study of more than 14,000 childhood malignancy survivors revealed a 2 fold increase in the incidence of cardiac dysfunction in individuals who received a cumulative dose of > 250 mg/m2 [11]. A study evaluated left ventricular function in 38 children with leukaemia undergoing anthracycline treatment. Among them, DCM occurred in 3 patients, while 28.9% showed strain abnormalities in cardiac muscle. The risk of these complications was higher in children with anthracycline doses of more than 240 mg/m2 or who underwent radiotherapy [66]. Anthracycline-mediated cardiotoxicity often leads to the presentation of systolic dysfunction secondary to a DCM phenotype. These abnormalities are observed in 60% of cancer survivors, especially older patients who present with reduced LVEF and ventricular dilation [67].

Fluoropyrimidines

This is the third most used chemotherapy drug for patients with solid tumours such as adenocarcinoma. For the past five decades, fluoropyrimidines such as 5-fluorouracil (FU) and its prodrug, capecitabine, are associated with significant cardiac complications. The rate of occurrence of cardiotoxicity is between 1 and 19%, and the survival rate of patients experiencing cardiotoxicity is reported to be 1.6–10.2%. Long-term patient exposure can cause angina, arrhythmias, and myocardial infarction [21]. Despite extensive clinical observation, there is a notable lack of consistent risk factors for predicting fluoropyrimidine-induced cardiotoxicity. Some factors that appear to increase susceptibility include combination chemotherapy regimens, a history of pre-existing cardiac conditions, and advanced age [68]. For instance, in a retrospective study comparing the cardiotoxicity between 5-FU and capecitabine, the incidence rates were 4% and 5%, respectively [69]. In a survey of 644 patients who received 5-FU and capecitabine, a total of 4% developed cardiac abnormalities, and 5-FU was associated with a greater risk of cardiotoxicity than capecitabine (10% vs 0.8–4%) [70].

Symptoms such as coronary vasospasm, ischemic heart disease, and myocardial infarction were observed in 4.5% of the 177 patients receiving 5-FU in a case–control study [22]. Emerging evidence suggests that genetic predisposition and clinical factors may play a role in fluoropyrimidine-induced cardiotoxicity. Mutations that increase enzyme activity may lower treatment effectiveness, while those that decrease enzyme activity can boost treatment response but raise the risk of side effects. Deficiencies in the enzyme dihydropyrimidine dehydrogenase (DPD), caused by variations in the *DPYD* gene, result in impaired drug metabolism [23, 71]. A study of 132 patients treated with fluoropyridines identified the *DPYD* c.2194G > A variant as being strongly associated with adverse drug risks, particularly relating to cardiotoxic, gastrointestinal and haematological toxicities [24]. A case report stated the role of thymidylate synthase gene variants in influencing severe cardiotoxic effects in a patient with fluoropyrimidine treatment [72]. Therefore, incorporating preventive genetic testing and integrating pre-treatment protocols could allow for dose adjustments or alternative therapies, potentially reducing adverse outcomes. Current data are insufficient to establish clear criteria linking cardiovascular risk factors to fluoropyrimidine-related cardiotoxicity for identifying high-risk patients, making it difficult to recommend discontinuation of fluoropyrimidine therapy based solely on cardiovascular risk [73].

Taxanes

Taxanes such as taxol or paclitaxel are used to treat patients with solid cancer types such as ovarian, breast, and prostate cancer, but the clinical significance of taxanes is limited by their cardiotoxicity [74, 75]. Serious cardiac complications, including cardiac ischemia, left ventricular dysfunction, and tachycardia, have been observed with an incidence rate of 5–20% in patients treated with this class of drugs [25, 26]. Increased arterial stiffness and oxidative stress are identified in women with breast cancer (BC) treated with taxanes [76]. In a study of thirty women with BC in which DOX was combined with paclitaxel, an estimated 50% of patients developed left ventricular dysfunction, and 20% developed chronic heart failure (CHF) [27]. In recent decades, cardiotoxicities associated with docetaxel have been reported at an incidence rate of 2.3–8% [77, 78]. However, limited data are available concerning the cardiotoxicity of docetaxel and its combination with DOX for treating patients with solid cancer types.

Alkylating agents

Cisplatin and cyclophosphamide treat lymphoma, myeloma, Hodgkin's disease, and sarcomas. Cisplatin-induced cardiotoxicity is observed in patients at a rate of 6–30% [28].

Cyclophosphamide, a crucial alkylating agent, has shown evidence of dose-related cardiotoxicity in the 7–28% at a 180 mg/kg dose. The notable causes associated with cyclophosphamide induced cardiotoxicity are apoptosis, inflammation, and mitochondrial damage, leading to cardiomyocyte damage [29].

Targeted therapy

Monoclonal antibodies

Antibodies such as trastuzumab, which are used to treat HER-2 positive BC, stomach, and prostate cancer, inhibit the dimerisation of HER2 receptors and are known to cause several cardiac complications like hypertension and CHF. CHF incidence rates range between 2 and 7% in early-stage BC patients and increase to 2.8% when targeted therapy is combined with anthracyclines [30]. Analysis of BC patients over 2 years showed 4.22% higher chances of CHF when treated with adjuvant trastuzumab therapy [79]. Trastuzumab therapy is associated with a 4–5% absolute risk increase in CHF over 2 years in adjuvant therapy settings. A 2-year analysis reported a 4.33% higher CHF risk in trastuzumab-treated BC patients [31]. Pertuzumab in combination with trastuzumab and chemotherapy for HER2-positive cancer, nearly doubles the risk of CHF (risk ratio: 1.97) however, it does not significantly increase the risk of asymptomatic or minimally symptomatic left ventricular systolic dysfunction [80].

Tyrosine kinase inhibitors (TKIs)

TKIs such as imatinib, sorafenib (SOR), sunitinib, and bevacizumab are used to treat non-small cell lung cancer (NSCLC), chronic lymphocytic leukaemia, and melanoma. It prevents the binding of tyrosine kinases to its receptors, inhibiting the phosphorylation of key substrates in the cells [81]. TKIs cause a variety of toxic effects, including irregular heart rhythms such as an extended QT interval, high blood pressure, and systolic dysfunction. Clinical trials found that < 50% of TKI patients experienced a decline in LVEF of < 10%, followed by MI, atrial fibrillation, and CHF [34, 35]. Cardiac complications of bevacizumab treatment, such as hypertension, were reported in more than 45% of clinical trials, and when combined with drugs such as 5-FU, irinotecan, and leucovorin, the effects are increased 8 fold [82]. SOR and sunitinib are widely used oral drugs for hepatocellular carcinoma and renal carcinoma and they may induce cardiotoxicity in long-term survivors of these cancers [83, 84]. Among gastrointestinal stromal tumour patients treated with repeating cycles of sunitinib in phase I/II trial, 11% had cardiovascular events, with CHF reported in 8% of patients [36]. In another study, hypertension was observed in up to 43% of cases, while CHF is a long-term side effect

showing probable late cardiotoxicity [85]. Further research is needed to identify the underlying pathological mechanisms and long-term adverse impact on cardiomyocytes that contribute to cardiac toxicity with TKI treatment.

Immune checkpoint inhibitors (ICIs)

Cancer immunotherapy has emerged as an effective cancer treatment in recent years. Monoclonal antibodies such as ipilimumab, durvalumab, and nivolumab target cytotoxic T lymphocytes associated antigen 4 (CTLA-4) and programmed cell death 1 (PD1) and its ligand (PDL1) to increase T-cell activity in cancer treatment [86]. Nearly 40% of patients treated with combined ipilimumab and nivolumab developed immune-related cardiac complications [87]. Several cases of myocarditis and CHF are reported in patients receiving ICIs in recent years, either as a single treatment or in combination with other drugs [88–91]. Clinical trials indicate that the incidence of ICIs-induced myocarditis ranges from 0.1 to 1.3%, with severe cases accounting for up to 0.5% and a high mortality rate in untreated patients. Myocarditis is notably more prevalent in dual checkpoint blockade regimens, such as anti-PD combined with anti-CTLA-4 therapy [39, 40]. Of the 30 cases of solid cancer types like bladder and colorectal cancer, ICIs-induced cardiotoxicity, 25–50% are due to anti-PD-1/anti-PDL-1 inhibitors [92]. In contrast, anti-PDL1 inhibitor cemiplimab has shown no cardiotoxic effects [93, 94].

Certain anticancer drugs are known to be more cardiotoxic than others. Factors such as the duration and dose of the treatment and the type and stage of the cancer also influence CTR-CVT. The incidence rate of cardiac toxicity among anthracyclines, TKIs, and proteasome inhibitors is as high as 20–40% [95]. The combination of anthracycline and radiotherapy poses a 15 fold more significant risk of heart failure [96]. In a 5-year follow-up study of non-Hodgkin lymphoma survivors, the incidence of heart failure was recorded at 17% while undergoing anthracycline treatment [97]. Although cancer treatment-induced cardiotoxicity is fatal, in a few cases, the deaths are driven by non-cardiac causes. This may be due to poor outcomes related to fatal cancer types and delays in treatment caused by the manifestation of cardiotoxicity at the time of therapy even at a low-dose administration [76, 98].

Chemotherapy-induced cardiotoxicity mechanisms

Chemotherapy-induced cardiotoxicity can cause an acute or delayed onset cardiac dysfunction, with a higher incidence observed in patients receiving high doses of anthracyclines or those with pre-existing CVD [99, 100]. Chemotherapeutic agents contribute to cardiotoxicity via oxidative stress, mitochondrial dysfunction, and DNA damage. These processes often result in cardiomyocyte loss, leading to pathological remodelling of the myocardium, resulting in arrhythmia and cardiomyopathy [101–103]. A summary of different cancer therapies and CTR-CVT has been illustrated in Fig. 1.

Anthracycline-mediated cardiotoxicity mechanisms

Anthracycline exposure causes two significant events that lead to cardiomyocyte injury/death (Fig. 1). First, anthracyclines bind to cardiomyocytes, and their quinone moiety is reduced to a semiquinone radical, which oxidises in the presence of molecular oxygen to reform its parent state. This redox cycling in anthracycline-iron complexes generates ROS. Second, the formation of the topoisomerase-anthracycline complex prevents the resealing of phosphate bonds in DNA, causing DNA damage [18–20, 104]. This activates pro-apoptotic and pro-inflammatory cytokines, which degrade mitochondrial structure and function in cardiomyocytes [105]. DNA damage activates extracellular signal-regulated kinase1/2 (ERK1/2), enhances p53 phosphorylation, a crucial cell-cycle regulator, and upregulates pro-apoptotic genes such as *PUMA* and *NOXA* [106, 107]. *PUMA* activates *BAX/BAK,* which disrupts mitochondrial integrity, leading to the release of pro-apoptotic factors like cytochrome c, *SMAC*, and *AIF*, which activate caspases and initiate cell death [108]. Alternatively, DOX induce apoptosis in cardiomyocytes by activating NF-kB, which upregulates *PUMA*, highlighting the dependency of *PUMA* on both the p53 and NF-kB pathways [107]. External ligand binding of Fas-L and tumour necrosis factor to their respective receptors stimulates cell death signalling, contributing to cardiomyocyte damage/injury [109].

The cardiotoxic effect of anthracycline on endothelial dysfunction disrupts vascular health and leads to the development of conditions majorly into atherosclerosis, cardiomyopathy, vasoconstriction [110, 111]. This endothelial dysfunction is driven by the production of ROS which impairs blood flow, diminishes NO availability, and accelerates the progression of build-up plaque in the walls of arteries [112]. Several molecular (endothelin-1) and genetic factors (genetic polymorphism of endothelial nitric oxide synthase, NADPH oxidase) play a crucial role in the development of vascular toxicity and endothelial damage, eventually leading to HF [110]. Anthracyclines downregulate antioxidant defences like *SVCT-2* and *GPX* [113]. Mitochondrial dysfunction is also caused by iron accumulation via upregulation of transferrin receptor expression, iron regulatory proteins, and downregulation of *ABCB8* [114, 115]. This reduces peroxisome proliferated-activated receptor (PPAR) expression, which affects Acetyl CoA carboxylase (ACC), leading to excessive malonyl-CoA production and ATP consumption [116, 117]. Anthracyclines promote mitochondrial fission and inhibit fusion. This is due to enhanced mitophagy
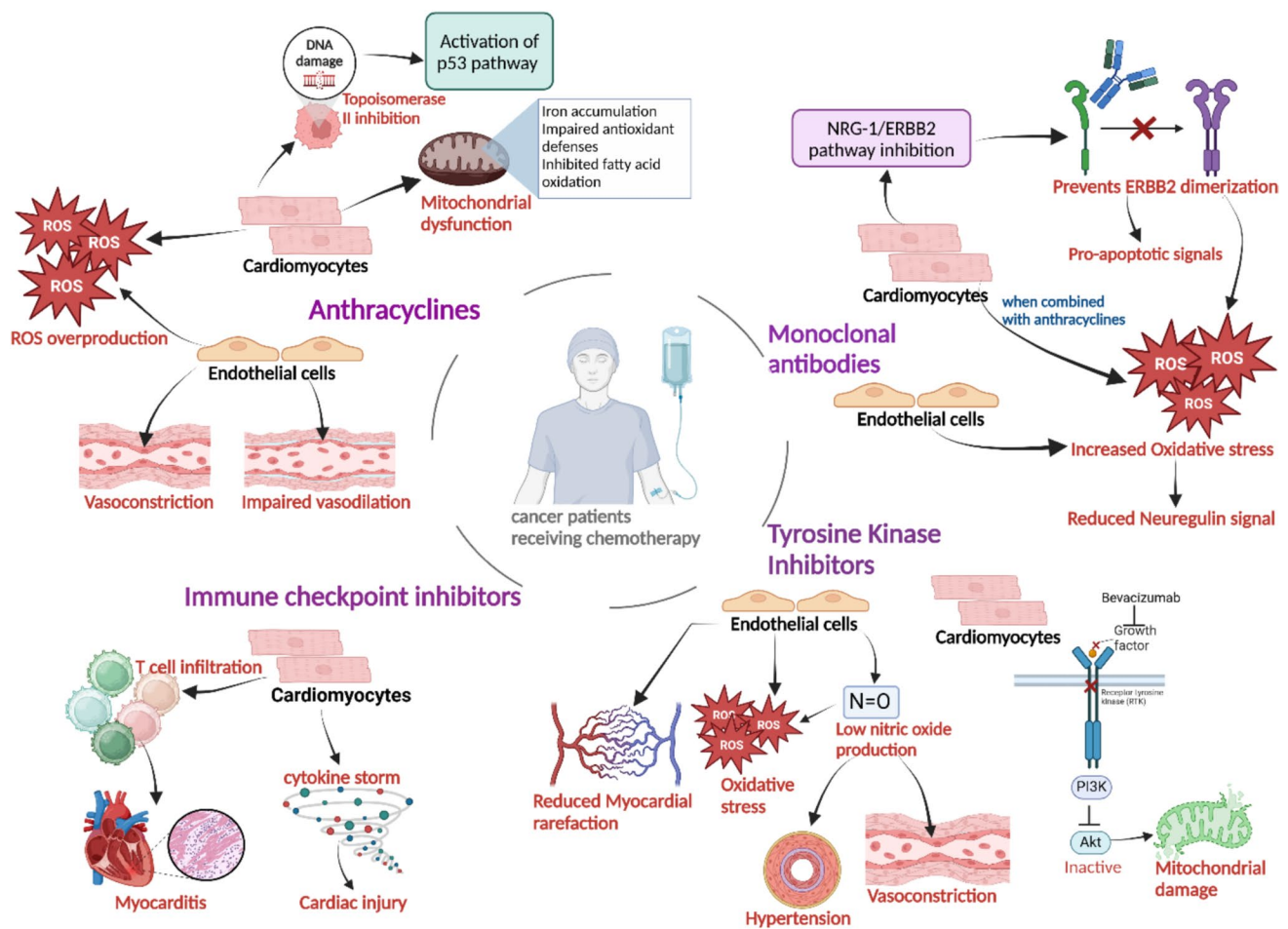
Fig. 1 Cancer therapies and cancer therapy-related cardiovascular toxicity. Anthracyclines induce cardiotoxicity via increased ROS production, topoisomerase II poisoning, and mitochondrial disruption. Monoclonal antibodies disrupts NRG-1/ERBB2 signalling, inducing oxidative stress and apoptotic pathways, especially when combined with anthracyclines. TKIs impair endothelial NO synthase activity, causing endothelial dysfunction, and vasoconstriction, while also promoting mitochondrial dysfunction in cardiomyocytes. ICIs induce myocarditis through T-cell infiltration and cytokine-mediated inflammation. (Tyrosine kinase inhibitors- TKIs, immune checkpoint inhibitors- ICIs, nitric oxide- NO, electron transport chain- ETC, reactive oxygen species- ROS)

resulting from the *PINK1*/Parkin pathway activation via increased *Drp-1* levels and reduced *MFN1/2* and *OPA1* expression [118].

Targeted therapy-mediated cardiotoxicity mechanisms

ERBB2 is a receptor protein known for its significant role in cell signalling, especially in response to Neuregulin (NRG-1) within cardiomyocytes. NRG-1 leads to the dimerization of ERBB2/4, unlocking the cell survival signalling pathway under adaptation and stress conditions in cardiomyocytes. The NRG-1/ERBB2 signalling is responsible for cardiac tissue development and proliferation [32, 119]. However, trastuzumab binding to HER2/ERBB2 receptors inhibits NRG-1-mediated ERBB2/4 dimerization. This triggers NRG-1 release from the cardiac endothelial cells, leading to disrupted cardiomyocytes through oxidative stress and pro-apoptotic signals [33]. Increased ROS accumulation and oxidative stress have been observed in patients with trastuzumab in combination with anthracycline, resulting in cardiac dysfunction and the development of CHF and left ventricular dysfunction [120].

Cardiomyocyte damage from TKIs such as bevacizumab arises from mechanisms involving cardiomyocyte and endothelial dysfunction [37]. They suppress endothelial nitric oxide (NO) synthase activity and reduce NO levels, contributing to oxidative stress and endothelial cell apoptosis [121]. Chronic endothelial dysfunction also leads to microvascular rarefaction mediated hypertension and myocardial strain. It also reduces myocardial perfusion and increases susceptibility to ischemic injury [38, 122]. By affecting cardiomyocyte survival pathways such as PI3 K/Akt signalling, vascular endothelial growth factor (VEGF) inhibition

accelerates mitochondrial dysfunction and apoptosis within cardiac cells [123]. SOR causes cardiomyocyte death via the accumulation of lipid-mediated ROS in the endoplasmic reticulum [124]. Unlike anthracyclines, ICIs cause immune mediated cardiotoxicity, which typically manifests shortly after the first two cycles of treatment [92]. This severe myocarditis is linked to a surge of T cells infiltrating the heart, due to increased levels of pro-inflammatory cytokines, contributing to cardiac damage and direct myocardial toxicity over time through oxidative stress and mitochondrial disruption [41].

Radiotherapy

External beam radiotherapy is important for treating 60% of cancer patients. During radiotherapy of the cancers of breast, head and neck, oesophagus, lung, and Hodgkin lymphoma, the heart is exposed to radiation, and the dose varies depending on the technique and individual patient's anatomy. A major consequence of radiotherapy generally observed in patients is late cardiotoxicity [45, 125]. The clinical presentation comprises coronary artery atherosclerosis, valvular disease, pericarditis, cardiomyopathy, and conduction defects. The estimated prevalence of radiotherapy-induced cardiomyopathy is > 10%, with an increased incidence of heart failure compared to that of the general population [45]. Cancer survivors who underwent mediastinal irradiation showed pathological myocardial remodelling leading to a DCM-mediated systolic dysfunction or restrictive cardiomyopathy-mediated diastolic dysfunction [126, 127].

The risk of radiotherapy-induced cardiotoxicity is influenced by the type of cancer, dose, patient's age, medical history, smoking status and high blood pressure [44]. Women with left-sided BC radiotherapy have a higher chance of developing ischemic heart disease, especially under combination therapy [128]. Over the decades, advances in radiotherapy techniques have reduced the mean heart dose to 4.7 Gy by the 1990 s to 2.6 Gy in 2006 [129]. Although the mean heart dose is a suitable parameter, it does not imply that lowering the dose will not have any effect on the cardiac system, especially when the areas, like the left anterior descending artery and left ventricle (LV), receive high doses [130].

The Pediatric Normal Tissue Effects in the Clinic (PENTEC) initiative found that higher cardiac radiation in combination with anthracycline doses significantly increases the risk of late cardiac disease in childhood cancer survivors. A mean heart dose < 10 Gy at standard fractionation poses a low 30-year risk without anthracycline exposure [131].

Recent advancements in radiotherapy focus on improving precision, reducing toxicity and enhancing outcomes; however, cardiotoxicity remains a predominant factor with advancements like hypofractionation. Damaging effects on the heart can be seen after doses as low as 2 Gy, and there is no apparent "safe" dose [132]. Doses of 40 Gy, 42.5 Gy, and 39 Gy have equivalent efficiency to the regular fractionation regime of 50 Gy, and it is shown to cause less cardiac damage [133]. A study of 5,58,871 subjects recorded over 20 years revealed that women with left-side BC receiving radiotherapy had a 90% higher risk of cardiac death compared to right-sided BC patients [134].

Radiation therapy-induced cardiotoxicity mechanisms

Proposed pathogenic mechanisms of radiation-induced CVD include endothelial cell damage with accelerated atherosclerosis, pro-thrombotic alterations in the coagulation pathway, inflammation, and fibrosis of the myocardial, pericardial, valvular, and conduction tissues [135]. A summary of the mechanisms of radiation induced cardiotoxicity is illustrated in Fig. 2. Radiation-induced oxidative stress in cardiomyocytes causes increased levels of malondialdehyde, xanthine oxidase, and adenosine deaminase, causing microvascular injury, reduced myocardial capillary density, and decreased oxygen [136]. Patients with pre-existing CVD develop cardiotoxicity due to microvascular injury, leading to rapid pericardial effusion [137].

Radiation induces inflammation through cyclooxygenase-2 (COX-2), an enzyme that converts prostaglandin from arachidonic acid [42]. After radiation exposure, damage response signals are activated from nuclear DNA and mitochondria via the upregulation of ROS and genes like *ATM*, *p53*, *p16*, and *p21*. ROS production activates NF-κB that transcribes senescence-associated secretory phenotype (SASP), leading to senescence. Activating these pathways damages cells in and around the cardiomyocytes causing chronic inflammation and disruption of cardiac tissue structure [43, 138].

A similar mechanism is seen in endothelial cells, initiating endothelial senescence and inflammation. Endothelial dysfunction begins with the accumulation of apolipoprotein B, a low-density lipoprotein in the arteries, which triggers the recruitment of monocytes and macrophages into the endothelium and then transforms into macrophages and develops a fatty streak in the inner lining of the endothelium. This marks the beginning of atherosclerosis, leading to myocardial infarction and fibrosis due to ischaemia and cell death [43, 139]. The blood vessel elasticity is impaired due to the accumulation of extracellular matrix components. Several inflammatory molecules and cytokines contribute to this process, including tumour necrosis factor, interleukin (IL)−1, IL-6, and platelet-derived growth factors. Further, monocyte chemotactic factor and transforming growth factor are also known to play a role in this process [140].
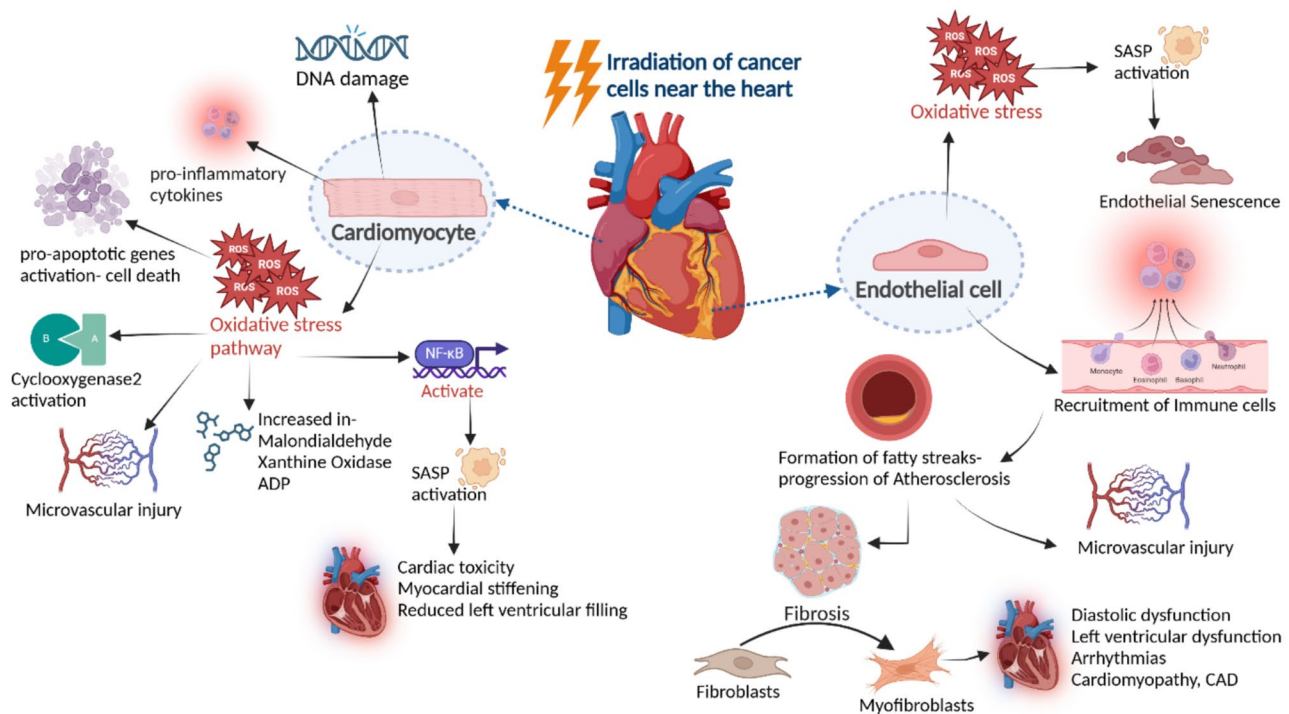
Fig. 2 The diagram illustrates the mechanisms of radiation-induced cardiac toxicity. Radiation-induced cardiomyocyte damage occurs due to oxidative stress, and DNA damage. Oxidative stress triggers pro-inflammatory cytokines, pro-apoptotic gene activation, increased malondialdehyde and xanthine oxidase, and cyclooxygenase-2 activation, resulting in microvascular injury, cell death, myocardial stiffening, and reduced left ventricular filling. In endothelial cells, oxidative stress promotes senescence, SASP activation, and immune cell recruitment, contributing to fibrosis through fibroblast activation, fatty streak formation, and atherosclerosis progression. These processes result in microvascular damage, diastolic dysfunction, arrhythmias, cardiomyopathy, and CAD, highlighting the interconnected pathways in radiation-induced cardiac toxicity. (reactive oxygen species- ROS, senescence-associated secretory phenotype- SASP, coronary artery disease (CAD)

Myocardial metabolic alterations may play an important role in the pathogenesis of radiation-induced cardiotoxicity. Radiation leads to bioenergetics failure in cardiomyocytes and metabolic alterations such as a shift from fatty acid oxidation to glycolysis, as observed in ischemic heart failure [141].

Cardiomyocyte loss secondary to radiation leads to myocardial replacement fibrosis, which causes pathological remodelling of the heart and changes its structure and function. The formation of myofibroblasts from cardiac fibroblasts signals the onset of cardiac fibrosis, with several signalling pathways, including PI3 K/AKT, TGF-β/Smad3, and MAP/ERK2 playing a role [142]. Interstitial fibrosis of the myocardium can cause cardiomyopathies, arrhythmias, coronary artery disease (CAD) and valvulopathies. Cardiomyopathies are progressive disorders which lead to heart failure, and arrhythmias can cause sudden cardiac death. Pericardial fibrosis can lead to thickening of the pericardium and cause abnormalities in cardiac function [143, 144].

Cardioprotective strategies

The growing understanding of the cardiotoxic mechanisms of various cancer treatment modalities has resulted in several treatment strategies which ameliorate cardiotoxicity [102]. A list of studies that established these cardioprotective treatments is summarised in Table 2.

Using fewer cardiotoxic chemotherapeutics or lower drug dosages while maintaining treatment effectiveness has been the most commonly accepted cardioprotective strategy in chemotherapy [102, 135]. Pharmacological approaches such as angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), β-blockers, dexrazoxane, and statins confer cardioprotective effects by maintaining normal heart function and preventing the development of cardiotoxicity. β-blockers treat hypertension by slowing the heart rate and relaxing blood vessels. Using β-blockers as a standalone treatment for cancer patients experiencing cardiotoxicity has yielded mixed results. In one study, carvedilol and nebivolol improved diastolic dysfunction in anthracycline-treated patients [145]. Another study, using

Table 2 A table summarising the cardioprotective strategies, their mechanisms, and key findings from clinical studies. (renin-angiotensin system, angiotensin-converting enzymes-ACE, angiotensin-receptor blocker- ARBs, intensity-modulated radiation therapy-IMRT, Deep inspiration breath-hold- DIBH, left ventricular ejection fraction- LVEF, Doxorubicin- DOX, Left ventricle-LV)

Cardioprotective Strategy	Mechanism/Effect	Key findings	References
Pharmacological approaches			
β-blockers	Treat hypertension by slowing heart rate and relaxing blood vessels	Mixed results for cardiotoxicity in cancer patients; Carvedilol and nebivolol improved diastolic dysfunction	[145, 146]
RAS inhibitors (ACE inhibitors and ARBs)	Control hypertension, oxidative stress, and cardiac fibrosis	Reduce hospitalization rates more effectively than β-blockers but may cause complications like hyperkalemia and angioedema in renal disease patients	[147–150]
Dexrazoxane	Reduces cardiotoxicity by inducing DNA repair mechanisms and inhibiting mitochondrial damage and ROS formation	Effective in patients receiving high-dose anthracyclines	[151, 152]
Combination therapy	Synergistic effects e.g., β-blockers and RAS inhibitors	Improves outcomes such as reduced left ventricular hypertrophy and cardiac dysfunction; PRADA trial showed early benefits with candesartan and metoprolol, but long-term benefits were modest. MANTICORE-101 trial showed no benefit in LV remodelling	[153–156]
Statins	Lower cholesterol, reduce oxidative stress, and inflammation	No significant cardioprotective properties observed in PREVENT, SPARE-HF, and STOP-CA trials; recommended for high-risk patients per ESC guidelines	[157–159]
Radiation therapy advances			
Intensity-modulated radiation therapy (IMRT) and proton therapy	Precisely target cancer and spare healthy tissue	Minimize cardiac exposure and reduce cardiotoxicity	[138]
FLASH radiotherapy	Delivers ultra-high doses in a single fraction, reducing tissue damage	Experimental stage with promising results in reducing cardiotoxicity	[160]
Deep inspiration breath-hold (DIBH)	Inflates lungs to shift the heart away from the treatment area	Minimizes cardiac radiation risk, especially in breast and lung cancer treatments	[161, 162]
Natural compounds			
Chia seed oil	Reduces oxidative stress, enhances antioxidant enzymes	Cardioprotective against DOX in rats	[163]
Ajwa date nanopreparation	Increases antioxidant capacity, suppresses inflammation, reduces ischemia	Cardioprotective against DOX-induced cardiotoxicity	[164–166]
Curcumin	Potent antioxidant derived from *Curcuma longa*	Mitigates DOX-induced cardiotoxicity; improves cardiac function	[167]
Flavonoids	Antioxidant, cardioprotective, and anti-tumor properties	Mechanisms need further exploration	[168]
Cannabidiol	Antioxidant and anti-inflammatory properties	Evaluated in mouse models of anthracycline-induced cardiomyopathy	[169, 170]
Lifestyle modification and Exercise			
Exercise	Enhances cardiovascular health, restores cardiomyocyte homeostasis	Reduced mortality in cancer patients by 48%; improves VO2 peak in BC patients, but LVEF impact remains unclear	[171, 172]
Lifestyle changes	Smoking cessation, reduced alcohol intake, healthy weight maintenance	Crucial for prevention in cardiovascular toxicity, especially in hepatocellular carcinoma patients	
Tailored interventions (e.g., yoga, qigong)	Improves quality of life	Requires more research to confirm cardioprotective mechanisms	[173]

echocardiogram strain-guided imaging, found that carvedilol had no significant advantage as a cardioprotective drug in terms of heart function or CTR-CVD prevention. However, the study also stated that cardiac strain changes alone may not warrant immediate intervention with cardioprotective therapy, especially in patients at low risk of cardiac dysfunction [146]. Older patients may experience fatigue, bradycardia, and exercise intolerance when using β-blockers, making personalised treatment necessary [147]. Renin-Angiotensin system (RAS) inhibitor drugs like ACE inhibitors and ARBs such as captopril, enalapril, lisinopril, and valsartan are well-known to confer cardioprotection by controlling hypertension, oxidative stress, and cardiac fibrosis [148–150]. Comparative trials show that RAS inhibitors reduce hospitalisation rates more effectively than β-blockers, although the latter fares better in arrhythmia prevention [174]. Patients with a history of renal disease do not tolerate this treatment as it can cause significant complications like hyperkalemia and angioedema [147]. Dexrazoxane helps reduce cardiotoxicity by inducing DNA repair mechanisms, inhibiting mitochondrial damage and ROS formation in patients of all ages receiving high-dose anthracycline treatment [151, 152].

A recent study found that combination therapy provides better cardioprotective outcomes than standalone drug treatments, particularly in reducing mortality in heart failure patients; however, the treatment must be tailored specifically to the patient's needs [152]. Combining β-blockers and RAS inhibitors can reduce left ventricular hypertrophy, diastolic, and systolic dysfunction. However, long-term outcomes are determined by specific heart failure subtypes and aetiologies [153]. In the PRADA trial, metoprolol was used in combination with candesartan to assess the cardioprotective effects on BC patients treated with adjuvant therapy. Cardiotoxicity causes acute myocardial damage, which can be measured using cardiac troponin biomarkers [175]. Overall outcomes were measured as LVEF preservation and cardiac troponin readings. Early measurements in the study showed metoprolol did not significantly impact LVEF but attenuated the increase in cardiac troponin, while candesartan treatment showed LVEF preservation but no effect on cardiac troponin levels [154]. Extended follow-up after 2 years revealed a slight decrease in LVEF but no significant long-term preservation of LVEF with candesartan treatment; however, there was a modest reduction in left ventricular end-diastolic volume and preserved global longitudinal strain. These findings suggest that while candesartan provides short-term benefits, a universal cardioprotective approach during adjuvant therapy may not be necessary for most patients without pre-existing CVD, highlighting the importance of individualised cardiac risk assessment [155]. The MANTICORE 101- trial was conducted in HER2-positive BC patients to study the efficacy of the combination of ACE inhibitors and β-blockers in preventing trastuzumab-mediated cardiotoxicity. Perindopril and bisoprolol effectively attenuated LVEF decline; however, neither prevented trastuzumab-mediated LV remodelling, which was the primary outcome [156].

Drug combinations of targeted therapies with taxanes yield better cardiac safety profiles with minimal cardiotoxicity. The CLEOPATRA trial conducted during 2015–2020 demonstrated the cardiac safety of combining pertuzumab, trastuzumab, and docetaxel in treating HER2-positive metastatic BC. This combinatorial treatment achieved an 8-year overall survival rate of 37% [176]. Another study confirmed that treatment with the combination of paclitaxel, trastuzumab, and pertuzumab was cardio-safe [177]. Statins, which lower cholesterol levels by terminating the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, help reduce oxidative stress and inflammation [157]. These effects make them potentially beneficial in reducing the risk of heart failure during anthracyclines and trastuzumab therapies [158]. Three randomized controlled trials; PREVENT, SPARE-HF, and STOP-CA have investigated the cardioprotective properties of statins. While the evidence indicates that statins do not reduce clinical heart failure rates, the current European Society of Cardiology (ESC) guideline recommends their use for patients at high or very high risk [159].

In radiotherapy, advanced radiation techniques, such as intensity-modulated radiation therapy (IMRT), and proton therapy, can target cancer more precisely and spare healthy tissue [138]. Charged particle therapy, using protons and heavy ions, minimises damage due to the Bragg peak and higher relative biological effectiveness compared to conventional radiation. FLASH radiotherapy delivers ultrahigh doses in a single fraction and shows reduced tissue damage through rapid oxygen depletion, although clinical application remains experimental [160]. The breath-holding technique, particularly deep inspiration breath-hold (DIBH), is widely used to reduce cardiac exposure. By inflating the lungs, the heart is shifted away from the treatment area, minimising radiation risk to the heart, particularly in breast and lung cancer treatments [161, 162]. Several studies concluded that DIBH significantly reduces the negative impact of radiation doses to critical organs like the heart and left anterior descending artery [178–180]. S. Tanguturi's study indicated that the effectiveness of DIBH varied across patients, with better outcomes seen in younger patients with a higher BMI and larger changes in lung volume during inspiration [181]. Despite its beneficial aspects, in a comparative study between DIBH and IMPT, DIBH was not feasible for some patients due to long treatment duration and age, highlighting its limitation in real-world applicability [182]. A study over 3 years compared Volumetric modulated arc therapy (VMAT) and helical tomography (HT) in left BC patients undergoing radiotherapy found no significant deterioration

in cardiac function, as assessed by LVEF. The results suggested both VMAT and HT can effectively limit cardiac exposure without causing noticeable damage [183]. Several studies have evaluated the impact of radiation on the cardiac conduction system, the sinoatrial node (SA) and atrioventricular node (AV) nodes. P. Loap et al., demonstrated that both these nodes are exposed during breast irradiation with VMAT, while Intensity-modulated proton therapy (IMPT) offers a potential dosimetric benefit as it delivers virtually no dose to SA and AV nodes [184].

Natural compounds are reliable sources of cardioprotection. Chia seed oil, rich in omega-3 fatty acids, is an effective chemoprotective agent against DOX in rats. It reduces oxidative stress, enhances superoxide dismutase and catalase, and neutralises free radicals generated by DOX [163]. Nanopreparation of ajwa dates showed cardioprotection against DOX-induced cardiotoxicity by increasing cardiac antioxidant capacity, suppressing inflammatory pathways mediated by cytokines and alleviating ischemia by upregulating glutathione and reducing malondialdehyde levels [164–166]. Curcumin, derived from *Curcuma longa*, is a potent antioxidant that mitigates DOX-induced cardiotoxicity. It reduces oxidative stress and improves cardiac function, promising an adjunctive strategy for cancer therapies [167]. Certain flavonoids have shown both cardioprotective and anti-tumour properties; however, their mechanisms are still to be discovered [167]. While traditional strategies help mitigate cardiotoxicity, a recent alternative to traditional Chinese medicine has gained attention for its potential in cardioprotection. Particularly, flavonoids, having both antiprotective and anti-tumour properties highlights the need to explore their mechanism in alleviating cardiotoxicity [168]. Non-psychotropic constituent of *Cannabis sativa*, cannabidiol, has antioxidant and anti-inflammatory properties, as was evaluated in mouse models of anthracycline-induced cardiomyopathy [169, 170].

Lifestyle modifications and exercise can improve cardiovascular health and reduce the impact of cancer treatment on the heart. Cancer patients develop deteriorated muscle strength due to radio/chemo drug exposure. Studies have shown that physical strength restores cardiomyocyte homeostasis and the heart's tolerance to chemotherapeutic agents [185]. Recent findings of a systematic review and meta-analysis of randomised controlled trials found exercise reduced cardiac mortality risk in cancer patients by 48%, although limitations included a small sample number (n = 3), moderate quality, and unclear definitions of cardiac mortality [171]. Aerobic exercise improved VO2 peak in BC patients, but its direct impact on LVEF remains uncertain due to small sample sizes and protocol variability, emphasising the need for high-quality trials to confirm its role in preventing cardiotoxicity [172]. Additionally, tailored interventions such as psychological treatments, including yoga, exercise, and

qigong/Tai Chi have been proven to enhance the quality of life, though more research is needed to assess their cardioprotective mechanism [173]. A summary of different cardioprotective strategies in cancer therapy is illustrated in Fig. 3.

Conclusion

Cancer treatment-induced cardiotoxicity is a notable concern in managing cancer patients and can significantly impact the quality of life of cancer survivors. The clinical manifestation of cardiotoxicity varies; it is primarily progressive and depends on the type and duration of cancer therapy. The clinical manifestations of CTR-CVT can range from acute symptoms to chronic heart dysfunction, with late-onset cardiotoxicity presenting significant challenges for cancer survivors. Several in vitro and preclinical models have advanced our study of the effects of cardiotoxicity of these cancer treatment modalities, but they have certain limitations. In vitro cultures, such as 2D cardiomyocytes lack replicability of in vivo cardiac environments. HiPSC-CMs are emerging as a transformative tool for pre-clinical cardiotoxicity assessments; however, much progress must be made in translating this innovation into clinical reality. Their current challenges, such as variability in reprogramming quality, epigenetic memory affecting differentiation efficiency, and unpredictable reactions during cell reprogramming, highlight the unmet need for refined techniques. Preclinical animal model is hindered by interspecies differences in cardiovascular physiology and drug responses, as well as their inability to replicate the genetic and metabolic diversity of the human population.

The mechanistic insights reveal that chemotherapy, targeted therapy, and radiotherapy exert cardiotoxicity primarily by oxidative stress and cellular damage. Other mechanisms include alterations in apoptosis, epigenetic modifications, and genetic susceptibility leading to cardiomyocyte and endothelial damage. TKIs induce cardiotoxicity by suppressing NO levels necessary for vascular homeostasis. This causes a strain on the myocardium, resulting in vasoconstriction. The loss of cardiomyocytes leads to pathological remodelling of the myocardium, leading to arrhythmias and cardiomyopathies. On the other hand, ICIs cause T-cell infiltration that manifests in myocarditis and acute cardiac injury. The damage to endothelial cells can lead to atherosclerosis and CAD.

To alleviate the significant cardiotoxic effects of cancer therapies, new mitigating strategies are being developed and tested. Cardio-oncology has seen considerable advancements, including multidisciplinary collaborations and the establishment of tailored clinical trials. For example, the PRADA trial evaluated the efficacy of ACE inhibitors and β-blockers in reducing chemotherapy-induced cardiotoxicity,

Fig. 3 Strategies to mitigate cardiotoxicity in cancer treatments
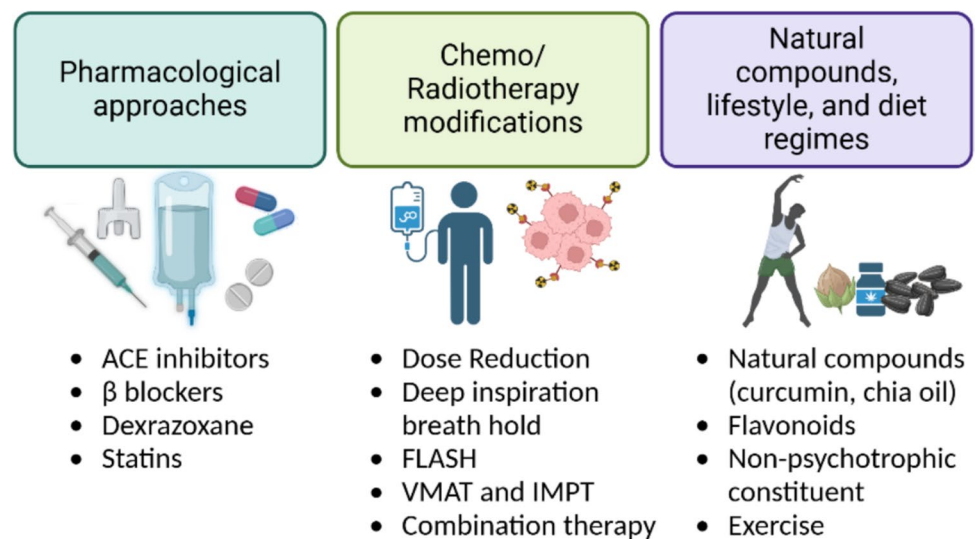
while the CLEOPATRA trial highlighted the cardiac safety of combining targeted therapy with taxanes for HER2-positive BC. These combination therapies have shown synergistic effects on reducing oxidative stress and improving cardiac output, albeit with limited long-term outcomes. Moreover, novel compounds, exercise, and lifestyle modifications show promising results to counter cancer therapy's toxic cardiac effects. Efforts to develop biomarkers like troponin and advanced imaging techniques hold promise but require further validation for widespread clinical adoption. In radiotherapy, DIBH techniques, and proton therapy offer a potential dosimetric benefit to reduce cardiac toxicity, although limitations like real-life applicability remain. Developing newer biomarkers and imaging techniques for continuous monitoring of clinical symptoms and identifying the early cardiotoxic effects can be helpful in preventing severe toxicities.

Future research should focus on understanding the mechanisms of cancer therapy-induced cardiotoxicity and develop more effective strategies to bridge the gap between mechanistic insights and clinical applications. This would require sustained efforts in interdisciplinary research, innovation, and collaboration from multiple oncology specialties, cardiology, radiation therapy, physiotherapy, and nutrition science. Studies should be conducted to incorporate preventive genetic testing and integrate pre-treatment protocols that could allow for dose adjustments or alternative therapies, potentially reducing adverse outcomes. A foremost focus on developing optimised prevention methods enhanced diagnostic accuracy, and personalised treatments will increase patients'quality of life during and post cancer treatment.

Authors' contributions KDM and PK conceptualised the framework and scope of the review. SS conducted an extensive literature review, wrote the draft, and designed the figures. KDM and PK critically reviewed and revised the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

Competing interests The authors declare no competing interests.

References

1. Gegechkori N, Haines L, Lin JJ (2017) Long Term and Latent Side Effects of Specific Cancer Types. Med Clin North Am 101(6):1053–1073

2. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D et al (2016) Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin 66(4):309–325

3. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH (2007) Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer. J Clin Oncol 25(25):3808–3815

4. Armstrong GT, Kawashima T, Leisenring W, Stratton K, Stovall M, Hudson MM et al (2014) Aging and Risk of Severe, Disabling, Life-Threatening, and Fatal Events in the Childhood Cancer Survivor Study. J Clin Oncol 32(12):1218–1227

5. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V et al (2005) Reversibility of Trastuzumab-Related Cardiotoxicity: New Insights Based on Clinical Course and Response to Medical Treatment. J Clin Oncol 23(31):7820–7826

6. American College of Cardiology [Internet]. [cited 2025 Jan 17]. Type I and Type II Cardiomyopathy Classifications Are Complete Nonsense: PRO. Available from: https://www.acc.org/latest-in-cardiology/articles/2018/05/04/08/41/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2018%2f05%2f04%2f08%2f41%2ftype-i-and-type-ii-cardiomyopathy-classifications-are-complete-nonsense-pro

7. Sawyer DB, Zuppinger C, Miller TA, Eppenberger HM, Suter TM (2002) Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1beta and anti-erbB2: potential mechanism for trastuzumab-induced cardiotoxicity. Circulation 105(13):1551–1554

8. Suter TM, Ewer MS (2013) Cancer drugs and the heart: importance and management. Eur Heart J 34(15):1102–1111

9. Florescu M, Cinteza M, Vinereanu D (2013) Chemotherapy-induced Cardiotoxicity. Maedica 8(1):59–67

10. Shakir DK, Rasul KI (2009) Chemotherapy Induced Cardiomyopathy: Pathogenesis, Monitoring and Management. J Clin Med Res 1(1):8–12

11. Volkova M, Russell R (2011) Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment. Curr. Cardiol Rev 7(4):214–220

12. Zamorano JL, Gottfridsson C, Asteggiano R, Atar D, Badimon L, Bax JJ et al (2020) The cancer patient and cardiology. Eur J Heart Fail 22(12):2290–2309

13. Lancellotti P, Suter TM, López-Fernández T, Galderisi M, Lyon AR, Van der Meer P et al (2019) Cardio-Oncology Services: rationale, organization, and implementation. Eur Heart J 40(22):1756–1763

14. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J et al (2022) 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). Eur Heart J 43(41):4229–4361

15. Koutsoukis A, Ntalianis A, Repasos E, Kastritis E, Dimopoulos MA, Paraskevaidis I (2018) Cardio-oncology: A Focus on Cardiotoxicity. Eur Cardiol Rev 13(1):64–69

16. Ewer MS, Ewer SM (2015S) Cardiotoxicity of anticancer treatments. Nat Rev Cardiol 12(9):547–558

17. Swain SM, Whaley FS, Ewer MS (2003) Congestive heart failure in patients treated with doxorubicin. Cancer 97(11):2869–2879

18. Menna P, Salvatorelli E, Minotti G (2010) Anthracycline Degradation in Cardiomyocytes: A Journey to Oxidative Survival. Chem Res Toxicol 23(1):6–10

19. Agunbiade TA, Zaghlol RY, Barac A (2019) Heart Failure in Relation to Anthracyclines and Other Chemotherapies. Methodist DeBakey Cardiovasc J 15(4):243–249

20. Narezkina A, Narayan HK, Zemljic-Harpf AE (2021) Molecular mechanisms of anthracycline cardiovascular toxicity. Clin Sci 135(10):1311–1332

21. Jurczyk M, Król M, Midro A, Kurnik-Łucka M, Poniatowski A, Gil K (2021) Cardiotoxicity of Fluoropyrimidines: Epidemiology, Mechanisms, Diagnosis, and Management. J Clin Med 10(19):4426

22. Raber I, Warack S, Kanduri J, Pribish A, Godishala A, Abovich A et al (2020) Fluoropyrimidine-Associated Cardiotoxicity: A Retrospective Case-Control Study. Oncologist 25(3):e606–e609

23. de Moraes FCA, de Almeida Barbosa AB, Sano VKT, Kelly FA, Burbano RMR (2024) Pharmacogenetics of DPYD and treatment-related mortality on fluoropyrimidine chemotherapy for cancer patients: a meta-analysis and trial sequential analysis. BMC Cancer 24(1):1210

24. Ardizzone A, Bulzomì M, De Luca F, Silvestris N, Esposito E, Capra AP. Dihydropyrimidine Dehydrogenase Polymorphism c.2194G>A Screening Is a Useful Tool for Decreasing Gastrointestinal and Hematological Adverse Drug Reaction Risk in Fluoropyrimidine-Treated Patients. Curr Issues Mol Biol. 2024 Sep;46(9):9831–43.

25. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC (1991) Cardiac disturbances during the administration of taxol. J Clin Oncol 9(9):1704–1712

26. Osman M, Elkady M (2017) A Prospective Study to Evaluate the Effect of Paclitaxel on Cardiac Ejection Fraction. Breast Care 12(4):255–259

27. Dombernowsky P, Gehl J, Boesgaard M, Paaske T, Jensen BV (1996) Doxorubicin and paclitaxel, a highly active combination in the treatment of metastatic breast cancer. Semin Oncol 23(5 Suppl 11):23–27

28. El-Awady ESE, Moustafa YM, Abo-Elmatty DM, Radwan A (2011) Cisplatin-induced cardiotoxicity: Mechanisms and cardioprotective strategies. Eur J Pharmacol 650(1):335–341

29. Iqubal A, Iqubal MK, Sharma S, Ansari MohdA, Najmi AK, Ali SM, et al. Molecular mechanism involved in cyclophosphamide-induced cardiotoxicity: Old drug with a new vision. Life Sci. 2019 Feb 1;218:112–31.

30. Valiyaveettil D, Joseph D, Malik M (2023) Cardiotoxicity in breast cancer treatment: Causes and mitigation. Cancer Treat Res Commun 1(37)

31. Schlam I, Swain SM (2021) HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now. Npj Breast Cancer 7(1):1–12

32. Odiete O, Hill MF, Sawyer DB (2012O 26) Neuregulin in Cardiovascular Development and Disease. Circ Res 111(10):1376–1385

33. Pentassuglia L, Graf M, Lane H, Kuramochi Y, Cote G, Timolati F et al (2009A 15) Inhibition of ErbB2 by receptor tyrosine kinase inhibitors causes myofibrillar structural damage without cell death in adult rat cardiomyocytes. Exp Cell Res 315(7):1302–1312

34. Orphanos GS, Ioannidis GN, Ardavanis AG (2009) Cardiotoxicity induced by tyrosine kinase inhibitors. Acta Oncol 48(7):964–970

35. Force T, Krause DS, Van Etten RA (2007) Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer 7(5):332–344

36. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L et al (2007) Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. The Lancet 370(9604):2011–2019

37. D'Adamo DR, Anderson SE, Albritton K, Yamada J, Riedel E, Scheu K et al (2005) Phase II Study of Doxorubicin and Bevacizumab for Patients With Metastatic Soft-Tissue Sarcomas. J Clin Oncol 23(28):7135–7142

38. Dobbin SJH, Petrie MC, Myles RC, Touyz RM, Lang NN (2021) Cardiotoxic effects of angiogenesis inhibitors. Clin Sci Lond Engl 1979. 135(1):71–100.

39. Xiao J, Li X, Wang X, Guan Y, Liu H, Liang J et al (2023) Clinical characteristics and management of immune checkpoint inhibitor-related cardiotoxicity: A single-center experience. Front Cardiovasc Med 6(10):1093383

40. Hu J, Tian R, Ma Y, Zhen H, Ma X, Su Q et al (2021) Risk of Cardiac Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-Analysis. Front Oncol 27(11)

41. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM et al (2018) Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol 71(16):1755–1764

42. Cheki M, Yahyapour R, Farhood B, Rezaeyan A, Shabeeb D, Amini P et al (2018) COX-2 in Radiotherapy: A Potential Target for Radioprotection and Radiosensitization. Curr Mol Pharmacol 11(3):173–183

43. Ell P, Martin JM, Cehic DA, Ngo DTM, Sverdlov AL (2021) Cardiotoxicity of Radiation Therapy: Mechanisms, Management, and Mitigation. Curr Treat Options Oncol 22(8):70

44. Siaravas KC, Katsouras CS, Sioka C (2023) Radiation Treatment Mechanisms of Cardiotoxicity: A Systematic Review. Int J Mol Sci 24(7):6272

45. Ellahham S, Khalouf A, Elkhazendar M, Dababo N, Manla Y (2022) An overview of radiation-induced heart disease. Radiat Oncol J 40(2):89–102

46. Asensio-López MC, Soler F, Pascual-Figal D, Fernández-Belda F, Lax A (2017) Doxorubicin-induced oxidative stress: The protective effect of nicorandil on HL-1 cardiomyocytes. PLoS ONE 12(2)

47. Strigun A, Wahrheit J, Niklas J, Heinzle E, Noor F (2012) Doxorubicin Increases Oxidative Metabolism in HL-1 Cardiomyocytes as Shown by 13C Metabolic Flux Analysis. Toxicol Sci 125(2):595–606

48. Dimitrakis P, Romay-Ogando MI, Timolati F, Suter TM, Zuppinger C (2012) Effects of doxorubicin cancer therapy on autophagy and the ubiquitin-proteasome system in long-term cultured adult rat cardiomyocytes. Cell Tissue Res 350(2):361–372

49. Polonchuk L, Chabria M, Badi L, Hoflack JC, Figtree G, Davies MJ et al (2017) Cardiac spheroids as promising in vitro models to study the human heart microenvironment. Sci Rep 7(1):7005

50. Truitt R, Mu A, Corbin EA, Vite A, Brandimarto J, Ky B et al (2018) Increased Afterload Augments Sunitinib-Induced Cardiotoxicity in an Engineered Cardiac Microtissue Model. JACC Basic Transl Sci 3(2):265–276

51. Shead KD, Huethorst E, Burton F, Lang NN, Myles RC, Smith GL (2024) Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes for Preclinical Cardiotoxicity Screening in Cardio-Oncology. JACC CardioOncology 6(5):678–683

52. Di Baldassarre A, Cimetta E, Bollini S, Gaggi G, Ghinassi B (2018) Human-Induced Pluripotent Stem Cell Technology and Cardiomyocyte Generation: Progress and Clinical Applications. Cells 7(6):48

53. Gintant G, Burridge P, Gepstein L, Harding S, Herron T, Hong C et al (2019) Use of Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes in Preclinical Cancer Drug Cardiotoxicity Testing. Circ Res 125(10):e75-92

54. Joshi J, Albers C, Smole N, Guo S, Smith SA (2024) Human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) for modeling cardiac arrhythmias: strengths, challenges and potential solutions. Front Physiol 12(15):1475152

55. Yang H, Yang Y, Kiskin FN, Shen M, Zhang JZ (2023) Recent advances in regulating the proliferation or maturation of human-induced pluripotent stem cell-derived cardiomyocytes. Stem Cell Res Ther 14(1):228

56. Zhu K, Bao X, Wang Y, Lu T, Zhang L (2023) Human induced pluripotent stem cell (hiPSC)-derived cardiomyocyte modelling of cardiovascular diseases for natural compound discovery. Biomed Pharmacother 1(157)

57. Burridge PW, Li YF, Matsa E, Wu H, Ong SG, Sharma A et al (2016) Human induced pluripotent stem cell–derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity. Nat Med 22(5):547–556

58. Kitani T, Ong SG, Lam CK, Rhee JW, Zhang JZ, Oikonomopoulos A et al (2019) Human-Induced Pluripotent Stem Cell Model of Trastuzumab-Induced Cardiac Dysfunction in Patients With Breast Cancer. Circulation 139(21):2451–2465

59. Bauer M, Cheng S, Jain M, Ngoy S, Theodoropoulos C, Trujillo A et al (2011) Echocardiographic Speckle-Tracking Based Strain Imaging for Rapid Cardiovascular Phenotyping in Mice. Circ Res 108(8):908–916

60. Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y et al (2002) ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 8(5):459–465

61. Chintalgattu V, Rees ML, Culver JC, Goel A, Jiffar T, Zhang J, et al. Coronary Microvascular Pericytes Are the Cellular Target of Sunitinib Malate–Induced Cardiotoxicity. Sci Transl Med. 2013 May 29;5(187):187ra69–187ra69.

62. Zeiss CJ, Gatti DM, Toro-Salazar O, Davis C, Lutz CM, Spinale F, et al. Doxorubicin-Induced Cardiotoxicity in Collaborative Cross (CC) Mice Recapitulates Individual Cardiotoxicity in Humans. G3 GenesGenomesGenetics. 2019 Aug 1;9(8):2637–46.

63. Gal án AC, Lobo M, V ílchez TJP, L ópez GJ, de MIA, P érez MC, et al. Serial Magnetic Resonance Imaging to Identify Early Stages of Anthracycline-Induced Cardiotoxicity. J Am Coll Cardiol. 2019 Feb 26;73(7):779–91.

64. Asnani A, Zheng B, Liu Y, Wang Y, Chen HH, Vohra A, et al. Highly potent visnagin derivatives inhibit Cyp1 and prevent doxorubicin cardiotoxicity. JCI Insight. 3(1):e96753.

65. Sawicki KT, Sala V, Prever L, Hirsch E, Ardehali H, Ghigo A (2021) Preventing and Treating Anthracycline Cardiotoxicity: New Insights. Annu Rev Pharmacol Toxicol 61(1):309–332

66. Rique A, Cautela J, Thuny F, Michel G, Ovaert C, El Louali F (2024) Left Ventricular Longitudinal Strain Abnormalities in Childhood Exposure to Anthracycline Chemotherapy. Children 11(3):378

67. Schultheiss HP, Fairweather D, Caforio ALP, Escher F, Hershberger RE, Lipshultz SE et al (2019) Dilated cardiomyopathy. Nat Rev Dis Primer 5(1):1–19

68. Shiga T, Hiraide M (2020M) Cardiotoxicities of 5-Fluorouracil and Other Fluoropyrimidines. Curr Treat Options Oncol 21(4):27

69. Dyhl-Polk A, Vaage-Nilsen M, Schou M, Vistisen KK, Lund CM, Kümler T et al (2020) Incidence and risk markers of 5-fluorouracil and capecitabine cardiotoxicity in patients with colorectal cancer. Acta Oncol 59(4):475–483

70. Kosmas C, Kallistratos MS, Kopterides P, Syrios J, Skopelitis H, Mylonakis N et al (2008) Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. J Cancer Res Clin Oncol 134(1):75–82

71. Maslarinou A, Manolopoulos VG, Ragia G (2023) Pharmacogenomic-guided dosing of fluoropyrimidines beyond DPYD: time for a polygenic algorithm? Front Pharmacol 15(14):1184523

72. Raber I, Frazer MB, Zerillo JA, Asnani A (2020) Uridine Triacetate for Severe Fluoropyrimidine Cardiotoxicity in a Patient With Thymidylate Synthase Gene Variants. JACC CardioOncology 2(2):329–332

73. Shiga T, Hiraide M (2020) Cardiotoxicities of 5-Fluorouracil and Other Fluoropyrimidines. Curr Treat Options Oncol 21(4):27

74. Marupudi NI, Han JE, Li KW, Renard VM, Tyler BM, Brem H (2007) Paclitaxel: a review of adverse toxicities and novel delivery strategies. Expert Opin Drug Saf 6(5):609–621

75. Chirca A, Sanda NA, Mihalcea DJ, Vinereanu D, Costea RV (2022F 1) Taxane induced cardiotoxicity in a patient with breast cancer. Eur J Surg Oncol 48(2)

76. Florescu M, Mihalcea D, Enescu OA, Radu E, Chirca A, Acasandrei AM, et al. Taxanes-induced cardiotoxicity is related to increased arterial stiffness and oxidative stress. Eur Heart J. 2013 Aug 1;34(suppl_1):P3006.

77. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C et al (2005) Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 352(22):2302–2313

78. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M et al (2005) Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Administered As First-Line Treatment: The M77001 Study Group. J Clin Oncol 23(19):4265–4274

79. Long HD, Lin YE, Zhang JJ, Zhong WZ, Zheng RN (2016) Risk of Congestive Heart Failure in Early Breast Cancer Patients Undergoing Adjuvant Treatment With Trastuzumab: A Meta-Analysis. Oncologist 21(5):547–554

80. Alhussein MM, Mokbel A, Cosman T, Aghel N, Yang EH, Mukherjee SD et al (2021) Pertuzumab Cardiotoxicity in Patients With HER2-Positive Cancer: A Systematic Review and Meta-analysis. CJC Open 3(11):1372–1382

81. Lamore SD, Kohnken RA, Peters MF, Kolaja KL (2020) Cardiovascular Toxicity Induced by Kinase Inhibitors: Mechanisms and Preclinical Approaches. Chem Res Toxicol 33(1):125–136

82. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W et al (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350(23):2335–2342

83. Gounder MM, Mahoney MR, Van Tine BA, Ravi V, Attia S, Deshpande HA et al (2018D 20) Sorafenib for Advanced and Refractory Desmoid Tumors. N Engl J Med 379(25):2417–2428

84. Goodman VL, Rock EP, Dagher R, Ramchandani RP, Abraham S, Gobburu JVS et al (2007) Approval Summary: Sunitinib for the Treatment of Imatinib Refractory or Intolerant Gastrointestinal Stromal Tumors and Advanced Renal Cell Carcinoma. Clin Cancer Res 13(5):1367–1373

85. Rini BI, Cohen DP, Lu DR, Chen I, Hariharan S, Gore ME et al (2011) Hypertension as a Biomarker of Efficacy in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib. JNCI J Natl Cancer Inst 103(9):763–773

86. Lobenwein D, Kocher F, Dobner S, Gollmann-Tepeköylü C, Holfeld J (2021) Cardiotoxic mechanisms of cancer immunotherapy – A systematic review. Int J Cardiol 323:179–187

87. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD et al (2015) Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 373(1):23–34

88. Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, Tawbi H et al (2016) Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer 4(1):50

89. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY et al (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. The Lancet 387(10027):1540–1550

90. Semper H, Muehlberg F, Schulz-Menger J, Allewelt M, Grohé C (2016) Drug-induced myocarditis after nivolumab treatment in a patient with PDL1- negative squamous cell carcinoma of the lung. Lung Cancer 1(99):117–119

91. Tadokoro T, Keshino E, Makiyama A, Sasaguri T, Ohshima K, Katano H et al (2016) Acute Lymphocytic Myocarditis With Anti-PD-1 Antibody Nivolumab. Circ Heart Fail 9(10)

92. Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A (2020) Immune Checkpoint Inhibitor Myocarditis: Pathophysiological Characteristics, Diagnosis, and Treatment. J Am Heart Assoc 9(2)

93. Safi M, Ahmed H, Al-Azab M, Xia Y long, Shan X, Al-radhi M, et al. (2021) PD-1/PDL-1 Inhibitors and Cardiotoxicity; Molecular, Etiological and Management Outlines. J Adv Res. 29:45–54.

94. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R et al (2017) Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. N Engl J Med 377(20):1919–1929

95. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M et al (2016) 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 37(36):2768–2801

96. Hall PS, Harshman LC, Srinivas S, Witteles RM (2013) The Frequency and Severity of Cardiovascular Toxicity From Targeted Therapy in Advanced Renal Cell Carcinoma Patients. JACC Heart Fail 1(1):72–78

97. Limat S, Daguindau E, Cahn JY, Nerich V, Brion A, Perrin S et al (2014) Incidence and risk-factors of CHOP/R-CHOP-related cardiotoxicity in patients with aggressive non-Hodgkin's lymphoma. J Clin Pharm Ther 39(2):168–174

98. Lalario A, Del Mestre E, Lo Casto M, Nuzzi V, Manca P, Bromage DI et al (2022) Clinical characterization and natural history of chemotherapy-induced dilated cardiomyopathy. ESC Heart Fail 9(5):3052–3059

99. Saidi A, Alharethi R (2011) Management of chemotherapy induced cardiomyopathy. Curr Cardiol Rev 7(4):245–249

100. Stone JR, Kanneganti R, Abbasi M, Akhtari M (2021M) Monitoring for Chemotherapy-Related Cardiotoxicity in the Form of Left Ventricular Systolic Dysfunction: A Review of Current Recommendations. JCO Oncol Pract 17(5):228–236

101. Moudgil R, Yeh ETH (2016) Mechanisms of Cardiotoxicity of Cancer Chemotherapeutic Agents: Cardiomyopathy and Beyond. Can J Cardiol 32(7):863-870.e5

102. Morelli MB, Bongiovanni C, Da Pra S, Miano C, Sacchi F, Lauriola M et al (2022) Cardiotoxicity of Anticancer Drugs: Molecular Mechanisms and Strategies for Cardioprotection. Front Cardiovasc Med 15(9)

103. Veeder JA, Hothem LN, Cipriani AE, Jensen BC, Rodgers JE (2021) Chemotherapy-associated cardiomyopathy: Mechanisms

of toxicity and cardioprotective strategies. Pharmacother J Hum Pharmacol Drug Ther 41(12):1066–1080

104. Vejpongsa P, Yeh E (2014) Topoisomerase 2β: A Promising Molecular Target for Primary Prevention of Anthracycline-Induced Cardiotoxicity. Clin Pharmacol Ther 95(1):45–52

105. Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF et al (2012) Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 18(11):1639–1642

106. Nakano K, Vousden KH (2001M 1) PUMA, a Novel Proapoptotic Gene, Is Induced by p53. Mol Cell 7(3):683–694

107. Zhang DX, Ma DY, Yao ZQ, Fu CY, Shi YX, Wang QL et al (2016J) ERK1/2/p53 and NF-κB dependent-PUMA activation involves in doxorubicin-induced cardiomyocyte apoptosis. Eur Rev Med Pharmacol Sci 20(11):2435–2442

108. Peña-Blanco A, García-Sáez AJ (2018) Bax, Bak and beyond — mitochondrial performance in apoptosis. FEBS J 285(3):416–431

109. Niu J, Azfer A, Wang K, Wang X, Kolattukudy PE (2009) Cardiac-targeted expression of soluble fas attenuates doxorubicin-induced cardiotoxicity in mice. J Pharmacol Exp Ther 328(3):740–748

110. Grakova EV, Shilov SN, Kopeva KV, Berezikova EN, Popova AA, Neupokoeva MN et al (2021) Anthracycline-Induced Cardiotoxicity: The Role of Endothelial Dysfunction. Cardiology 146(3):315–323

111. Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G et al (2013) The Vascular Endothelium and Human Diseases. Int J Biol Sci 9(10):1057–1069

112. Terwoord JD, Beyer AM, Gutterman DD (2022) Endothelial dysfunction as a complication of anti-cancer therapy. Pharmacol Ther 1(237)

113. Ludke AR, Sharma AK, Akolkar G, Bajpai G, Singal PK (2012) Downregulation of vitamin C transporter SVCT-2 in doxorubicin-induced cardiomyocyte injury. Am J Physiol-Cell Physiol 303(6):C645–C653

114. Ichikawa Y, Ghanefar M, Bayeva M, Wu R, Khechaduri A, Prasad SVN et al (2014) Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. J Clin Invest 124(2):617–630

115. Muckenthaler MU, Galy B, Hentze MW (2008) Systemic Iron Homeostasis and the Iron-Responsive Element/Iron-Regulatory Protein (IRE/IRP) Regulatory Network. Annu Rev Nutr. 28:197–213.

116. Tokarska-Schlattner M, Zaugg M, da Silva R, Lucchinetti E, Schaub MC, Wallimann T et al (2005) Acute toxicity of doxorubicin on isolated perfused heart: response of kinases regulating energy supply. Am J Physiol-Heart Circ Physiol 289(1):H37-47

117. Huang L, Zhang K, Guo Y, Huang F, Yang K, Chen L et al (2017) Honokiol protects against doxorubicin cardiotoxicity via improving mitochondrial function in mouse hearts. Sci Rep 7(1):11989

118. Li H, Wang M, Huang Y (2024) Anthracycline-induced cardiotoxicity: An overview from cellular structural perspective. Biomed Pharmacother 1(179)

119. Rupert CE, Coulombe KL (2015A 8) The Roles of Neuregulin-1 in Cardiac Development, Homeostasis, and Disease. Biomark Insights 10(Suppl 1):1–9

120. Wattenberg MM, Kwilas AR, Gameiro SR, Dicker AP, Hodge JW (2014) Expanding the use of monoclonal antibody therapy of cancer by using ionising radiation to upregulate antibody targets. Br J Cancer 110(6):1472–1480

121. Hsu PY, Mammadova A, Benkirane-Jessel N, Désaubry L, Nebigil CG (2021) Updates on Anticancer Therapy-Mediated Vascular Toxicity and New Horizons in Therapeutic Strategies. Front Cardiovasc Med 27(8)

122. Barachini S, Ghelardoni S, Varga ZV, Mehanna RA, Montt-Guevara MM, Ferdinandy P et al (2023) Antineoplastic drugs inducing cardiac and vascular toxicity – An update. Vascul Pharmacol 1(153)

123. Lee WS, Kim J (2018) Cardiotoxicity associated with tyrosine kinase-targeted anticancer therapy. Mol Cell Toxicol 14(3):247–254

124. Jiang H, Wang C, Zhang A, Li Y, Li J, Li Z et al (2022) ATF4 protects against sorafenib-induced cardiotoxicity by suppressing ferroptosis. Biomed Pharmacother 1(153)

125. Jahng JWS, Little MP, No HJ, Loo BW, Wu JC (2024) Consequences of ionizing radiation exposure to the cardiovascular system. Nat Rev Cardiol 21(12):880–898

126. Mrotzek SM, Rassaf T, Totzeck M (2020) Cardiovascular Damage Associated With Chest Irradiation. Front Cardiovasc Med 20(7):41

127. Heidenreich PA, Hancock SL, Vagelos RH, Lee BK, Schnittger I (2005) Diastolic dysfunction after mediastinal irradiation. Am Heart J 150(5):977–982

128. Wennstig AK, Wadsten C, Garmo H, Fredriksson I, Blomqvist C, Holmberg L et al (2020) Long-term risk of ischemic heart disease after adjuvant radiotherapy in breast cancer: results from a large population-based cohort. Breast Cancer Res 22(1):10

129. Taylor CW, Nisbet A, McGale P, Darby SC (2007) Cardiac Exposures in Breast Cancer Radiotherapy: 1950s–1990s. Int J Radiat Oncol 69(5):1484–1495

130. Becker-Schiebe M, Stockhammer M, Hoffmann W, Wetzel F, Franz H (2016) Does mean heart dose sufficiently reflect coronary artery exposure in left-sided breast cancer radiotherapy? Strahlenther Onkol 192(9):624–631

131. Bates JE, Rancati T, Keshavarz H, Gagliardi G, Aznar MC, Howell RM et al (2024) Cardiac Disease in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review. Int J Radiat Oncol 119(2):522–532

132. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D et al (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 368(11):987–998

133. Piroth MD, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R et al (2019) Heart toxicity from breast cancer radiotherapy: Current findings, assessment, and prevention. Strahlenther Onkol 195(1):1

134. Henson KE, McGale P, Taylor C, Darby SC (2013) Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. Br J Cancer 108(1):179–182

135. Koutroumpakis E, Deswal A, Yusuf SW, Abe J ichi, Nead KT, Potter AS, et al. Radiation-Induced Cardiovascular Disease: Mechanisms, Prevention, and Treatment. Curr Oncol Rep. 2022 May 1;24(5):543–53.

136. Mansour HH, Tawfik SS (2012) Early treatment of radiation-induced heart damage in rats by caffeic acid phenethyl ester. Eur J Pharmacol 692(1):46–51

137. Sárközy M, Varga Z, Gáspár R, Szűcs G, Kovács MG, Kovács ZZA et al (2021) Pathomechanisms and therapeutic opportunities in radiation-induced heart disease: from bench to bedside. Clin Res Cardiol 110(4):507–531

138. Sarkar RR, Hatamipour A, Panjwani N, Courtney PT, Cherry DR, Salans MA et al (2021) Impact of Radiation on Cardiovascular Outcomes in Older Resectable Esophageal Cancer Patients With Medicare. Am J Clin Oncol 44(6):275

139. Baselet B, Sonveaux P, Baatout S, Aerts A (2019) Pathological effects of ionizing radiation: endothelial activation and dysfunction. Cell Mol Life Sci 76(4):699–728

140. Díaz-Gavela AA, Figueiras-Graillet L, Luis ÁM, Salas Segura J, Ciérvide R, del Cerro Peñalver E, et al. Breast

Radiotherapy-Related Cardiotoxicity. When, How, Why. Risk Prevention and Control Strategies. Cancers. 2021 13(7):1712.

141. Choksey A, Timm KN (2022) Cancer Therapy-Induced Cardiotoxicity—A Metabolic Perspective on Pathogenesis, Diagnosis and Therapy. Int J Mol Sci 23(1):441

142. Yu Z, Xu C, Song B, Zhang S, Chen C, Li C et al (2023) Tissue fibrosis induced by radiotherapy: current understanding of the molecular mechanisms, diagnosis and therapeutic advances. J Transl Med 21(1):708

143. Belzile-Dugas E, Eisenberg MJ (2021) Radiation-Induced Cardiovascular Disease: Review of an Underrecognized Pathology. J Am Heart Assoc 10(18)

144. Toste JC (2022) Cardio-oncology: Understanding the different mechanisms of cardiovascular toxicity. Rev Port Cardiol 41(7):587–597

145. Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M et al (2013) Protective effects of nebivolol against anthracycline-induced cardiomyopathy: A randomized control study. Int J Cardiol 167(5):2306–2310

146. Gong FF, Grunblatt E, Voss WB, Rangarajan V, Raissi S, Chow K et al (2024D) A strain-guided trial of cardioprotection in early-stage breast cancer patients on anti-HER2 therapy (PROTECT HER2). Cardio-Oncol 10(1):1–11

147. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ. 2013 Jan 28;346(jan28 1):f360–f360.

148. Gupta V, Kumar Singh S, Agrawal V, Bali ST (2018) Role of ACE inhibitors in anthracycline-induced cardiotoxicity: A randomized, double-blind, placebo-controlled trial. Pediatr Blood Cancer 65(11)

149. Janbabai G, Nabati M, Faghihinia M, Azizi S, Borhani S, Yazdani J (2017) Effect of Enalapril on Preventing Anthracycline-Induced Cardiomyopathy. Cardiovasc Toxicol 17(2):130–139

150. Nakamae H, Tsumura K, Terada Y, Nakane T, Nakamae M, Ohta K et al (2005) Notable effects of angiotensin II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. Cancer 104(11):2492–2498

151. Ganatra S, Nohria A, Shah S, Groarke JD, Sharma A, Venesy D et al (2019) Upfront dexrazoxane for the reduction of anthracycline-induced cardiotoxicity in adults with preexisting cardiomyopathy and cancer: a consecutive case series. Cardio-Oncol 5(1):1

152. Kourek C, Touloupaki M, Rempakos A, Loritis K, Tsougkos E, Paraskevaidis I et al (2022) Cardioprotective Strategies from Cardiotoxicity in Cancer Patients: A Comprehensive Review. J Cardiovasc Dev Dis 9(8):259

153. Strauss MH, Hall AS, The NK, Combination of Beta-Blockers and ACE Inhibitors Across the Spectrum of Cardiovascular Diseases. Cardiovasc Drugs Ther [Internet]. (2021) cited 2023 Jul 11. Available from: https://doi.org/10.1007/s10557-021-07248-1

154. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW et al (2016) Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 37(21):1671–1680

155. Heck SL, Mecinaj A, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW et al (2021) Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Extended Follow-Up of a 2×2 Factorial, Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Candesartan and Metoprolol. Circulation 143(25):2431–2440

156. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ et al (2017) Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101–Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity. J Clin Oncol 35(8):870–877

157. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH (2012) Effect of Statin Therapy on the Risk for Incident Heart Failure in Patients With Breast Cancer Receiving Anthracycline Chemotherapy. J Am Coll Cardiol 60(23):2384–2390

158. Calvillo-Argüelles O, Abdel-Qadir H, Michalowska M, Billia F, Suntheralingam S, Amir E et al (2019) Cardioprotective Effect of Statins in Patients With HER2-Positive Breast Cancer Receiving Trastuzumab Therapy. Can J Cardiol 35(2):153–159

159. American College of Cardiology [Internet]. [cited 2025 Jan 24]. Statins For Cardioprotection From Anthracycline Cardiotoxicity. Available from: https://www.acc.org/Latest-in-Cardiology/Articles/2023/09/07/12/43/http%3a%2f%2fwww.acc.org%2fLatest-in-Cardiology%2fArticles%2f2023%2f09%2f07%2f12%2f43%2fStatins-For-Cardioprotection-From-Anthracycline-Cardiotoxicity

160. Kim JW. Cutting-edge technologies in external radiation therapy. Ewha Med J [Internet]. 2024 Oct 31 [cited 2025 Jan 4];47(4). Available from: https://synapse.koreamed.org/articles/1516088857

161. Busschaert SL, Kimpe E, Gevaert T, De Ridder M, Putman K (2024) Deep Inspiration Breath Hold in Left-Sided Breast Radiotherapy: A Balance Between Side Effects and Costs. JACC CardioOncology 6(4):514–525

162. Mader T, Pace R, Boucas da Silva RT, Erwin Johannes Adam L, Näf G, Charles Winter C et al (2024) Deep inspirational breast hold (DIBH) for right breast irradiation: Improved sparing of liver and lung tissue. Clin Transl Radiat Oncol. 45

163. Ahmed AZ, Mumbrekar KD, Satyam SM, Shetty P, D'Souza MR, Singh VK (2021) Chia Seed Oil Ameliorates Doxorubicin-Induced Cardiotoxicity in Female Wistar Rats: An Electrocardiographic. Biochemical and Histopathological Approach Cardiovasc Toxicol 21(7):533–542

164. Abdelghffar EA, Obaid WA, Mohammedsaleh ZM, Ouchari W, Eldahshan OA, Sobeh M. (2022) Ajwa dates (*Phoenix dactylifera* L.) attenuate cisplatin-induced nephrotoxicity in rats via augmenting Nrf2, modulating NADPH oxidase-4 and mitigating inflammatory/apoptotic mediators. Biomed Pharmacother. 156:113836.

165. Al-Jaouni S, Abdul-Hady S, El-Bassossy H, Salah N, Hagras M (2019) Ajwa Nanopreparation Prevents Doxorubicin-Associated Cardiac Dysfunction: Effect on Cardiac Ischemia and Antioxidant Capacity. Integr Cancer Ther 1(18):1534735419862351

166. Khan F, Khan TJ, Kalamegam G, Pushparaj PN, Chaudhary A, Abuzenadah A, et al. (2017) Anti-cancer effects of Ajwa dates (Phoenix dactylifera L.) in diethylnitrosamine induced hepatocellular carcinoma in Wistar rats. BMC Complement Altern Med. 17:418.

167. Arruda FS, Tomé FD, Milhomem AC, Franco PIR, Justino AB, Franco RR et al (2024) Curcumin Attenuates Doxorubicin-Induced Cardiac Oxidative Stress and Increases Survival in Mice. Pharmaceutics 16(8):1105

168. Shi H, Duan L, Tong L, Pu P, Wei L, Wang L et al (2024) Research Progress on Flavonoids in Traditional Chinese Medicine to Counteract Cardiotoxicity Associated with Anti-Tumor Drugs. Rev Cardiovasc Med 25(3):74

169. Hao E, Mukhopadhyay P, Cao Z, Erdélyi K, Holovac E, Liaudet L et al (2015) Cannabidiol Protects against Doxorubicin-Induced Cardiomyopathy by Modulating Mitochondrial Function and Biogenesis. Mol Med 21(1):38–45

170. Mohammed KAEH, Soliman NA, Eldahmy SI, Shalaby A (2024) Eventual Medicinal Benefits of Cannabidiol Oil alleviates Doxorubicin-Related Cardiac injuries. Bull Fac Sci Zagazig Univ 2024(2):168–173

171. Morishita S, Hamaue Y, Fukushima T, Tanaka T, Fu JB, Nakano J (2020) Effect of Exercise on Mortality and Recurrence in

Patients With Cancer: A Systematic Review and Meta-Analysis. Integr Cancer Ther 1(19):1534735420917462

172. Tsai YL, Chuang YC, Chen CP, Lee YC, Cheng YY, Ou-Yang LJ (2023A 1) Feasibility of Aerobic Exercise Training to Mitigate Cardiotoxicity of Breast Cancer Therapy: A Systematic Review and Meta-Analysis. Clin Breast Cancer 23(6):576–590

173. D'Andre SD, Ellsworth LL, Kirsch JL, Montane HN, Kruger MB, Donovan KA et al (2024D) Cancer and Stress: Understanding the Connections and Interventions. Am J Lifestyle Med 6:15598276241304372

174. Taylor AA, Siragy H, Nesbitt S (2011) Angiotensin Receptor Blockers: Pharmacology, Efficacy, and Safety. J Clin Hypertens 13(9):677–686

175. Sorodoc V, Sirbu O, Lionte C, Haliga RE, Stoica A, Ceasovschih A et al (2022) The Value of Troponin as a Biomarker of Chemotherapy-Induced Cardiotoxicity. Life 12(8):1183

176. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V et al (2020) Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 21(4):519–530

177. Yu AF, Manrique C, Pun S, Liu JE, Mara E, Fleisher M et al (2016) Cardiac Safety of Paclitaxel Plus Trastuzumab and Pertuzumab in Patients With HER2-Positive Metastatic Breast Cancer. Oncologist 21(4):418–424

178. Tamilarasu S, Saminathan M (2022) Dosimetric comparison of normal breathing and deep inspiration breath hold technique for synchronous bilateral breast cancer using 6MV flattened beam and flattening filter free beam. Rep Pract Oncol Radiother 27(1):63–75

179. Wikström K, Isacsson U, Nilsson K, Ahnesjö A (2018) Reproducibility of heart and thoracic wall position in repeated deep inspiration breath holds for radiotherapy of left-sided breast cancer patients. Acta Oncol 57(10):1318–1324

180. Lai J, Hu S, Luo Y, Zheng R, Zhu Q, Chen P et al (2020) Meta-analysis of deep inspiration breath hold (DIBH) versus free breathing (FB) in postoperative radiotherapy for left-side breast cancer. Breast Cancer 27(2):299–307

181. Tanguturi SK, Lyatskaya Y, Chen Y, Catalano PJ, Chen MH, Yeo WP et al (2015) Prospective assessment of deep inspiration breath-hold using 3-dimensional surface tracking for irradiation of left-sided breast cancer. Pract Radiat Oncol 5(6):358–365

182. Salim N, Popodko A, Tumanova K, Stolbovoy A, Lagkueva I, Ragimov V (2023) Cardiac dose in the treatment of synchronous bilateral breast cancer patients between three different radiotherapy techniques (VMAT, IMRT, and 3D CRT). Discov Oncol 14(1):29

183. Hou PY, Hsieh CH, Wu LJ, Hsu CX, Kuo DY, Lu YF et al (2022) Cardiac Function after Modern Radiation Therapy with Volumetric Modulated Arc Therapy or Helical Tomotherapy for Advanced Left-Breast Cancer Receiving Regional Nodal Irradiation. Bioengineering 9(5):213

184. Loap P, Fourquet A, Kirova Y (2021) Evaluation of Cardiac Conduction System Exposure with Breast Volumetric Modulated Arc Therapy and Intensity Modulated Proton Therapy. Int J Radiat Oncol. 111(3)

185. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM et al (2010) American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors. Med Sci Sports Exerc 42(7):1409–1426