Medicine Plus 2 (2025) 100074

Medicine Plus

Anthracycline-induced cardiotoxicity: emerging mechanisms and therapies

Guanjing Ling[a,1], Fei Ge[a,1], Weili Li[a], Yan Wei[a], Shujuan Guo[a], Yuqin Zhang[a], Yilin Li[a], Yawen Zhang[a], Heng Liu[a], Yunxia Wu[a], Wei Wang[a,c,d,e,*], Yong Wang[a,b,c,d,*]

[a] *College of Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China*

[b] *Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing 100029, China*

[c] *Beijing Key Laboratory of TCM Syndrome and Formula, Beijing 100029, China*

[d] *Key Laboratory of Beijing University of Chinese Medicine, Ministry of Education, Beijing 100029, China*

[e] *Guangzhou University of Chinese Medicine, Guangzhou 510006, China*

ARTICLE INFO

Keywords:
Anthracycline
Cardiotoxicity
Cardio-oncology
Mechanism
Therapy

ABSTRACT

Chemotherapy-induced cardiovascular disease has become one of the main causes of death in cancer survivors. Several international authoritative societies have developed a number of guidelines to standardize clinical practice for the emerging discipline of cardio-oncology, aiming to allow patients to receive cancer treatment while reducing the risk of cardiovascular events. Anthracyclines, as the earliest first-line chemotherapy drugs, have attracted much attention from researchers due to their severe cardiotoxicity. Although targeted therapy and immunotherapy strategies improve anticancer efficacy, they also increase the risk of cardiotoxicity. Therefore, anthracyclines are still indispensable in cancer treatment, and in-depth understanding of the mechanism of cardiotoxicity will help to develop effective therapeutic strategies. This review aims to summarize the new mechanisms of cardiotoxicity caused by anthracyclines and current emerging therapeutic strategies.

* Corresponding authors.
E-mail addresses: wangwei26960@163.com (W. Wang), wangyong@bucm.edu.cn (Y. Wang).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.medp.2025.100074
Received 8 December 2024; Received in revised form 17 February 2025; Accepted 19 February 2025
Available online 28 February 2025

1. Introduction

Over the past decades, the survival and prognosis of cancer patients have been significantly improved due to the continuous development of innovative cancer therapies. At the same time, the complex sequelae related to cancer therapies continue to occur in clinical practice. Among them, cardiovascular diseases caused by cancer therapies have attracted much attention, leading to high hospitalization and mortality rates of cancer patients.[1–3] Cardio-oncology has emerged as a new interdisciplinary field and a clinical frontier hotspot. In recent years, authoritative societies such as the European Society of Cardiology (ESC), the American Society of Clinical Oncology (ASCO), the Canadian Cardiovascular Society (CCS), and the Chinese Society of Clinical Oncology (CSCO) have successively developed a series of consensus documents and guidelines aimed at standardizing the identification, surveillance, management, prevention, and treatment of cardiovascular complications associated with cancer therapies. These efforts are designed to ensure that cancer patients receive optimal care, thereby minimizing the risk to their cardiac health during clinical treatment.[4–10]

Anthracycline chemotherapy, one of the earliest chemotherapy strategies, inhibits the proliferation and survival of tumor cells through cytotoxic effects, and their therapeutic effects have indeed received positive feedback in clinical applications, improving the overall survival of patients with various types of cancer.[11] However, the severe cardiotoxicity caused during this process, known as Cancer Therapy-Related Cardiac Dysfunction (CTRCD), cannot be ignored in terms of drug safety.[12] A study indicated that during the follow-up period, 37.5% of patients treated with anthracyclines suffered from cardiotoxicity.[13] Anthracycline-induced cardiotoxicity (AIC) is classified into acute and chronic based on the time of onset, with chronic cardiotoxicity potentially occurring within a year or several years after the completion of anthracycline treatment. The cardiotoxicity is almost exclusively chronic, and only a small proportion is acute and typically reversible upon discontinuation of anthracycline treatment.[14] Concurrently, this cardiotoxicity is a progressive process, initially manifesting as subclinical myocardial injury, and gradually progressing to early asymptomatic left ventricular ejection fraction (LVEF) reduction, ventricular wall thickness increase, and myofibrillar disarray. Prolonged exposure may ultimately result in dilated cardiomyopathy and irreversible heart failure.[15,16] Both early and long-term cardiotoxicity contribute to the occurrence of poor prognosis in cancer patients.

With a deeper understanding of the mechanisms of cancer development, there has been substantial progress in other cancer therapies to further enhance the efficacy of cancer treatment and mitigate the relative cardiotoxicity, such as targeted therapy, immunotherapy, and other therapies. Targeted therapy drugs, such as monoclonal antibodies trastuzumab and pertuzumab, have been proven to significantly improve the prognosis of patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, they also inevitably increase the risk of cardiac dysfunction and heart failure in cancer patients, especially when used in combination with anthracyclines, where the incidence of cardiac dysfunction is much higher than with anthracyclines alone.[11,17] Immunotherapy, particularly the use of immune checkpoint inhibitors, has been widely applied in the treatment of various types of cancer over the past decade due to its ability to overcome tumor immune escape. However, the non-specific activation of the immune system by these agents leads to a broad spectrum of immune-related adverse cardiovascular events, with myocarditis being the most severe and carrying an extremely high fatality rate.[18,19] In addition to targeted therapy and immunotherapy, other cancer therapies such as radiation therapy and hormone therapy can also cause varying degrees and types of cardiotoxicities, severely affecting patients' survival, prognosis, and quality of life. More importantly, there is a lack of large-scale and high-level evidence-based medical evidence for cardiac protection strategies developed in response to cardiotoxicity induced by these therapies.[20,21]

Although anthracycline drugs may cause severe cardiotoxicity, their significant advantages, such as high efficacy at low doses, broad-spectrum antitumor activity, and inhibitory effects on tumor cells in different cell cycles, have made anthracyclines the first-line treatment for many types of cancers in clinical practice for more than fifty years.[22,23] Therefore, AIC continues to hold a significant position in clinical practice, prompting clinicians and basic researchers to delve deeply into its pathogenic mechanisms and develop safer and more effective therapeutic strategies to prevent and mitigate cardiotoxicity. This study aims to review the latest advances in the mechanisms of AIC and emphasize the emerging therapeutic strategies.

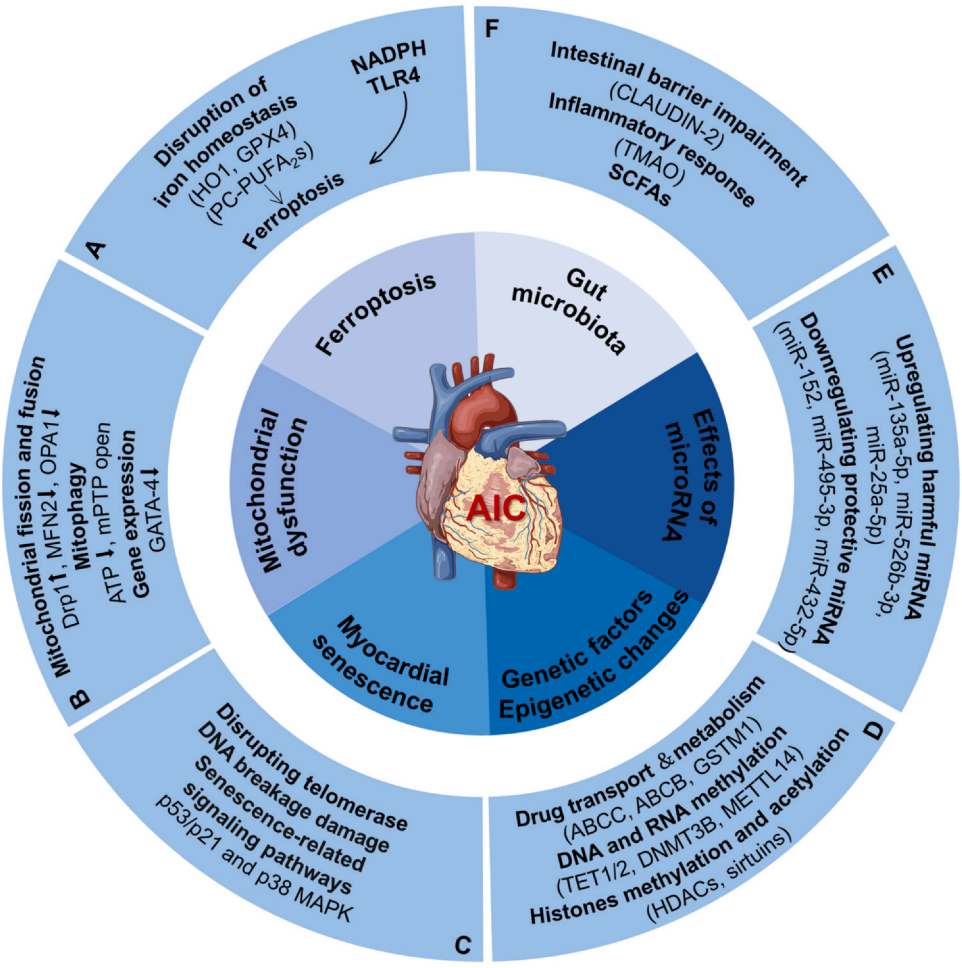

Fig. 1. Overview of the emerging mechanisms of AIC. (A) Anthracyclines cause mitochondrial dysfunction and cardiotoxicity in cardiomyocytes by interfering with mitochondrial division and fusion balance, disrupting mitophagy, mitochondrial substrate metabolism and electron transport chains. (B) Anthracyclines induce lipid peroxidation and myocardial damage by disrupting intracellular iron balance and increasing intracellular free iron content in cardiomyocytes. (C) Anthracyclines accelerate the senescence phenotype of cardiomyocytes by disrupting telomere-binding proteins and telomerase, causing DNA breakage damage, and activating senescence-related signaling pathways, leading to cardiotoxicity. (D, E) Genetic factors and epigenetic modifications play an important role in AIC, involving multifaceted mechanisms such as drug transport, metabolism, DNA and RNA methylation, histone modification, and non-coding RNA. (F) Anthracycline-induced dysregulation of the gut microbiota may lead to cardiotoxicity through mechanisms such as affecting intestinal barrier integrity, inflammatory response, short-chain fatty acids, and so on. ABCB: ATP-binding cassette, sub-family B; ABCC: ATP-binding cassette, sub-family C; AIC: anthracycline-induced cardiotoxicity; ATP: adenosine triphosphate; DNA: deoxyribonucleic acid; DNMT3B: DNA methyltransferase 3B; Drp1: dynamin-related protein 1; GATA-4: GATA binding protein 4; GPX4: glutathione peroxidase 4; GSTM1: glutathione S-transferase mu 1; HDACs: histone deacetylases; HO1: heme oxygenase 1; MAPK: mitogen-activated protein kinase; METTL14: methyltransferase-like protein 14; MFN2: mitofusin 2; mPTP: mitochondrial permeability transition pore; NADPH: nicotinamide adenine dinucleotide phosphate; OPA1: optic atrophy 1; PC-PUFA$_2$s, polyunsaturated fatty acids with 2 double bonds in phosphatidylcholine; RNA: ribonucleic acid; SCFAs: short-chain fatty acids; TET1/2: ten-eleven translocation 1/2; TLR4: toll-like receptor 4; TMAO: trimethylamine N-oxide. This figure was created using image from Servier Medical Art under a CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

2. Emerging mechanisms of AIC

The mechanisms of cardiotoxicity caused by anthracyclines are complex and varied. In addition to the previously reported mechanisms of inhibiting topoisomerase, causing oxidative stress, damaging mitochondrial structure and function, disrupting autophagy and mitophagy, and so on, the researchers have recently discovered emerging pathogenic mechanisms involving cellular aging, genetic factors, and organ interactions such as intestinal flora, which we summarized (Fig. 1).

2.1. Mitochondrial dysfunction

Mitochondria are the main site of energy production in cardiomyocytes and a major source of reactive oxygen species (ROS) and reactive nitrogen species (RNS).[24] An increasing number of studies have shown that anthracyclines, especially doxorubicin (DOX), perturb the mitochondrial quality-control system, which is considered to be a central and critical factor in mitochondrial function and cellular homeostasis.[24–27] Specifically, anthracyclines can affect the dynamic balance of mitochondrial fission and fusion and increase the expression of the mitochondrial fission protein dynamin-related protein 1 (Drp1), inhibit the expression of mitochondrial fusion proteins such as mitofusin 2 (MFN2) and optic atrophy 1 (OPA1), induce dysregulation of mitochondrial autophagy and contribute to the fragmentation and dysfunction of mitochondria, which can cause cardiotoxicity.[24,28] Anthracyclines can also interfere with the mitochondrial substrate metabolism especially fatty acid metabolism and electron transport chain, which can result in the blockage of adenosine triphosphate (ATP) synthesis, and induce the opening of mitochondrial permeability transition pore (mPTP), ultimately lead to cell apoptosis.[29,30] In addition, anthracyclines affect mitochondrial gene expression, especially inhibiting the GATA binding protein 4 (*GATA-4*) gene, which suppresses mitochondrial synthesis and metabolism, further exacerbating cardiotoxicity.[31] Given the vital role of energetics in the heart, the mechanism of mitochondrial disorders has always been the focus of researchers.

2.2. Ferroptosis

As the mechanism of anthracyclines inducing various forms of cell death, such as apoptosis, pyroptosis, and necroptosis, has been extensively investigated, strategies to inhibit cell death have been developed to improve the survival rate of cardiomyocytes.[32] However, inhibition of these cell death pathways has been shown to only partially improve the survival of cardiomyocytes,[33] suggesting the possibility and importance of other cell death pathways in this process. Ferroptosis is a form of cell death proposed by Dr. Brent R. Stockwell of Columbia University in 2012.[34] It has gradually become a hot research topic in the cardiovascular field in recent years.[35–37] Several studies have shown that ferroptosis as a specific type of cell death plays a key role in AIC. Anthracyclines disrupt such as heme oxygenase 1 (HO1) and glutathione peroxidase 4 (GPX4)-induced intracellular iron homeostasis, resulting in the increase of free iron in cardiomyocytes, lipid peroxidation in cell membranes and mitochondria, inducing cellular iron death and myocardial injury, and this process persists during treatment.[38–40] To mitigate the ferroptosis induced by anthracyclines, there are some strategies have been proposed. Iron chelators such as dexrazoxane, deferoxamine, ciclopirox and low-iron diets are recommended to attenuate iron accumulation, protect mitochondrial structure and function, and reduce the incidence of cardiotoxicity.[32,41,42] Recently, it has been found that the activation of molecules such as nicotinamide adenine dinucleotide phosphate (NADPH) and Toll-like receptor 4 (TLR4) promotes anthracycline-induced ferroptosis.[36] In addition, phospholipids containing a single polyunsaturated fatty acyl tail (PL-$PUFA_1$s) have been reported to facilitate ferroptosis.[43] Further, a novel perspective has been proposed that diacyl-PUFA phosphatidylcholines (PC-$PUFA_2$s) promote ferroptosis by activating ROS production in mitochondria and lipid peroxidation in endoplasmic reticulum,[35] which provides a potential therapeutic target for ferroptosis-related diseases, including anthracycline-induced ferroptosis.

2.3. Myocardial senescence

Cell senescence refers to the irreversible arrest of the cell cycle, thereby permanently losing the ability to proliferate.[44] Cellular senescence is considered a major risk factor for cardiovascular disease, leading to abnormal changes in cardiac structure and function, such as left ventricular (LV) hypertrophy, diastolic dysfunction, and myocardial fibrillation.[45,46] The biological characteristics of senescence in various cell types, including cardiomyocytes, are manifested by the up-regulation of senescence signaling pathways such as p53/p21 signaling pathway, activation of deoxyribonucleic acid (DNA) damage

response markers such as p38 mitogen-activated protein kinase (MAPK) and gamma H2A.X variant histone (γH2AX), silencing of proliferation-related genes, and release of senescence-related secretory phenotypes such as interleukin (IL)-1 and IL-6.[47]

Notably, since AIC patients develop cardiac abnormalities such as diastolic dysfunction, increased incidence of atrial fibrillation, and abnormal heart rate similar to elderly individuals, the hypothesis that anthracyclines accelerated the senescence phenotype of cardiomyocytes has been proposed.[48] First, in addition to disrupting telomere-binding proteins and telomerase,[49,50] anthracyclines cause DNA breakage damage, which has been shown to activate ataxia telangiectasia mutated-checkpoint kinase 2 (ATM-Chk2) and ataxia telangiectasia and Rad3-related protein-checkpoint kinase 1 (ATR-Chk1) and subsequently inhibit mouse double minute 2/4 (MDM2/4), the key factor in p53 ubiquitination degradation.[51] Besides, anthracyclines activate the p38 MAPK signaling pathway,[52] and these abnormal changes can activate the senescence phenotype. Another important feature of senescence is mitochondrial dysfunction. In senescent cells, the content of cardiolipin in the inner mitochondria is reduced, and the structure of the inner membrane ridge is damaged, thus disrupting the normal function of the electron transport chain.[53] In addition, abnormal changes such as loss of mitochondrial membrane potential, excessive production of ROS, disorder of mitophagy and mutation of mitochondrial DNA are also shown in senescent cells. Similarly, the above abnormal changes were observed in all AIC animal models, supporting the hypothesis that anthracyclines accelerated cardiomyocyte senescence.[48]

In summary, basic research suggests that age and tissue-specific expression of these senescence-related features or biomarkers is strongly associated with AIC,[45] and that senescence-associated secreting phenotype factors hold promise as potential biomarkers for identifying, monitoring, and predicting AIC outcomes.[54] Therefore, in-depth studies on myocardial senescence and senescence-related biomarkers are of great importance.

2.4. Genetic factors and epigenetic changes

The susceptibility of different patients to cardiotoxicity has led researchers to explore individual genetic factors. Recently, studies have revealed multifaceted mechanisms of genetic contribution to AIC, involving drug transport, drug metabolism, epigenetic changes, and so on,[14,55,56] which provides a new perspective on AIC.

The latest researches indicate that genes encoding proteins involved in drug transport, such as multiple variants of ATP-binding cassette, sub-family C (ABCC) and ATP-binding cassette, sub-family B, member 4 (ABCB4), are significantly associated with the risk of AIC. Variations in these genes lead to the accumulation of anthracyclines in the heart. Instead, coding in anthracycline-based drug efflux transporters of the *ABCB1* gene (rs1045642) of single nucleotide polymorphisms (SNPs) and genetic variants of the soluble carrier (SLC) transporter gene family seem to have cardioprotective effects.[14,52,57] In addition to drug transport distribution, drug metabolism also plays an important role in drug efficacy and safety. As mentioned above, metabolic disorders promote the occurrence and development of AIC, and genetic variation of some metabolism-related genes has been shown to be related to this process. Glutathione S-transferases (GSTs), as a class of phase II metabolic enzymes, play a key role in the detoxification of many carcinogens and drugs.[58] Clinical studies have shown that the deletion of glutathione S-transferase mu 1 (*GSTM1*) gene in both cardiomyocytes and peripheral blood is significantly related to the incidence of AIC,[59] providing a new strategy for the identification of AIC risk in children.

Epigenetic modifications include DNA and ribonucleic acid (RNA) methylation as well as histone modification and non-coding RNA (ncRNA). Anthracyclines have been reported to affect these processes and thus drive the development of cardiotoxicity.[56] DNA methylation is often associated with gene silencing. Studies have shown that anthracycline treatment leads to the upregulation of DNA demethylases such as ten-eleven translocation 1/2 (TET1/2) and the downregulation of DNA methyltransferase 3B (DNMT3B), resulting in significantly down-regulated methylation levels of genes associated with cardiac dysfunction in animal models and patient tissues, thus promoting the development of cardiac toxicity.[60,61] Anthracyclines also promote the expression of RNA methyltransferase-like protein 14 (METTL14), thereby inducing N6-methyladenosine (m6A) modification of circ-ZNF609, whose

inhibition has been shown to alleviate AIC.[62,63] In addition, anthracyclines affect the methylation and acetylation of histones. Previous studies have reported that anthracyclines can affect the expression of multiple subtypes of histone deacetylases (HDACs) and sirtuins, resulting in a series of injuries such as oxidative stress and apoptosis of cardiomyocytes.[56] Recent studies have revealed that the expression of histone-3 lysine-27 (H3K27) demethylase Jumonji domain-containing 3 (JMJD3) is upregulated in the hearts of patients and animal models treated with anthracyclines. Thus, the trimethylation level of H3K27 in the promoter region of ROS suppressor Sestrin2 is reduced, making its transcriptional repression.[64]

MicroRNAs (miRNAs) are short-stranded ncRNA molecules encoded by endogenous genes consisting of 21–23 nucleotides, which regulate gene expression and protein translation mainly by interacting with miRNA regulatory elements in the 3' untranslated regions (3' UTR) of target messenger RNAs (mRNAs), and then inhibiting the translation efficiency of the mRNAs or promoting their degradation.[65] In this process, miRNAs act as potential key regulators and therapeutic targets that affect cell proliferation, apoptosis, cell necrosis, and cell differentiation.[66–68] Studies have shown that anthracyclines, especially DOX, upregulate harmful miRNA and downregulate protective miRNA. To be precise, anthracyclines can upregulate the expression of cytotoxic miRNAs such as miR-135a-5p and miR-526b-3p, thus promoting oxidative stress and apoptosis of cardiomyocytes.[69,70] At the same time, anthracyclines downregulated the expression of protective miRNAs such as miR-152 and miR-495-3p, thereby aggravating AIC.[71,72] Recent studies have reported that anthracyclines can reduce the expression of miR-432-5p in cardiomyocytes, suggesting that exogenous supplementation of miR-432-5p reduces cardiotoxicity.[73] In addition, miR-25a-5p is found to exacerbate anthracycline-induced oxidative damage in cardiomyocytes.[74] These studies suggest that miRNAs, as important regulators of gene expression, may also serve as possible early diagnostic biomarkers and therapeutic targets, providing new ideas and approaches for the diagnosis and treatment of cardiac diseases.

In summary, genetic factors and epigenetic changes play an important role in the cardiotoxicity of anthracyclines and have important clinical implications for the development and optimization of therapeutic strategies.

2.5. Gut microbiota

Gut microbiota is a complex community that colonizes in the human intestinal tract and interdependent with the human body over a long period of time, which plays an important role in human health.[75] In recent years, a series of studies have revealed that there exists a complex and close relationship between gut microecology and the cardiovascular system, which has been referred to as the "gut-microbiota-heart (GMH) axis".[76–78] Previous studies have found that anthracyclines can cause dysbiosis in gut microbes. The transplantation of fecal microbiota from AIC mice into germ-free mice induced the development of cardiotoxicity,[79] revealing the key role of intestinal microbial dysbiosis in AIC. Although the mechanism by which anthracycline-induced dysbiosis is still unclear, recent studies have suggested several possible mechanisms, including but not limited to intestinal barrier impairment, inflammatory response, and alterations in short-chain fatty acids (SCFAs).[78] These complex mechanisms interact together to cause an imbalance of gut microbiota that possibly induces cardiotoxicity.

The integrity of the intestinal barrier is crucial to prevent the invasion of external microorganisms and harmful substances.[80] The regulation of tight junctions serves as the core of the intestinal barrier, which consists of a variety of transmembrane proteins, including the claudin family, zonula occludens (ZO) protein and occludin protein, which regulate the transmembrane transport of ions and water through different mechanisms, affecting the permeability of the intestinal barrier.[81] A clinical study found that the plasma level of zonulin was significantly increased in chemotherapy patients, indicating impaired intestinal permeability. Moreover, this change was positively correlated with the levels of markers for myocardial injury N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin T (cTnT). Notably, impaired intestinal permeability appeared to precede cardiotoxicity, as they observed a significant increase in zonulin levels in chemotherapy patients who had not yet developed cardiac dysfunction.[82] A study showed that DOX disrupted the normal arrangement of CLAUDIN-2 protein in

tissue, resulting in damage to the intestinal barrier, however, it is unclear whether this change is related to AIC.[83] Interestingly, trimethylamine N-oxide (TMAO), a metabolite of intestinal microbiota, exacerbates DOX-induced myocardial fibrosis by activating NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, providing a new target for anthracycline-induced myocardial fibrosis.[84] SCFAs are a metabolite of gut microbiota, which is involved in anti-inflammatory response and energy production.[85] Studies have shown that the reduction of SCFAs induces AIC by causing energy impairment of heart mitochondria, oxidative stress, and inflammation, which can be alleviated by oral SCFAs such as phenylalanine-butyramide, butyrate, etc.[86–88] Of note, the specific mechanism of these oral metabolites for AIC treatment still needs to be further explored.

In summary, interfering with the composition and function of intestinal microbes may provide a new therapeutic strategy for the GMH axis to reduce or reverse the toxic side effects of anthracyclines. Rational use of anthracyclines and attention to the balance of gut microbiota are of great significance for the treatment and rehabilitation of chemotherapy patients.

2.6. Novel biomarkers

Among the emerging mechanisms of AIC, multiple novel biomarkers have been shown to have an important impact on disease progression and treatment response. Researches show that markers of inflammation, fibrosis, and oxidative stress C-reactive protein (CRP), myeloperoxidase (MPO), growth differentiation factor 15 (GDF-15), and glycogen phosphorylase BB (GPBB), an essential enzyme for glucose metabolism, were elevated after anthracycline treatment and were associated with reduced risk of LVEF.[89,90] Elevated levels of placental growth factor (PGF), asymmetric dimethylarginine, and N-monomethylarginine were associated with an increased risk of CTRCD after chemotherapy with anthracyclines.[91,92] As mentioned earlier, epigenetic factors have been shown to be closely related to the pathological mechanism of anthracycline-induced cardiotoxicity, among which miRNAs have attracted more attention. miRNAs regulate the expression of about 30% of human essential genes and are closely related to various physiological and pathological processes.[93] Multiple clinical studies have shown that dysregulation of miRNAs, such as miRNA-34a, is associated with CTRCD risk in patients with anthracycline chemotherapy. However, there are discrepancies between some studies, which may be limited by the lack of a standardized method to isolate, quantify, and qualitatively identify miRNAs, and the need to consider the influence of individual differences and comorbidities.[6] In addition, changes in the blood metabolome were found 2 weeks after the end of DOX treatment, and most of the changes were associated with cardiac parameters, suggesting that changes in the blood metabolome can be used as potential markers of myocardial damage for anthracyclines.[94]

In recent years, it has seen a growing recognition of the significance of human induced pluripotent stem cells (hiPSCs) in elucidating pathogenic mechanisms and assessing disease risk. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) have been successfully employed to model the susceptibility of cancer patients to AIC, thereby providing an ideal platform for identifying individuals at high risk of AIC.[95] Patients with the solute carrier transporter family 28 member 3 (SLC28A3) variant have repeatedly been found to hold a low AIC susceptibility, however, this cardioprotective mechanism is unclear. By functional genomics, it was found that patient-derived iPSC-CMs carrying the protective SLC28A3 variant had significantly lower DOX uptake, to a certain extent, to provide a basis for identifying low AIC risk groups.[96] Moreover, hiPSC-CMs in conjunction with clustered regularly interspaced short palindromic repeats interference and activation (CRISPRi/a) system have successfully identified previously unreported pathogenic drivers of AIC, such as hematopoietic prostaglandin D synthase (HPGDS), Scm polycomb group protein homolog 1 (SCMH1), carbonic anhydrase 12 (CA12), and ATPase H^+/K^+ transporting subunit alpha (ATP4A), offering potential targets for drug development. However, it has also been reported that the mitochondrial content in hiPSC-CMs is lower than that in normal human cardiomyocytes, and the high proportion of mitochondria in cardiomyocytes is considered a key factor contributing to cardiac vulnerability to anthracyclines. Therefore, the impact of this difference in mitochondrial content on risk effect requires further evaluation.[95,97] In other words, these novel biomarkers provide a possible sensitive, specific, and cost-effective monitoring of patients receiving anthracyclines.

3. Traditional therapeutic strategies for AIC

3.1. Limiting cumulative dose, changing administration or non-anthracycline treatment regimens

Both acute and chronic cardiotoxicity caused by anthracyclines are dose-dependent. For example, studies have shown that when the cumulative dose of DOX exceeded 600 mg/m^2, the incidence of cardiotoxicity increased to 36%, of which, when the cumulative dose exceeded 550 mg/m^2, the incidence of heart failure reached 26%.[27] Therefore, reducing the cumulative dose of anthracyclines and changing the route of administration such as using continuous infusion instead of injection to reduce the occurrence of cardiotoxicity are recommended by international guidelines.[8,98] The lifetime cumulative dose of DOX is usually limited to 450 mg/m^2, or modified DOX analogs with higher limiting doses such as epirubicin are used.[99] The results of clinical practice also affirm this strategy. An early prospective randomized evaluation has shown that a 6-h continuous infusion of DOX has a lower risk of cardiotoxicity than a 15–20 min rapid infusion.[100] A meta-analysis also showed a lower risk of cardiotoxicity with epirubicin than with DOX.[101] In addition, non-anthracycline therapy may be used. However, the dose of chemotherapy drugs is closely related to the antitumor effect, and limiting cumulative dose may also reduce the damage to tumor cells while reducing cardiotoxicity.[102] And due to individual genetic differences, cardiotoxicity may still occur in some patients within the restricted dosage.[103] In addition, a previous clinical trial in pediatric cancer patients showed that continuous DOX infusion did not show a cardioprotective advantage over injection,[104] suggesting there may be some limitations to changing the route of administration to mitigate cardiotoxicity. Multiple factors need to be considered in the course of treatment to minimize cardiotoxicity while maintaining the maximum antitumor effect.

3.2. Changing the dosage forms

Nanotechnology has been used to modify anthracyclines, as researchers have tried to change the dosage form to preserve the efficacy of anthracyclines while improving drug safety. Various nanotechnological formulations of anthracyclines have been developed, such as PEGylated and non-PEGylated liposomes, chitosan nanoparticles, polymer micelles, dendrimers, etc. These polymer-anthracycline conjugates hold good pharmacokinetics, considerable anticancer activity, and low non-tissue-specific toxicity.[105] Among them, PEGylated liposomal doxorubicin (PLD) is the first nanomedicine approved by the US Food and Drug Administration (FDA) for cancer, which reduces toxic reactions by altering the pharmacokinetics of anthracyclines. Multiple clinical trials have shown that the incidence of early cardiotoxicity in the treatment of breast cancer with PLD combined with cyclophosphamide and trastuzumab is lower than that with DOX and cyclophosphamide alone.[106,107] Other clinical studies have shown PLD as an adjuvant chemotherapy regimen for breast cancer patients is comparable to DOX or epirubicin, but with a lower incidence of cardiotoxicity.[108–110] However, there have been reports of new toxic effects associated with PLD use in the short term, such as higher skin toxicity and risk of mucositis. Fortunately, appropriate supportive care can reverse this non-lethal adverse reaction.[111]

3.3. Cardioprotective agent—dexrazoxane

To reduce cardiotoxicity without compromising the effect of anticancer effect, the researchers also developed an iron chelator, dexrazoxane, as a cardioprotective agent against the cardiotoxicity of anthracyclines. Multiple adult randomized studies have shown that dexrazoxane used in patients with metastatic breast cancer who received a high cumulative dose of anthracyclines reduces the risk of heart failure and does not affect anti-cancer treatment outcomes.[112,113] Therefore, authoritative societies such as the ASCO, the ESC, and the CSCO recommend that dexrazoxane be considered as a cardioprotective strategy in patients at high risk of cardiotoxicity with anthracyclines.[8–10] However, it is rarely used in clinical practice, and some reports have analyzed the possible main reasons.[98] A study showed that in patients with pre-existing reduced LVEF or heart failure prior to cancer diagnosis, no change in

cardiovascular events was observed with dexrazoxane as a cardioprotective agent. Trial results to the contrary have been reported, but relative evidences are limited. In addition, some studies have shown that pediatric patients treated with dexrazoxane may have a higher risk of secondary malignancies (SMN),[113] although previous studies have shown that dexrazoxane does not cause SMN in pediatric patients. Therefore, clinicians and patients should weigh the cardioprotective effects of dexrazoxane against the risk of possible adverse effects under this safety controversy.

4. Emerging therapeutic strategies for AIC

4.1. Other cardioprotective agents

Because AIC can eventually develop into heart failure, many guidelines on cardio-oncology recommend the use of heart failure treatment drugs such as angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II receptor blockers (ARBs), and beta-blockers (BB) for high-risk patients receiving anthracyclines. These recommendations are based on multiple clinical trials demonstrating the effectiveness of the drugs. Recently, some meta-analyses reviewed multiple randomized controlled trials to evaluate the effects of these drugs on AIC. The results showed the beneficial effects of BB and ACE-I/ARB therapy on LVEF in anthracycline treatment regimens.[114,115] However, some randomized controlled trials have shown the opposite. The trial results showed that although BB and ACE-I/ARB treatment early in patients with breast cancer or non-Hodgkin lymphoma was associated with reduced left ventricular end-diastolic diameter (LVEDd) and retained global longitudinal strain (GLS), it did not alter the outcome of decreased LVEF, which is an important indicator to identify and monitor cardiotoxicity. More importantly, there were significant differences in cardiac troponin (cTn) concentrations with no change in LVEF before and after treatment with these cardioprotective agents, so they also question the guidelines recommendation to use cTn to identify and monitor patients at cardiovascular risk for anthracyclines.[116,117]

Statins, a distinctive class of lipid-lowering drugs, are recommended in the guidelines as new cardioprotective agents because they have demonstrated beneficial effects against the cardiotoxicity of anthracyclines. Nevertheless, similar to the aforementioned heart failure treatment drugs, the beneficial effects of statins on cardiotoxicity have presented diverse outcomes in different clinical trials.[118] Several studies have indicated the beneficial role of statins in preventing the cardiotoxicity of anthracyclines by reducing the incidence of cardiac dysfunction and hospitalization for heart failure in patients with breast cancer or lymphoma.[119,120] In contrast, a large-scale trial yielded negative results. The findings showed that the prospective use of statins in patients with breast cancer and lymphoma without indications of cardiovascular diseases did not prevent the decline in LVEF after 2 years of DOX treatment.[121] Therefore, despite guideline recommendations, there remain conflicting viewpoints on the cardioprotective effects of heart failure drugs or statins. This might be partly attributed to the inconsistencies in the recruitment criteria, trial size, and follow-up duration of relevant trials.

Since mitochondrial structure and function disorders are one of the key pathogenic mechanisms of AIC, many drugs targeting mitochondrial disorders have been developed. Studies have shown that the use of iron-chelating agents such as deferoxamine, antioxidants such as Mito-Q, vitamin E, and other compounds can inhibit the formation of ROS/RNS and reduce myocardial oxidative stress damage.[122] It has been reported that the novel angiotensin receptor antagonist LCZ696 can improve the mitochondrial quality control mechanism and promote electron transfer in the mitochondrial respiratory chain by inhibiting Drp1.[123] In addition, drugs used to treat metabolic diseases have also been shown to ameliorate anthracycline-induced mitochondrial disorders in recent years. Metformin is a class of oral hypoglycemic agents used in the treatment of type 2 diabetes. Studies have shown that metformin can inhibit the release of cytochrome C from mitochondria, reduce the production of ROS, and activate adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) pathway to inhibit mitochondrial oxidative stress damage caused by anthracyclines.[124,125] Studies have shown that sodium-glucose cotransporter (SGLT-2) inhibitors, also used as hypoglycemic agents, can improve cardiac mitochondrial dysfunction caused by anthracyclines and increase intracellular ATP levels.[126] Additionally, SGLT-2 has

been reported to be associated with a lower risk of cardiac events in patients treated with anthracyclines.[127,128] Significantly, more large-scale, high-level, and evidence-based medical evidence is required to substantiate the beneficial effects of these emerging cardioprotective agents.

4.2. New nanotechnology

Based on the typical traits of enhanced permeability and retention effect and specific receptors on the surface of tumor cells, a variety of nano-formulated anthracyclines have been developed, which employ nano-molecules to either passively target tumor cells (with larger liposomal drug volume) or actively target tumor cells (via specific ligands). This is done to enhance the specific delivery of drugs to tumor cells and minimize the toxic side effects on other tissues.[105] Among various ligands such as peptides, oligonucleotides, or antibodies, the combination of targeted antibodies and nanotechnology has gradually emerged as a mainstream cancer treatment strategy due to the high selectivity and affinity of monoclonal antibodies to tumor cell surface antigens. Monoclonal antibodies that can actively target specific receptors on cancer cells are covalently coupled with nanomedical drugs through chemical reactions, thereby achieving a therapeutic approach that targets cancer cells and mitigates toxic side effects simultaneously.[129] Recent studies have reported that myocardium-specific targeting peptide combined with 8P, an antioxidant active ingredient extracted from the natural compound *Eleutherococcus senticosus*, to construct a myocardium-targeting PLD can improve mitochondrial function, reduce oxidative stress, and thus alleviate AIC.[130] However, since the chemical reaction might affect the affinity of the antigen-antibody, the efficacy and release rate of the drug,[131] and more importantly, the emergence of drug-resistant cancer cell populations, the clinical application of combining monoclonal antibodies and nanomaterials has been unsatisfactory.[132–134] To overcome this limitation, researchers have developed multiple bispecific antibodies that bind to PEGylated liposomes to construct anthracycline targeting systems. By binding with two different antigens or two non-overlapping epitopes on the same antigen, they can enhance the sensitivity of cancer cells to chemotherapy, further inhibit the progression of solid tumors and non-solid tumors, and reduce the occurrence of off-target effects, thereby alleviating the occurrence of toxic side effects in various organs, including the heart. This type of bispecific antibody and anthracycline targeting drugs have demonstrated an enhancing efficacy and reducing toxicity effect in leukemia, breast cancer, non-small cell lung cancer, and other cancers.[135–139]

4.3. Stem cell therapy

Stem cell therapy, with its advantages such as autologous transplantation and no immunological rejection, has become an important novel therapy for treating a variety of diseases and has brought new hope for the treatment of heart diseases.[140]

The normal activity of mesenchymal stem cells (MSCs) is crucial for tissue and organ homeostasis. In the body, chemical messengers can be exchanged between organs to maintain the homeostasis of tissues and metabolic, a process known as interorgan crosstalk. These chemical messengers are packed into extracellular vesicles, which travel through various interstitial fluids and the blood, enabling paracrine communication between neighboring cells and distal tissues in both healthy and diseased states.[141,142] Studies indicate that paracrine effects mediated by bone marrow-derived MSCs have been evaluated as a cardiac repair strategy to prevent and reverse anthracycline-induced myocardial injury and heart failure.[143] Result from a SENECA trial showed that mesenchymal stem cells delivered mitochondria surrounded by extracellular vesicles to damaged cardiomyocytes via a paracrine mechanism, thereby alleviating mitochondrial dysfunction and subsequent cardiomyocyte apoptosis. The study highlighted that this effect was mainly generated by the specific uptake of exogenous mitochondria surrounded by extracellular vesicles by damaged cells, and extracellular vesicles lacking mitochondria did not show therapeutic effects, providing a possible strategy for cell-free therapy.[144] Subsequently, mitochondrial transplantation, a revolutionary intervention to improve the cardiotoxicity of anthracyclines, was introduced to improve cardiac function induced by DOX-induced cardiotoxicity by rescuing cardiac energy

depletion through transplantation of healthy mitochondria.[145–147] Unfortunately, at present, this technique has only been successfully implemented *in vitro* or in animals. It is expected that this intervention strategy can be successfully implemented in clinical practice with the support of more basic evidence and advanced technology in the future.

iPSCs are a type of regenerative cells with unlimited differentiation potential and self-renewal ability, which can differentiate into any cell type. They provide a powerful tool for constructing heart disease models, studying patient-specific physiology and pathology, and screening potential therapeutic drugs for heart disease. In the past decade, stem cell therapy based on iPSCs has made remarkable progress in the field of myocardial regeneration. An earlier study showed that iPCS-CMs created from Filipino cynomolgus monkey, were injected into major histocompatibility complex-matched cynomolgus monkey with myocardial infarction through an allogeneic transplantation strategy, improving the cardiac contractile function and showing electrical coupling with host cells. However, this allogeneic strategy could lead to immunological rejection without immunosuppression and temporarily cause ventricular tachycardia. Further efforts are needed to develop strategies to control these adverse reactions.[148] Fortunately, a study showed that transplanting the hPSC-CMs with depolarization-related genes hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 (*HCN4*), calcium voltage-gated channel subunit alpha1 H (*CACNA1H*), and solute carrier family 8 member A1 (*SLC8A1*) knocked out and hyperpolarization-related gene potassium inwardly rectifying channel subfamily J member 2 (*KCNJ2*) overexpressed into the body could reduce the risk of arrhythmia, providing hope for improving the safety of iPSC therapy.[149] Additionally, a study demonstrated that autologous iPSC-CMs could be successfully implanted and matured in two cynomolgus monkeys with subclinical chronic myocardial infarction without immunosuppression, providing evidence to reduce concerns about the immune response to autologous iPSC therapy.[150] Notably, a recent report showed that injecting hiPSC-CMs into non-human primates with myocardial infarction could restore cardiac contractile function with a low incidence of arrhythmia, providing another strong piece of evidence for the application of iPSCs in treating human heart diseases.[15]1However, there are currently no reports on the treatment of AIC based on iPSCs, and only small-scale clinical trials for treating heart diseases are ongoing in countries such as China and Japan. Since the results of these trials have not been published yet, the safety and efficacy of iPSC therapy in humans remain to be confirmed.[152] Nevertheless, these studies provide important theoretical foundations and experimental data for the application of iPSCs in treating AIC, demonstrating the potential of iPSC-based cardiac regenerative medicine in AIC treatment.

4.4. Chinese herbal formulas

Natural products play a key role in drug discovery, especially the application in cardiovascular medicine has a long history. Over the past few decades, nearly half of newly developed cardiovascular drugs have been based on natural products.[153] Recently, increasing reports have shown that the use of Chinese herbal formulas alone or in combination with chemical drugs can prevent and treat AIC, and significantly improve the prognosis and quality of life of patients. We reviewed relevant clinical studies in the last 3 years (Table 1).

Clinical trial has shown that total crocin tablet combined with micro-pump infusion of DOX effectively reduced the incidence of abnormal electrocardiogram, increased LVEF, and improved hemorheological indicators in patients with diffuse large B-cell lymphoma, thereby reducing heart damage.[154] Huangqi Shengmai decoction enhanced LV function and reduced myocardial damage in breast cancer patients treated with anthracyclines.[155] Modified Zhigancao decoction combined with Kaihe Liuqi acupuncture reduced the incidence of arrhythmia and improved cardiac function in breast cancer patients receiving anthracycline-treated chemotherapy.[156] Shengmai powder combined with Taohong Siwu decoction prevented myocardial damage and electrocardiogram abnormality in patients with non-Hodgkin lymphoma treated with DOX.[157] Wenxin Zhicao decoction reduced the electrocardiogram abnormality caused by DOX and reduced the incidence of cardiotoxicity in breast cancer patients.[158] Wenyang Yiqi formula reduced the incidence of abnormal electrocardiogram in breast cancer patients treated with epirubicin and alleviated the clinical symptoms of cardiac injury.[159] Qiliqiangxin capsule prevented cardiotoxicity in breast cancer patients induced by epirubicin, reduced the occurrence of heart failure, and improved the quality of life of patients.[160] Shenmai injection combined with dexrazoxane significantly reduced the occurrence of myocardial damage in acute leukemia patients during

Table 1
Summary of clinical trials of Chinese herbal formulas in the treatment of AIC.

Chinese herbal formulas	Cancer types (cases, *n*)	Chemotherapy drugs	Outcomes
Crocin tablet[154]	Diffuse large B-cell lymphoma (92)	Doxorubicin	Electrocardiogram, CK-MB, cTnI, NT-proBNP, LVEF, hemorheological indexes
Huangqi Shengmaiyin[155]	Breast cancer (50)	Anthracyclines	E/a', E/e', GWI, GCW, GWW, GWE
Modified Zhigancao decoction[156]	Breast cancer (100)	Epirubicin	Electrocardiogram, LVEF, LVEDs/d
Shengmai powder combined with Taohong Siwu decoction[157]	Non-Hodgkin lymphoma (60)	Doxorubicin	AST, LDH, CK, LVEF, LVEDd, cTnI, BNP, Mb, electrocardiogram
Wenxin Zhicao decoction[158]	Breast cancer (68)	Doxorubicin	NT-proBNP, cTnI, electrocardiogram
Wenyang Yiqi decoction[159]	Breast cancer (88)	Epirubicin	LVEF, CK-MB, cTnI, BNP, electrocardiogram
Qiliqiangxin capsule[160]	Breast cancer (88)	Epirubicin	LVEF, LVEDs/d, NT-proBNP
Shenmai injection[161]	Acute leukemia (60)	Daunorubicin	CK, CK-MB, LDH, AST, electrocardiogram, LVEF, BNP, cTnT

a', late diastolic velocity of mitral annulus obtained by tissue Doppler imaging; AIC: anthracycline-induced cardiotoxicity; AST: aspartate aminotransferase; CK-MB: creatine kinase isoenzyme MB; cTn: cardiac troponin; E, mitral inflow early diastolic velocity obtained by pulsed wave; e', early diastolic velocity of the mitral annulus obtained by tissue doppler imaging; GCW: global constructive work; GWE: global work efficiency; GWI: global work index; GWW: global wasted work; LDH: lactate dehydrogenase; LVEDs/d: left ventricular end-systolic/diastolic diameter; LVEF: left ventricular ejection fraction; Mb: myoglobin; *n*, number of cases; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

chemotherapy and alleviated cardiotoxicity.[161] In addition, more natural products or Chinese herbal formulas have been shown to significantly improve the cardiotoxicity induced by anthracyclines in basic studies, and the mechanisms of action are diverse.

Certainly, we must acknowledge its limitations. Firstly, the sample sizes of current studies on Chinese herbal formulas tend to be small, which may lead to insufficient statistical significance of the results, and thus affect the universal applicability of the conclusions. In addition, although some studies have provided preliminary evidence that Chinese herbal formulas can enhance cardiac function or mitigate cardiotoxicity, these studies generally lack long-term follow-up and large-scale randomized controlled trials. Therefore, we should remain cautious when comprehensively evaluating the effects of Chinese herbal formulas and look forward to future clinical practice of higher quality to fill the knowledge gaps in this area.

4.5. Distal ischaemic preconditioning

Transient, reversible ischemia-in-perfusion treatment at the distal tissue has been shown to induce a systemic protective phenotype,[162] which is closely related to cardiac protection.[163] Preclinical study in large animals has shown that distal ischemic preconditioning prior to each anthracycline treatment could alleviate dysregulation of mitochondrial cleavage and autophagy, thereby alleviating cardiac dysfunction.[164] Some randomized clinical trials have been conducted on this basis. However, two trials in children and adults, respectively, did not show a beneficial effect of distal ischemic preconditioning. An important reason was that the recruited patients, both children and adults, had a low risk of cardiotoxicity, which might limit the beneficial effects of these interventions.[165,166] Given that this intervention has been shown to have a beneficial effect on the heart in clinical studies in other cardiovascular areas,[167] it remains a very promising therapeutic strategy against the cardiotoxicity of anthracyclines. It is important to include a larger number of people at higher risk of cardiotoxicity in future clinical trials. Such a study is currently underway in a large clinical trial to evaluate the safety and efficacy of distal ischemic preconditioning in high-risk populations receiving anthracyclines.[168,169] Of note, it is reported that distal ischaemic preconditioning may promote cancer progression,[170] and this will require clinicians

to further validate and weigh the risks and benefits.

4.6. Physical exercise and monitoring

In addition to drug therapy, exercise training has also been included in non-drug interventions for AIC. Both clinical and preclinical studies have shown that exercise interventions are associated with a lower risk of cardiotoxicity with anthracyclines.[171,172] There are also some tests, however, suggest that exercise to prevent AIC was not significant. But no doubt that exercise has a positive effect on cardiopulmonary function.[173] It is important to note that security issues must be taken seriously. For example, intense exercise itself may put a strain on the heart. Patient frailty caused by cancer treatment should also be taken into account. Therefore, exhausting exercise should be avoided. At the same time, cardiopulmonary exercise testing should be performed before exercise to evaluate the patient's exercise tolerance, and cardiac function should be monitored regularly during exercise to develop a reasonable exercise plan.[174]

4.7. Treatment monitoring and personalized therapy

Monitoring cardiac serum biomarkers in cancer patients during anthracycline treatment is critical for assessment, early diagnosis, and prevention of cardiotoxicity. The *2022 Cardiovascular Oncology Guideline* of the ESC recommends that in addition to cardiac imaging for anthracycline-based chemotherapy patients, continuous monitoring such as cardiac serum troponin and natriuretic peptide should be needed for risk stratification to promote early diagnosis and treatment. However, experts have raised potential limitations of these traditional biomarkers, including troponin and natriuretic peptide as nonspecific markers susceptible to patient gender, race, weight, and other comorbidities.[6] To overcome the limitations of traditional biomarkers, researchers are exploring more specific and sensitive biomarkers. In addition to the novel circulating biomarkers mentioned above, galactin-3 associated with myocardial fibrosis has shown good predictive value in animal models, but a clear association with reduced LVEF has not been observed in clinical studies, which might be related to the inability of echocardiography to accurately assess myocardial fibrosis.[175] In addition, fms-like tyrosine kinase-1 and immunoglobulin E have been reported as candidate biomarkers.[8] To ensure antitumor efficacy while minimizing the risk of cardiotoxicity, dynamic monitoring of treatment response using biomarkers can optimize treatment choice and further evaluate prognosis. For example, combining traditional biomarkers (such as cTnT, NT-proBNP) with novel biomarkers (such as miRNAs, MPO) can significantly improve the sensitivity and specificity of early diagnosis and prognosis assessment of AIC.[176] The investigation into the emerging mechanisms of AIC offers a robust theoretical foundation for the development of more sensitive and specific biomarkers, as well as innovative therapeutic strategies. By leveraging hiPSC-CMs technology and integrating novel biomarkers such as inflammatory markers, metabolomic indicators, and epigenetic signatures, the risk assessment of cardiotoxicity in patients exposed to anthracyclines can be significantly enhanced. This approach provides stronger support for clinical decision-making and facilitates personalized treatment regimens. However, further research is essential to address existing challenges and propel the ongoing advancement of AIC treatment strategies.

5. Feasibility and challenges of emerging therapeutic strategies

While emerging therapeutic strategies for mitigating AIC hold significant promise, they have also ignited discussions surrounding ethical considerations, cost challenges, and barriers to implementation.

The earliest use of embryonic stem cell therapy strategies has sparked intense ethical controversy because it involves the destruction of embryos. Adult stem cells such as MSCs avoid ethical problems, but their sources and differentiation potential are relatively limited. Although the newly developed iPSCs can avoid the above problems, they also face new challenges, such as the complicated preparation process, and the risk of immunological rejection, arrhythmia, and tumorigenesis. Fortunately, there are reports that these challenges can be overcome,

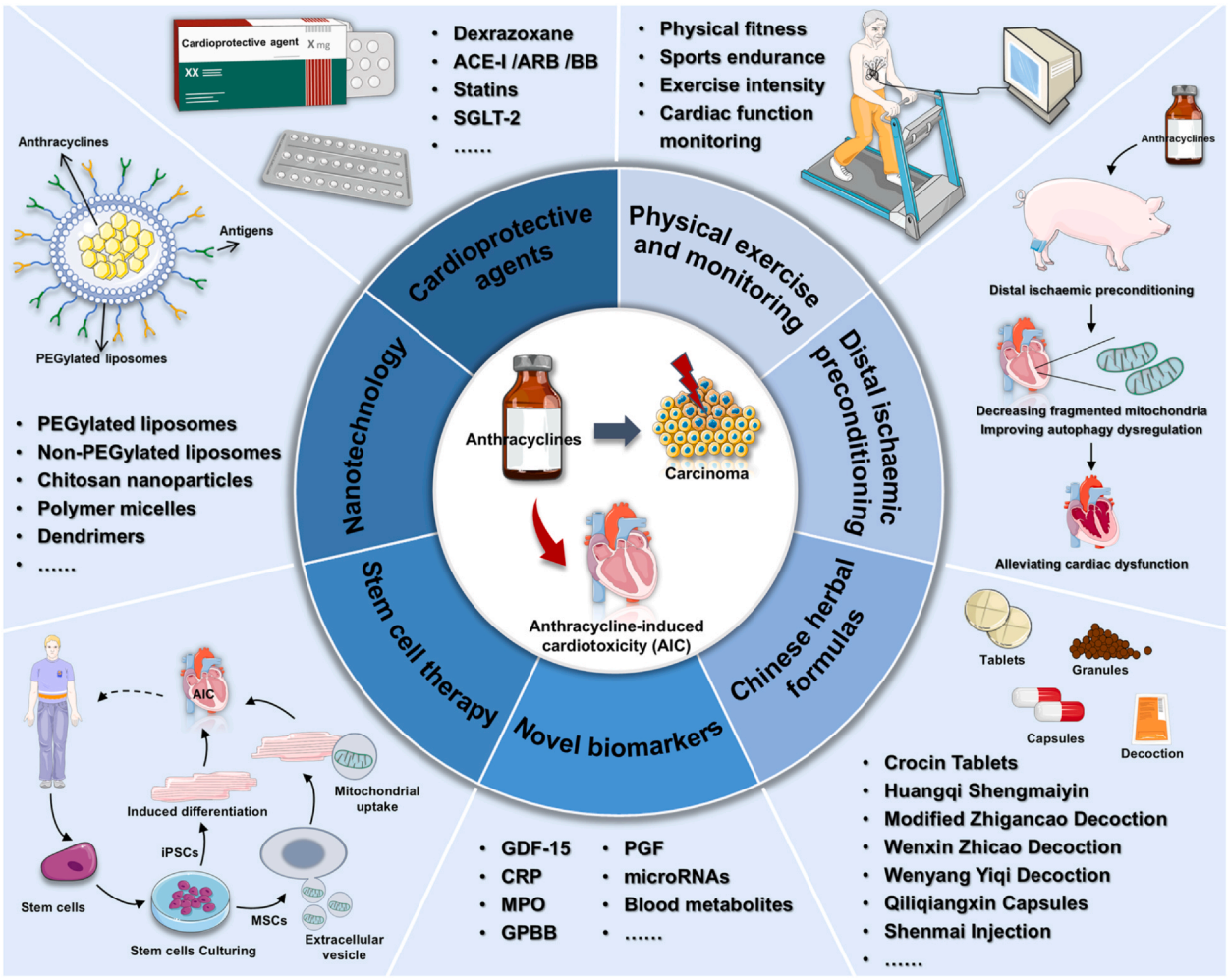

Fig. 2. Therapeutic strategies for AIC. ACE-I: angiotensin-converting enzyme inhibitor; AIC: anthracycline-induced cardiotoxicity; ARBs: angiotensin II receptor blockers; BB: beta-blockers; CRP: C-reactive protein; GDF-15: growth differentiation factor 15; GPBB: glycogen phosphorylase BB; iPSCs: induced pluripotent stem cells; MPO: myeloperoxidase; MSCs: mesenchymal stem cells; PGF: placental growth factor; SGLT-2: sodium-glucose cotransporter. This figure was created using images from Servier Medical Art under a CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

but more reliable data is needed to support their safety and effectiveness.[177,178] For interventions such as remote ischemic preconditioning, the potential risk and individual differences of patients need to be fully considered in clinical trials to avoid exposing low-risk patients to possible ineffective interventions.[179] Moreover, the issue of cost presents a significant challenge that we cannot overlook. The development and application of high-tech means such as new nanotechnology require huge financial investment, which may lead to high treatment costs, making it unaffordable for some patients.[180] At the same time, although clinical trials have shown that Chinese herbal formulas are significantly effective, pollution, misidentification, and improper processing of formulas may cause health problems, and the implementation obstacles should not be ignored.[181] Interestingly, studies have shown that exercise adherence is influenced by a variety of factors. For example, patients with heart failure are often motivated by improved health, performance in activities of daily living, and body image. On the other hand, patient efforts, social support from family members, and medical care all play an integral role. However, it is worth noting that these factors, while promoting adherence, may also potentially become an obstacle for patients to maintain exercise habits for a long time.[182]

In summary, in exploring novel therapeutic strategies to combat AIC, it is imperative to take into account ethical considerations, cost constraints, and the obstacles pertaining to their implementation.

6. Prospect and conclusion

Anthracyclines have consistently played a significant role in cancer treatment, and their adverse cardiovascular effects have always been a matter of concern. Tremendous efforts have been exerted to develop novel strategies to safeguard cancer patients from cardiovascular risks (Fig. 2). Guidelines suggest the utilization of heart failure medications such as ACE-I/ARBs, BB, statins, etc., as a preventive measure. However, the actual administration of these cardioprotective agents remains controversial due to the uncertain protective effects demonstrated in clinical trials. Nevertheless, the therapeutic potential of these medications cannot be denied, but more high-level evidence-based medical evidence is needed to continuously support this beneficial effect.

The early identification of the risk of cardiovascular events is of crucial importance for early prevention and treatment, and the challenge lies in accurately identifying patients at risk. Monitoring cardiac serum biomarkers is an essential tool for the identification and early diagnosis of cardiovascular events, and there is greater value in developing potential markers that are sensitive and predictable at an early stage, and have a good correlation with pathological mechanisms. Additionally, new biomarkers should be customized to specific populations to avoid being influenced by factors such as individual differences and cancer types. Epigenetic factors have been proved to be crucial to AIC, and epigenetic therapeutic strategies have shown broad application prospects in combating AIC. However, few clinical studies have been reported on the efficacy of drugs based on this strategy, and more clinical trials are needed to confirm the efficacy and safety of epigenetic drugs for AIC treatment. In recent years, gene therapy holds potential in the treatment of heart diseases, especially in terms of gene modification or replacement for certain inherited heart disorders. However, gene therapy for the cardiotoxicity of anthracyclines has not been reported in clinical practice. With the growing recognition of the genetic susceptibility to the cardiotoxicity of anthracyclines, gene therapy may become a new therapeutic strategy for preventing and treating the cardiotoxicity of anthracyclines in the future.[183] It is necessary to formulate an individual treatment plan based on the genetic background of the patient and to explore a personalized comprehensive treatment strategy.

Both conventional and emerging therapeutic strategies for the cardiotoxicity caused by anthracyclines have potential benefits and risks, and more research is required to support the safety, efficacy, and rationality of these therapeutic strategies. These research challenges highlight the complexity of the cardiotoxicity of anthracyclines, necessitating interdisciplinary collaboration and continuous research to reduce the risk of cardiotoxicity in cancer patients while enhancing their quality of life.

CRediT authorship contribution statement

Guanjing Ling: Writing–original draft, Conceptualization. **Fei Ge:** Writing–original draft, Conceptualization. **Weili Li:** Writing–review & editing, Supervision. **Yan Wei:** Writing–original draft. **Shujuan Guo:** Writing–original draft. **Yuqin Zhang:** Writing–original draft. **Yilin Li:** Writing–original draft. **Yawen Zhang:** Writing–original draft. **Heng Liu:** Writing–original draft. **Yunxia Wu:** Writing–review & editing. **Wei Wang:** Writing–review & editing, Supervision. **Yong Wang:** Writing–review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0502605), the National Natural Science Foundation of China

(82374420 and 82174364), the Beijing-Tianjin-Hebei Basic Research Cooperation project (J230033), the Science and Technology Department of Beijing University of Chinese Medicine (2022-JYB-JBZR-001), the Science and Technology Department of Beijing University of Chinese Medicine (BZY-BZX-2022-08), and the Beijing University of Chinese Medicine Graduate Independent Project (ZJKT2023042).

References

1. Karlstaedt A, Moslehi J, de Boer RA. Cardio-onco-metabolism: metabolic remodelling in cardiovascular disease and cancer. *Nat Rev Cardiol.* 2022;19(6):414–425.
2. Herrmann J. From trends to transformation: where cardio-oncology is to make a difference. *Eur Heart J.* 2019;40(48):3898–3900.
3. Salloum FN, Tocchetti CG, Ameri P, et al. Priorities in cardio-oncology basic and translational science: GCOS 2023 symposium proceedings: JACC: cardiooncology state-of-the-art review. *JACC CardioOncol.* 2023;5(6):715–731.
4. Herrmann J, López-Fernández T, Lyon AR. The year in cardiovascular medicine 2021: cardio-oncology. *Eur Heart J.* 2022;43(9):857–862.
5. Zheng H, Zhan H. Cardio-oncology guidelines and strength of the evidence. *JACC CardioOncol.* 2023;5(1):149–152.
6. Boen HM, Cherubin M, Franssen C, et al. Circulating microRNA as biomarkers of anthracycline-induced cardiotoxicity: JACC: cardiooncology state-of-the-art review. *JACC CardioOncol.* 2024;6(2):183–199.
7. Virani SA, Dent S, Brezden-Masley C, et al. Canadian Cardiovascular Society guidelines for evaluation and management of cardiovascular complications of cancer therapy. *Can J Cardiol.* 2016;32(7):831–841.
8. Lyon AR, López-Fernández T, Couch LS, et al. 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). *Eur Heart J.* 2022;43(41):4229–4361.
9. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2017;35(8):893–911.
10. Guidelines of Chinese Society of Clinical Oncology (CSCO) clinical practice guideline of cardio-oncology 2023. Beijing: People's Medical Publishing House; 2023.
11. Omland T, Heck SL, Gulati G. The role of cardioprotection in cancer therapy cardiotoxicity: JACC: cardiooncology state-of-the-art review. *JACC CardioOncol.* 2022;4(1):19–37.
12. Moslehi JJ. Cardio-oncology: a new clinical frontier and novel platform for cardiovascular investigation. *Circulation.* 2024;150(7):513–515.
13. López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, et al. Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. *Eur Heart J.* 2020;41(18):1720–1729.
14. Camilli M, Cipolla CM, Dent S, et al. Anthracycline cardiotoxicity in adult cancer patients: JACC: cardiooncology state-of-the-art review. *JACC CardioOncol.* 2024;6(5):655–677.
15. Nebigil CG, Désaubry L. Updates in anthracycline-mediated cardiotoxicity. *Front Pharm.* 2018;9:1262.
16. Christidi E, Brunham LR. Regulated cell death pathways in doxorubicin-induced cardiotoxicity. *Cell Death Dis.* 2021;12(4):339.
17. Jacobse JN, Schaapveld M, Boekel NB, et al. Risk of heart failure after systemic treatment for early breast cancer: results of a cohort study. *Breast Cancer Res Treat.* 2021;185(1):205–214.
18. Makunts T, Saunders IM, Cohen IV, et al. Myocarditis occurrence with cancer immunotherapy across indications in clinical trial and post-marketing data. *Sci Rep.* 2021;11(1):17324.
19. Rubio-Infante N, Ramírez-Flores YA, Castillo EC, et al. A systematic review of the mechanisms involved in immune checkpoint inhibitors cardiotoxicity and challenges to improve clinical safety. *Front Cell Dev Biol.* 2022;10:851032.
20. Totzeck M, Schuler M, Stuschke M, et al. Cardio-oncology - strategies for management of cancer-therapy related cardiovascular disease. *Int J Cardiol.* 2019;280:163–175.
21. Liang Z, He Y, Hu X. Cardio-oncology: mechanisms, drug combinations, and reverse cardio-oncology. *Int J Mol Sci.* 2022;23(18):10617.
22. Mattioli R, Ilari A, Colotti B, et al. Doxorubicin and other anthracyclines in cancers: activity, chemoresistance and its overcoming. *Mol Asp Med.* 2023;93:101205.
23. Zheng H, Zhan H. Preventing anthracycline-associated heart failure: what is the role of dexrazoxane? *JACC CardioOncol.* 2024;6(2):318–321.
24. Wu L, Wang L, Du Y, et al. Mitochondrial quality control mechanisms as therapeutic targets in doxorubicin-induced cardiotoxicity. *Trends Pharm Sci.* 2023;44(1):34–49.
25. Osataphan N, Phrommintikul A, Chattipakorn SC, et al. Effects of doxorubicin-induced cardiotoxicity on cardiac mitochondrial dynamics and mitochondrial function: Insights for future interventions. *J Cell Mol Med.* 2020;24(12):6534–6557.
26. Huang J, Wu R, Chen L, et al. Understanding anthracycline cardiotoxicity from mitochondrial aspect. *Front Pharm.* 2022;13:811406.

27. Wallace KB, Sardão VA, Oliveira PJ. Mitochondrial determinants of doxorubicin-induced cardiomyopathy. *Circ Res.* 2020;126(7):926–941.
28. Chen R, Niu M, Hu X, et al. Targeting mitochondrial dynamics proteins for the treatment of doxorubicin-induced cardiotoxicity. *Front Mol Biosci.* 2023;10:1241225.
29. Dhingra R, Margulets V, Chowdhury SR, et al. Bnip3 mediates doxorubicin-induced cardiac myocyte necrosis and mortality through changes in mitochondrial signaling. *Proc Natl Acad Sci USA.* 2014;111(51):E5537–E5544.
30. Du Q, Zhu B, Zhai Q, et al. Sirt3 attenuates doxorubicin-induced cardiac hypertrophy and mitochondrial dysfunction via suppression of Bnip3. *Am J Transl Res.* 2017;9(7):3360–3373.
31. Qiu Y, Jiang P, Huang Y. Anthracycline-induced cardiotoxicity: mechanisms, monitoring, and prevention. *Front Cardiovasc Med.* 2023;10:1242596.
32. Fang X, Wang H, Han D, et al. Ferroptosis as a target for protection against cardiomyopathy. *Proc Natl Acad Sci USA.* 2019;116(7):2672–2680.
33. Zhang T, Zhang Y, Cui M, et al. CaMKII is a RIP3 substrate mediating ischemia- and oxidative stress-induced myocardial necroptosis. *Nat Med.* 2016;22(2):175–182.
34. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell.* 2012;149(5):1060–1072.
35. Qiu B, Zandkarimi F, Bezjian CT, et al. Phospholipids with two polyunsaturated fatty acyl tails promote ferroptosis. *Cell.* 2024;187(5):1177–1190.
36. Chen X, Xu S, Zhao C, et al. Role of TLR4/NADPH oxidase 4 pathway in promoting cell death through autophagy and ferroptosis during heart failure. *Biochem Biophys Res Commun.* 2019;516(1):37–43.
37. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol.* 2021;22(4):266–282.
38. Li X, Liang J, Qu L, et al. Exploring the role of ferroptosis in the doxorubicin-induced chronic cardiotoxicity using a murine model. *Chem Biol Inter.* 2022;363:110008.
39. Tadokoro T, Ikeda M, Ide T, et al. Mitochondria-dependent ferroptosis plays a pivotal role in doxorubicin cardiotoxicity. *JCI Insight.* 2023;8(6):e169756.
40. Pan J, Xiong W, Zhang A, et al. The imbalance of p53-Park7 signaling axis induces iron homeostasis dysfunction in doxorubicin-challenged cardiomyocytes. *Adv Sci.* 2023;10(15):e2206007.
41. Wu L, Zhang Y, Wang G, et al. Molecular mechanisms and therapeutic targeting of ferroptosis in doxorubicin-induced cardiotoxicity. *JACC Basic Transl Sci.* 2024;9(6):811–826.
42. Xie LH, Fefelova N, Pamarthi SH, et al. Molecular mechanisms of ferroptosis and relevance to cardiovascular disease. *Cells.* 2022;11(17):2726.
43. Shan K, Feng N, Zhu D, et al. Free docosahexaenoic acid promotes ferroptotic cell death via lipoxygenase dependent and independent pathways in cancer cells. *Eur J Nutr.* 2022;61(8):4059–4075.
44. Mao Z, Ke Z, Gorbunova V, et al. Replicatively senescent cells are arrested in G1 and G2 phases. *Aging.* 2012;4(6):431–435.
45. Bao H, Cao J, Chen M, et al. Biomarkers of aging. *Sci China Life Sci.* 2023;66(5):893–1066.
46. Yan M, Li J, Shen T. Structural and functional changes and their cellular and molecular mechanisms during cardiac senescence (in Chinese). *Chin J Geriatr.* 2021;40(11):1437–1443.
47. Chen MS, Lee RT, Garbern JC. Senescence mechanisms and targets in the heart. *Cardiovasc Res.* 2022;118(5):1173–1187.
48. Linders AN, Dias IB, López Fernández T, et al. A review of the pathophysiological mechanisms of doxorubicin-induced cardiotoxicity and aging. *NPJ Aging.* 2024;10(1):9.
49. Spallarossa P, Altieri P, Aloi C, et al. Doxorubicin induces senescence or apoptosis in rat neonatal cardiomyocytes by regulating the expression levels of the telomere binding factors 1 and 2. *Am J Physiol Heart Circ Physiol.* 2009;297(6):H2169–H2181.
50. Maejima Y, Adachi S, Ito H, et al. Induction of premature senescence in cardiomyocytes by doxorubicin as a novel mechanism of myocardial damage. *Aging Cell.* 2008;7(2):125–136.
51. Aubrey BJ, Kelly GL, Janic A, et al. How does p53 induce apoptosis and how does this relate to p53-mediated tumour suppression? *Cell Death Differ.* 2018;25(1):104–113.
52. Linders AN, Dias IB, Ovchinnikova ES, et al. Evaluation of senescence and its prevention in doxorubicin-induced cardiotoxicity using dynamic engineered heart tissues. *JACC CardioOncol.* 2023;5(3):298–315.
53. Lesnefsky EJ, Chen Q, Hoppel CL. Mitochondrial metabolism in aging heart. *Circ Res.* 2016;118(10):1593–1611.
54. Tang X, Li P, Chen H. Cardiomyocyte senescence and cellular communications within myocardial microenvironments. *Front Endocrinol.* 2020;11:280.
55. Qi Y, Wei Y, Li L, et al. Genetic factors in the pathogenesis of cardio-oncology. *J Transl Med.* 2024;22(1):739.
56. Liu X, Li Z. The role and mechanism of epigenetics in anticancer drug-induced cardiotoxicity. *Basic Res Cardiol.* 2025;120(1):11–24.
57. Xie S, Sun Y, Zhao X, et al. An update of the molecular mechanisms underlying anthracycline induced cardiotoxicity. *Front Pharm.* 2024;15:1406247.
58. Ferreira MJ, Rodrigues TA, Pedrosa AG, et al. Glutathione and peroxisome redox homeostasis. *Redox Biol.* 2023;67:102917.

59. Singh P, Wang X, Hageman L, et al. Association of GSTM1 null variant with anthracycline-related cardiomyopathy after childhood cancer-A Children's Oncology Group ALTE03N1 report. *Cancer.* 2020;126(17):4051–4058.
60. Nguyen N, Lienhard M, Herwig R, et al. Epirubicin alters DNA methylation profiles related to cardiotoxicity. *Front Biosci.* 2022;27(6):173.
61. Robinson EL, Ameri P, Delrue L, et al. Differential expression of epigenetic modifiers in early and late cardiotoxic heart failure reveals DNA methylation as a key regulator of cardiotoxicity. *Front Cardiovasc Med.* 2023;10:884174.
62. Yu P, Wang J, Xu G, et al. RNA m6A-regulated circ-ZNF609 suppression ameliorates doxorubicin-induced cardiotoxicity by upregulating FTO. *JACC Basic Transl Sci.* 2023;8(6):677–698.
63. Wang L, Yu P, Wang J, et al. Downregulation of circ-ZNF609 promotes heart repair by modulating RNA N6-methyladenosine-modified Yap expression. *Research.* 2022;2022:9825916.
64. Wang P, Lan R, Guo Z, et al. Histone demethylase JMJD3 mediated doxorubicin-induced cardiomyopathy by suppressing SESN2 expression. *Front Cell Dev Biol.* 2020;8:548605.
65. Zhou S, Jin J, Wang J, et al. miRNAs in cardiovascular diseases: potential biomarkers, therapeutic targets and challenges. *Acta Pharm Sin.* 2018;39(7):1073–1084.
66. Kimura M, Kothari S, Gohir W, et al. MicroRNAs in infectious diseases: potential diagnostic biomarkers and therapeutic targets. *Clin Microbiol Rev.* 2023;36(4):e0001523.
67. Olson EN. MicroRNAs as therapeutic targets and biomarkers of cardiovascular disease. *Sci Transl Med.* 2014;6(239):239ps3.
68. Ambros V. The functions of animal microRNAs. *Nature.* 2004;431(7006):350–355.
69. Wang X, Cheng Z, Xu J, et al. Circular RNA Arhgap12 modulates doxorubicin-induced cardiotoxicity by sponging miR-135a-5p. *Life Sci.* 2021;265:118788.
70. Zhang L, Liu L, Li X. MiR-526b-3p mediates doxorubicin-induced cardiotoxicity by targeting STAT3 to inactivate VEGFA. *Biomed Pharm.* 2020;123:109751.
71. Meng J, Xu C. MicroRNA-495-3p diminishes doxorubicin-induced cardiotoxicity through activating AKT. *J Cell Mol Med.* 2022;26(7):2076–2088.
72. Zhang W, Lai X, Guo X. Activation of Nrf2 by miR-152 inhibits doxorubicin-induced cardiotoxicity via attenuation of oxidative stress, inflammation, and apoptosis. *Oxid Med Cell Longev.* 2021;2021:8860883.
73. Geng W, Yan S, Sang D, et al. Downregulating miR-432-5p exacerbates adriamycin-induced cardiotoxicity via activating the RTN3 signaling pathway. *Aging.* 2024;16(16):11904–11916.
74. Liu R, Lv Y, Jiang C, et al. The miR-25a-5p aggravating anthracycline-induced myocardial damage in breast cancer treatment (in Chinese). *J Guangxi Med Univ.* 2024;41(01):26–31.
75. Schirmer M, Garner A, Vlamakis H, et al. Microbial genes and pathways in inflammatory bowel disease. *Nat Rev Microbiol.* 2019;17(8):497–511.
76. Bui TVA, Hwangbo H, Lai Y, et al. The gut-heart axis: updated review for the roles of microbiome in cardiovascular health. *Korean Circ J.* 2023;53(8):499–518.
77. Zhang Z, Lv T, Wang X, et al. Role of the microbiota-gut-heart axis between bile acids and cardiovascular disease. *Biomed Pharm.* 2024;174:116567.
78. Huang C, Li X, Li H, et al. Role of gut microbiota in doxorubicin-induced cardiotoxicity: from pathogenesis to related interventions. *J Transl Med.* 2024;22(1):433.
79. An L, Wuri J, Zheng Z, et al. Microbiota modulate doxorubicin induced cardiotoxicity. *Eur J Pharm Sci.* 2021;166:105977.
80. Lewis CV, Taylor WR. Intestinal barrier dysfunction as a therapeutic target for cardiovascular disease. *Am J Physiol Heart Circ Physiol.* 2020;319(6):H1227–H1233.
81. Horowitz A, Chanez-Paredes SD, Haest X, et al. Paracellular permeability and tight junction regulation in gut health and disease. *Nat Rev Gastroenterol Hepatol.* 2023;20(7):417–432.
82. Li Z, Xing J, Ma X, et al. An orally administered bacterial membrane protein nanodrug ameliorates doxorubicin cardiotoxicity through alleviating impaired intestinal barrier. *Bioact Mater.* 2024;37:517–532.
83. Cray P, Sheahan BJ, Cortes JE, et al. Doxorubicin increases permeability of murine small intestinal epithelium and cultured T84 monolayers. *Sci Rep.* 2020;10(1):21486.
84. Li X, Geng J, Zhao J, et al. Trimethylamine N-oxide exacerbates cardiac fibrosis via activating the NLRP3 inflammasome. *Front Physiol.* 2019;10:866.
85. van der Hee B, Wells JM. Microbial regulation of host physiology by short-chain fatty acids. *Trends Microbiol.* 2021;29(8):700–712.
86. Huang K, Liu Y, Tang H, et al. Glabridin prevents doxorubicin-induced cardiotoxicity through gut microbiota modulation and colonic macrophage polarization in mice. *Front Pharm.* 2019;10:107.
87. Russo M, Guida F, Paparo L, et al. The novel butyrate derivative phenylalanine-butyramide protects from doxorubicin-induced cardiotoxicity. *Eur J Heart Fail.* 2019;21(4):519–528.
88. Al-Qadami GH, Secombe KR, Subramaniam CB, et al. Gut microbiota-derived short-chain fatty acids: impact on cancer treatment response and toxicities. *Microorganisms.* 2022;10(10):2048.
89. Todorova VK, Hsu PC, Wei JY, et al. Biomarkers of inflammation, hypercoagulability and endothelial injury predict early asymptomatic doxorubicin-induced cardiotoxicity in breast cancer patients. *Am J Cancer Res.* 2020;10(9):2933–2945.

90. Xiao H, Wang X, Li S, et al. Advances in biomarkers for detecting early cancer treatment-related cardiac dysfunction. *Front Cardiovasc Med.* 2021;8:753313.
91. Finkelman BS, Putt M, Wang T, et al. Arginine-nitric oxide metabolites and cardiac dysfunction in patients with breast cancer. *J Am Coll Cardiol.* 2017;70(2):152–162.
92. Putt M, Hahn VS, Januzzi JL, et al. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. *Clin Chem.* 2015;61(9):1164–1172.
93. Zhang J, He J, Zhang L. The down-regulation of microRNA-137 contributes to the up-regulation of retinoblastoma cell proliferation and invasion by regulating COX-2/PGE2 signaling. *Biomed Pharm.* 2018;106:35–42.
94. Thonusin C, Osataphan N, Leemasawat K, et al. Changes in blood metabolomes as potential markers for severity and prognosis in doxorubicin-induced cardiotoxicity: A study in HER2-positive and HER2-negative breast cancer patients. *J Transl Med.* 2024;22(1):398.
95. Burridge PW, Li YF, Matsa E, et al. Human induced pluripotent stem cell-derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity. *Nat Med.* 2016;22(5):547–556.
96. Lo Sardo V, Kamp TJ. Preventing anthracycline-induced cardiotoxicity using functional genomics and human-induced pluripotent stem cell-derived cardiomyocytes. *Circulation.* 2022;145(4):295–298.
97. Liu C, Shen M, Liu Y, et al. CRISPRi/a screens in human iPSC-cardiomyocytes identify glycolytic activation as a druggable target for doxorubicin-induced cardiotoxicity. *Cell Stem Cell.* 2024;31(12):1760–1776.
98. Upshaw JN, Parson SK, Buchsbaum RJ, et al. Dexrazoxane to prevent cardiotoxicity in adults treated with anthracyclines: JACC: cardiooncology controversies in cardio-oncology. *JACC CardioOncol.* 2024;6(2):322–324.
99. Sawicki KT, Sala V, Prever L, et al. Preventing and treating anthracycline cardiotoxicity: new insights. *Annu Rev Pharm Toxicol.* 2021;61:309–332.
100. Shapira J, Gotfried M, Lishner M, et al. Reduced cardiotoxicity of doxorubicin by a 6-hour infusion regimen. A prospective randomized evaluation. *Cancer.* 1990;65(4):870–873.
101. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer.* 2010;10:337.
102. Early Breast Cancer Trialists' Collaborative Group. Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100,000 women from 86 randomised trials. *Lancet.* 2023;401(10384):1277–1292.
103. Levis BE, Binkley PF, Shapiro CL. Cardiotoxic effects of anthracycline-based therapy: what is the evidence and what are the potential harms? *Lancet Oncol.* 2017;18(8):e445–e456.
104. Lipshultz SE, Giantris AL, Lipsitz SR, et al. Doxorubicin administration by continuous infusion is not cardioprotective: the Dana-Farber 91-01 acute lymphoblastic leukemia protocol. *J Clin Oncol.* 2002;20(6):1677–1682.
105. Iervolino A, Spadafora L, Spadaccio C, et al. Myocardial cell preservation from potential cardiotoxic drugs: the role of nanotechnologies. *Pharmaceutics.* 2022;15(1):87.
106. Martín M, Sánchez-Rovira P, Muñoz M, et al. Pegylated liposomal doxorubicin in combination with cyclophosphamide and trastuzumab in HER2-positive metastatic breast cancer patients: efficacy and cardiac safety from the GEICAM/2004-05 study. *Ann Oncol.* 2011;22(12):2591–2596.
107. Rayson D, Suter TM, Jackisch C, et al. Cardiac safety of adjuvant pegylated liposomal doxorubicin with concurrent trastuzumab: a randomized phase II trial. *Ann Oncol.* 2012;23(7):1780–1788.
108. O'Brien MER, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol.* 2004;15(3):440–449.
109. Safra T, Muggia F, Jeffers S, et al. Pegylated liposomal doxorubicin (Doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m^2. *Ann Oncol.* 2000;11(8):1029–1033.
110. Zhang J, Jiang H, Zhang J, et al. Effectiveness and safety of pegylated liposomal doxorubicin versus epirubicin as neoadjuvant or adjuvant chemotherapy for breast cancer: A real-world study. *BMC Cancer.* 2021;21(1):1301.
111. Ansari L, Shiehzadeh F, Taherzadeh Z, et al. The most prevalent side effects of pegylated liposomal doxorubicin monotherapy in women with metastatic breast cancer: a systematic review of clinical trials. *Cancer Gene Ther.* 2017;24(5):189–193.
112. Marty M, Espié M, Llombart A, et al. Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (cardioxane) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy. *Ann Oncol.* 2006;17(4):614–622.
113. de Baat EC, Mulder RL, Armenian S, et al. Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines. *Cochrane Database Syst Rev.* 2022;9(9):CD014638.
114. Gao Y, Wang R, Jiang J, et al. ACEI/ARB and beta-blocker therapies for preventing cardiotoxicity of antineoplastic agents in breast cancer: a systematic review and meta-analysis. *Heart Fail Rev.* 2023;28(6):1405–1415.
115. Lewinter C, Nielsen TH, Edfors LR, et al. A systematic review and meta-analysis of beta-blockers and renin-angiotensin system inhibitors for preventing left ventricular dysfunction due to anthracyclines or trastuzumab in patients with breast cancer. *Eur Heart J.* 2022;43(27):2562–2569.
116. Heck SL, Mecinaj A, Ree AH, et al. 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.* 2021;143(25):2431–2440.

117. Henriksen PA, Hall P, MacPherson IR, et al. Multicenter, prospective, randomized controlled trial of high-sensitivity cardiac troponin I-guided combination angiotensin receptor blockade and beta-blocker therapy to prevent anthracycline cardiotoxicity: the cardiac CARE trial. *Circulation.* 2023;148(21):1680–1690.
118. Moreno-Arciniegas A, Cádiz L, Galán-Arriola C, et al. Cardioprotection strategies for anthracycline cardiotoxicity. *Basic Res Cardiol.* 2025;120(1):71–90.
119. Neilan TG, Quinaglia T, Onoue T, et al. Atorvastatin for anthracycline-associated cardiac dysfunction: the STOP-CA randomized clinical trial. *JAMA.* 2023;330(6):528–536.
120. Abdel-Qadir H, Bobrowski D, Zhou L, et al. Statin exposure and risk of heart failure after anthracycline- or trastuzumab-based chemotherapy for early breast cancer: a propensity score-matched cohort study. *J Am Heart Assoc.* 2021;10(2):e018393.
121. Hundley WG, D'Agostino R, Crotts T, et al. Statins and left ventricular ejection fraction following doxorubicin treatment. *NEJM Evid.* 2022;1(9):EVIDoa2200097.
122. Saad SY, Najjar TA, Al-Rikabi AC. The preventive role of deferoxamine against acute doxorubicin-induced cardiac, renal and hepatic toxicity in rats. *Pharm Res.* 2001;43(3):211–218.
123. Xia Y, Chen Z, Chen A, et al. LCZ696 improves cardiac function via alleviating Drp1-mediated mitochondrial dysfunction in mice with doxorubicin-induced dilated cardiomyopathy. *J Mol Cell Cardiol.* 2017;108:138–148.
124. Ajzashokouhi AH, Bostan HB, Jomezadeh V, et al. A review on the cardioprotective mechanisms of metformin against doxorubicin. *Hum Exp Toxicol.* 2020;39(3):237–248.
125. Timm KN, Tyler DJ. The role of AMPK activation for cardioprotection in doxorubicin-induced cardiotoxicity. *Cardiovasc Drugs Ther.* 2020;34(2):255–269.
126. Oh CM, Cho S, Jang JY, et al. Cardioprotective potential of an SGLT2 inhibitor against doxorubicin-induced heart failure. *Korean Circ J.* 2019;49(12):1183–1195.
127. Abdel-Qadir H, Carrasco R, Austin PC, et al. The association of sodium-glucose cotransporter 2 inhibitors with cardiovascular outcomes in anthracycline-treated patients with cancer. *JACC CardioOncol.* 2023;5(3):318–328.
128. Gongora CA, Drobni ZD, Quinaglia Araujo Costa Silva T, et al. Sodium-glucose co-transporter-2 inhibitors and cardiac outcomes among patients treated with anthracyclines. *JACC Heart Fail.* 2022;10(8):559–567.
129. Ahmad A, Khan F, Mishra RK, et al. Precision cancer nanotherapy: evolving role of multifunctional nanoparticles for cancer active targeting. *J Med Chem.* 2019;62(23):10475–10496.
130. Zhao M, Liu C, Liu Z, et al. Myocardium-targeted liposomal delivery of the antioxidant peptide 8P against doxorubicin-induced myocardial injury. *Int J Pharm.* 2024;663:124569.
131. Jiang CT, Chen KG, Liu A, et al. Immunomodulating nano-adaptors potentiate antibody-based cancer immunotherapy. *Nat Commun.* 2021;12(1):1359.
132. Beishenaliev A, Loke YL, Goh SJ, et al. Bispecific antibodies for targeted delivery of anti-cancer therapeutic agents: A review. *J Control Release.* 2023;359:268–286.
133. Loi S, Giobbie-Hurder A, Gombos A, et al. Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b-2 trial. *Lancet Oncol.* 2019;20(3):371–382.
134. Collins DM, Bossenmaier B, Kollmorgen G, et al. Acquired resistance to antibody-drug conjugates. *Cancers.* 2019;11(3):394.
135. Ju Y, Li S, Tan AEQ, et al. Patient-specific nanoparticle targeting in human leukemia blood. *ACS Nano.* 2024;18(42):29021–29035.
136. Moles E, Chang DW, Mansfeld FM, et al. EGFR targeting of liposomal doxorubicin improves recognition and suppression of non-small cell lung cancer. *Int J Nanomed.* 2024;19:3623–3639.
137. Ho KW, Chen IJU, Cheng YA, et al. Double attack strategy for leukemia using a pre-targeting bispecific antibody (CD20 Ab-mPEG scFv) and actively attracting PEGylated liposomal doxorubicin to enhance anti-tumor activity. *J Nanobiotechnol.* 2021;19(1):16.
138. Chen IJ, Cheng YA, Ho KW, et al. Bispecific antibody (HER2 × mPEG) enhances anti-cancer effects by precise targeting and accumulation of mPEGylated liposomes. *Acta Biomater.* 2020;111:386–397.
139. Moles E, Howard CB, Huda P, et al. Delivery of PEGylated liposomal doxorubicin by bispecific antibodies improves treatment in models of high-risk childhood leukemia. *Sci Transl Med.* 2023;15(696):eabm1262.
140. Yahyazadeh R, Baradaran Rahimi V, Askari VR. Stem cell and exosome therapies for regenerating damaged myocardium in heart failure. *Life Sci.* 2024;351:122858.
141. Newman AAC, Von Itter R, Moore KJ. Extracellular vesicles: bridging the heart and tumor in reverse cardio-oncology. *Circulation.* 2024;149(22):1749–1751.
142. Herrlich A, Kefaloyianni E, Rose-John S. Mechanisms of interorgan crosstalk in health and disease. *FEBS Lett.* 2022;596(5):529–533.
143. Zhang Y, Yu Z, Jiang D, et al. iPSC-MSCs with high intrinsic MIRO1 and sensitivity to TNF-α yield efficacious mitochondrial transfer to rescue anthracycline-induced cardiomyopathy. *Stem Cell Rep.* 2016;7(4):749–763.
144. O'Brien CG, Ozen MO, Ikeda G, et al. Mitochondria-rich extracellular vesicles rescue patient-specific cardiomyocytes from doxorubicin injury: insights into the SENECA trial. *JACC CardioOncol.* 2021;3(3):428–440.
145. Sun X, Chen H, Gao R, et al. Mitochondrial transplantation ameliorates doxorubicin-induced cardiac dysfunction via activating glutamine metabolism. *iScience.* 2023;26(10):107790.
146. Maleki F, Salimi M, Shirkoohi R, et al. Mitotherapy in doxorubicin induced cardiotoxicity: a promising strategy to reduce the complications of treatment. *Life Sci.* 2022;304:120701.

147. Maleki F, Rabbani S, Shirkoohi R, et al. Allogeneic mitochondrial transplantation ameliorates cardiac dysfunction due to doxorubicin: an *in vivo* study. *Biomed Pharm.* 2023;168:115651.
148. Shiba Y, Gomibuchi T, Seto T, et al. Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts. *Nature.* 2016;538(7625):388–391.
149. Marchiano S, Nakamura K, Reinecke H, et al. Gene editing to prevent ventricular arrhythmias associated with cardiomyocyte cell therapy. *Cell Stem Cell.* 2023;30(4):396–414.
150. Lin Y, Sato N, Hong S, et al. Long-term engraftment and maturation of autologous iPSC-derived cardiomyocytes in two rhesus macaques. *Cell Stem Cell.* 2024;31(7):974–988.
151. Kobayashi H, Tohyama S, Ichimura H, et al. Regeneration of nonhuman primate hearts with human induced pluripotent stem cell-derived cardiac spheroids. *Circulation.* 2024;150(8):611–621.
152. Mallapaty S. Revealed: Two men in China were first to receive pioneering stem-cell treatment for heart disease. *Nature.* 2020;581(7808):249–250.
153. Zhao C, Li S, Zhang J, et al. Current state and future perspective of cardiovascular medicines derived from natural products. *Pharm Ther.* 2020;216:107698.
154. Dong K, Liang Y, Li S, Cao M, Liu D, Fei X. Clinical observation on crocin tablets combined with micropump infusion of doxorubicin for prevention of acute cardiotoxicity in patients with diffuse large B-cell lymphoma (in Chinese). *Chin J Exp Tradit Med Formula.* 2024;30(17):131–137.
155. Yang K, Zhang Z, Yuan X. Non-invasive myocardial work assessment of the clinical efficacy of Huangqi Shengmaiyin in preventing and treating anthracycline-induced myocardial toxicity (in Chinese). *Jiangxi Med J.* 2024;59(6):573–576.
156. Zhou C, Zhang Y, Gan X, et al. Effect of Modified Zhigancao Decoction combined with Kaihe Liuqi Acupuncture on arrhythmia induced by chemotherapy in breast cancer (in Chinese). *J Hubei Univ Chin Med.* 2023;25(6):29–32.
157. Yi Y, Liu X, Xiao W, et al. Protective effect of Shengmai Powder combined with Taohong Siwu decoction on myocardium in patients with non-Hodgkin lymphoma (in Chinese). *Med Innov China.* 2023;20(32):99–103.
158. Li T, Han D, Fu X, et al. Effect of Wenxin Zhicao decoction on cardiotoxicity related to adriamycin chemotherapy in breast cancer (in Chinese). *Inf Tradit Chin Med.* 2023;40(7):67–70 76.
159. Xie X, Chen Y, Jie Li. Study on the intervention of therapy for warming yang and supplementing qi on cardiotoxicity of anthracycline chemotherapy drugs (in Chinese). *Mod J Integr Tradit Chin West Med.* 2023;32(6):786–791.
160. Shao Y, Han F. Clinical efficacy observation of Qiliqiangxin capsules in preventing and treating cardiac toxicity induced by epirubicin in breast cancer patients (in Chinese). *Prev Treat Cardiovasc Dis.* 2023;13(4):19–21.
161. Hu J. The impact of Shenmai injection combined with dexrazoxane on cardiac toxicity in acute leukemia patients undergoing chemotherapy (in Chinese). *Prev Treat Cardiovasc Dis.* 2022;12(30):18–20.
162. Heusch G, Bøtker HE, Przyklenk K, et al. Remote ischemic conditioning. *J Am Coll Cardiol.* 2015;65(2):177–195.
163. Bromage DI, Pickard JMJ, Rossello X, et al. Remote ischaemic conditioning reduces infarct size in animal *in vivo* models of ischaemia-reperfusion injury: a systematic review and meta-analysis. *Cardiovasc Res.* 2017;113(3):288–297.
164. Galán-Arriola C, Villena-Gutiérrez R, Higuero-Verdejo MI, et al. Remote ischaemic preconditioning ameliorates anthracycline-induced cardiotoxicity and preserves mitochondrial integrity. *Cardiovasc Res.* 2021;117(4):1132–1143.
165. Cheung YF, Li VWY, So EKF, et al. Remote ischemic conditioning in pediatric cancer patients receiving anthracycline chemotherapy: a sham-control single-blind random trial. *JACC CardioOncol.* 2023;5(3):332–342.
166. Mallouppas M, Chung R, Ghosh AK, et al. Anthracyclines and biomarkers of myocardial injury: the effect of remote ischemic conditioning. *JACC CardioOncol.* 2023;5(3):343–355.
167. Thielmann M, Kottenberg E, Kleinbongard P, et al. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet.* 2013;382(9892):597–604.
168. Moreno-Arciniegas A, García A, Kelm M, et al. Rationale and design of RESILIENCE: a prospective randomized clinical trial evaluating remote ischaemic conditioning for the prevention of anthracycline cardiotoxicity. *Eur J Heart Fail.* 2024;26(10):2213–2222.
169. Ibáñez B, Gomes-Silva M. Remote ischemic conditioning for anthracycline cardiotoxicity: the need to protect the most vulnerable. *JACC CardioOncol.* 2023;5(3):356–359.
170. Heusch G. Cardioprotection in cardio-oncology: a case for concern? *Cardiovasc Res.* 2023;119(12):e144–e145.
171. Foulkes SJ, Howden EJ, Haykowsky MJ, et al. Exercise for the prevention of anthracycline-induced functional disability and cardiac dysfunction: the BREXIT study. *Circulation.* 2023;147(7):532–545.
172. Naaktgeboren WR, Binyam D, Stuiver MM, et al. Efficacy of physical exercise to offset anthracycline-induced cardiotoxicity: a systematic review and meta-analysis of clinical and preclinical studies. *J Am Heart Assoc.* 2021;10(17):e021580.
173. Murray J, Bennett H, Bezak E, et al. The role of exercise in the prevention of cancer therapy-related cardiac dysfunction in breast cancer patients undergoing chemotherapy: systematic review. *Eur J Prev Cardiol.* 2022;29(3):463–472.
174. Wilson RL, Christopher CN, Yang EH, et al. Incorporating exercise training into cardio-oncology care: current evidence and opportunities: JACC: cardiooncology state-of-the-art review. *JACC CardioOncol.* 2023;5(5):553–569.
175. Tian Y, Lv W, Lu C, et al. Galectin-3 inhibition attenuates doxorubicin-induced cardiac dysfunction by upregulating the expression of peroxiredoxin-4. *Can J Physiol Pharm.* 2020;98(10):700–707.

176. Alexandraki A, Papageorgiou E, Zacharia M, et al. New insights in the era of clinical biomarkers as potential predictors of systemic therapy-induced cardiotoxicity in women with breast cancer: a systematic review. *Cancers.* 2023;15(13):3290.
177. Liew LC, Ho BX, Soh BS. Mending a broken heart: current strategies and limitations of cell-based therapy. *Stem Cell Res Ther.* 2020;11(1):138.
178. Protze SI, Lee JH, Keller GM. Human pluripotent stem cell-derived cardiovascular cells: from developmental biology to therapeutic applications. *Cell Stem Cell.* 2019;25(3):311–327.
179. Zhao W, Hausenloy DJ, Hess DC, et al. Remote ischemic conditioning: challenges and opportunities. *Stroke.* 2023;54(8):2204–2207.
180. Kenchegowda M, Rahamathulla M, Hani U, et al. Smart nanocarriers as an emerging platform for cancer therapy: a review. *Molecules.* 2021;27(1):146.
181. Wang JW, Shao H, Zhang YN, et al. Traditional Chinese medicine as a protective strategy against chemotherapy-induced cardiotoxicity: an overview of the literature. *J Tradit Complement Med.* 2024;15(2):107–118.
182. Del Buono MG, Arena R, Borlaug BA, et al. Exercise intolerance in patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019;73(17):2209–2225.
183. Cejas RB, Petrykey K, Sapkota Y, et al. Anthracycline toxicity: light at the end of the tunnel? *Annu Rev Pharm Toxicol.* 2024;64:115–134.