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REVIEW

Natural Products From Traditional Chinese Medicine: Potential Therapeutic Agents in Cancer Therapy-Induced Cardiotoxicity

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Abstract: Cancer therapy-induced cardiotoxicity (CTIC) is a serious and increasingly recognized cause of death and disability among cancer survivors. It frequently necessitates the withdrawal or dose reduction of effective anticancer drugs, limiting therapeutic options and affecting patient outcomes. While CTIC poses a major health risk, the precise cellular and molecular mechanisms responsible for this toxicity remain elusive, which complicates the development of preventive and therapeutic strategies. In recent years, natural products derived from Traditional Chinese Medicine (TCM) have gained attention as potentially beneficial agents for CTIC management. These TCM natural products consist of biologically active compounds that often act on multiple therapeutic targets, offering a comprehensive approach to mitigating cardiotoxicity during cancer treatment. This review aims to provide a concise overview of CTIC associated with various anticancer drugs and examine the emerging research on TCM natural products in reducing the cardiotoxic effects related to cancer therapies, highlighting areas where further investigation is needed. In addition, we also provide the challenges and coping strategies faced by basic research and clinical transformation of Chinese medicine monomers.

Keywords: traditional chinese medicine, cancer therapy-induced cardiotoxicity, cardio-oncology, natural products, therapeutic agents

Introduction

Cancer is a significant threat to human health and survival. With recent advancements in cancer diagnostics and therapeutics, cancer is increasingly managed as a chronic condition.[1] However, this progress has also brought the unintended consequence of treatment-associated cardiotoxicity. Cardiotoxic events can complicate therapeutic regimens and, in some cases, necessitate treatment discontinuation, thereby increasing mortality risk among cancer patients. Cardiotoxic complications associated with chemotherapeutic agents have been reported as the second leading cause of mortality among cancer patients, which has garnered increasing attention in the field of oncology and cardiology.[2] A 2024 meta-analysis involving over 35,000 cancer patients found that the incidence of chemotherapy-related cardiac dysfunction reached 63.21 per 1000 person-years, highlighting the high cardiovascular risk associated with anticancer treatments.[3]

In recent years, cardio-oncology has emerged as a new interdisciplinary field, aiming to study the heart damage and cardiotoxicity faced during tumor treatment. Among them, traditional chemotherapy drugs represented by doxorubicin, tumor-targeted drugs such as TKI (Tyrosine Kinase Inhibitor) inhibitors and monoclonal antibodies, and new immune-checkpoint inhibitors such as PD1 and PDL-1 monoclonal antibodies, which have been extensively investigated in

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cardio-oncology research. Furthermore, in recent years, the role of TCM and TCM natural products in tumor-related cardiotoxicity has received widespread attention. An increasing number of studies suggest that these compounds can ameliorate tumor-associated cardiotoxicity and possess significant clinical application value.

Traditional Chinese Medicine, as a core component of traditional medicine, has a history spanning several millennia. Currently, research in TCM is often focused on chemical monomers with biological activity within Chinese medicines, specifically TCM natural products. In contrast to single-compound Western pharmaceuticals, TCM natural products exhibit chemical diversity and exert multi-target, multi-pathway pharmacological activities. These properties enable systemic regulation, contributing to their therapeutic efficacy.[4] In recent years, thanks to the progress of modern medicine and biotechnology, the research on TCM natural products in fields such as oncology, cardiovascular disease, and metabolic disease has received wide attention. Isolated active constituents, including flavonoids, terpenoids, alkaloids, and phenolic acids, have been extracted and identified from Traditional Chinese Medicines with antioxidant, anti-inflammatory, lipid-regulating, and anti-tumor effects. These components have shown promising therapeutic potential in oncology treatment, cardiovascular diseases, and metabolic diseases.[5,6] These diverse and complex TCM natural products hold great potential and clinical application value in the treatment of diseases. This offers novel perspectives for the development of modern therapeutic strategies.

Currently, specific studies have identified the potential of TCM natural products in reducing the cardiotoxic effects of chemotherapeutic drugs on healthy cells.[7] While tumor chemotherapeutic drugs have shown significant efficacy in inhibiting the proliferation of cancer cells, they are also accompanied by toxic side effects on healthy cardiomyocytes, leading to frequent cardiotoxicity problems. Studies on active ingredients extracted from various Chinese herbal medicines have demonstrated that these natural compounds can significantly attenuate chemotherapy-induced cardiotoxicity and preserve cardiomyocyte function.

This review summarizes the latest research in cardiotoxicity associated with tumor therapies and the cardioprotective effects of active ingredients derived from Traditional Chinese Medicine (TCM). Further introduce these active ingredients that mitigate cardiotoxicity and evaluate their current clinical application and potential strategies to enhance their translational use.

To ensure that this review is comprehensive and up-to-date, we conducted a literature search using multiple databases, mainly focusing on PubMed. The search covered publications from January 2013 to March 2024. Various combinations of the following keywords were used: “cardiotoxicity”, “cancer”, “chemotherapy”, “tyrosine kinase inhibitors”, “traditional Chinese medicine”, “cardiac dysfunction”, and “anticancer drugs”. Only articles published in English were included.

Overview of Cardio-Oncology

Research Scope and Treatment Goals of CTIC

Cardio-oncology is a rapidly evolving interdisciplinary field in medicine that pertains to the cardiovascular evaluation, management, and post-treatment care of patients with cancers (Figure 1). Its primary objective is to prevent, promptly diagnose, stratify risk, and effectively manage cardiovascular disease associated with cancer treatment.[8,9] Cancer therapy-induced cardiotoxicity (CTIC) is one of the main focuses of oncology cardiology research and clinical intervention. It has emerged as a significant cause of mortality among cancer survivors due to the shared risk factors between cancer and cardiovascular diseases, including hyperlipidemia, hypertension, diabetes mellitus, and immune dysregulation.[10,11] The spectrum of cardiac complications resulting from CTIC includes myocarditis, heart failure (HF), coronary artery disease, valvular heart disease, arrhythmias, arterial hypertension, peripheral vascular diseases and stroke.[12] As a result of improved treatment and prognosis across various kinds of malignancies, there is a gradual shift towards increased CTIC.[13] Hence, the field of cardio-oncology is progressively expanding, necessitating the stratification and monitoring of cardiovascular risk in patients with malignancies prior to treatment (CTIC risk assessment), during treatment (CTIC detection), and post-treatment completion (CTIC survivorship).[14] The ultimate goal is to optimize antitumor efficacy while minimizing cancer therapy-related cardiac events through comprehensive care for both oncological and cardiovascular health.[15]

Increasing research efforts have been directed toward the development of strategies to prevent or mitigate CTIC. The potential cardiotoxicity of chemotherapeutics, exemplified by anthracyclines (such as doxorubicin, pirarubicin,

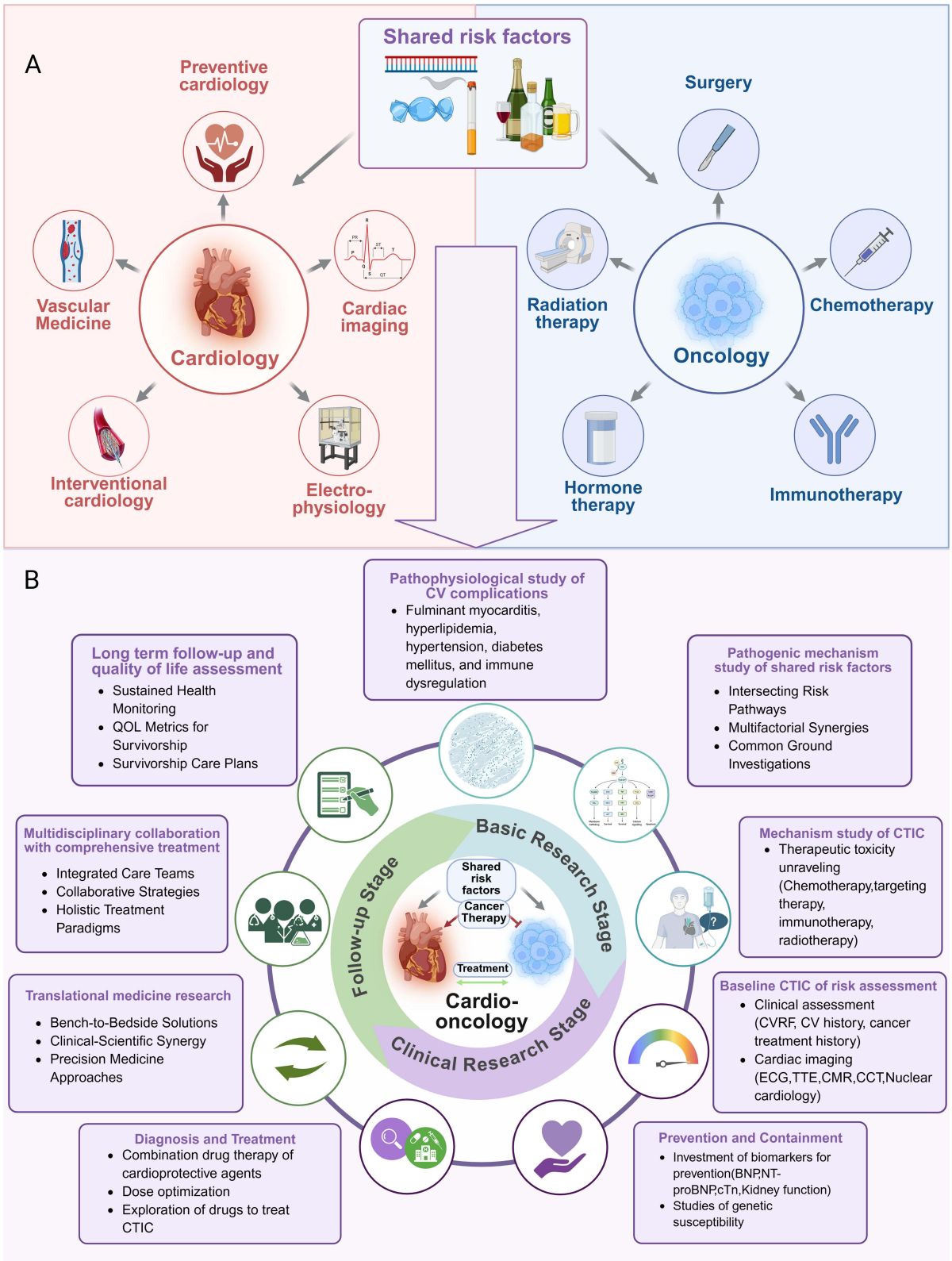

Figure 1 The composition and research content of cardio-oncology. (**A**) Shared risk factors and integrated approaches to Cardiology & Oncology. Shared risk factors correlate cardiovascular diseases and cancer. Holistic treatment paradigms should integrate therapies including cardiology (vascular medicine, interventional cardiology, novel imaging, etc.) with oncology (chemotherapy, immunotherapy, hormone therapy, etc.). (**B**) Comprehensive Research on Cardio-oncology. Comprehensive cardio-oncology research spans basic, clinical and follow-up phases, delving into cardiotoxicity etiology, assessment, management, treatment and prognosis.

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cyclophosphamide, 5-fluorouracil, paclitaxel, and cisplatin), has garnered significant attention and has been comprehensively investigated from diverse perspectives.[16] Anthracycline therapy involves multiple processes including topoisomerase II inhibition, generation of reactive oxygen radicals, suppression of apoptotic pathways initiation, and DNA intercalation. Doxorubicin serves as the typical anthracycline that elevates the risk of systolic dysfunction and HF through mechanisms involving DNA damage, oxidative stress, and mitochondrial dysfunction.[17,18] Arsenic trioxide, as a treatment for solid tumors, demonstrates a distinct regulatory mechanism from standard chemotherapy and holds promising clinical application prospects.[19] It is also the most cost-effective targeted therapy for tumors, carrying significant social and economic value.[20] Its mode of action involves the restoration of mutant TP53 protein structure, with approximately half of all tumors exhibiting TP53 mutations.[21] TP53 plays a crucial role in cell autophagy and metabolism, particularly in glucose metabolism, making it one of the most vital tumor suppressor factors within cells.[22] Moreover, the impact of tumor-targeting drugs to induce CTIC, represented by TKIs, such as sunitinib, and sorafenib, are also a matter of concern. However, studies on this topic are scarce and still in the early stages, which may be related to the drug's iterative development. Among tumor-targeted drugs, HER2 molecular-targeted therapies and VEGF (Vascular Endothelial Growth Factor) inhibitors, have been associated with an increased risk of HF and left ventricular dysfunction.[23] VEGF blockers can induce microvascular changes that lead to reduced myocardial capillary network and impaired contractility. Anti-VEGF functions performed by TKIs including pazopanib, axitinib, vandetanib, regorafenib, cabozantinib, and lenvatinib, can also affect vascular endothelial cells and trigger hypertension.[24] Mitogen-activated protein kinase (MEK) inhibitor and dasatinib, a multi-targeted TKI, have been associated with cardiomyopathy. The histone deacetylase inhibitor panobinostat and several TKIs, particularly ALK (Anaplastic lymphoma kinase) inhibitors such as crizotinib and ceritinib, followed by sunitinib, sorafenib and pazopanib, have been correlated with QT interval prolongation, a critical determinant of arrhythmia.[25,26] In addition, immune-checkpoint inhibitors (ICIs) have precipitated a fundamental transformation in cancer treatment, rendering them a viable treatment option for almost half of patients with malignancies. Initial observations have highlighted the potential for ICIs to induce fulminant myocarditis, while recent studies have reported other immune-related cardiac adverse events (irAEs), encompassing an elevation in cardiac dysfunction, vascular inflammation, thrombogenesis, and atherosclerosis.[27] The utility of ICIs disrupts immune system regulation and can trigger cell-mediated cytotoxicity targeting host tissues inadvertently. Typical targets of ICIs include cytotoxic T lymphocyte associated antigen 4 (CTLA4), programmed cell death protein 1 (PD1), PD1 ligand 1 (PDL1), and lymphocyte activation gene 3 (LAG3), a recently-identified target that correlates with fatigue status of CD4+ and CD8+ T cells.[28] Furthermore, radiotherapy can also induce cardiotoxicity. Mechanisms of radiation-induced cardiotoxicity include oxidative stress, DNA damage, protein oxidation, lipid peroxidation, and molecular signaling pathway damage, such as the TGF-β (Transforming Growth Factor Beta) pathway, PI3K/Akt (Phosphatidylinositol 3-kinase/Protein kinase B) pathway, MAPK/ERK (Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase) pathway, JAK/STAT (Janus kinase/Signal Transducer and Activator of Transcription) pathway, and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway.[29,30]

Current Situation of Laboratory Research and Clinical Studies

Cardio-oncology research primarily encompasses two domains: clinical studies targeting early-stage intervention in diagnosis and laboratory-based studies. Clinical investigations primarily focus on early detection and the implementation of timely interventional strategies. Progress in cardiovascular imaging has underscored the crucial need for reliable methodologies to identify, monitor, and prognosticate the risks of CTIC. The American Heart Association has put forward guidelines and consensus on cardiovascular imaging for CTIC. Echocardiography is the primary modality for evaluating cardiac function, and it should be conducted before cancer therapy to evaluate baseline left ventricular ejection fraction (LVEF) and peak systolic longitudinal strain. Assessment of right ventricular function should also be included in echocardiographic evaluations due to its prognostic significance. Three-dimensional echocardiography is the recommended approach for obtaining 3D LVEF. For patients with abnormal baseline LVEF, it is advisable to explore alternative cancer treatment modalities associated with reduced cardiotoxicity.[31,32] Besides, results from echocardiography should be combined with findings from other cardiovascular imaging techniques including cardiac magnetic resonance imaging (CMR), which offers more detailed information about cardiac function including myocardial fibrosis, edema, and

myocarditis, in addition to Cardiac Computed Tomography Angiography (CTA) to assess valvular diseases, coronary artery disease, and non-cardiovascular complications associated with radiation therapy, followed by Nuclear Medicine Imaging used to evaluate myocardial perfusion and metabolism by detecting ischemia and myocarditis. These multi-modality imaging methods complement each other while providing a comprehensive assessment of cardiac condition for detecting and monitoring CTIC of cancer patients.[33]

Research in the laboratory includes the exploration of biomarkers for early diagnosis, genetic studies of cancer susceptibility, and the exploration of drugs to treat CTIC. Natriuretic peptides (NPs), including B-type NP (BNP) or N-terminal pro-BNP (NT-proBNP) and cardiac troponin (cTn) are widely-recognized biomarkers of heart damage and stress whose increased levels have resulted in CTIC.[34] It is advisable to conduct NP assessment at the beginning of treatment in patients at high risk who are receiving chemotherapeutics, ICIs and proteasome inhibitors (PIs). Other potential biomarker for CTIC include microRNAs (miRNAs), Galectin-3 (Gal-3), C-Reactive Protein (CRP).[35,36] Growth differentiation factor-15 (GDF-15), myeloperoxidase (MPO) and asymmetric dimethylarginine also have been postulated as useful biomarkers due to their involvement in metabolism of nitric oxide, which are possible mechanisms of anthracycline-induced cardiotoxicity.[37] Moreover, as a result of recent developments in -omics technology, the therapeutic significance of phenotyping has been significantly increased in both amplitude and spectrum.[38] The -omics disciplines, including genomics, proteomics, metabolomics, lipidomics, and immunomics, aim to employ computational techniques for identifying patterns within extensive datasets, with the purpose of elucidating the underlying pathophysiological mechanisms.[39] In cases of CTIC, -omics technologies can reveal novel disease measurements that may contribute to customizing medical treatment in the field of cardio-oncology.[40] For genetic screening, it has been found that there are multiple cancer-related cardiotoxic genes. Several studies have found that certain single nucleotide polymorphisms (SNPS) in the ERBB2 (also known as HER2) gene are related to trastuzumab-induced cardiotoxicity.[41] And human leukocyte antigen (HLA) genes, participating in the regulation of the immune system, are related to cardiotoxicity caused by chemotherapeutics.

To note, the development of pharmaceuticals or possible therapeutic targets for CTIC treatment is advancing at a rapid pace. Some non-coding RNAs, such as circular RNA (circRNA), have been identified as potential targets for ameliorating CTIC.[42] It was reported that circITCH can alleviate DOX-induced cardiotoxicity by combining with miR-330-5p to prevent the degradation of target genes including SERCA2a, Survivin and SIRT6.[43] Moreover, CircFOXO3 accelerates the advancement of glioblastoma by functioning as a competitive endogenous RNA against NFAT5.[44] By sequestering ID1, E2F1, FAK and HIF1α, thereby impeding their nuclear translocation and anti-aging function, circFOXO3 also exacerbates DOX-induced cardiomyopathy.[45] Furthermore, an increasing number of TCM natural products have demonstrated efficacy in managing cardiotoxicity resulting from diverse cancer treatment modalities.[46] Research discovered that Isorhapontigenin (Isor), a novel derivative of stilbene, effectively alleviated DOX-induced apoptosis in cardiomyocytes in vitro by upregulating YAP1 expression.[47] In current practice, CTIC is mainly managed by adjusting cancer drugs and adding heart-protective medications. For high-risk patients, ACE inhibitors, beta-blockers, and diuretics are recommended. Cardiac interventions and managing complications may also be needed, and treatment may be paused if necessary.[48] For instance, in cases of hypertension induced by TKIs targeting VEGF pathway, antihypertensive medications such ACEIs or calcium channel blockers can be employed for blood pressure control.[49,50] Treatment of ICI-related myocarditis usually starts with high-dose corticosteroids like prednisone or methylprednisolone.[51] Based on the evaluation of clinical response and patterns in multiple biomarkers, it may be appropriate to contemplate the use of other immunomodulatory agents (abatacept and plasa pheresis).[52,53] However, current strategies for ameliorating CTIC remain inadequate. Currently, dexrazoxane remains the only FDA- and EMA-approved cardioprotective agent for anthracycline-induced cardiotoxicity due to its ability to chelate iron and limit oxidative stress without compromising anticancer efficacy. Furthermore, randomized trials and meta-analyses have shown that β-blockers and ACE inhibitors or ARBs can help reduce CTIC.[54,55] But these interventions are not universally effective, and some evidence shows inconsistent outcomes for ACEI/ARB monotherapy. Meanwhile, one network meta-analyses suggest potential benefits of combined prophylaxis regimens, including molecular agents and traditional Chinese medicine formulations, though high-quality trials are still needed.[56]

Natural Products From Traditional Chinese Medicine in CTIC

In recent years, natural products derived from Traditional Chinese Medicines have garnered increasing attention in tumor cardiology research. These natural compounds have been shown to exert protective effects in cardio-oncology by modulating the immune response, inhibiting tumor cell proliferation, and improving cardiovascular function, thereby demonstrating significant research value and promising clinical application potential.[57] Through experimental studies, we have found that TCM natural products play a great role in alleviating the cardiotoxicity caused by anticancer drugs. These include traditional chemotherapy drugs as anthracyclines (eg, doxorubicin, pirarubicin), fluoropyrimidines (eg, 5-fluorouracil), alkylating agents (eg, cyclophosphamide, cisplatin), as well as newer treatments like arsenic trioxide, molecularly targeted drugs (eg, TKIs such as sorafenib and sunitinib, proteasome inhibitors such as bortezomib and carfilzomib), and monoclonal antibodies (eg, trastuzumab).

Traditional chemotherapy drugs refer to cytotoxic agents that primarily target rapidly dividing cells by interfering with DNA synthesis or mitosis. In contrast molecularly targeted drugs are therapeutics designed to specifically inhibit oncogenic pathways by targeting.

Notably, certain TCM-derived natural compounds have been reported to exert synergistic effects with anticancer agents, thereby enhancing the overall efficacy of tumor therapy.[58,59]

Cardiotoxicity Associated with Traditional Chemotherapy Drugs

Doxorubicin-Induced Cardiotoxicity

Anthracyclines (ie doxorubicin, daunorubicin, epirubicin, idarubicin) are widely used in the treatment of hematological malignancies and solid tumors, such as acute leukemias, lymphomas, breast cancers, gastric cancers, soft-tissue sarcomas, and ovarian cancers.[60,61] They have made significant improvements in the overall survival of cancer patients and are one of the most effective cytostatic drugs for the treatment of various malignancies.[62] However, with the widespread use of anthracyclines, it has been found that the toxic effects of these drugs are not limited to tumor cells, but can also affect cardiac cells. Members of the anthracycline family have been found to be a significant cause of both acute and chronic cardiotoxicity,[63,64] with approximately one-third of deaths attributable to long-term cardiotoxicity, compared to 51% of tumor-related mortality.[64]

Clinical studies have found that anthracycline-induced cardiac disorders (eg, cardiac insufficiency, arrhythmias, and, rarely, acute myocarditis) occur in up to 20% of all anthracycline-treated patients, and up to 48% of patients treated with high-dose anthracyclines.[64] Therefore, addressing anthracycline-induced cardiotoxicity is of great clinical significance. Through the literature, we have found that TCM natural products are able to ameliorate anthracycline-induced cardiotoxicity and improve the efficacy of oncology treatment to a certain extent.

Currently, doxorubicin (DOX) is the most extensively studied anthracycline, particularly with regard to its cardiotoxic effects. In the process of summarizing the research on the treatment of DOX cardiotoxicity with TCM natural products, we found that many Traditional Chinese Medicines can alleviate the cardiotoxicity it causes (Figure 2), such as *Panax ginseng, Salvia miltiorrhiza, Lonicera japonica Thunb., Astragalus membranaceus, Coptis chinensis root, Scutellaria baicalensis, Magnolia bark, Evodia rutaecarpa*, t*uckahoe, Veratrum nigrum, Mentha haplocalyx, Aconitum carmichaelii*, etc., have certain chemically active substances that have a certain effect in reducing the cardiotoxicity caused by anthracyclines (Table 1).

Matrine and sophocarpine both can be extracted from *Sophora flavescens*. Sophocarpine reduces the oxidative stress of cardiomyocytes and reduces the apoptosis of cardiomyocytes through the Nrf2/HO-1 (Nuclear factor erythroid 2–related factor 2/Heme oxygenase-1) signaling pathway;[83] matrine can reduce the cardiotoxicity caused by DOX through the AMPKα/UCP2 (AMP-activated protein kinase alpha/uncoupling protein 2) pathway.[84] Berberine is an important extract of *Coptis chinensis*, it can relieve DOX-induced cardiotoxicity through multiple pathways. Studies have found that berberine can reduce the MBA level in cardiac cells, mitochondrial damage in the heart, cardiac fibrosis, and cardiac oxidative stress levels by decreasing the expression of SIRT1, p66Shc proteins, and related pathways and genes.[89,90,95]

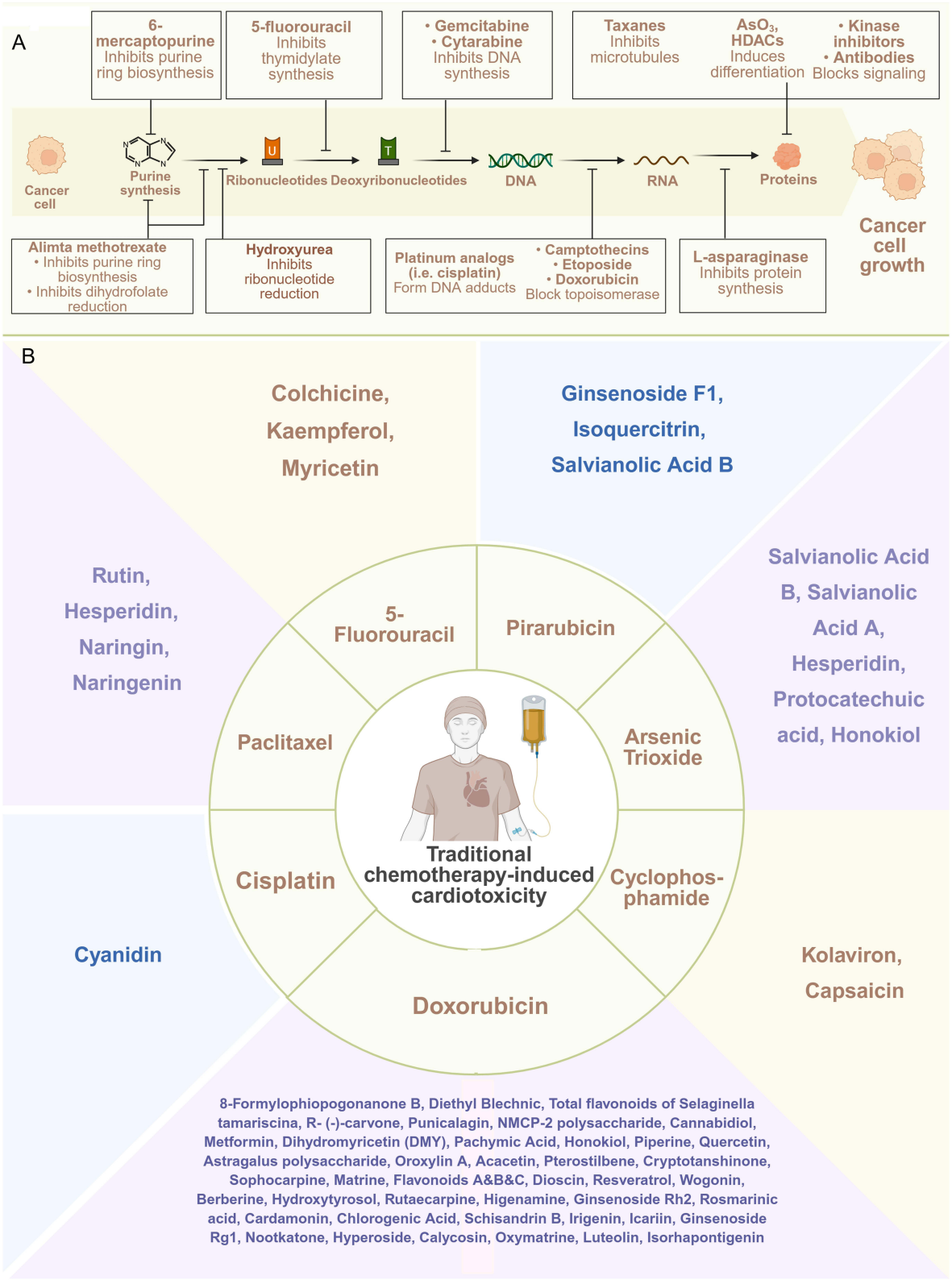

Figure 2 Relationship between traditional chemotherapeutic drugs in inhibiting cancer cell proliferation and their induced cardiotoxicity. (**A**) How chemotherapy drugs act on cancer cells. Various types of chemotherapy drugs (5-fluorouracil, 6-mercaptopurine, A2O3, taxanes, cytarabine, etc.) inhibit the growth of cancer cells by affecting each stage of cellular protein synthesis (purine ring biosynthesis, DNA synthesis, etc). (**B**) Comprehensive overview of the protective effects of natural products. Comprehensive research on the protective effects of natural products from different traditional Chinese medicines various chemotherapeutic drugs, including doxorubicin, 5-fluorouracil, cisplatin, cyclophosphamide, pirarubicin, and paclitaxel.

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Table 1 Cardiotoxicity of Traditional Chemotherapy Drugs

Research Model	Research Subjects	Natural Compounds	Sources	Intervention Methods (in vitro)	Intervention Methods (in vivo)	Effects	Targets or Pathways	References
DOX cardiotoxicity	Male C57BL/6 mice	8-Formylophiopogonanone B	*Ophiopogon japonicus*	None	DOX (20mg/kg), 8-FOB (20mg/kg)	Cardiac atrophy↓, Cardiac dysfunction↓, Collagen content in cardiac tissues↓, Cardiac contractility↑	HMOX1 expression↓	D Qin et al (2021)[65]
DOX cardiotoxicity	H9c2 cells, Sprague-Dawley rats	Diethyl Blechnic	*Salvia miltiorrhiza*	DB, DOX	DB, DOX	Cell death↓, Cardiac Cell apoptosis↓, P-p53 and Cyt c expression↓, Bcl-2 and Bcl-xl expression↑, Bax expression↓	ROS↓, JNK1/2 signaling pathway↑	J Yu et al (2018)[66]
DOX cardiotoxicity	Male C57BL/6 mice, H9c2 cells	Total flavonoids of Selaginella tamariscina	*Selaginella tamariscina*	DOX+TFST (6,8,10μg/mL)	TFST+DOX (70,140mg/kg), DOX (20 mg/kg)	Mitochondrial dysfunction↓, ER stress↓	MFN2/PERK pathway↑	LY Gao et al (2022)[67]
DOX cardiotoxicity	Male BALB/c mice, H9C2 cells, MCF 7 cells	R- (-)-carvone	*Mentha canadensis L.*	R-(-)-carvone (100μM-6.25μM), DOX (100μM-6.25μM)	DOX (20mg/kg), -(-)-carvone (75,150mg/kg)	CK and LDH↓, Toxicity on normal heart cells↓		Abbas MM et al (2020)[68]
DOX cardiotoxicity	H9c2 cells	Punicalagin	*Punica granatum L.*	PUN (50,100,200μM), DOX (5μM)	None	LDH in H9c2 cells↓, apoptotic cells↓, ROS production↓	Expression of nuclear Nrf2↑, Nrf2/HO-1 signaling↑	MF Ye et al (2019)[69]
DOX cardiotoxicity	H9C2 cells, female BALB/c mice	NMCP-2 Polysaccharide	*Morchella conica*	NMCP-2 (5,10,15,20μg/mL), DOX (1,2,4μM)	NMCP-2 (50mg/kg), DOX (5mg/kg)	Cell activity of H9C2↑, Heart weight↓, Oxidative stress↓, Apoptotic damage↓	Activities of serum markers (CK-MB, AST, and ALT) ↓, Antioxidant enzymes↑	N Xu et al (2021)[70]
DOX cardiotoxicity	Male C57BL/6J mice	Cannabidiol	*Cannabis sativa L.*	None	DOX, CBD (10mg/kg)	Myocardial cell death↓, Metalloproteinases 2 and 9↑	Mitochondrial biogenesis↑	EK Hao et al (2015)[71]
DOX cardiotoxicity	Male Wistar Albino rats	Metformin	*Syringa oblata Lindl.*	None	Metformin (250mg/kg/day), Dox (16mg/kg)	Left ventricular functions↑, CNP levels↓	Adenosine monophosphate↓	M Argun et al (2016)[72]
DOX cardiotoxicity	H9C2 cells, U937cells, HL-60 cells, K-562cells, Neonatal SD rats, ICR mice, BALB/C mice	Dihydromyricetin (DMY)	*Ampelopsis grossedentata*	DMY, ADR	DMY (500,250,125,50mg/kg), ADR (2mg/kg)	Primary cardiomyocytes apoptosis↓, Reactive oxygen species↓	MDM2-mediated ubiquitylated degradation of ARC↓	H Zhu et al (2014)[73]
DOX cardiotoxicity	Male Albino rats	Pachymic Acid	*Poria cocos*	None	PA (10mg/kg), LN (10mg/kg), DOX (3.5mg/kg)	Cardiac hypertrophy↓, Cardiac fiber↑, Mitochondria↓	miR24↓, expression of RyR-2 and SERCA-2a genes↓, Protein expression of JP-2↓	N Younis et al (2021)[74]
DOX cardiotoxicity	Male C57BL/6 J mice, H9c2 cells	Honokiol	*Magnolia bark*	Honokiol (2.5,5μM)	Honokiol (0.2 mg/kg/day), DOX (5 mg/kg/week, 3 mg/kg/day)	Mitochondrial respiration↑, Myocardial reactive oxygen species levels↓	PPARγ signaling↑	LZ Huang et al (2017)[75]
DOX cardiotoxicity	C57BL/6 mice, H9c2 cells	Piperine	*Piper nigrum L., Piper longum L.*	Piperine (20μmol/l), PPAR-γ antagonist (10μmol/l)	Piperine (50mg/kg), DOX (15mg/kg), PPAR-γ inhibitor (0.35mg/kg/d)	Cardiac injury↓, Cardiac contractility↑, Inflammation accumulation↓, Cardiac oxidative stress↓, Cardiomyocytes apoptosis↓	PPARγ receptor↑	J Yan et al (2019)[76]
DOX cardiotoxicity	H9c2 cells, C57BL/6 female mice	Quercetin	*Crataegus pinnatifida, Hippophae rhamnoides L.*	Quercetin (50–100μM), DOX (0–16μM)	Quercetin (100mg/kg), DOX (20mg/kg)	Apoptosis↓, Mitochondrial dysfunction↓, ROS generation↓, Oxidative stress↓	Bmi-1 expression↑	QH Dong et al (2014)[77]
DOX cardiotoxicity	Male C57BL/6 mice	Astragalus polysaccharide	*Astragalus membranaceus*	None	APS (1.5g/kg/day), DOX (20mg/kg)	Autophagosome formation↓, Apoptosis↓, Heart function↑, Normal autophagic↑	Caspase-3 activation↓, LC3B activation↓, AMPK/mTOR pathway↑	Y Cao et al (2017)[78]

DOX cardiotoxicity	Male C57BL/6 mice, H9c2 cells	Oroxylin A	*Scutellaria radix*	OA (40μmol/l), DOX (5μmol/l), H89 (10μmol/l), 2'5'-dd-Ado (200μmol/L)	OA (40 mg/kg), Tamoxifen (25mg/kg/day), DOX (20mg/kg)	Oxidative damage in cardiac tissues↓, Inflammatory cytokines↓, Myocardial apoptosis↓	Sirtuin 1 signaling pathways↑	WB Zhang et al (2021)[79]
DOX cardiotoxicity	Male C57BL/6 mice, H9C2 cells	Acacetin	*Robinia pseudoacacia L.*	Acacetin (0.3,1,3μM)	Acacetin prodrug (15mg/kg), DOX (2.5mg/kg/day)	Ventricular fibrosis↓, Myocardial collagen I and collagen III protein↑	ROS production↓, AMPK/Nrf2 pathway↑, Nrf2 siRNA↑	WY Wu et al (2020)[80]
DOX cardiotoxicity	H9c2 cells, male C57BL/6 mice	Pterostilbene	*Pterocarpus santalinus*	Pterostilbene (10μM), DOX (1μM)	Pterostilbene (10 mg/kg/day), Dox (20mg/kg), Compound C (20mg/kg/day), EX527 (5mg/kg/day)	Mitochondrial damage↓, Oxidative stress↓	AMPK, SIRT1 and PGC1α signaling↑	D Liu et al (2019)[81]
DOX cardiotoxicity	H9C2 cells	Cryptotanshinone	*Salvia miltiorrhiza*	Cts (5,10,25μM), DOX (1μM)	None	Mitochondrial apoptosis↓, Oxidative stress↓	Akt and GSK-3β↑, Phosphorylation of GSK-3β↓, p-GSK-3β↑	XP Wang et al (2021)[82]
DOX cardiotoxicity	H9C2 cells, male C57BL/6J mice	Sophocarpine	*Sophora flavescens*	Sophocarpine (1,2,5μM), DOX (1μg/mL), DOX+SOP (1,2,5μM)	SOP (5,10,15,30mg/kg), DOX (5 mg/kg)	Heart injury biomarkers↓, Oxidative stress↓, Apoptosis↓	Nrf2/HO-1 signaling pathway↑	HJ Zhang et al (2024)[83]
DOX cardiotoxicity	Male C57/B6 mice, H9C2 cells	Matrine	*Sophora flavescens*	Matrine (200μmol/L), DOX (1μmol/L)	Martine (200 mg/kg/day), Geni pin (30mg/kg), DOX (4mg/kg)	MDA level and NADPH oxidase↓, Cardiomyocyte apoptosis↓	AMPKα/UCP2 pathway↑	C Hu et al (2019)[84]
DOX cardiotoxicity	H9c2 Cells	Flavonoid A, B, C	*Hippophae rhamnoides Linn*	F-A, F-B, F-C (0.1,1.0,5.0,10,20,40,80,160μM), DOX (2.5μM)	None	Cell apoptosis↓, Mitochondrial dysfunction↓	Myocardial GSH-Px and SOD↑, MDA content↓, JNK activation↓	WN Zhou et al (2023)[85]
DOX cardiotoxicity	Male SD mice, H9c2 cells	Dioscin	*Dioscorea polystachya Turczaninow*	Dioscin (0–8μM), DOX (0–10μM)	DOX + Dioscin (60mg/kg/day), DOX (2.5mg/kg/week)	Cardiac injury ↓, dysfunction↓, Cardiac ferroptosis↓	Nrf2/GPX4 signaling pathway↑	J Liu et al (2024)[86]
DOX cardiotoxicity	Male C57BL/6J mice, H92c cells	Resveratrol	*Veratrum album*	DOX (1μM), Res (20μM)	DOX (24mg/kg), Res (20mg/kg/day)	Cardiac ferroptosis↓, Cardiac dysfunction↓	MAPK signaling pathway↓	L Chen et al (2024)[87]
DOX cardiotoxicity	H9c2 Cells, male SD mice	Wogonin	*Scutellaria baicalensis*	WG (10μM), DOX (5μM)	WG (100mg/kg), DOX (3mg/kg)	Myocardial injury↓, Oxidative stress↓, Mitochondrial Cytochrome c release↓	Mitochondrial cytochrome c release↓, Caspase activation↓	YJ Wei et al (2022)[88]
DOX cardiotoxicity	H9c2 Cells, Sprague-Dawley mice	Berberine	*Coptis chinensis Franch*	DOX (1μM), Ber (0.1,1,10μM)	DOX (20 mg/kg/day), Ber (20 mg/kg)	CAT, SOD, and GSH-PX activities↑, Levels of MDA↓, Oxidative stress↓	SIRT1 expression↑, p66Shc expression↓	YZ Wu et al (2019)[89]
DOX cardiotoxicity	NRCMs Cells, Sprague-Dawley mice	Berberine	*Coptis chinensis Franch*	DOX (1μM), Ber (0.06,0.25,1.0,4.0μM)	DOX (20 mg/kg), Ber (30,60,90mg/kg)	Cardiomyocyte apoptosis↓, AMPK and p53 activation↑, Mitochondrial membrane loss↓	Cardiomyocyte apoptosis↓, Bcl-2 expression↑	XX Lv et al (2012)[90]
DOX cardiotoxicity	H9c2 Cells	Hydroxytyrosol	*Canarium album (Lour). Rauesch.*	HT (50μM), DOX (0.1μM)	None	DNA damage↓, toxicity in H9c2 Cardiomyoblasts↓, ROS production↓, SOD2 activation↓	-H2AX protein levels↓, Bax pro-apoptotic pathway↓	I Sirangelo et al (2022)[91]
DOX cardiotoxicity	Male C57BL/6 mice	Rutaecarpine	*Evodia rutaecarpa*	None	DOX + Rut (20,40mg/kg), DOX (5mg/kg)	Cardiac dysfunction↓, Fibrosis↓, Oxidative stress and apoptosis↓	AKT /Nrf-2 signaling pathway↑	ZQ Liao et al (2022)[92]
DOX cardiotoxicity	Male C57BL/6 mice	Higenamine	*Aconitum carmichaelii Debeaux root*	None	DOX (5mg/kg), HG (10mg/kg)	Cardiac injury↓, Cardiomyocyte apoptosis↓, Oxidative stress injury↓	AMPK activation↑, ROS production↓	CL Jin et al (2022)[93]

(*Continued*)

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Table 1 (Continued).

Research Model	Research Subjects	Natural Compounds	Sources	Intervention Methods (in vitro)	Intervention Methods (in vivo)	Effects	Targets or Pathways	References
DOX cardiotoxicity	BALB/c female mice, H9c2 cells	Ginsenoside Rh2	*Panax ginseng*	DOX (100μM), Rh2 (10μg/mL)	DOX (2mg/kg), Rh2 (20,30mg/kg)	Histological damage↓, Heart inflammation↓, Cardiac fibrosis↓	Premature senescence↓, Myofibroblast transition↓, Endothelial-mesenchymal transition↓	JG Hou et al (2022)[94]
DOX cardiotoxicity	Male SD mice	Berberine	*Coptis chinensis Franch*	None	DOX (2.5mg/kg), Ber (60mg/kg)	Oxidative stress↓, Mitochondrial injury↓, Cardiomyocyte apoptosis↓, Differentiation of CFs into myofibroblasts↓, MMP Loss↓	Nrf2-mediated pathway↑	YY Wang et al (2023)[95]
DOX cardiotoxicity	C57/B6 male mice, NRCMs cells	Rosmarinic acid	*Rosmarinus officinalis L., Mentha haplocalyx Briq., Perilla frutescens (L). Britt*	DOX (1μM), rh Fas L (5μg/mL), RA (30μg/mL)	DOX (15mg/kg), RA (100mg/kg/d)	Cardiomyocyte apoptosis↓, Paracrine interplay between CMs and CFs↓, Fas L expression and release↓	MMP7 expression↓, NFAT activation↓	X Zhang et al (2019)[96]
DOX cardiotoxicity	Male C57BL/6 J mice, H9C2 cells, HL-1 cells	Cardamonin	*Alpinia galanga*	CAR (0,12.5,25,50,100μM)	DOX (5 mg/kg/week), DOX+ CAR (20,40,80 mg/kg/Day)	Anti-oxidative capacity↑, Cell death in HL-1 cells↓, Inflammatory response↓	Expression of Nrf2↑, Keap1 activity↓	Q Wang et al (2020)[97]
DOX cardiotoxicity	Male Wistar Albino rats	Chlorogenic Acid	*Crataegus monogyna, Vaccinium angustifolium*	None	DOX (15mg/kg), CGA (100mg/kg/day)	DOX-induced LPO↓, oxidative stress↓, Caspase-3 expression↓	Nrf2/HO-1 pathway↑	B Cicek et al (2023)[98]
DOX cardiotoxicity	Male C57BL/6 JAX mice	Schisandrin B	*Schisandra chinensis*	None	DOX (20mg/kg), Sch B (25,50,100 mg/kg/d)	MDA level↓, Nitrite level↓, ROS production↓, Oxidative stress↓, Cytokine production↓, Expression of MMP-2, 9↓	MAPK/p53 signaling↓	Thandavarayan et al (2015)[99]
DOX cardiotoxicity	Male C57BL/6 mice, HL-1 cells	Irigenin	*Belamcanda chinensis*	None	DOX (5 mg/kg), DOX +IR (10,20mg/kg/d), DOX+Car (10 mg/kg)	Oxidative stress↓, Inflammation↓, ROS generation↓	miR-425 expressions↑	LT Guo et al (2020)[100]
DOX cardiotoxicity	H9c2 cells	Icariin	*Epimedii Herba*	Ica (1,5,10,20μM), DOX (1μM)	None	ROS production↓, O_2-overproduction↓, mPTP opening↓, PDE5a activity↓	Cav-1 expression↓	M Scicchitano et al (2021)[101]
DOX cardiotoxicity	Male C57BL/6J mice	Ginsenoside Rg1	*Panax ginseng*	None	DOX (6mg/kg), Rg1 (50mg/kg/day)	Cardiac fibrosis↓, Cardiac autophagy↓, Endoplasmic reticulum stress↓	Expression of GFAT1↑, Expression of JNK1 and P70S6k↑	ZM Xu et al (2018)[102]
DOX cardiotoxicity	Male C57B6/J mice	Nootkatone	*Citrus maxima (Burm). Merr.*	None	DOX (20mg/kg), NK (90mg/kg)	Heart GAL-3↓, Heart DNA/RNA oxidative damage↓, Cardiac injury↓	NF-κB or GAL-3↓	Al-Salam S et al (2022)[103]
DOX cardiotoxicity	HL-1 cells	Hyperoside	*Hypericum perforatum L*	Hyperoside (100μM), DOX+Hyperoside (1μM+100μM), DOX (1μM)	None	Oxidative stress↓, SOD activity↑, HL-1 cells apoptosis↓, Apoptosis-related proteins↓, Anticancer property of DOX↑	ASK1/p38 signaling pathway↓	LX Chen et al (2023)[104]
DOX cardiotoxicity	H9c2 cells, C57BL/6J male mice	Calycosin	*Astragalus membranaceus*	DOX (0.5–20μM), CAL (5–160μg/mL), Nigericin (0.5–20μM)	DOX (5mg/kg/week), CAL (50mg/kg)	Mitochondrial injury↓, Oxidative stress↓, NLRP3 Inflammasome-mediated pyroptosis↓	NLRP3 inflammasome↓	L Zhang et al (2022)[105]
DOX cardiotoxicity	Male SD mice, H9c2 cells	Oxymatrine	*Sophora flavescens Aiton*	DOX+Oxymatrine, DOX (1μM)	DOX (3mg/kg), DOX + Oxymatrine (12.5,25,50mg/kg)	Oxidative stress↓, release of LDH and CK-MB↓, Cardiac CAT, SOD and GSH-Px activities↑	Apoptotic pathway↓, Stabilization of cell membrane↑	YY Zhang et al (2017)[106]

DOX cardiotoxicity	Male Wistar rats	Luteolin	*Lonicera japonica Thunb, Chrysanthemum*	None	DOX (4mg/kg), LUT (50,100mg/kg)	Serum marker levels↓, Oxidative stress↓, Apoptosis mediators↓, Bcl2/Bax ratio↑, Expression of caspase family proteins↓, phlpp1 protein expression↑, p-AKT protein expression↑	AKT/Bcl-2 signal pathway↑	Zhang, Y. et al (2020)[107]
DOX cardiotoxicity	Human heart samples, NRCMs, male C57BL/6 mice	Isorhapontigenin	*Belamcanda chinensis (L). Redouté*	DOX (1μmol/L), Isor (1–40μmol/L)	DOX (24 mg/kg), Isor (30mg/kg/day)	Cardiomyocytes apoptosis↓, Cardiac dysfunction↑	YAP1 expression↑	Wang, P et al (2020)[47]
Pirarubicin cardiotoxicity	Male Wistar rats, H92c cells	Ginsenoside F1	*Panax ginseng*	GF1 (0,10,20,40,60,80μM), THP (1,3,5,7,9 μM)	THP + GF1 (25,50mg/kg/d)	Rat body weight↑, LVSP↑, Oxidative stress↓, Vacuole degeneration↓	AKT/Bcl-2 signaling pathways↑	Y Zhang et al (2023)[108]
Pirarubicin cardiotoxicity	Male Wistar rats, H9c2 cells, HCM cells	Isoquercitrin	*Amomum villosum, Morus alba*	IQC (5,10,25,50,70,90,100,200,500μM)	THP+IQC (50,100mg/kg/d), THP (3mg/kg)	Rat body weight↑, Cardiotoxicity myocardial enzymes↓, Oxidative stress↓	Phlpp1/AKT/Bcl-2 signaling pathway↑	L Wang et al (2024)[109]
Pirarubicin cardiotoxicity	Male SD rats, CCK-8 cells, H9C2 cells	Salvianolic Acid B	*Salvia miltiorrhiza*	Sch B (25,50,100,200μM), THP (5μM)	THP + Sch B (50mg/kg)	Myocardial tissue↑, Blood biochemical indexes↓, Expression of apoptosis-related proteins↓	mPTP opening↓	HW Shi et al (2021)[110]
Arsenic Trioxide cardiotoxicity	Male BALB/c mice, HepG2 cells, HeLa cells	Salvianolic Acid B	*Salvia miltiorrhiza*	ATO (4μM), Sal B (10μM)	ATO (1mg/kg), Sal B (2 mg/kg)	Myocardial damage↓, Antioxidant capacity↑, Expression of pro-survival proteins↑	Akt and Bcl-2 proteins↑	M Wang et al (2013)[111]
Arsenic Trioxide cardiotoxicity	Male BALB/c mice	Salvianolic Acid A	*Salvia miltiorrhiza*	None	ATO (2mg/kg/day), Sal A (3mg/kg/day)	Antioxidant enzyme activities↑, SERCA activity↑, Antioxidant activity↑	Ca^{2+}-related protein expression↑	RY Wang et al (2019)[112]
Arsenic Trioxide cardiotoxicity	Male Kunming mice	Hesperidin	*Tangerine peel*	None	ATO (7.5mg/kg/day), HES (100,300mg/kg/day)	Release of the myocardial enzymes↓, ATO-induced pro-inflammatory cytokines↓	p62-Keap1-Nrf2 pathway↑	YX Jia et al (2021)[113]
Arsenic Trioxide cardiotoxicity	H9C2 cells	Protocatechuic Acid	*Hibiscus mutabilis, Salvia miltiorrhiza*	DOX (0.25–4μM), ATO (5–60μM), PCA (1–100μM)	None	Hydroperoxides levels↓, Antioxidant capacity↑, Cytotoxicity↓	TLR4 and dependent pathways↓	Shafiee, F et al (2023)[114]
Arsenic Trioxide cardiotoxicity	C57BL/6 male mice	Honokiol	*Magnolia officinalis*	None	ATO (4mg/kg), HKL (0.2mg/kg)	Oxidative stress↓, cardiomyocytes apoptosis↓, ROS generation↓, Oxidative stress↓	Sirt3/AMPK signaling pathway↑, JNK signaling↓	AL Huang et al (2022)[115]
Arsenic Trioxide cardiotoxicity	H9c2 cells, male BALB/c mice	Salvianolic Acid A	*Salvia miltiorrhiza*	ATO (2.5,10μM), Sal A (25μM)	ATO (1,2,4mg/kg), Sal A (3mg/kg)	Myocardial mitochondrial damage↓, Mitochondrial biosynthesis↑	Akt/GSK-3β signaling↑	JY Zhang et al (2018)[116]
Cyclophosphamide cardiotoxicity	Male Wistar mice	Kolaviron	*Garcinia hanburyi*	None	Cyc (50mg/kg/d), KV (200,400mg/kg/d)	Oxidative stress↓, Antioxidant enzymes↑	Lipid peroxidation↓	Omole, J. G et al (2018)[117]
Cyclophosphamide cardiotoxicity	Male Wistar rats	Capsaicin	*Capsicum annuum*	None	Capsaicin (10,20mg/kg), Cyc (200mg/kg)	Content of troponin-I↓, Content of LDH↓, Lipid peroxidation↑, Triglycerides level↓, Caspase 3 level↓	Free radicals generation↓, Inflammatory cytokines↓, Apoptotic pathway↓	Ahmed, R. An et al (2023)[118]
5-Fluorouracil cardiotoxicity	Male Wistar rats	Colchicine	*Colchicum autumnale*	None	5-FU (100mg/kg), COL (5 mg/kg)	RBC levels↑, CK enzyme↓, Oxidative stress↓, Body weight↑	MDA levels↓, TCA levels↑	Safarpour, S et al (2022)[119]
5-Fluorouracil cardiotoxicity	Male Wistar rats	Kaempferol	*Kaempferol galanga*	None	5-FU (100 mg/kg), KPF (1 mg/kg/day), KPF-NPs (1 mg/kg/day)	RBC levels↑, WBC levels↓, Oxidative stress↓, Serum cardiac enzymes↓	VEGF expression↑, Src-kinase activity↓	Safarpour, S et al (2022)[120]
5-Fluorouracil cardiotoxicity	Experimental animals	Myricetin	*Morella rubra*	None	5-FU (150mg/kg), Myricetin (25,50mg/kg b.wt).	GSH and its dependent enzymes↓, Oxidative stress↓, ROS production↓	HSP-72↑	Arafah, A et al (2022)[121]

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Table 1 (Continued).

Research Model	Research Subjects	Natural Compounds	Sources	Intervention Methods (in vitro)	Intervention Methods (in vivo)	Effects	Targets or Pathways	References
Paclitaxel cardiotoxicity	Male Wistar rats	Rutin and Hesperidin	*Tangerine peel*	None	Paclitaxel (2mg/kg), Rutin (10 mg/kg), Hesperidin (10 mg/kg)	Levels of CK-MB↓, Levels of LDH↓, Heart GSH↓	CK-MB and LDH activities↓	Ali, Y. A et al (2023)[122]
Paclitaxel cardiotoxicity	Male Wistar Rats	Naringin and Naringenin	*Citrus maxima*	None	Paclitaxel (2 mg/kg), Naringin (10 mg/kg), Naringenin (10 mg/kg)	LDH activity↓, SOD and GPx activities↑, Oxidative Stress↓	LPO levels↓, GSH levels↑, Free radicals↓	Khaled, S. S et al (2022)[123]
Cisplatin cardiotoxicity	H9c2 cells	Cyanidin	*Glycine max*	Cisplatin (5,10,20,40μM), Cyanidin (40,80μM)	None	Myocardial cells viability↑, Apoptotic rate↓, Activation of caspases↓, Expression of anti-apoptotic protein↑	ERK signaling pathway↑, Mitochondrial pathway↑	P Qian et al (2018)[124]

Notes: ↑, upregulation; ↓, downregulation; Italicized text indicates botanical sources (Latin names); Bold text represents table headers.
Abbreviations: DOX, Doxorubicin; ATO, Arsenic Trioxide; THP, Pirarubicin; APS, Astragalus polysaccharide.

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Scutellaria baicalensis, like *Coptis chinensis* and *Sophora flavescens*, is also a heat-clearing medicine. Baicalin and lignin A in it can reduce myocardial damage and oxidative stress levels in myocardial cells. They achieve this by decreasing the activity of Cytochrome-c and caspase in cardiomyocytes and activating the sirtuin 1 signaling pathway.[88]

In addition, substances in Traditional Chinese Medicines with tonic effects, such as *Panax ginseng, Astragalus membranaceus, Schisandra chinensis, Epimedium pubescens, and Ophiopogon japonicus*, can also improve the effects of related cardiotoxicity.

Ginsenoside Rg1 in *Panax ginseng* can improve the expression of GFAT1, JNK1, and P70S6k-related kinases to reduce cardiac toxicity.[102] Although the mechanism of ginsenoside Rh2 has not been clarified in current research, in vivo and in vitro experiments have found that Rh2 can reduce cardiac inflammation, cardiac fibrosis, and cardiac tissue damage.[94] Astragalus polysaccharide in *Astragalus tongolensis* can reduce cardiomyocyte apoptosis by inhibiting the activation of Caspase-3 and LC3B and activating the AMPK/mTOR (AMP-activated protein kinase/mechanistic target of rapamycin) pathway.[78]

Schisandrin B in *Schisandra chinensis* can also reduce myocardial cell apoptosis.[99] It can weaken the conduction of the MAPK/p53 (Mitogen-Activated Protein Kinase/Tumor Protein p53) signaling pathway, reduce the levels of MDA (Malondialdehyde) and nitrite in the heart, and reduce the level of oxidative stress in the heart.[99] Icariin in *Epimedium* can weaken the expression of Cav-1, inhibit the opening of mPTP (Mitochondrial permeability transition pore) and the activity of PDE5a (phosphodiesterase 5a), and reduce the level of oxidative stress in the heart.[101] Natural isoflavone 8-Formylophiopogonanone-B in *Ophiopogon japonicus* can weaken the expression of HMOX1 (heme oxygenase 1), thereby reducing the heart atrophy and cardiac dysfunction caused by DOX.[65]

Beyond the above-mentioned chinese medicines, our research summary found that a variety of TCM natural products, such as pachymic acid in *Poria cocos*,[74] honokiol in *Magnolia officinalis*,[75] cryptotanshinone in *Salvia miltiorrhiza*,[82] resveratrol in *Veratrum*,[87] cardamonin in *Alpinia officinalis*,[97] luteolin in *Lonicera japonica* and *Chrysanthemum*,[107] and hyperoside in chinese medicine such as *Forsythia suspensa, Polygonum multiflorum, and Evodia rutaecarpa*,[104] all can improve DOX-induced cardiotoxicity by affecting related signaling pathways or the expression of proteins or genes.

In general, the topic of Chinese herbal natural products alleviating DOX-induced cardiotoxicity has received much attention from researchers. Herbs such as *Panax ginseng, Astragalus membranaceus, Salvia miltiorrhiza, Scutellaria baicalensis, Coptis chinensis, and Epimedium brevicornum* contain active compounds including ginsenosides, astragalus polysaccharides, berberine, baicalin, and icariin, which have been shown to alleviate myocardial injury, reduce oxidative stress, and improve cardiac function in experimental models. Other compounds, such as honokiol, cryptotanshinone, resveratrol, cardamonin, luteolin, and hyperoside, also exhibit cardioprotective properties. These findings highlight the potential of TCM-derived natural products as promising agents in the prevention and management of DOX-induced cardiotoxicity.

Pirarubicin-Induced Cardiotoxicity

Pirarubicin (THP) is another anthracycline antibiotic that is widely used in clinical practice for the treatment of malignant tumors due to its high efficacy and broad spectrum.[125] However, it has been identified to cause various toxicity,[125] which limits its medical use.[126] The most serious toxicity of THP is its cardiotoxicity, and the mechanism of its cardiotoxicity is still under investigation, study found that cardiotoxicity caused by THP is closely associated with the occurrence of oxidative stress in cardiomyocytes.[127–129] Summarizing multiple studies, we found that natural products from TCM can be used to treat THP-induced cardiotoxicity.[108]

As another commonly used anthracycline, the research on the cardiotoxicity of pirarubicin has also attracted much attention (Figure 2). Chemicals from *Panax ginseng, Amomum villosum, Morus alba, and Salvia miltiorrhiza* can be used to treat pirarubicin cardiotoxicity. Ginsenoside F1 from *Panax ginseng* can activate AKT/Bcl-2 signaling pathways and reduce cardiac oxidative stress levels.[108] Isoquercitrin from *Amomum villosum* and *Morus alba* can activate Phlpp1/AKT/Bcl-2 signaling pathway and reduce myocardial toxicity and cardiac oxidative stress levels.[110] Salvianolic Acid B from *Salvia miltiorrhiza* can inhibit the opening of mPTP and weaken the expression of apoptosis-related proteins in the heart[110] (Table 1). These findings suggest that Chinese herbal natural products may have therapeutic potential to alleviate THP treatment-related cardiotoxicity.

Arsenic Trioxide-Induced Cardiotoxicity

Arsenic trioxide has shown a strong anti-tumor effect when used in the treatment of acute promyelocytic leukemia (APL) and glioma.[130] Arsenic trioxide can inhibit tumor growth by inducing changes in cancer cell apoptosis signals.[131] However, current clinical studies have found that Arsenic Trioxide can affect the mitochondrial membrane potential of cardiomyocytes, causing heart problems in patients.[132]

Regarding the cardiotoxicity caused by arsenic trioxide, studies have found that TCM natural products have good therapeutic effects. Salvianolic Acid A and Salvianolic Acid B in *Salvia miltiorrhiza* can improve the antioxidant capacity of the heart and reduce mitochondrial damage by affecting the expression of proteins and related signaling pathways, such as Ca^{2+}-related proteins and AKT/GSK-3β.[111,112,116] Protocatechuic acid in commonly used Chinese medicine such as Hibiscus mutabilis and *Salvia miltiorrhiza*, hesperidin in dried orange peel, and honokiol in *Magnolia officinalis* can reduce oxidative stress and damage to cardiomyocytes by affecting different signaling pathways, thereby alleviating the symptoms of cardiac toxicity caused by arsenic trioxide[113–115] (Figure 2) (Table 1).

In general, arsenic trioxide, while effective in treating certain cancers such as acute promyelocytic leukemia and glioma, has been associated with cardiotoxicity due to its effects on mitochondrial function in cardiomyocytes. TCM Natural products have shown promising protective effects against this toxicity. These findings suggest that TCM natural products may serve as potential candidates for mitigating arsenic trioxide-induced cardiotoxicity.

5-FU-Induced Cardiotoxicity

5-Fluorouracil (5-FU) is a fluoropyrimidine (FP) antimetabolite that can be used to treat a variety of solid tumors. Clinical and literature studies have shown that 5-FU has potential cardiotoxicity and may cause coronary artery spasm and other symptoms; and in severe cases, it can lead to sudden cardiac death.[133] The incidence of 5-FU cardiotoxicity is only second to anthracyclines in terms of cardiotoxicity.[120]

Comprehensive experimental studies have demonstrated that certain TCM-derived natural compounds can mitigate 5-fluorouracil-induced cardiotoxicity (Figure 2). By summarizing the literature, we found that colchicine, myricetin, and kaempferol all have the effect of reducing the cardiotoxicity caused by this type of drug. These active substances reduce the oxidative stress of myocardial cells by regulating the expression of various kinases, heat shock proteins, and growth factors[119–121] (Table 1).

In summary, while 5-fluorouracil remains a cornerstone chemotherapeutic agent for various solid tumors, its notable cardiotoxic risk-second only to anthracyclines-necessitates effective protective strategies. Accumulating evidence from experimental studies highlights that TCM-derived natural compounds such as colchicine, myricetin, and kaempferol exhibit cardioprotective effects by modulating oxidative stress pathways and key molecular targets, offering promising adjunctive options to mitigate 5-FU-induced cardiotoxicity.

Paclitaxel-Induced Cardiotoxicity

Paclitaxel is a diterpene alkaloid compound with anticancer activity. It is extensively utilized in the treatment of breast cancer, ovarian cancer, certain head and neck malignancies, as well as lung cancer.[134] Clinical records show that paclitaxel has a certain degree of cardiotoxicity, but its cardiotoxicity is rarer than that of anthracyclines and 5--fluorouracil.[135] Paclitaxel-induced cardiotoxicity is mainly manifested as subacute or acute bradycardia, heart block, and atrial or ventricular arrhythmias.[135]

Due to the low incidence of paclitaxel-induced cardiotoxicity, research on this topic remains limited (Figure 2). In terms of treating and alleviating paclitaxel-induced cardiotoxicity, TCM natural products have achieved good experimental results. We found that rutin and hesperidin from tangerine peel can reduce the levels of CK-MB (Creatine Kinase MB Isoenzyme) and LDH (Lactate dehydrogenase) in cardiomyocytes by reducing CK-MB and LDH activities, thereby improving the cardiotoxicity caused by doxorubicin.[122] Whereas naringin and naringenin in *Citrus maxima* can improve the oxidative stress and LDH activity of cardiomyocytes by affecting the levels of LPO, GSH, and free radicals[123] (Table 1).

In summary, paclitaxel, though less cardiotoxic than anthracyclines, can cause arrhythmias and bradycardia, and emerging studies suggest that natural compounds from Traditional Chinese Medicine, such as rutin, hesperidin, and naringin, may help alleviate its cardiotoxic effects by reducing oxidative stress and cardiac injury markers.

Cisplatin-Induced Cardiotoxicity

Cisplatin is a broad-spectrum chemotherapeutic agent employed in the treatment of various malignancies, including small-cell lung cancer, ovarian cancer, lymphoma, and germ cell tumors.[131] However, clinical studies have found that cisplatin has severe, acute and cumulative cardiotoxicity.[136] Experiments have found that cisplatin-induced cardiac dysfunction is associated with mitochondrial membrane depolarization and mitochondrial ultrastructural abnormalities. Based on this, mitochondrial-targeted antioxidants can be used for treatment, and substances in TCM natural products can play a similar role.[137]

At present, research on the treatment of cisplatin-induced cardiac toxicity with TCM natural products has also received much attention. According to a study, it was found that both cyanide and icariin could show protective effects against cisplatin mediated cardiotoxicity through ROS mediated oxidative stress injury[124,138] (Figure 2). Taking cyanidin as an example, cyanidin which is abstracted from *Glycine max*. It can activate the ERK signaling pathway and mitochondrial pathway, increase the expression of anti-apoptotic proteins in cardiomyocytes and inhibit the activity of caspase, and thus improve the survival rate of cardiomyocytes[124] (Table 1).

Notably, cisplatin—despite its broad anticancer use—induces cardiotoxicity linked to mitochondrial damage, and studies have shown that TCM natural products such as cyanidin and icariin can mitigate this toxicity by targeting oxidative stress and apoptosis-related pathways.

Cyclophosphamide-Induced Cardiotoxicity

Cyclophosphamide is an alkylating anticancer agent with strong cytotoxicity and immunosuppressive activity.[139] It is a widely effective anticancer agent. Studies have found that cyclophosphamide has a certain degree of cardiotoxicity for patients. Manifestations of cyclophosphamide-induced cardiotoxicity include pericardial effusions, myocarditis, pericarditis, and HF. The cardiotoxicity caused by cyclophosphamide is dose-dependent. When the patient receives a cyclophosphamide dose greater than 150 mg/kg or 1.55 g/m2/day, there is a higher risk of cardiac damage.[140]

The precise mechanisms underlying cyclophosphamide-induced cardiotoxicity remain unclear. However, studies have indicated that reactive oxygen species generated by cyclophosphamide play a critical role in impairing cardiac endothelial function.[141] The use of cyclophosphamide affects the ability of cardiac mitochondria to retain accumulated calcium, causing severe oxidative stress and nitrative stress in the heart.[117,142] Kolaviron from *Garcinia hanburyi* and capsaicin from *Capsicum annuum* can reduce cyclophosphamide-induced oxidative and nitrative stress by affecting the apoptosis pathway of cardiac myocytes and regulating inflammatory factors and free radicals, etc.[66,118] (Table 1 and Figure 2).

All in all, while cyclophosphamide is a widely used alkylating agent, its dose-dependent cardiotoxicity manifesting as pericardial effusion, myocarditis, and heart failure has been linked to oxidative and nitrative stress, and TCM-derived compounds such as kolaviron and capsaicin have shown potential in alleviating these effects by modulating apoptosis and inflammation-related pathways.

Summary

Although conventional chemotherapy agents have demonstrated substantial efficacy in tumor treatment, their clinical utility is frequently limited by cardiotoxicity, which can compromise therapeutic outcomes. Adriamycin and pirarubicin, represented by anthracyclines, as well as traditional chemotherapy drugs such as arsenic trioxide, fluorouracil, paclitaxel, cisplatin and cyclophosphamide, can cause cardiotoxicity by inducing oxidative stress, mitochondrial damage, and apoptosis. A number of studies have found that TCM active ingredients can alleviate the cardiotoxicity induced by these drugs. Currently, anthracycline drugs are mostly used to treat the cardiotoxicity caused by traditional chemotherapy drugs with TCM natural products. The active ingredients of TCM involved in relevant studies mainly include saponins, polyphenols, flavonoids, etc. These active ingredients can reduce oxidative stress, inflammatory reaction, and cardiomyocyte apoptosis by regulating related signaling pathways (such as AMPK, SIRT1, Akt, etc). However, at present, the specific mechanism of various active ingredients to alleviate cardiotoxicity is still unclear, and more clinical trials are needed to further explore.

Chemotherapy Targeted Drugs-Induced Cardiotoxicity

In recent years, targeted therapies have shown promising efficacy in cancer treatment. These agents primarily act on aberrant tumor signaling pathways and are characterized by high specificity, reduced toxicity, and an improved therapeutic index.[143] However, long-term use of targeted drugs can lead to systemic toxicity, especially cardiovascular toxicity.[144] The mechanism of action remains unclear. There are many types of tumor-targeting drugs, including HER2+ targeted therapy, tyrosine kinase inhibitors, proteasome inhibitors, MEK/BRAF inhibitors, etc. This article mainly introduces the treatment of TKI and proteasome inhibitor-related cardiotoxicity with TCM natural products.[144]

Commonly used TKIs include sorafenib, sunitinib, imatinib, etc. The cardiotoxicity associated with these types of targeted drugs is relatively rare. This article primarily focuses on the treatment of sorafenib and sunitinib with TCM natural products (Table 2). Sunitinib has more clinical applications, and its cardiotoxicity has also been studied extensively. Studies have found that polydatin in *Reynoutria japonica*, and astragaloside IV in *Astragalus membranaceus* reduce oxidative stress and inflammatory damage in cardiomyocytes by regulating NLRP3-MyD88 pathway and COUP-TFII expression, respectively.[145,146] In the study of Sorafenib cardiotoxicity, it was found that hesperetin in tangerine peel reduces cardiomyocyte apoptosis through regulating TLR4/NLRP3 signaling pathway.[147]

Cardiotoxicity of proteasome inhibitors (PIs) mainly occurs in the use of bortezomib and carfilzomib.[151] In contrast, a clinical meta-analysis found that the cardiotoxicity caused by carfilzomib is equivalent to that of bortezomib and is potentially lethal.[151] For carfilzomib-induced cardiotoxicity, zingerone in *Zingiber officinale* can reduce apoptosis of cardiac cells and inhibit the occurrence of cardiac autophagy by regulating Nrf2/HO-1 signaling pathways[148] (Figure 3).

Targeted drugs show strong selectivity and therapeutic effect in tumor treatment, but long-term use will lead to cardiotoxicity. This article reviews the cardiotoxic mechanisms of tyrosine kinase inhibitors (sorafenib and sunitinib) and proteasome inhibitors (bortezomib and caffezomib). Studies have shown that resveratrol glucoside, astragaloside IV, hesperidin and other TCM ingredients can reduce oxidative stress, inflammatory reaction and cardiomyocyte apoptosis by regulating key signaling pathways (such as NRLP3-MyD88, COUP-TFII, TLR4/NLRP3). Although TCM natural products provide a potential solution for drug-induced cardiotoxicity, the research on the mechanism of action of TCM natural products is still in the preliminary stage, and the mechanism of cardiotoxicity of targeted drugs is still exploring.[152] It is necessary to further study the mechanism of action of targeted drugs' cardiotoxicity and related TCM active ingredients, so as to better intervene the targeted drug-related toxicity (Table 2).

Overall, although the mechanisms underlying cardiotoxicity caused by targeted therapies remain under investigation, current studies have shown that several TCM natural products may be able to offer promising cardioprotective effects. Active ingredients such as polydatin, astragaloside IV, hesperetin, and zingerone have shown the ability to alleviate oxidative stress, inflammation, and cardiomyocyte apoptosis induced by tyrosine kinase inhibitors and proteasome inhibitors in preclinical studies. These findings suggest that TCM natural products may serve as potential adjuvant therapies to mitigate the cardiovascular risks associated with long-term use of targeted anticancer agents.

Monoclonal Antibody Anticancer Drugs-Induced Cardiotoxicity

Monoclonal antibodies (mAbs) are a major component of cancer therapy, and their mechanism of action is mainly focused on stimulating innate immune effects. Currently, the commonly used mAbs in clinical practice are mainly divided into conjugated and unconjugated types. Conjugated mAbs have a single pathway of action, usually relying on the direct cytotoxic effect of their payload, which is taken up by endocytosis of the receptor-bound conjugated mAbs.[153] The mechanism triggered by unconjugated mAbs is relatively complex. Different unconjugated mAbs directly bind to Fcγ receptors (FCGRs) on different types of immune cells, directly triggering different immune responses, which are mediated by differences in the binding ratio (A:I ratio) of activating and inhibitory FCGRs, which varies depending on the antibody isotype.[154] After FCGR activation, phagocytes engulf antibody-bound pathogens or cells, which is called antibody-dependent cellular phagocytosis (ADCP). FCGR (Fc Gamma Receptor) engagement and signaling activities also stimulate cell stimulation of different classes of immune cells (such as DCs, macrophages, or neutrophils), further changing the adaptive immune response. In addition, the Fc portion of the conjugated antibody can also stimulate other innate immune cells, such as natural killer (NK) cells, to directly lyse well-opsonized targets, known as antibody-

Table 2 Cardiotoxicity of Tumor-Targeted Drugs & Antibody Drugs

Research Model	Research Subjects	Natural Compounds	Sources	Intervention Methods (in vitro)	Intervention Methods (in vivo)	Effects	Targets or Pathways	References
Sorafenib cardiotoxicity	Male Swiss mice	Hesperetin	*Tangerine peel*	None	Sorafenib (100mg/kg/day), Hesperetin (50mg/kg/day, orally)	TGFβ levels↓, Caspase-3 expression↓, Collagen deposition↓	TLR4/NLRP3 signaling pathway↓, NF-kB activation↓	Zaafar, D et al (2022)[147]
Sunitinib cardiotoxicity	AC-16cells, H9C2 cells	Polydatin	*Reynoutria japonica*	Sunitinib (5,10,25,50μM), polydatin (50,100,200,400μM)	None	Leukotrienes B4↓, Reactive oxygen species and MDA↓, NLRP3 inflammasome↓	NLRP3-MyD88 pathway↓	Quagliariello, V et al (2021)[145]
Sunitinib cardiotoxicity	Male C57BL/6 mice, H9c2 cells	Astragaloside IV	*Astragalus membranaceus*	SU (4μM), ASIV (50μM)	SU (40 mg/kg/day), ASIV (10,50mg/kg/day)	Myocardial injury↓, Myocardial oxidative stress↓	COUP-TFII expression↓	WT Qin et al (2024)[146]
Carfilzomib cardiotoxicity	Male Wistar albino rats	Zingerone	*Zingiber officinale*	None	Carfilzomib (4 mg/kg), Zingerone (50 mg/kg)	Cardiac GSH, CAT, and SOD levels↑, TNFα level↓, Caspase-3 level↓	NF-kB signaling pathways↓, IL-1β and IL-6↓	Alam, M. F. et al (2022)[148]
Trastuzumab cardiotoxicity	Wistar rats	Zingerone	*Zingber officinale*	None	TZB (6 mg/kg/week), Zingerone (50,100mg/kg)	TBARS↓, Non-enzymatic antioxidant↑, Inflammatory cytokines↓	IL-2 and TNF-α expression↓	Khan G et al (2023)[149]
Trastuzumab cardiotoxicity	Male Wistar rats, HCMs cells	Ginsenoside Rg2	*Panax ginseng*	Rg2 (200μM)	TZM (6,12 mg/kg/day), Rg2 (15mg/kg)	TZM-induced apoptosis↓, TZM-induced LV dysfunction↓	Expression of proapoptotic proteins ↓, PI3K/Akt pathway↑	G Liu et al (2022)[150]

Notes: ↑, upregulation; ↓, downregulation; Italicized text indicates botanical sources (Latin names); Bold text represents table headers.
Abbreviations: TZB, Trastuzumab; SU, Sunitinib; ASIV, Astragaloside IV.

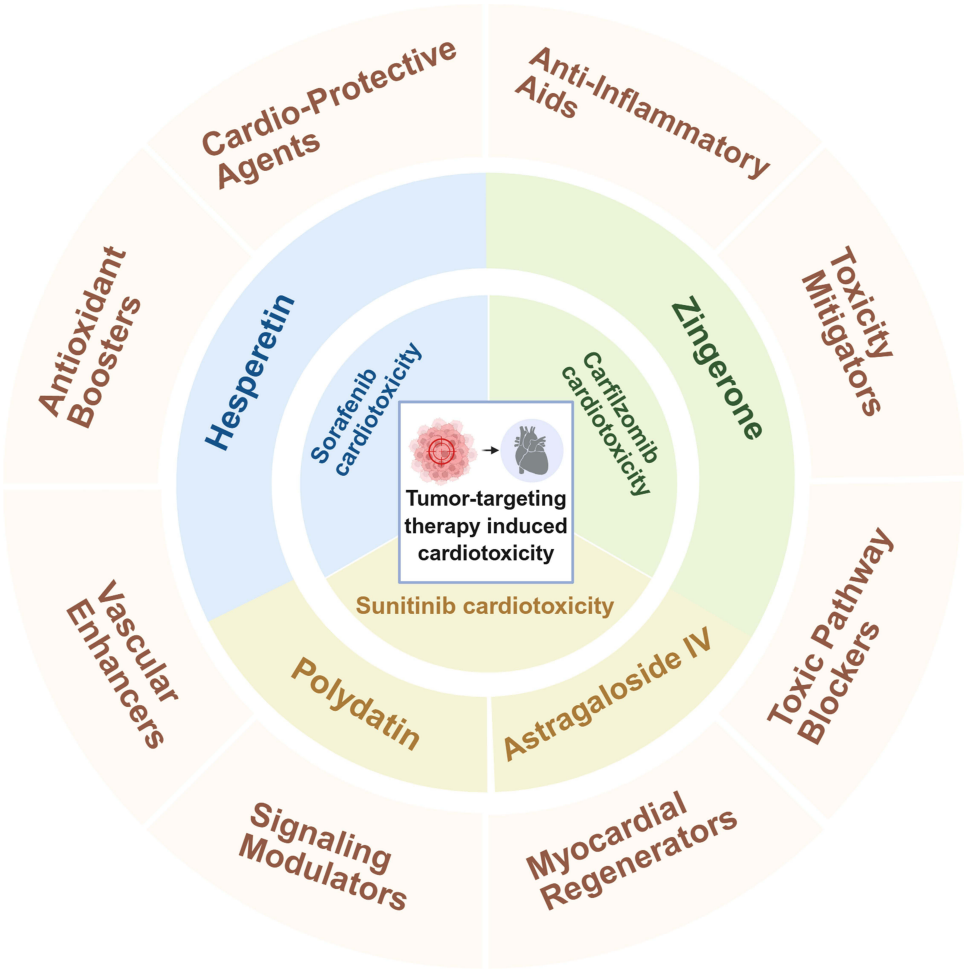

Figure 3 Protective effects of TCM (Traditional Chinese Medicine) natural products on the cardiotoxicity of tumor-targeted drugs. The general mechanism of the protective effect of TCM natural products (zingerone, astragaloside IV, polydatin, etc.) on the cardiotoxicity caused by different types of tumor targeted drugs (sorafenib, sunitinib, carfilzomib, etc.).

dependent cellular cytotoxicity (ADCC). In addition, the Fc portion of the mAb can also trigger the activation of serum proteins, such as the complement family.[155] This ability of unconjugated mAbs to block interactions and internalize receptors inhibits the transduction of oncogenic signaling and suppresses tumor growth.

Although monoclonal antibodies are currently widely used in cancer treatment, they can also cause significant cardiotoxicity. A typical example is the HER2-specific monoclonal antibody, which is a humanized antibody against HER2 (also known as ERBB2), which is overexpressed in 15–20% of breast cancers.[156] HER2 signaling increases cancer cell proliferation, tumor growth, and metastatic spread.[157] HER2-specific monoclonal antibodies often directly damage cardiomyocytes. Clinically, it has been found that the incidence of HER2-specific monoclonal antibody-induced cardiotoxicity, trastuzumab, is 15–20%, and the incidence of HF is <5%. In a continuous patient data set, 40–45% of patients treated with trastuzumab had a decrease in cardiac function of ≥10%,[158,159] and up to 75% of patients treated with trastuzumab may experience irreversible decrease in cardiac function.[160]

Other studies have found that cardiotoxicity occurs when trastuzumab is administered alone or in combination with anti-tumor drugs (especially anthracyclines),[161] and the cardiotoxicity caused by combined use is greatly increased.[161] At present, the relevant mechanism is still unclear. Experimental studies have shown that when trastuzumab is used in combination with doxorubicin, it may affect the signaling pathway related to cell autophagy, thereby affecting the normal functioning of the heart[162] (Figure 4).

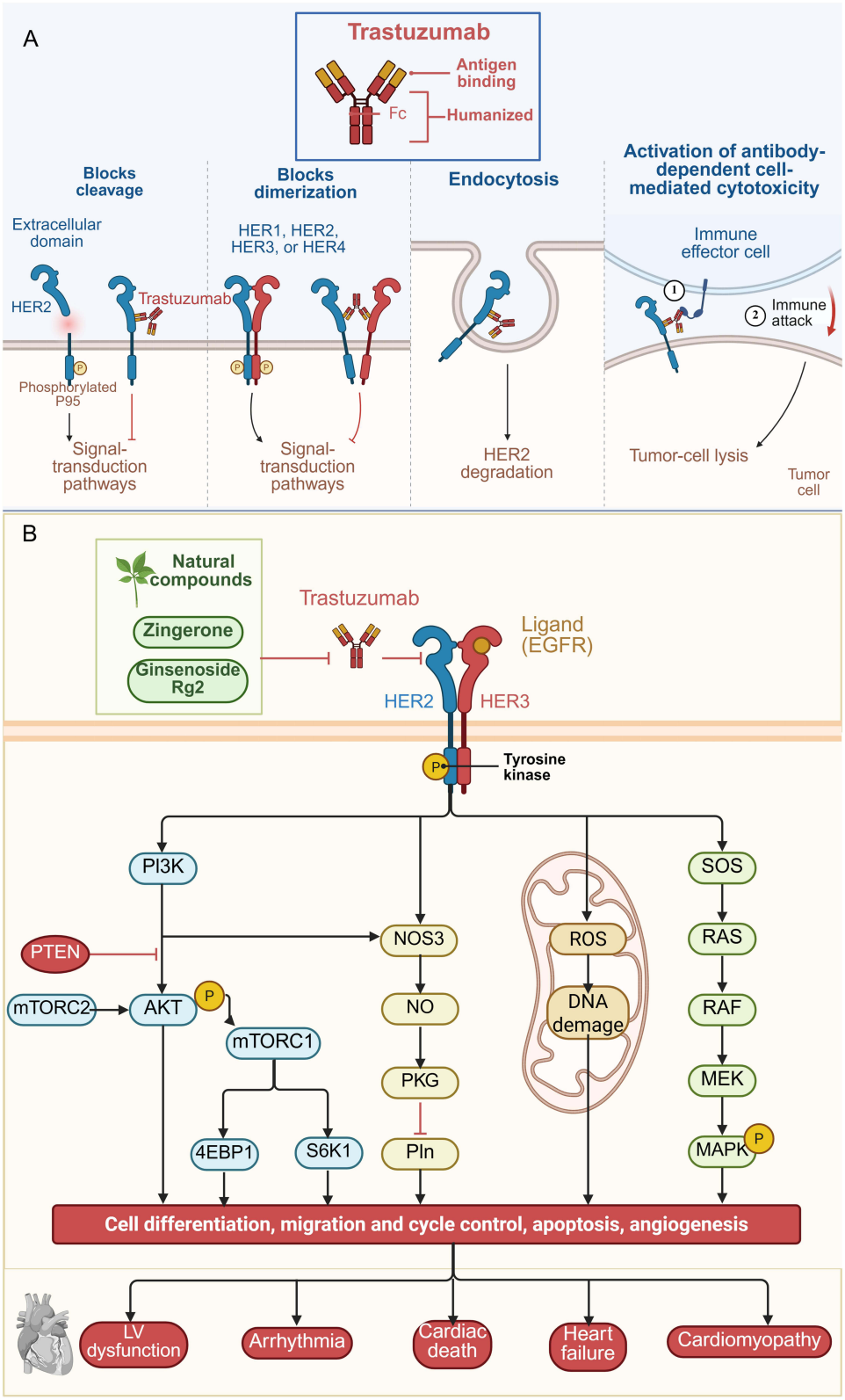

Figure 4 The mechanism of action of trastuzumab and its effect on the cardiovascular system. (**A**) Mechanism of action of trastuzumab in HER2-positive cancer cells. Trastuzumab inhibits signal transduction pathways and prevents tumor proliferation by blocking cleavage, blocking dimerization, endocytosis, and activating antibody-dependent cell-mediated cytotoxicity. (**B**) Mechanisms of natural products against trastuzumab-induced cardiotoxicity. Natural compounds such as Zingerone and Ginsenoside Rg2 inhibit multiple signaling pathways downstream of trastuzumab, including PI3K/AKT (Phosphoinositide 3-kinase/Protein kinase (**B**) and RAS/MAPK (Rat sarcoma/Mitogen-activated protein kinase), and alleviate adverse reactions caused by these signaling pathways.

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At present, cases of heart-related death are uncommon in patients receiving trastuzumab monotherapy or combination therapy.[161] However, considering the enormous burden it brings to cancer patients, the treatment of trastuzumab-induced cardiac toxicity has attracted much attention, and TCM natural products have shown good efficacy in alleviating the cardiac toxicity caused by this type of monoclonal antibody (Table 2).

Experimental studies have found that zingerone in *Zingiber officinale* can increase the expression of IL-2 and TNF-α in the heart, reduce the expression of cardiac apoptotic proteins, and thus reduce the induction of cell apoptosis by trastuzumab,[149] ginsenoside Rg2 in *Panax ginseng* can enhance the conduction of PI3K/AKT pathway and reduce the occurrence of cardiac oxidative stress and cardiac inflammation.[150]

Monoclonal antibodies (mAbs) now play an important role in tumor therapy. However, their cardiotoxicity, especially HER2-specific monoclonal antibody (trastuzumab), has become an urgent problem in the treatment of cancer patients. To address this problem, TCM natural products provide new ideas and directions for cardiotoxicity intervention with their unique advantages of multi-targets and multi-mechanisms.

The above findings indicated that TCM natural products have good effects in alleviating monoclonal antibody-induced cardiotoxicity. This not only provides a new adjuvant strategy for the comprehensive treatment of tumor patients, but also opens up a new direction for research in the field of cardio protection. Since the mechanism of action of TCM natural products in alleviating monoclonal antibody-associated cardiotoxicity is still not clear enough. Therefore, it is necessary to further clarify the mechanism of various TCM natural products in alleviating mAb-induced cardiotoxicity in order to better realize clinical application.

Current Clinical Applications

At present, the research on the anti-tumor cardiotoxicity of TCM natural products is still mainly based on basic experiments at the animal model and cell level, and human clinical research on single active ingredients is still very scarce. The clinical studies published so far are mostly focused on the evaluation of the intervention effect of whole extracts of one herd or compound injections.

For example, Shenmai injection extracted from ginseng has been shown in multiple randomized controlled trials to significantly improve electrocardiogram abnormalities (such as ST-T changes, QT interval prolongation) and myocardial enzyme indicators (such as CK-MB levels) in patients with anthracycline-induced cardiotoxicity.[163] Whole Chinese medicine extracts represented by ginseng have also been shown to delay LVEF decline and play a protective role in cardiac function in patients with breast cancer chemotherapy,[164] providing preliminary evidence for the clinical transformation of TCM natural products in the direction of anti-tumor cardiotoxicity.

Combining the mechanism research results revealed by the current basic research and the clinical efficacy of whole extracts in the population, we believe that natural products of TCM have important research value, good application potential and development prospects in the prevention and treatment of chemotherapy-related cardiotoxicity. With the continuous optimization of research design and the accumulation of evidence-based evidence, its role in precision medicine and personalized tumor treatment is also worth further anticipation.

Discussion

Clinical case studies have demonstrated that a wide range of anticancer drugs—whether traditional anthracyclines like DOX or newer immunosuppressive agents—can induce cardiovascular complications. The underlying mechanisms of such cardiotoxicity are multifactorial, involving various forms of regulated cell death in cardiomyocytes, including autophagy, apoptosis, necroptosis, ferroptosis, and pyroptosis. Due to the limited targets of conventional Western drugs, recent research efforts have increasingly shifted toward TCM natural products. With their multi-component, multi-target, and holistic regulatory characteristics, TCM offers promising potential for alleviating tumor-induced cardiotoxicity.[165–167]

Recent experimental studies have identified an increasing number of TCM-derived natural products with potential in the prevention of CTIC. These TCM natural products affect various aspects of cardiotoxicity, including inhibiting myocardial oxidative stress, alleviating myocardial ischemia-reperfusion injury, inhibiting myocardial fibrosis, regulating apoptosis and autophagy of cardiomyocytes, and alleviating myocardial mitochondrial dysfunction. The molecules and pathways involved include ROS, Noxs, Nrf2, TGF-β/Smad, NF-κB, NLRP3, P53, PI3K/AKT, MAPK, AMPK, PI3K/

AKT/mTOR, AMPK/mTOR/Ulk1, Beclin1, LC3, Atg, ERS Pathway, etc. These show the comprehensive intervention effect of TCM natural products on CTIC. Notably, the natural bioactive compounds currently under investigation include ginsenosides (Ginsenoside Rg, Ginsenoside F, etc), salvianolic acids, coptis berberine, schisandrin B, zingerone, astragalus polysaccharide, astragaloside, cryptotanshinone, matrine, sophocarpine, etc. Specifically, ginseng is extensively utilized in treating cardiovascular diseases, nervous system diseases, cancer, diabetes, and other diseases. Ginsenosides are triterpenoid glycoside compounds extracted from ginseng, which are the main active ingredients of ginseng. Among them, ginsenoside Rh2 reduces the pathological remodeling of the myocardium by reducing the transformation of fibroblasts to myofibroblasts (FMT) and endothelial-mesenchymal transition in the heart.[94] *Salvia miltiorrhiza* is a commonly used anticancer in Chinese medicine. Salvianolic acid and tanshinone in it have been found to have strong anticancer effects. Additional studies have demonstrated that its constituents can mitigate ischemia-reperfusion injury and preserve mitochondrial function, thereby reducing cardiotoxicity.[168,169] Berberine is a commonly used antibacterial natural product of TCM. It can reduce cardiotoxicity by reducing cardiac fibrosis and increasing SOD to reduce cardiac oxidative stress.[95]

Conclusions and Perspectives

In conclusion, this review systematically highlights the potential of TCM natural products in mitigating CTIC. A comprehensive analysis of preclinical studies indicates that natural compounds such as ginsenosides, salvianolic acids, and berberine exhibit multi-target cardioprotective effects by modulating oxidative stress, apoptosis, and key signaling pathways (eg, AMPK, SIRT1, Nrf2). These findings support the potential application of TCM-derived agents as adjunctive therapies to improve the cardiovascular safety profile of anticancer regimens.

With the support of modern technology, the research on TCM natural products has made significant progress, but there are also some limitations. The absence of standardized and objective quantitative evaluation criteria has resulted in TCM being classified as complementary or alternative medicine in most Western countries. Despite the accumulation of substantial basic and clinical research data, the clinical translation of TCM remains limited.[170] Moreover, potential herb-drug interactions between certain TCM formulations and conventional cardiovascular medications necessitate careful evaluation of the patient's medical history and contraindications prior to combined administration.[171] Furthermore, many clinical trials involving TCM suffer from methodological limitations, including small sample sizes, short follow-up durations, and dependence on surrogate endpoints.[170] These factors lead to uncertainty in the intervention of TCM natural products on tumor-associated cardiotoxicity. This may partially explain why, despite favorable preclinical findings, the clinical efficacy of TCM-derived natural products in managing tumor-related cardiotoxicity has yet to gain widespread recognition. Moreover, a substantial gap exists between the controlled conditions of experimental research and the complex, dynamic nature of human physiology in clinical settings. Although these natural products have shown promising effects in experimental studies, additional evidence is required to support their routine application in clinical practice. Overcoming these challenges necessitates comprehensive elucidation of the molecular interactions between TCM natural products and the complex mechanisms underlying tumor-induced cardiotoxicity. Advanced techniques such as in situ hybridization, immunohistochemistry, and gene chip analysis can facilitate the elucidation of the mechanisms of action and direct molecular targets of TCM natural product candidates. Or rely on modern analytical methods and translational models, such as using network pharmacology to analyze the possible targets of TCM natural products. These will provide the necessary preclinical basis for the widespread application of TCM natural products.

Abbreviations

CTIC, Cancer therapy-induced cardiotoxicity; TCM, Traditional Chinese Medicine; TP53, Tumor protein 53; LVEF, left ventricular ejection fraction; LAG3, lymphocyte activation gene 3; CTLA4, cytotoxic T lymphocyte associated antigen 4; ICI, immune-checkpoint inhibitor; irAE, immune-related cardiac adverse event; ALK, Anaplastic lymphoma kinase; MEK, mitogen-activated protein kinase; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; HF, heart failure; PDL1, PD1 ligand 1; PD1, programmed cell death protein 1; CTA, computed tomography angiography; NP, natriuretic peptides; NT-proBNP, N-terminal pro-BNP; cTn, cardiac troponin; PI, proteasome inhibitor; CRP, C-Reactive protein; Isor, Isorhapontigenin; DOX, doxorubicin; HMOX1, heme oxygenase 1; MDA, malondialdehyde; mPTP, mitochondrial permeability transition pore; PDE5A, phosphodiesterase 5A; THP, pirarubicin; APL, acute promyelocytic

leukemia; 5-FU, 5-Fluorouracil; LDH, Lactate dehydrogenase; mAb, monoclonal antibody; ADCP, antibody-dependent cellular phagocytosis; FCGR, Fc Gamma Receptor; NK, natural killer; ADCC, antibody-dependent cellular cytotoxicity.

Data Sharing Statement

All data generated or analyzed during this study are included in this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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