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Research Progress on Integrated Traditional Chinese and Western Medicine for the Prevention and Treatment of Anthracycline-Induced Cardiac Toxicity: A Multi-Target Regulatory Network and Clinical Translation Perspective

Yuan Wang[1], Yinhai Dai[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Department of Oncologly Surgery, The Second Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
Correspondence Author

Abstract: ***Anthracyclines form the cornerstone of chemotherapy for numerous solid tumours and haematological malignancies. However, their dose-dependent and cumulative cardiotoxicity severely limits their clinical efficacy. In Western medicine, dexrazoxane remains the only proven agent capable of effectively preventing anthracycline-induced cardiac toxicity. However, it diminishes the antitumour efficacy of anthracyclines and is associated with a range of adverse reactions, including bone marrow suppression, decreased appetite, nausea and vomiting, and diarrhoea. Against this backdrop, traditional Chinese medicine (TCM), guided by its principles of holistic thinking and syndrome differentiation, demonstrates unique potential in preventing and treating chemotherapy side effects due to its multi-component, multi-target action characteristics. It has consequently emerged as a research focus in the field of oncocardiology. Analysis in this paper indicates that traditional Chinese medicines exhibit favourable feasibility and safety profiles, offering valuable insights for developing clinical strategies to prevent and manage anthracycline-induced cardiac toxicity.***

Keywords: Anthracyclines, Cardiotoxicity, Prevention and treatment strategies, Traditional Chinese medicine, Combination therapy.

1. Introduction

Anthracyclines, such as doxorubicin (DOX) and epirubicin, form the cornerstone of chemotherapy for various solid tumours and haematological malignancies. However, their dose-dependent and cumulative cardiotoxicity, including reduced left ventricular ejection fraction (LVEF), dilated cardiomyopathy, and congestive heart failure, severely limits clinical efficacy and constitutes a major cause of long-term morbidity and mortality among cancer survivors [1]. Despite the application of cardioprotective agents such as right-sided reserpine, ongoing debates regarding their potential impact on antitumour efficacy and limitations in applicability have spurred academic circles to continually explore safer and more effective prevention and treatment strategies. Against this backdrop, Traditional Chinese Medicine (TCM), guided by its principles of holistic thinking and syndrome differentiation, has demonstrated unique potential in preventing and treating chemotherapy side effects due to its multi-component, multi-target action characteristics. Consequently, it has gradually emerged as a research focus within the field of oncocardiology.

This paper aims to systematically review recent advances in Chinese and Western medicine (particularly TCM) approaches to preventing anthracycline-induced cardiotoxicity (AIC). The review will focus on the following core perspectives: Firstly, it will conduct an in-depth analysis of the key pathological mechanisms of AIC, providing a framework for understanding the biological basis of TCM interventions; Second, systematically summarising and cross-comparing the multidimensional protective networks revealed by various TCM interventions (including compound formulas, single herbs, and acupuncture), elucidating their paradigm shift from single-target regulation to multi-system homeostasis restoration. Third, critically evaluating the strength of the evidence chain and translational bottlenecks from preclinical models to clinical studies. Literature analysis reveals that current research collectively supports the core view that TCM interventions exert cardioprotective effects by synergistically modulating multiple pathways, including oxidative stress, cell death (apoptosis, autophagy, pyroptosis, ferroptosis), mitochondrial dysfunction, and inflammatory fibrosis [1,2]; their mechanisms frequently involve epigenetic or post-transcriptional regulation of key signalling nodes (e.g., Nrf2, PI3K/Akt, AMPK, SIRT3) [2-4]; Moreover, most studies indicate that under appropriate intervention protocols, TCM protectants do not interfere with, and may even synergise with, the antitumour activity of anthracyclines [5-7]. This review will explore these areas of consensus and divergence, aiming to provide reference for deepening mechanistic research and optimising clinical practice in this field.

2. Key Pathological Mechanisms of Anthracycline-Induced Cardiac Toxicity: Biological Foundations for Dialogue Between Chinese and Western Medicine

A thorough understanding of the complex pathophysiology of anthracyclines is fundamental to evaluating and interpreting the efficacy of any protective strategy, including traditional Chinese medicine interventions. The existing literature

generally recognises that anthracycline toxicity is not driven by a single mechanism, but rather by multiple interrelated pathological processes that form a "toxicity network" [1,2]. At the core of this network lies mitochondrial dysfunction. Anthracyclines can embed themselves within mitochondrial DNA, inhibiting electron transport chain complexes I and II. This triggers explosive generation of reactive oxygen species (ROS), thereby inducing oxidative stress [8,9]. Persistent oxidative damage not only directly disrupts myocardial cell lipids, proteins, and DNA but further compromises mitochondrial membrane integrity. This leads to cytochrome c release, activating the intrinsic apoptosis pathway [10,11]. Notably, oxidative stress is closely associated with iron metabolism disorders and can induce ferroptosis—a regulated form of cell death characterised by iron-dependent accumulation of lipid peroxides. Research confirms that DOX downregulates key antioxidant defence proteins such as glutathione peroxidase 4 (GPX4), leading to ferroptosis, which plays a significant role in [12-14].

Beyond classical apoptosis and the emerging ferroptosis, other cell death pathways are also involved. Autophagy, acting as a double-edged sword, exhibits protective effects when moderately activated. However, DOX can cause autophagy flux blockage, leading to the accumulation of damaged organelles (particularly mitochondria) and protein aggregates, thereby exacerbating cellular damage [15-17]. Furthermore, inflammatory cell death pathways such as pyroptosis and the more complex PANoptosis (a cell death pathway integrating features of pyroptosis, apoptosis, and necrotic apoptosis) have been demonstrated to participate in AIC processes [18,19]. These cell death events ultimately converge on cardiomyocyte loss and cardiac remodelling. Concurrently, DOX persistently activates inflammatory pathways such as NF-κB, promoting the release of pro-inflammatory factors including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6. This recruits inflammatory cells and synergistically drives myocardial fibroblast activation and excessive extracellular matrix deposition alongside factors like transforming growth factor-β (TGF-β), leading to myocardial fibrosis and ventricular stiffness [20-22]. Impaired mitochondrial biogenesis and energy metabolism reprogramming (such as fatty acid oxidation inhibition) further diminish cardiac compensatory capacity [1,6,23]. In summary, AIC constitutes a vicious cycle involving redox imbalance, multi-modal cell death, chronic inflammation, and metabolic disorder. Traditional Chinese Medicine's holistic perspective and therapeutic principle of "strengthening the healthy and expelling the pathogenic" align precisely with the need to counteract this multi-targeted, networked toxicity. Its interventions often aim to disrupt this vicious cycle at multiple junctures, restoring cardiac homeostasis.

3. The Multidimensional Protective Network of TCM Interventions: Paradigm Shift from Single-Target to Multisystem Regulation

Building upon insights into the complex mechanisms of AIC, extensive research has focused on elucidating the protective effects and molecular basis of various TCM interventions. Collectively, these studies have delineated a multi-tiered, multi-target protective network. Its operational paradigm is evolving from "target inhibition" — targeting single pathological pathways — towards "network regulation" — modulating pivotal hub proteins to restore multi-system equilibrium.

3.1 Systemic Regulation by Compound Formulas and Patent Medicines: Paradigms of Multi-Component Synergy

TCM compound formulas constitute the primary clinical application form, employing the "sovereign, minister, assistant, and messenger" formulation principle to achieve synergistic enhancement and toxicity reduction through multi-component cooperation. In AIC prevention and treatment research, numerous classical formulas, empirical prescriptions, and modern proprietary Chinese medicines demonstrate significant protective potential.

3.1.1 Precision Intervention

Targeting Cell Death Pathways: Different formulas exhibit regulatory preferences for specific cell death patterns. For instance, Danggui Buxue Tang has been demonstrated to effectively mitigate DOX-induced myocardial injury and functional deterioration in both in vitro and in vivo models by inhibiting ZBP1 protein, thereby blocking the formation of the downstream PANoptosis complex [18]. Huangqi Guizhi Wuwu Tang has been demonstrated to simultaneously inhibit both the classical pyroptosis pathway mediated by the NLRP3 inflammasome and the non-classical pyroptosis pathway mediated by caspase-11. Network pharmacology analysis suggests IL-1β and IL-18 as key downstream targets [19]. Regarding ferroptosis regulation, both Xinjiekang and Shengmai Decoction have been reported to activate the nuclear factor E2-related factor 2 (Nrf2) signalling axis, thereby upregulating downstream antioxidant proteins such as heme oxygenase-1 (HO-1) and GPX4. This counteracts lipid peroxidation and iron accumulation, protecting cardiomyocytes [12,24]. Research on Qishen Granules has revealed a more intricate mitochondrial quality control mechanism: it promotes both the autophagic clearance of damaged mitochondria (mitochondrial autophagy) via the MDM2-p53 pathway and the biosynthesis of new mitochondria through factors such as PGC-1α, thereby maintaining mitochondrial network health in a bidirectional manner [25].

3.1.2 Hub Regulation of Core

Signalling Nodes: The efficacy of numerous compound preparations can be traced to their regulation of several core signalling nodes. E2-related factor 2, serving as a primary regulator of antioxidant stress, constitutes a common target in multiple formulations (e.g., Xinjiekang, Shengmai Injection) [12,26]. Linggui Zhugan Decoction has been demonstrated to improve mitochondrial function, reduce ROS production, and inhibit apoptosis by targeting the BTG2 protein to activate the AMPK-FOXO3a pathway [27]. Another study on Astragalus and Ginseng Granules emphasised the role of the deacetylase Sirtuin 3 (SIRT3), which enhances mitochondrial antioxidant defence by activating the SIRT3/Ac-SOD2 pathway [3]. Compound Danshen Droplet Pills and Astragalus-Salvia Cardio-Strengthening Capsules extensively involve activation

of the PI3K/Akt/mTOR pathway, which plays a central role in inhibiting apoptosis, regulating autophagy, and promoting cell survival [28,29]. Based on the theory of "heart-kidney disharmony", Huanglian Ajiao Tang was found to upregulate Ubiquilin 1 (UBQLN1) expression while alleviating myocardial cell apoptosis and autophagy dysregulation, demonstrating the alignment between traditional Chinese medical theory and modern molecular mechanisms [30].

3.1.3 Multi-omics technologies reveal synergistic mechanisms and material foundations

Modern techniques such as metabolomics and network pharmacology are extensively applied to elucidate the synergistic effects of compound formulas. Research on the Astragalus-Aconite pair demonstrated superior protective effects when combined compared to either herb alone. Metabolomics revealed this synergy stems from more comprehensive regulation of multiple metabolic pathways, including energy and amino acid metabolism [31]. Similarly, employing a strategy combining UHPLC-Q-TOF-MS/MS, network pharmacology, and experimental validation, studies have elucidated the principal active component groups within formulations such as Buxus Chinensis Powder [32], Fuzheng Huangkang Decoction [33], and Qishen Huanwu Capsules [34]. These studies have also uncovered their network-based mechanisms of action, which involve regulating multiple pathways including oxidative stress and inflammation.

3.2 Single-Drug and Active Component Target Exploration: Breakthroughs in Mechanism Elucidation

Isolating single active components from traditional Chinese medicines is pivotal for elucidating the material basis and action targets of TCM efficacy. Research into these components often yields greater depth of understanding regarding mechanisms.

3.2.1 Broad protective effects of saponins and flavonoids

Astragaloside IV, a primary active component of Astragalus membranaceus, ranks among the most extensively studied constituents. It reduces ROS production at its source by inhibiting NADPH oxidase (NOX2/NOX4) [9], inhibit ferroptosis by activating E2-related factor 2 signalling [14], and improve fatty acid metabolism by upregulating PGC-1α/PPARα [6]. Formononetin (derived from Astragalus, Aquilaria, etc.) exhibits synergistic effects when combined with Astragaloside IV [6,35]. Calycosin has been reported to mitigate cardiomyocyte pyroptosis by inhibiting NLRP3 inflammasome activation [36]. Ophiopogonin D, extracted from Ophiopogon japonicus, inhibits ferroptosis by restoring the β-catenin/GPX4 pathway [13]. Ginsenoside Rg1, loaded into engineered vesicles for targeted delivery, demonstrated anti-apoptotic potential [37].

3.2.2 Unique mechanisms of other component types

Tanshinone IIA, a representative lipophilic component of Salvia miltiorrhiza, inhibits DOX-induced apoptosis by activating the Akt pathway [10]. Its water-soluble component, Salvianolic acid A, has been found to directly target the mitochondrial enzyme GOT2, improving NADH/NAD+ balance by activating the malate-aspartate shuttle, thereby alleviating oxidative stress and exhibiting antitumour synergism with DOX. Dehydroandrographolide from Andrographis paniculata restores autophagic flux by modulating the mTOR-TFEB axis [7,15]. Cyclovirobuxine D from Buxus [8] and Tetramethylpyrazine from Ligusticum wallichii [38] primarily target improvements in mitochondrial dysfunction and oxidative damage. These studies not only validate the efficacy of specific compounds but also provide lead compounds for drug development based on natural product structures.

3.3 Acupuncture and Physical Therapy: Unique Pathways as Complementary Non-Pharmacological Interventions

Acupuncture, as a non-pharmacological therapy within TCM, has also accumulated research evidence in AIC prevention and treatment. Electroacupuncture stimulation of the Neiguan point (PC6) has demonstrated distinct cardioprotective effects. Mechanistic studies indicate that electroacupuncture modulates autophagy, inhibits apoptosis and inflammation by activating the PI3K/Akt/mTOR/ULK1 pathway while suppressing the AMPK/mTOR/ULK1 pathway [4]. Another study found that electroacupuncture at PC6 optimises nitric oxide metabolism by regulating the balance between inducible nitric oxide synthase (iNOS) and arginase 2 (ARG2), thereby mitigating cardiac injury [39]. Moreover, moxibustion has been reported to alleviate oxidative stress by reducing myocardial malondialdehyde (MDA) levels and enhancing superoxide dismutase (SOD) activity, thereby improving cardiac function in rats with DOX-induced cardiomyopathy. These studies offer potential adjunctive therapeutic options for patients unable or unwilling to increase oral medication.

4. From Evidence to Practice: Preclinical - Clinical Evidence Chain and Translational Bottlenecks

Despite the accumulation of substantial evidence from preclinical studies regarding the mechanisms of TCM in preventing and treating AIC, its translation into clinical practice faces a series of challenges. This necessitates an objective assessment of the strength and gaps within the existing evidence chain.

4.1 Consistency and Limitations of Preclinical Models

The vast majority of existing literature comprises preclinical studies, encompassing diverse animal models such as mice, rats, and zebrafish, alongside cell lines including H9c2 cardiomyocytes. These investigations provide consistent evidence across multiple levels: functionally, TCM interventions (e.g., Astragalus and Ginseng Granules [40] and Xinmai Long Injection [41]) significantly improve DOX-induced reductions in LVEF and left ventricular shortening fraction (FS);At the biochemical level, they reduce serum levels of myocardial injury markers including cardiac troponin I/total troponin T (cTnI/cTnT), creatine kinase MB isoenzyme (CK-MB), lactate dehydrogenase (LDH), and brain natriuretic peptide/N-terminal pro-brain natriuretic peptide (BNP/NT-proBNP) [21]; at the histopathological level, it mitigates myocardial cell vacuolation, necrosis,

inflammatory infiltration, and fibrosis [20,42]. These findings have been replicated across different laboratories and interventions, establishing a robust foundation for therapeutic efficacy.

Nevertheless, the limitations of preclinical models warrant attention. Firstly, most studies employ prophylactic administration (prior to or concurrent with DOX), differing from clinical practice where protective interventions often commence only after signs of cardiotoxicity emerge. Secondly, animal models typically utilise healthy young subjects, failing to replicate the complex background conditions frequently present in cancer patients, such as metabolic disorders and immunosuppression. A limited number of studies have attempted to validate protective effects in tumour-bearing models without compromising antitumour efficacy. Examples include investigations into Astragaloside IV combined with mangiferin in breast cancer models [6] and Danphenolic acid A in lung cancer models [7]. While such research holds greater clinical relevance, its volume remains insufficient.

4.2 Clinical Research Evidence: From Case Reports to Systematic Reviews

Clinical evidence primarily derives from randomised controlled trials (RCTs) and their meta-analyses, case reports, and a limited number of observational studies.

4.2.1 Randomised Controlled Trials and Meta-analyses

A meta-analysis encompassing 10 RCTs involving 748 patients demonstrated that adjunctive treatment with Chinese herbal compound formulations significantly improved LVEF in patients with acute myocardial infarction (AMI), whilst reducing serum levels of cTnI, CK-MB, and CK [42]. Another meta-analysis of Shenmai Injection (16 RCTs, 2140 patients) indicated its efficacy in improving ECG ST-T segment changes, reducing cardiac enzymes, and decreasing arrhythmias, though its effect on LVEF improvement was not statistically significant [43]. A network meta-analysis (50 RCTs) comparing eight TCM injections indicated that different formulations may exhibit distinct advantages in improving specific indicators such as ECG abnormalities, LVEF, and elevated cTnI levels [36]. These systematic reviews provide preliminary evidence-based medical support for TCM in preventing and treating AIC. Ongoing multicentre RCTs, such as the study on saffron total glycosides tablets [44], represent the direction for developing higher-quality clinical evidence.

4.2.2 Case studies and mechanism exploration

Case reports provide vivid illustrations, such as a patient with severe anthracycline-induced heart failure who experienced significant improvement in cardiac function and symptoms following treatment with Modified Fried Licorice Decoction [45]. Some clinical studies also explore mechanisms, such as the reduced incidence of cardiac toxicity observed with the combination of Shenqi Fuzheng Injection and CHOP regimen (containing anthracyclines) for lymphoma treatment [22].

5. Translational Bottlenecks and Challenges Facing Integrated Chinese and Western Medicine

Despite promising prospects, clinical translation of TCM for AIC prevention and treatment faces significant bottlenecks. Firstly, clinical research quality varies considerably. Most published RCTs feature small sample sizes and suboptimal methodological rigour, including inadequate randomisation and blinding, and inconsistent endpoint definitions (frequently using surrogate endpoints rather than hard endpoints like heart failure incidence or cardiovascular mortality), resulting in limited evidence quality [43,44]. Secondly, the impact on tumour efficacy remains a core concern. While most preclinical studies (e.g., on genistein [5], Fuzheng Huangkang Decoction [33], and Diaoxin Kang Capsules [42]) report that TCM interventions do not impair, and may even enhance, the antitumour effects of DOX, other research suggests caution is warranted. For instance, dandelion was found to protect the heart by promoting DOX efflux via P-glycoprotein (P-gp) activation, yet it simultaneously enhanced tumour cell efflux of DOX, potentially diminishing its antitumour efficacy [46]. This underscores that an ideal cardioprotective agent should exhibit tissue selectivity or synergise with DOX in antitumour activity. Thirdly, the tension between standardisation and individualisation. TCM emphasises syndrome differentiation and treatment, yet modern clinical research and application demand standardised formulations, dosages, and treatment courses. Integrating syndrome differentiation elements appropriately within large-scale randomised controlled trials (RCTs) presents a significant challenge. Finally, dosage forms and routes of administration. Chinese herbal injections (e.g., Shenmai Injection, Aidi Injection) are widely used clinically with extensive research [47,48]. However, their complex composition demands stringent quality control and safety monitoring. Optimising oral formulations (granules, capsules, decoctions) for compliance and pharmaceutical properties (e.g., bioavailability) remains a priority.

6. Discussion and Outlook

A comprehensive analysis of existing literature indicates that research into the prevention and treatment of AIC through integrated Chinese and Western medicine has progressed from descriptive observations to mechanism exploration, establishing preliminary evidence bridges from laboratory to clinical settings. Research consensus strongly supports the unique advantage of traditional Chinese medicine in counteracting the complex network toxicity of AIC through multi-targeted, multi-pathway synergistic actions. However, advancing towards higher levels of evidence-based medical support and widespread clinical application necessitates addressing common deficiencies in current research.

The foremost common shortcoming in current research lies in the superficial nature of mechanism studies. Numerous studies employ network pharmacology to predict dozens or even hundreds of potential targets and pathways. Yet subsequent experimental validation often remains confined to

examining expression changes in a handful of known proteins (e.g., E2-related factor 2, PI3K/Akt, Bcl-2/Bax), lacking confirmation of key target functions (e.g., through gene knockout/knockdown complementation experiments) and failing to provide in-depth analysis of dynamic interactions within signalling networks [2,49,50]. For instance, numerous compound formulations have been reported to activate E2-related factor 2, yet few studies have examined how different formulations activate the upstream sensing mechanisms of E2-related factor 2 or their specific regulatory effects on distinct downstream gene programmes. Secondly, disease models remain disconnected from clinical contexts. As previously noted, evaluations of protective effects under complex pathophysiological conditions—such as tumour progression or immunotherapy—are lacking, as are direct comparative studies against established protective agents (e.g., leuco-resveratrol). Thirdly, there exists a pronounced translational gap. On one hand, numerous promising active compounds (e.g., danphenolic acid A [7]) remain without clinically suitable formulations. On the other, clinical efficacy observations are often disconnected from fundamental mechanism investigations, with clinical samples rarely utilised for reverse validation or the discovery of novel biomarkers and mechanisms.

Given these shortcomings, future research should focus on three directions: Firstly, developing disease models and research paradigms closer to clinical practice. This includes encouraging the use of patient-derived organoids, humanised tumour models, and animal models reflecting ageing and comorbidities. Research designs should shift from a singular focus on "prevention" to a balanced emphasis on "prevention + treatment," systematically evaluating the impact of TCM interventions on cardiac toxicity associated with emerging anticancer therapies (e.g., immune checkpoint inhibitors, ADC drugs) and potential interactions. Second, initiate rigorously designed prospective clinical trials. Large-scale, multicentre, double-blind, placebo-controlled randomised controlled trials (RCTs) are required, with patient-centred hard endpoints such as heart failure incidence, cardiovascular mortality, and quality of life as primary outcomes. Trials should detail standardised protocols for interventions (particularly acupuncture and individualised decoctions) and actively explore biomarkers associated with protective effects (e.g., circulating miRNAs, metabolites) to enable efficacy prediction and patient stratification [2]. Thirdly, advance the modernisation and precision of traditional Chinese medicine. Employing systems biology and artificial intelligence methodologies, conduct in-depth analyses of synergistic and antagonistic networks within effective compound formulas — specifically component-component and component - target - pathway interactions—to identify core bioactive substance groups. Building upon this foundation, develop novel TCM formulations featuring defined components, controlled quality, and targeted delivery systems (e.g., nanodelivery systems [51-53]), thereby enhancing therapeutic efficacy, reducing toxicity, and overcoming challenges related to interactions with chemotherapeutic agents.

7. Conclusion

In summary, the prevention and treatment of anthracycline-induced cardiac toxicity using traditional Chinese medicine represents a dynamic and fruitful field of research. Substantial evidence indicates that interventions such as TCM formulas, active monomers, and acupuncture form a multidimensional protective network by regulating key pathological pathways including oxidative stress, ferroptosis, autophagy and cell death, mitochondrial function, and inflammatory fibrosis. The core mechanism lies in restoring the heart's intrinsic homeostasis rather than blocking single targets. This multi-system regulatory characteristic aligns closely with the complex pathogenesis of anthracycline-induced cardiomyopathy (AIC), offering a highly promising "Chinese solution" to overcome the clinical application challenges of anthracyclines.

Nevertheless, it must be recognised that the journey from potential to becoming a widely accepted standard treatment remains arduous. Current research evidence chains exhibit critical shortcomings, including insufficient depth in elucidating fundamental mechanisms, room for improvement in clinical trial design quality, and unclear pathways for translational application. Future success hinges on closer collaboration between basic scientists and clinicians, alongside employing more rigorous scientific methodologies and advanced biotechnologies to interpret and optimise traditional wisdom. We recommend that academia should dedicate efforts to both mechanism-deepening "exploratory" research and clinically-oriented "applied" studies; industry should focus on developing innovative drugs based on clearly identified active ingredients; and clinical guideline developers should, after thoroughly evaluating existing high-level evidence, prudently consider incorporating certain TCM interventions with proven efficacy and assured safety into comprehensive cardiac oncology management pathways. The ultimate objective is to provide cancer patients with treatment regimens that effectively combat tumours while maximising cardiac health preservation.

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