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Journal of
Cancer and Tumor Research

ISSN 3068-4137

Short Review

Long-Term Consequences Of Chemotherapy On Cardiac Dysfunctions And Toxicity In Cancer Survivors: Latest News And Updates On The Role Of Chronic Inflammatory Mechanisms And The Anti-Inflammatory Therapeutic Potential Of Natural Compounds And Related Analogs.

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Abstract

It is well-recognized that secondary malignancies, heart damage, short- and long-term fatigue, osteoporosis, peripheral neuropathy, hearing loss, and infertility are some of the long-term health consequences of chemotherapy in cancer survivors. Recent advances reveal new insights into the cellular mechanisms underlying the development of cardiotoxicity associated with chronic inflammation in survivors. The role of specific food ingredients, nutrients, and natural health products in preventing some of the underlying pathophysiological mechanisms is increasingly being explored as potentially promising safe and efficient solutions against those debilitating health concerns. Recent developments in chemotherapy-induced cardiotoxicity studies focus on new therapeutic targets such as mitochondrial protection. Research also emphasizes early detection with biomarker analysis and the exploration of novel cardioprotective agents that may have a better profile of safety and efficacy than dexrazoxane, the first FDA-approved (1995) therapy.

Keywords: Chemotherapy, cardiotoxicity, chemotherapy-induced cardiotoxicity (CIC), long-term effects, cancer, chronic inflammation, dietary supplement, food ingredient, natural health product, cancer survivors.

INTRODUCTION

Cardiotoxicity, cardiovascular diseases (CVDs), and hypertension emerging months or even years after undergoing chemotherapy and/or radiotherapy are well-documented phenomena within the medical community. Anthracyclines, introduced in the late 1960s, were among the first treatments identified to cause dose-dependent cardiotoxicity, frequently resulting in conditions such as cardiomyopathy and heart failure. Despite some progress made through epidemiological research since then, critical questions remain unresolved regarding the global prevalence, at-risk populations, underlying cellular mechanisms, and effective prevention strategies. For example, the exact proportion of cancer survivors who succumb to heart failure following chemotherapy or radiotherapy is still a matter of deliberation. Furthermore, to date, no cardioprotective agents have been universally approved by regulatory bodies to address this pressing issue. While dexrazoxane received approval from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 1995, its use was significantly restricted in 2011 due to reports linking it to secondary acute myeloid leukemia and myelodysplastic syndrome.

CVDs continue to be the leading cause of mortality worldwide. According to the World Health Organization (WHO), approximately 17 million individuals die annually from CVDs, accounting for nearly 30% of global deaths [1]. Cancer ranks as the second leading cause of death globally, claiming close

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Received: 01-Dec-2025, Manuscript No. JOCTR - 5287**; Editor Assigned:** 02-Dec-2025 **; Reviewed:** 30-Dec-2025, QC No. JOCR - 5287 **; Published:** 01-July-2026.
Citation: Pierre Guertin. Integrating Phenology As A Leading Indicator In Climate–Health Surveillance For Early Warning Of Seasonal Pollen And Respiratory Risk. Journal of Cancer and Tumor Research. 2026 July; 18(1).
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to nine million lives each year. Alarmingly, cancer incidence is anticipated to rise by about 70% over the next two decades, as per WHO projections [2,3]. At present, half of all people initially diagnosed with cancer survive for at least a decade, and experts predict this survival rate will significantly improve with time. However, as survival improves, so too does the likelihood of long-term complications associated with cancer therapies, including life-threatening conditions like therapy-induced CVDs. Given this trend, the burden of chemotherapy- and radiotherapy-associated CVDs is expected to escalate considerably in the years ahead [4].

A notable connection exists between chemotherapy-induced cardiotoxicity (CIC) and other debilitating issues such as fatigue—both increasingly acknowledged as significant side effects of cancer treatment. These complications often arise from shared biological pathways, including oxidative stress, inflammation, and compromised heart function. Cardiotoxicity itself can manifest through symptoms such as abnormal fatigue, shortness of breath, and swelling, all of which contribute to a patient's overall sense of physical exhaustion and reduced quality of life.

METHODS

Key terms such as cardiotoxicity, chemotherapy, 2025, inflammation, natural health products, dietary supplements, nutrients, and food ingredients were utilized to identify original articles published between January 1, 2025, and November 24, 2025. The search was conducted across databases including PubMed, Google Scholar, and ClinicalTrials.gov.

CHEMOTHERAPY-INDUCED CARDIOTOXICITY (CIC)

The first drugs found (1971) to cause dose-dependent cardiotoxicity (e.g., cardiomyopathy, heart failure) in cancer survivors were anthracyclines. Unfortunately, the mechanisms of CIC remain incompletely understood although significant advances have been made in recent years. We now know that oxidative stress from reactive oxygen species (ROS), direct cardiac injury via DNA damage (particularly with anthracyclines and platinum compounds), and mitochondrial dysfunction play an important role. In 2025, scientists reported evidence suggesting unsuspected roles for sodium glucose cotransporter 2 (SGLT2) inhibitors, PCSK9 inhibitors, and related combinatorial therapeutic approaches in treating long-term CIC [5]. Other natural substances (listed below) with comparable therapeutic effects have also been identified this year (**Table 1**).

Table 1. Paradigms of studies (2025) with natural/natural-derived ingredients on CIC.

Names	Type	Doses	Duration	Models	References 2025
SGLT2i	flavonoid	-	-	-	Quadriariello&al
PCSK9i	antibody	-	-	-	Quadriariello&al
TNFAIP8	cardamonin-ind.*	-	-	KO mice	Cheng&al
Exendin-4	salivary peptide	20nM	3 hours	H9C2 rat cell	Khine&al
Vitamin B17	apricot seed	300mg/kg	14 days	mice	Salama&al
Melanoxetin	polyphenolic	10mg/kg	14 days	rats	Hassan&al
Glycitein	isoflavone-soya	-	24 hours	rats	Jingya&Peng
Imperatorin	furocoumarin	12-25mg/kg	6 weeks	rats	Zhang&al
Lycopene	carotenoid	5mg/kg	-	mice vivo,cell	Huang&al
Puerarin	isoflavonoid	15mg/kg	1 day	mice vivo,cell	Feng&al
AVL	perennials-onion	-	-	H9C2 mice cell	Song&al
C3G	anthrocyan.-corn	135uM	48 hours	HL-1 cell	Cappellini&al
Blueberry	anthrocyan.berry	80mg/kg	14 days	rats	Shaker&al

** 'Ind.' means 'induced inhibitor or activator'*

SGLT2i

Originally designed to lower blood glucose, the SGLT2 inhibitor class of medications has lately been demonstrated indeed to produce clinically relevant effects for heart failure and renal protection. First identified in 1835 as phloretin-2'-O-glucoside or phlorizin, this flavonoid glycoside molecule was extracted from apple tree bark. Due to its relatively low biovailability, first phlorizin-based analogs derived from C glucoside were developed 15 years ago (e.g., canagliflozin [6]). Subsequently, canagliflozin was promptly authorized for sales in the United States (2013) and Europe (2012) to treat hyperglycemia. In 2025, a potential role for this class of drugs in cancer therapy has been explored (Quadriariello et al. 2025) – e.g., a few clinical trials are currently being conducted indeed (e.g., NCT06443645, NCT07018622, NCT06341842, NCT070765, NCT06888505) to assess clinically the effects of

SGLT2 inhibitors against anthracyclines-induced toxicity in vital organs such as the heart.

PCSK9i

The proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor is another class of compounds derived from natural ingredients – especially berberine found in goldenseal, barberry, and Oregon grape. It is known originally as a substance capable of lowering cholesterol levels (e.g., alirocumab FDA-approved in 2015). In 2025, it was postulated for the first time to potentially play a role as adjuvant in cancer therapy especially when used in combination. Indeed, SGLT2 + PCSK9 inhibitors were found to exert synergistic effects on endothelial function in diabetics [7]. Given 1) that SGLT2i and PCSK9i exhibit mechanistically, complementary and potentially synergistic actions across several shared pathophysiological pathways and, 2) that a dual therapeutic strategy targeting both glucose and lipid axes, via SGLT2i and PCSK9i, emerges as a biologically sound and clinically compelling intervention for cardioprotection in cancer, it was postulated in 2025 that their used as a combination therapy may probably yield additive effects on atherosclerotic plaque regression, endothelial repair, and arterial stiffness reduction in a wide variety of indications although no clinical trial has yet been launched to assess this novel promising hypothesis [5].

TNFAIP8 and cardamonin

Tumor necrosis factor-alpha-induced protein 8 or TNFAIP8 is a recently identified human protein, a downstream product of TNF alpha, known for its role in regulating cell death, inflammation, and immunity. Although it is not found in food, plants or natural ingredients, there is compelling evidence suggesting that its expression can be inhibited by cardamonin, a chalcone-type flavonoid found in plants such as the Alpinia katsumadai and Alpinia conchigera [8]. Interestingly, blocking the expression of TNFAIP8 in KO mice was reported to significantly reduce doxorubicin (DOX)-induced cardiotoxicity in adult animals [9].

Exendin-4

Exendin-4 (Ex-4), a glucagon-like peptide-1 (GLP-1) receptor agonist emerged as a potent modulator of mitochondrial dysfunction and cellular stress through suppression of the p53 and NF-κB pathways. It is not found in food or natural ingredients although it is a peptide originally isolated from a natural compound – that is the saliva of the Gila monster. A synthetic version, called exenatide, has already been FDA-approved for type-2 diabetes. Hnin Ei Ei Khine and colleagues found that Ex-4 administration markedly restored mitochondrial bioenergetics that was correlated with upregulation of markers involved in mitochondrial biogenesis (PGC1α, NRF1, ATP5A) and fusion process (OPA1, MFN1), accompanied by downregulation of mitochondrial fission markers (DNM1, FIS1) in adult rodents [10]. Its role in preventing or reducing chemotherapy-induced cardiotoxicity was tested in cardiomyoblast cell lines treated with cisplatin suggesting the existence of a clinically relevant role for cancer survivors.

Vitamin B17

Interestingly, natural food ingredients have also been found to provide protection against cardiac toxicity. Vitamin B17 was found in rodents to lower elevated troponin I levels and to normalize creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH). Oxidative stress was reduced, evidenced by a 50% decrease in MDA and increases in GSH and SOD activities. Gene analysis showed reduced expression of pro-inflammatory and fibrotic markers (IL-1β, NF-κB, TGF-β, MMP-9) and enhanced P53 expression [11].

Melanoxetin

Melanoxetin (MEL) is a natural polyphenolic compound with diverse biological abilities shown capable to largely reverse cardiac toxicity induced by flumethrin by virtue of its anti-inflammatory, antioxidative and anti-apoptotic effects on Toll-like receptor 4 (TLR4), nuclear factor-kappa B (NF-κB), NLRP3, high mobility group box 1 (HMGB1), tumor necrosis factor-α (TNF-α), receptor for advanced glycation end-products (RAGE) interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2) & interleukin-6 (IL-6), reactive oxygen species (ROS) and malondialdehyde (MDA)[12].

Glycitein

Glycitein treatment was found to scavenge free radicals induced by DOX and to render lipid-lowering, anti-inflammatory, antiapoptotic, and cardioprotective effects in the DOX-administered rats [13].

Imperatorin

Imperatorin (IMP), a furocoumarin ingredient extracted from Angelica dahurica, was found to partially prevent anthracycline (e.g., DOX)-induced cardiotoxicity [14]. 25 mg/kg and 12.5 mg/kg IMP relieved or suppressed DOX-induced reductions in heart weight, cardiac histopathology, elevated serum levels of LDH, AST and CK-MB as well as upregulated mRNA levels of NLRP3, CASP1, GSDMD, ASC, IL-1β and IL-18, elevated protein expressions of NLRP3, ASC, GSDMD-FL, GSDMD-N, pro caspase 1, caspase 1 p20, pro IL 1β and IL 1β in heart tissues, as well as increased serum levels of pro-inflammatory cytokines including IL-1β and IL-18.

Lycopene

Lycopene (LYC) is a dietary nutrient that plays a protective role in various cardiovascular diseases [15]. It was found to reduce

collagen content and fibrosis by inhibiting the expression of matrix metalloproteinase 2 (MMP-2) and MMP-9. Additionally, LYC inhibited reactive oxygen species (ROS) production by upregulating antioxidant enzymes expression. LYC enhanced B-cell lymphoma 2 (Bcl-2), but reduced apoptosis positive cells by reducing tumor protein 53 (p53), Bcl-2 associated X protein (Bax), and cleaved-Caspase 3 (c-Casp3) levels. Besides, LYC reduced inflammatory cytokine levels through activating peroxisome proliferator activated receptor gamma (PPARγ)

Puerarin

Although Puerarin (Pue), a known effective inhibitor of tumor cell proliferation, failed to be developed clinically because of poor water solubility and bioavailability, a novel puerarin nanoparticle(nanoPue)wasshowntoalsostronglyinhibittumor growth and enhance the chemotherapeutic effect of DOX in HCC models. It increased the perivascular coverage within the tumors, decreased the expressions of NSUN2, p-AKT, VEGFA, and MMP-9, and reduced endothelial cell tube formation [16].

Allium victorialis L.

The water extract of Allium victorialis L. (AVE), also known as alpine leek or victory onion, was generally known for its pain-relieving effects. It was found this year to also normalize DOX-induced abnormal heart rate, RR interval, cQT prolongation, and segmentation in mouse cardiomyocytes (H9c2 cells) via unclear mechanisms [17].

C3G

Cyanin-3-O-glucoside or C3G is a specific flavonoid and a polyphenol found in several types of fruits and vegetables (e.g., black soybeans, purple corn, cranberries, red cabbage). An ACN-rich diet from purple corn, which mainly contains cyanidin 3-glucoside (C3G) and its acetylated derivatives, has been shown to be effective in reducing DOX-induced cardiotoxicity in mice via actions upon AMPK and P53 mediated mechanisms [18].

Blueberry extract

Blueberry extracts are polyphenols (anthrocyanins) generallly known for significant antioxidant properties. Furthermore, 80.0 mg/kg blueberry extract was shown recently to attenuate DOX-induced oxidative stress in rats via actions upon elevated serum biomarkers cTnT, NT-proBNP, MPO and cardiac MDA, TOP II [19].

DISCUSSION

This concise review highlights new evidence indicating that a persistent inflammatory response triggered by chemotherapy, driven by mechanisms such as oxidative stress and cytokine release, results in cardiomyocyte loss, fibrosis, endothelial dysfunction, and an elevated risk of heart failure. The findings point to a range of well-established and newly emerging cellular pathways that contribute to the protective effects of dietary supplements and natural health products against chemotherapy-induced cardiotoxicity (CIC). Key mechanisms and markers involved include cTnT, NT-proBNP, MPO, cardiac MDA, TOP II, AMPK, P53, NSUN2, p-AKT, VEGFA, MMP-9, MMP-2, ROS, Bcl-2, Bax, c-Casp3, PPARγ, LDH, AST, CK-MB, NLRP3, Casp-1, GSDMD, ASC, IL-1β, IL-18, pro-caspase 1, caspase 1 p20, TLR4, NF-κB, HMGB1, TNF-α, COX-2, IL-6, CK-MB TGF-β, PGC1α, NRF1, ATP5A, OPA1, MFN1, DNM1, and FIS1.

It is not unreasonable to consider that the mechanisms mentioned above could play a role in both protecting against CIC and reducing CRF, either directly or indirectly. While cancer is often associated with aging, it is important to recognize that many younger individuals also face specific forms of cancer, such as lymphomas. Chronic inflammation, which is particularly prevalent in older adults—referred to as inflammaging—is characterized by elevated levels of IL-6 and CRP. This suggests that the impact of chronic inflammation and the potential advantages of the aforementioned products might be more pronounced in elderly patients. Moreover, although pediatric patients are known to be susceptible to cardiotoxicity, older individuals with concurrent risk factors may experience a lower threshold for cardiotoxic effects [20].

CONCLUSION

In recent years, various nutrients such as coenzyme Q10, selenium, Vitamin E, omega-3 fatty acids, and berberine have been reported to provide some degree of protection against chemotherapy-induced cardiotoxicity (CIC). New research findings from 2025 offer additional evidence indicating that other food components and nutrients might also play a significant therapeutic role in mitigating cardiotoxicity among cancer survivors. These include blueberry extract, purple corn extract, Allium victorialis L., nanopuerarin, lycopene, imperatorin, glycitein, melanoxetin, Vitamin B17, and exendin-4. However, as most of these mechanisms have primarily been explored in animal models, further clinical trials and studies using human tissues are necessary to confirm and validate their effects.

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