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CONTEMPORARY REVIEW

Vitamin C as a Cardioprotective Agent Against Doxorubicin-Induced Cardiotoxicity

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ABSTRACT: Doxorubicin is used and highly effective chemotherapeutic agent; however, its clinical utility remains limited by dose-dependent cardiotoxicity, presenting a significant challenge in cancer management. Growing preclinical research and clinical evidence suggest that the antioxidant vitamin C (ascorbic acid) may confer cardioprotective effects against doxorubicin-induced cardiotoxicity. In this review, both preclinical and clinical research has been synthesized to assess the potential role of vitamin C in mitigating doxorubicin-induced cardiotoxicity. Preclinical data have routinely indicated that vitamin C can reduce oxidative stress, preserve mitochondrial function, and modulate proinflammatory cytokine levels. Additionally, animal models have demonstrated promising results in maintaining cardiomyocyte structural integrity. In this capacity, vitamin C may be an effective adjunctive therapeutic for attenuating cardiac injury. Conversely, the clinical data remain variable, with emerging evidence supporting the notion that vitamin C can serve as a safe adjunct that preserves cardiac function during anthracycline therapy. Further investigation is warranted to optimize dosing, timing, and delivery routes and better elucidate the exact molecular mechanisms of these protective effects. This review emphasizes key molecular mechanisms, such as oxidative and nitrosative stress, mitochondrial dysfunction, and inflammatory signaling, in the myocardium, and examines the role of vitamin C supplementation, alone or in combination with doxorubicin, on myocardial damage markers and cardiomyocyte viability.

Key Words: cardioprotection ■ doxorubicin-induced cardiotoxicity ■ oxidative stress ■ reactive oxygen species ■ vitamin C

Doxorubicin (Figure 1) is a widely used chemotherapeutic agent recognized for potent antitumor efficacy in a variety of cancers.[1] However, the clinical utility of doxorubicin has been historically constrained by dose-dependent adverse effects, most prominently its cardiotoxicity.[2] Doxorubicin-induced cardiotoxicity (DIC) is driven by oxidative stress, mitochondrial dysfunction, and apoptotic signaling that can lead to irreversible damage to cardiac tissues, ultimately resulting in congestive heart failure in some patients.[3,4]

Efforts to mitigate these adverse effects have focused on antioxidant strategies. Vitamin C (ascorbic acid) has been extensively studied and garnered attention in this context due to its established antioxidant properties and ability to neutralize reactive oxygen species (ROS).[5,6] One investigational strategy to mitigate DIC has involved the coadministration of vitamin C (Figure 1). Research in this area has explored whether vitamin C can preserve cardiac function while maintaining the therapeutic efficacy of doxorubicin.[5]

Despite promising preclinical data suggesting a protective role of vitamin C against DIC, clinical studies have yielded mixed results.[7] Some trials have demonstrated a reduction in cardiotoxicity markers with vitamin C supplementation, whereas others have shown no significant benefits.[8] These discrepancies highlight the need for further investigation into the mechanisms through which vitamin C interacts with doxorubicin in cardiac tissues.[1]

This literature review presents a comprehensive study of preclinical and clinical trials that consolidates existing information on the role and impact of vitamin C

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Nonstandard Abbreviations and Acronyms

DHA	dehydroascorbic acid
DIC	doxorubicin-induced cardiotoxicity
eNOS	endothelial nitric oxide synthase
KEAP1	Kelch-like ECH-associated protein 1
NO	nitric oxide
Nrf2	nuclear factor erythroid 2-related factor 2
p38	p38 mitogen-activated protein kinase
ROS	reactive oxygen species
SOD	superoxide dismutase
vitamin C	vitamin C

on DIC. The review examines various approaches and discoveries to elucidate the antioxidative processes of vitamin C, aiming to contribute to the management of cardiotoxicity in cancer by demonstrating the potential significance of vitamin C as a therapeutic adjunct in doxorubicin-based chemotherapy (Figure 2). Additionally, this analysis identifies current knowledge gaps and potential future research initiatives to enhance cardiovascular outcomes for cancer patients.

DOXORUBICIN OVERVIEW

Doxorubicin, an anthracycline antibiotic derived from *Streptomyces peucetius* var. *caesius*, serves as a cornerstone in treating various cancers, including solid tumors and hematologic malignancies.[9] This effective anticancer agent inhibits DNA replication and promotes apoptosis by intercalating into DNA and blocking topoisomerase II.[1] The pathogenesis of DIC involves the generation of reactive ROS, lipid peroxidation, mitochondrial dysfunction, and subsequent apoptosis of cardiac myocytes.[10] These effects occur as doxorubicin undergoes redox cycling in cardiac cells,

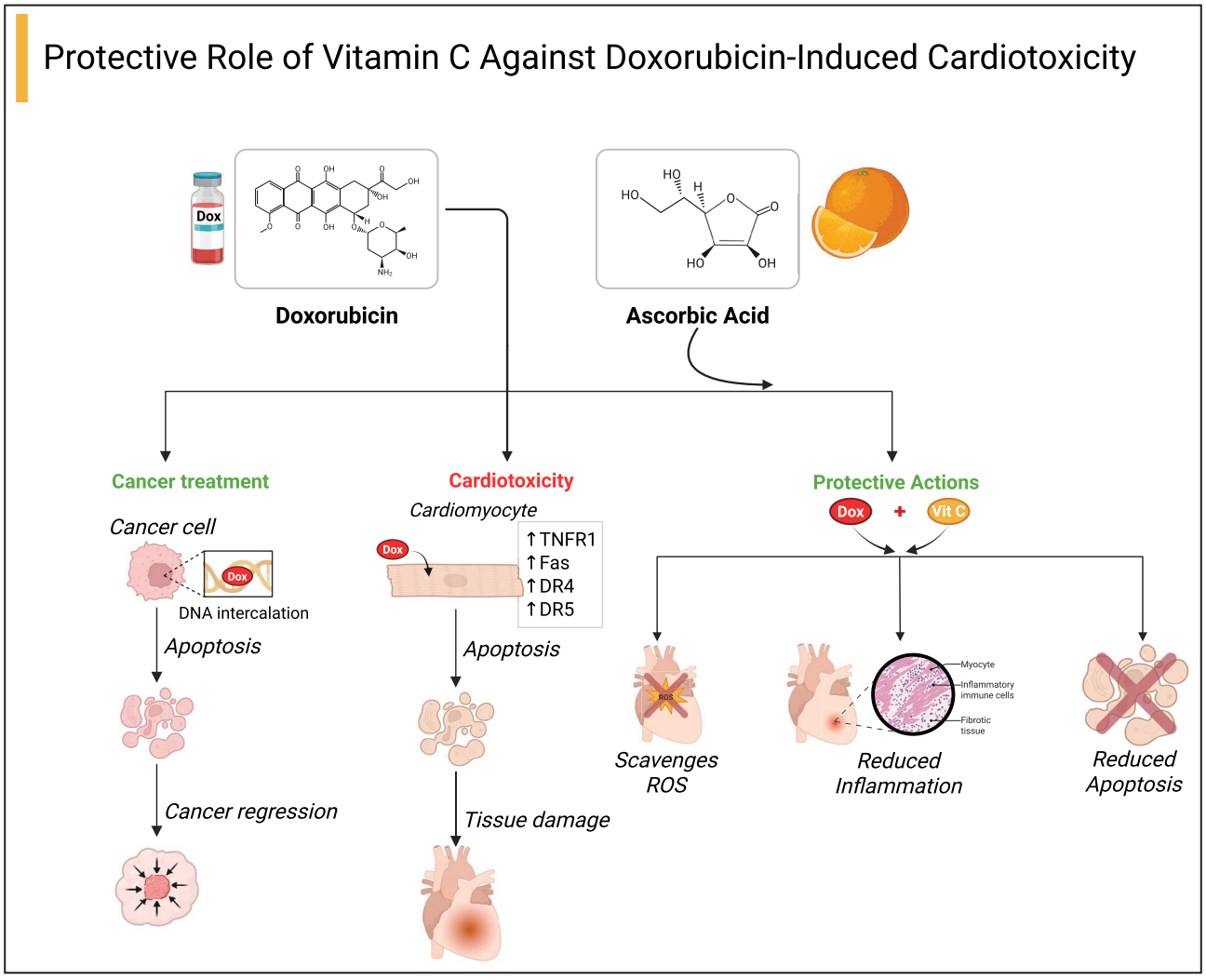

Figure 1. Schematic demonstration of the protective role of vitamin C against doxorubicin-induced cardiotoxicity.
DR indicates death receptor; ROS, reactive oxygen species; and TNFR1, tumor necrosis factor receptor 1.

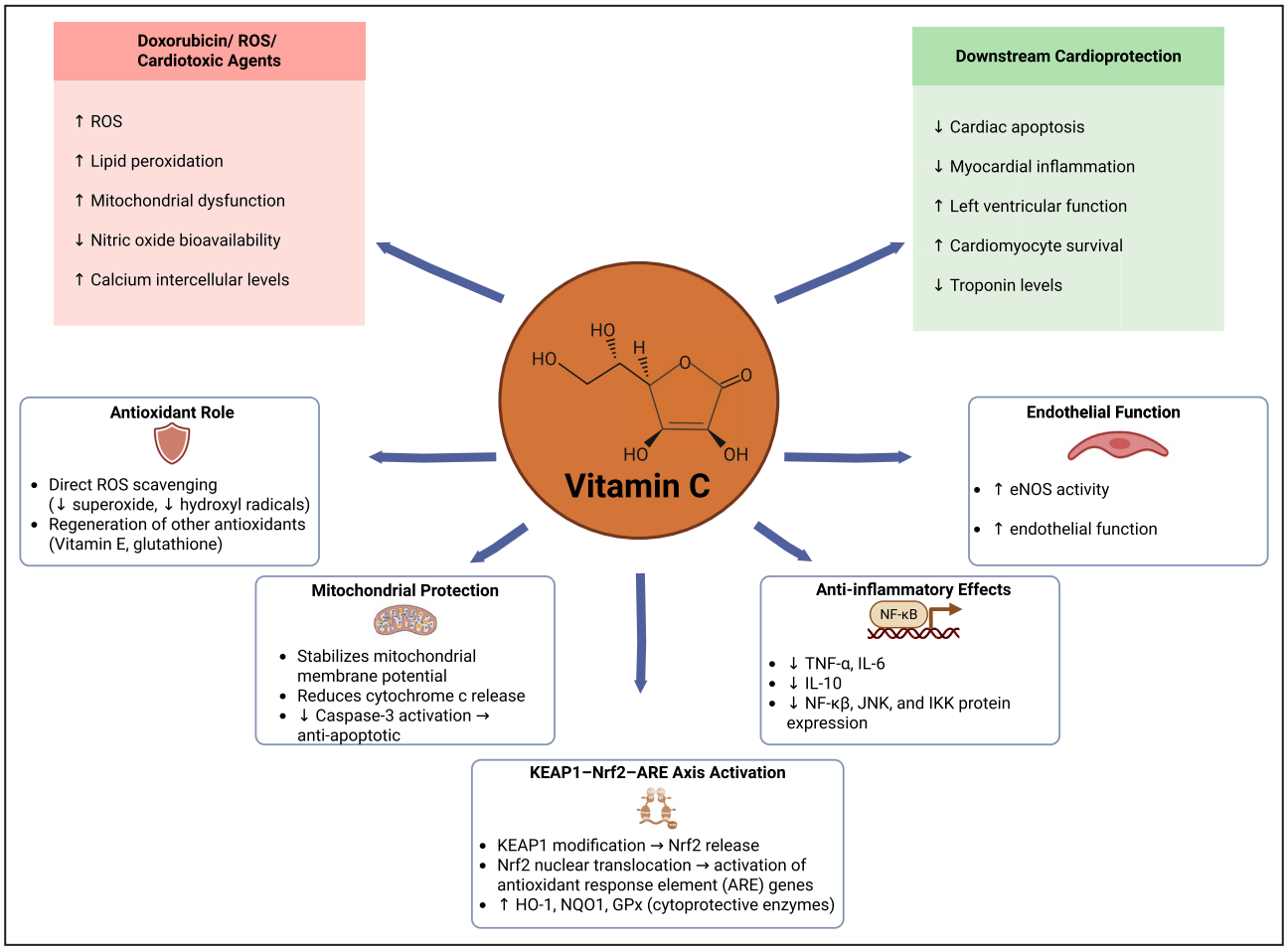

Figure 2. Schematic demonstration of the cardioprotective mechanisms vitamin C.
ARE indicates antioxidant response element; eNOS, endothelial nitric oxide synthase; GPx, glutathione peroxidase; HO-1, heme oxygenase-1; IKK, IκB kinase; IL, interleukin; JNK, c-Jun N-terminal kinase; KEAP1, Kelch-like ECH-associated protein 1; NF-κB, nuclear factor kappa B; NQO1, NAD(P)H:quinone oxidoreductase; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; and TNF- α, tumor necrosis factor alpha.

resulting in excessive production of ROS that overwhelm the limited antioxidant defenses of the heart.

Anticancer Mechanism of Action

Predominantly, doxorubicin enters cells by passive diffusion, and once inside it intercalates into DNA and inhibits topoisomerase II. These activities disrupt DNA replication and transcription, leading to DNA strand breaks and activating apoptotic pathways.[11] Furthermore, doxorubicin induces oxidative stress by increasing the production of ROS, which leads to further DNA damage and triggers lipid peroxidation, exacerbating cellular injury.[12,13]

DNA Intercalation and Topoisomerase II Inhibition

Doxorubicin preferentially intercalates in regions where GC base pairs are in proximity, likely because of the formation of hydrogen bonds between guanine and doxorubicin.[14] This intercalation causes the DNA to unwind, resulting in positive supercoiling of the DNA helix.[15] Clinically significant medication dosages are necessary to detect doxorubicin–DNA adducts[16]; however, these adducts are not believed to represent the primary mechanism by which doxorubicin exerts its anticancer effects.[11]

Topoisomerases are essential for preserving the proper DNA structure during transcription and replication. When supercoiling arises from the processes, topoisomerase type I or type II enzymes introduce single- or double-strand breaks, allowing the DNA to unwind and serve as an effective template.[17] Although doxorubicin inhibits topoisomerase I to some degree, its principal target is topoisomerase II. At very low concentrations <1 μmol/L, doxorubicin prevents DNA relegation by trapping topoisomerase II enzymes in its covalently bound state at double-strand breaks.[1] Moreover, treatment of cancer cells with doxorubicin leads to the

upregulation of DNA damage response pathway genes, a consequence of the formation of both single-strand breaks and double-strand breaks s in the DNA.[18]

Induction of Apoptosis in Cancer Cells

The electron transport chain and peroxisome metabolism produce ROS in aerobic organisms.[19] Although ROS normally functions as cellular messengers, an excess can damage DNA and lead to senescence, cell death, or halt in the cell cycle.[20] In cardiac cells, doxorubicin interacts with cardiolipin, a phospholipid in the inner mitochondrial membrane, thereby intensifying ROS production. This increase in oxidative stress results in mitochondrial damage and triggers apoptosis through mechanisms such as the upregulation of death receptors and ligands.[21]

Ceramide overproduction may improve the anticancer activity of doxorubicin by increasing ROS production, leading to a greater degree of DNA damage and apoptosis. Ceramides facilitate this process by stimulating the release of proapoptotic proteins from mitochondria, thereby amplifying apoptotic pathways.[22]

Mechanisms of Doxorubicin-Induced Cardiotoxicity

DIC limits the clinical use of this effective chemotherapeutic agent. Its complex pathophysiology is driven by several interrelated mechanisms.

Oxidative and Nitrosative Stress

Excessive lipid peroxidation and ROS generation in cardiac tissues are central to the development of DIC. In anthracyclines, the aglycone moiety forms complexes with iron that facilitate marked increases in ROS production and intensify oxidative damage in the heart.[23]

Increased NOS (nitric oxide synthase)-dependent ROS production is another critical culprit to DIC. When doxorubicin binds to the eNOS (endothelial NOS) reductase enzyme, a doxorubicin semiquinone radical is generated through a 1-electron reduction reaction catalyzed by flavoenzymes (ie, mitochondrial NADH [nicotinamide adenine dinucleotide] dehydrogenase and NADPH [nicotinamide adenine dinucleotide phosphate]-cytochrome P450 reductase).[13] This reaction disrupts the normal balance between NO and superoxide by reducing NO levels, increasing superoxide production, amplifying oxidative stress, and contributing to cardiotoxicity. Previous studies have demonstrated that doxorubicin decreases eNOS protein and mRNA levels, activating redox processes that cause cell death. Specifically, it has been shown that transgenic animals overexpressing eNOS produce higher levels of doxorubicin-induced cardiac ROS, whereas eNOS knockout models produce less ROS and use of antisense eNOS mRNA decreases caspase-3 activity, offering cardioprotection.[24,25]

Mitochondrial Dysfunction

Doxorubicin attaches to the mitochondrial membrane, producing an irreversible complex with cardiolipin, a critical protein for the normal functioning of the electron transport chain, which is required for energy generation. This binding affects cardiolipin function, causing superoxide radical production and mitochondrial dysfunction, worsening heart injury.[26] Furthermore, doxorubicin inhibits mitochondrial formation and metabolism by downregulating the expression of the *GATA4* gene, which triggers apoptosis.[21] Ceramide accumulation and DNA damage from doxorubicin can amplify apoptotic signaling in both cancer cells (as discussed in Section 2.1.2) but also in cardiac tissue. The conjunction of oxidative stress and mitochondrial injury is a hallmark of cardiomyocyte apoptosis in DIC.

Iron Accumulation and Iron-Mediated Oxidative Stress

Doxorubicin chelates iron ions, leading to their accumulation in cardiomyocytes. This excessive iron promotes oxidative stress via the Fenton process, which produces highly reactive hydroxyl radicals from hydrogen peroxide. In addition, both doxorubicin and its metabolite, doxorubicinol, disrupt iron homeostasis by altering the function of iron regulatory proteins such transferrin and IRP-1. These disturbances further enhance ROS generation, which contributes to cardiotoxicity.[26]

NADPH-Dependent ROS

NOX (NADPH oxidases) are key enzymes responsible for ROS production in the heart.[27] This multicomponent enzyme complex, comprising Rac1, cytosolic regulatory subunits, and membrane-bound cytochrome b-558, transfers electrons from NADPH to doxorubicin, facilitating the formation of the doxorubicin semiquinone radical.[28] Studies have shown that animals lacking NOX2 or gp91phox are resistant to DIC, exhibiting reduced superoxide production, whereas wild-type mice experience cardiac dysfunction, including atrophy, cell death, and fibrosis.[27] Moreover, eliminating the Rac1 gene in cardiac cells improves heart function by decreasing DNA damage, NOX2 activation, and apoptosis caused by doxorubicin.[26] In alignment with these findings, the Rac1 inhibitor NSC23766 has been shown to protect against DIC.[29]

Disruption of Calcium Homeostasis

Doxorubicin disrupts calcium handling in cardiomyocytes by altering influx and efflux mechanisms across

cellular membranes, resulting in dysregulation of intracellular calcium levels that impair contractile function and contribute to cardiac dysfunction.[30] In addition, doxorubicin increases intracellular calcium levels and produces ROS, which together cause cell death in cardiac muscle. Calcium chelators have been shown to prevent ROS formation and, subsequently, cell death.[31] Furthermore, doxorubicin metabolism produces the metabolite doxorubicinol, which inhibits the sodium-calcium exchanger essential for effective cardiac contraction.[32]

AMPK Signaling and Energetic Stress

Doxorubicin decreases the activity of the ACC (acetyl-CoA carboxylase) enzyme in the heart by inhibiting the AMPK (AMP-activated protein kinase) pathway. This AMPK inhibition triggers alternative signaling routes, including the MAPK (Mitogen-activated protein kinase) and Akt pathways, which can further contribute to DNA damage through genotoxic and oxidative stress mechanisms. As a result of AMPK inhibition, the cardiac tissue experiences elevated energy stress and hypertrophy, compounding the cardiotoxic effects of doxorubicin.[33]

Autophagy Disruption

Doxorubicin affects autophagy by causing autophagosome accumulation and impairing autophagic flux, which contribute to cell death.[34] In addition, doxorubicin interferes with key signaling pathways, including p53 (tumor-suppressor protein p53), Bcl-2 (B-cell lymphoma 2), and mTOR (mammalian target of rapamycin), that are responsible for regulating cell survival, resulting in cardiomyocyte damage and ROS production. However, curcumin has demonstrated cardioprotective effects by boosting autophagy and preventing apoptosis, suggesting that the dysfunction of autophagy by doxorubicin may play a role in cardiomyocyte mortality.[35–37]

Endothelial Dysfunction and Fibrosis

Chronic exposure to doxorubicin disrupts endothelial cell function, impairing vascular integrity and promoting fibrotic changes within cardiac tissues. This cardiac fibrosis, characterized by excessive deposition of extracellular matrix proteins, contributes to increased cardiac stiffness and overall cardiac dysfunction.[38]

VITAMIN C

Vitamin C is an essential water-soluble nutrient with profound biological significance. As a potent antioxidant, vitamin C plays a crucial role in protecting cells from oxidative stress by scavenging free radicals and ROS that can cause cellular damage.[4,39,40] Beyond the antioxidant properties of vitamin C, it is integral to collagen synthesis and aids in the maintenance of connective tissues and promotes wound healing. Moreover, vitamin C supports immune function by enhancing the immune cell activity and contributes to the synthesis of neurotransmitters and hormones.[41] The potential role of vitamin C in mitigating oxidative stress-related damage, including that induced by chemotherapeutic agents like doxorubicin, emphasizes its therapeutic potential in supporting overall health and well-being.[42]

Structure, Source

Vitamin C, chemically known as ascorbic acid (Figure 1), is essential for its antioxidant properties and serves as a cofactor in various enzymatic reactions involved in collagen synthesis, neurotransmitter production, and immune function.[43] Plant-based foods are considered the primary dietary sources of vitamin C, and alongside other plant components such as vitamin E (alpha-tocopherol), may be effective scavengers of ROS.[39,44] Diets, rich in plant-based sources, such as the Mediterranean diet, have been linked to protection against cancer and cardiovascular disease.[45] Although citrus fruits are considered the main source for vitamin C, studies have shown that Brassica vegetables can also contribute significantly, and up to 50% of the relative dietary intake of vitamin C could be provided naturally, depending on the daily habits of the consumers and regional dietary patterns.[46] In the study of García-Closas et al, fruits (particularly oranges) accounted for 51% of vitamin C intake, with vegetables like tomatoes and sweet peppers contributing 20%, followed by juices and drinks and potatoes with 7% and 4%, respectively.[47]

The human body relies entirely on dietary sources to meet the daily requirements of vitamin C. Because vitamin C is water soluble, excess is excreted through urine, necessitating regular dietary consumption to maintain adequate levels in the body.[48]

Pharmacological Application

Vitamin C acts as a potent antioxidant by scavenging free radicals and ROS in the body.[49] It works by transferring or donating electrons to neutralize oxidative damage, thereby reducing sulfur, nitrogen, and unstable oxygen radicals. Additionally, vitamin C plays an important role in the regeneration of other antioxidants (ie, vitamin E). Research has demonstrated that vitamin C can inhibit peroxide radical-induced lipid peroxidation in human plasma, affording further protection against oxidative stress.[50]

Vitamin C boosts immune function, helps avoid allergic reactions, and improves the absorption of iron,

calcium, and folic acid. Reduced intracellular vitamin C levels have been linked to immune suppression.[41] Moreover, vitamin C is necessary for the interferon synthesis, immunoglobulin synthesis and inhibition of IL-18 (interleukin-18), which is a factor in the regulation of malignant tumors.[51]

Vitamin C also supports gallbladder function by aiding in the production of bile and facilitating the elimination of steroid hormones.[52] It also serves as an essential cofactor for lysyl and prolyl hydroxylases enzymes that are essential for stabilizing and cross-linking type I and III collagen fibers.[53] Furthermore, vitamin C is essential for the intracellular signaling that encourages the proliferation of fibroblasts, which is necessary for tissue repair and wound healing.

In 1969, it was first reported that high concentrations of intravenously administered vitamin C could have a pro-oxidant effect on cancer cells[54] Recent studies by Yun et al have suggested that vitamin C might selectively kill cancer cells by inducing (H_2O_2) production. This selective action is thought to occur because cancer cells have lower levels of antioxidant enzymes compared with normal cells.[55,56] However, this theory remains controversial, as H_2O_2 is commonly produced by cells, especially in malignant conditions, and could be directly administered instead of vitamin C.[57]

Vitamin C plays a profound role in human skin health, when applied topically it can neutralize ROS generated by pollution, smoking, and sun radiation exposure.[58] In addition, vitamin C inhibits tyrosinase, the enzyme responsible for hydroxylating tyrosine into melanin precursors, making the use of vitamin C effective for treating sunspots, hyperpigmentation and melasma.[59] Furthermore, vitamin C enhances the cohesion between the dermis and epidermis and promotes the development of keratinocytes, thereby contributing to overall skin integrity and appearance.[60]

Recent studies have indicated that vitamin C influences epigenetic mechanisms, particularly DNA methylation, an inherited modification involved in gene silencing.[61] Mutations from UV radiation can alter methylation, leading to the silencing of genes crucial for cell differentiation and apoptosis. Apoptosis after UV exposure is vital for preventing malignancies like melanoma. Because methylation is reversible, research remains ongoing to explore the cellular protective role of vitamin C through these epigenetic mechanisms.[62]

A study on the potential of vitamin C in preventing male infertility was carried out in 2018 by Ilić et al.[63] Maintaining genetic material in sperm cells depends on the integrity of their DNA, which can be damaged by apoptotic processes and ROS. DNA fragmentation is facilitated by the enzyme DNase I (deoxyribonuclease I), which is dependent on calcium and magnesium ions. The study, using Site Finder and Molecular Docking techniques, discovered that, vitamin C can connect with specific locations on DNase I through hydrogen donor and acceptor interactions, inactivating the enzyme. Thus, preliminary findings imply that vitamin C may be helpful in shielding seminal DNA from harm.[63,64]

Beyond the profound antioxidant qualities of vitamin C, it is essential for cognitive function. In addition to promoting the manufacture of myelin and the maturation and differentiation of neurons, vitamin C functions as an enzyme cofactor in the synthesis of collagen, carnitine, tyrosine and peptide hormones.[65] Vitamin C deficiency has frequently been linked to the onset of various mental health disorders including schizophrenia, anxiety and depression as well as neurodegenerative diseases like Alzheimer's, Parkinson's, Huntington's, multiple sclerosis, and amyotrophic lateral sclerosis.[65] Additionally, vitamin C may have beneficial effects on cardiovascular health, potentially reducing the risk of cardiovascular diseases by improving endothelial function and reducing oxidative stress.[66–71]

VITAMIN C IMPACT ON DOXORUBICIN-INDUCED CARDIOTOXICITY

In exploring the critical impact of vitamin C supplementation on DIC, a growing body of research has investigated the dynamic relationship between doxorubicin and the potential protective effects of vitamin C on cardiac function (Figure 2). Additional studies have examined its potential as a prophylactic measure against DIC.[72] Both animal and clinical studies have suggested that vitamin C may confer protective benefits and improve cardiac function when administered alongside doxorubicin treatment.[73] However, responses to vitamin C supplementation vary among individuals, with factors such as the dose, timing relative to doxorubicin administration, preexisting cardiovascular conditions, and cancer type influencing effectiveness.[73] By example, Sacks et al reported that, in H9c2 myoblast, mitochondrial-targeted antioxidants like mitoquinone and SKQ1, not vitamin C, were effective in the mitigation of doxorubicin-induced damage.[74]

Biomarkers, Cardiac Enzymes, and Inflammation Factors

Biomarkers and cardiac enzymes play key roles in diagnosing and monitoring DIC. Elevated levels of troponins (troponin I and troponin T) in the blood indicate myocardial injury and are routinely measured for diagnosing acute coronary syndromes.[75] Like troponins, CK (creatine kinase) and CK-MB, a specific isoform predominantly found in cardiac muscle cells,

also indicate myocardial injury but their levels rise earlier than that of troponins.[76] Elevated blood levels of BNP (B-type natriuretic peptide), a hormone released from the ventricles of the heart, are indicative of heart failure and useful for diagnosing and assessing the severity of heart failure.[77] Myoglobin, a protein found in cardiac and skeletal muscle cells, can also indicate myocardial injury, but is considered less specific than both troponins or CK-MB.[78] Although CRP (C-reactive protein) is a definitive marker of inflammation, its presence is not specific to cardiac conditions, but CRP levels are often elevated in acute coronary syndromes and other inflammatory processes that affect the heart.[79] Lastly, the observance of elevated levels of LDH (lactate dehydrogenase) may indicate myocardial injury, but like CRP, is considered less specific.[80]

The cardiotoxic effects of doxorubicin are mediated, in part, by an inflammatory cascade that is kicked off by oxidative stress. Doxorubicin-induced ROS generation results in significant oxidative damage to cardiac tissues, which triggers the release of proinflammatory cytokines (TNF-α [tumor necrosis factor alpha] and IL-6) and recruitment of immune cells to the site of injury.[81] TNF-α is a proinflammatory cytokine produced by the compromised myocardium and its expression is further amplified by sympathetic nervous system activation.[82] Both, elevated TNF-α and IL-6 levels have been correlated with the progression toward heart failure and increased levels of soluble TNF-α have been documented during doxorubicin chemotherapy.[83] In preclinical small animal models, administration of vitamin C decreased the rise of key cardiac injury biomarkers, troponin, and CK, proposing a cardioprotective role in the context of doxorubicin-induced cardiotoxicity.[84–86]

Previous work conducted by Akolkar et al reported that doxorubicin increased the levels of proinflammatory cardiac (TNF-α, IL-1β, and IL-6) and attenuated levels of the anti-inflammatory (IL-10); however, concurrent treatment with vitamin C prevented this increase in proinflammatory cytokine levels, blunted the attenuation of IL-10, and were associated with improved survival outcomes in the treated rat groups.[72] Similarly, vitamin C pretreatment reduced doxorubicin-induced protein expression of NF-κβ (nuclear factor kappa B), JNK (c-Jun N-terminal kinase), and IKK (IκB kinase).[72] In a parallel study by Ludke et al, exposure of isolated adult rat cardiomyocytes to doxorubicin (10 μmol/L) for 24 hours resulted in a 98% increase in ROS production and CK release, alongside an approximate 20% decrease in cell viability. Notably, treatment with vitamin C (25 μmol/L) was able to relieve problematic doxorubicin-induced effects by reducing ROS and CK release by 50%, decreasing apoptosis, and improving cardiomyocytes viability.[87] Moreover, Swamy et al investigated both the potential preventive and curative role of vitamin C on DIC in Wistar rats. The result showed that pretreatment with vitamin C (20 mg/kg PO) significantly protected the myocardium from doxorubicin, evidenced by normalization of antioxidant enzyme activities (GSH [reduced glutathione], SOD [superoxide dismutase]. and CAT [catalase]) and reductions in malondialdehyde, creatine phosphokinase, LDH, aspartate aminotransferase, and alanine aminotransferase levels compared with doxorubicin-treated controls. Furthermore, posttreatment with vitamin C in doxorubicin-treated animals significantly enhanced tissue GSH, SOD, and CAT levels while reducing malondialdehyde, reinforcing the cardioprotective role of vitamin C in this model.[5]

Interestingly, both vitamin C (100 mM) and the p38 MAP kinase (p38 MAPK) inhibitor, SB203580 (10 mM), revealed a doxorubicin-induced enhancement of the contractile properties in male adult rat ventricular myocytes.[88] This observation highlights the role of ROS in contractile response associated with DIC. Specifically, doxorubicin exposure markedly increased ROS production, a response that was effectively abrogated by both vitamin C and SB203580.[88] These findings suggest that modulation of ROS, either through antioxidant supplementation or inhibition of p38 MAPK signaling, can influence myocardial contractility during doxorubicin treatment, offering a potential therapeutic strategy for mitigation of cardiac dysfunction.

Oxidative/Nitrosative Stress

DIC was initially thought to be attributed primarily to the generation of ROS and ensuing oxidative stress.[23] In this context, enzymes such as NADH dehydrogenase, cytochrome P-450 reductase, and xanthine oxidase contribute to formation of oxygen free radicals, promoting intracellular hydrogen peroxide and superoxide radicals. This oxidative milieu adversely affects eNOS, leading to reduced NO bioavailability.[89,90] Moreover, the oxidative and nitrosative stress, or the concomitant release of inflammatory cytokines, can activate NO synthase, which in turn may perpetuate both acute and chronic inflammatory responses, ultimately contributing to the progression toward heart failure.[91]

In addition to oxidative stress, DIC is also associated with doxorubicin-induced Ca^{2+} overload, which, in turn, leads to further oxidative damage and the activation of apoptotic and necrotic cell death pathways.[92] Additionally, doxorubicin has been reported to generate nitrosative stress through a reaction of superoxide with NO, increasing the production of powerful reactive nitrogen species like peroxynitrite.[93] In contrast, vitamin C has been hypothesized to reduce oxidative stress and protect the heart from doxorubicin-induced damage.[72] Importantly, vitamin C has also been reported to enhance the activity of eNOS, the enzyme responsible for producing NO in the endothelial inner

Table. Vitamin C Protective Effects Against Doxorubicin-Induced Cardiotoxicity

Type of study	Experimental model	Doxorubicin dose	Vitamin C dose	Treatment paradigm	Vitamin C impact on DIC	References
In vitro	H9c2 cardio myoblasts	0.5–50 μmol/L	1–1000 μmol/L	Cotreatment*	No measurable cardioprotection; only nitoquinone mesylate/plastoquinonyl-decyl-triphenylphosphonium prevented doxorubicin injury	[74]
In vitro	Human breast-cancer cell line breast cancer cells	1 μmol/L	200 μmol/L	Cotreatment* (proteomics)	Statistically significant change on 26 proteins linked to apoptosis, immunity, and redox control; suppression of MFC-7 proliferation; potential biomarkers for predicting response to therapy.	[95]
In vitro In vivo	RL (B-cell lymphoma) and K562 (chronic myelogenous leukemia) cell lines Imprinting-control-region severe combined immunodeficient mouse strain mice were xenografted with RL cells	600 nmol/L (75% inhibitory concentration) 1 mg/kg IP (8 doses on days 0, 2, 4, 6, 14, 16, 26, 28)	100–500 μmol/L (given as dehydroascorbic acid; intracellular conc.=8.5–18 mmol/L) 250 mg/kg IV (given 2 h before each doxorubicin; intratumor conc.=5.5 mmol/L)	Prophylactic† In vitro: 1 h before doxorubicin In vivo: 2 h before each doxorubicin dose	In vitro: dose-dependent decrease in doxorubicin cytotoxicity and clonogenic death; reduced apoptosis; preserved mitochondrial membrane potential. In vivo: vitamin C pretreatment reduced doxorubicin efficacy 4-fold (tumors 4× larger than doxorubicin-only); protection linked to maintenance of mitochondrial membrane potential.	[42]
In vivo	Male Wistar rats (5 groups, n=6)	2.5 mg/kg IP (6 doses 15 mg/kg)	20 mg/kg PO	Prophylactic† (15 d before doxorubicin) Therapeutic‡ (15 d after doxorubicin)	Prophylactic/pretreatment: Normalized GSH, SOD, and CAT; Decreased malondialdehyde, creatine-phosphokinase, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase; myocardial architecture preserved; histology indistinguishable from controls. Therapeutic/posttreatment: significantly increased GSH, SOD, and CT; decreased malondialdehyde; partial histologic recovery, improved myocardial architecture but not fully normalized compared with the prophylactic group.	[5]
Ex vivo	Adult rat cardiomyocytes	10 μmol/L (for 24 h)	5–100 μmol/L	Cotreatment* Prophylactic† (vitamin C pretreatment for 1 h)	Reduced reactive oxygen species and creatine kinase; decreased phosphorylation of apoptosis-signal-regulating kinase 1 (–71%), p38 (–40%) and p53 (–40%); Reduced caspase-3 cleavage; normalized B-cell lymphoma-2-associated X protein:B-cell lymphoma-extra large ratio, decreased nuclear fragmentation and overall apoptosis; Preserved ATP/MTT signal; viability 90% vs 73% with doxorubicin alone.	[87]
Ex vivo	Adult rat cardiomyocytes	0.1–10 μmol/L	20 μmol/L (6–48 h time course)	Cotreatment* (vitamin C pretreatment for 1 h)	Protected against the activation oxidative stress that is induced by proteins, autophagy, and apoptosis; blocked activation of p38 mitogen-activated protein kinase, c-Jun N-terminal kinase, and tumor-suppressor protein p53 proteins.	[96]
Ex vivo	Adult rat cardiomyocytes	10 μmol/L	25 μmol/L	Prophylactic† (vitamin C pretreatment for 1 h)	Reduced protein nitrosylation and tumor necrosis factor-α; increased interleukin-10; decreased inducible NOS expression and NOS activity and total NOS activity, leading to lower intracellular NO and peroxynitrite levels.	[97]

(*Continued*)

Table. Continued

Type of study	Experimental model	Doxorubicin dose	Vitamin C dose	Treatment paradigm	Vitamin C impact on DIC	References
Ex vivo	Adult rat cardiomyocytes	10 µmol/L	25 µmol/L	Cotreatment* (vitamin C pretreatment for 1 h)	Blunted doxorubicin-induced sodium-dependent vitamin C transporter-2 downregulation followed by a reduction in lipid hydroperoxides and nitrosylation; increased total antioxidant capacity; restored glutathione peroxidase (full) and copper/zinc-dependent superoxide dismutase (partial); decreased B-cell lymphoma-2-associated X protein/cytochrome-c release and annexin-positive cells; increased cell viability (MTT).	[98]
In vivo	Male Wistar rats (250–300 g)	20 mg/kg	250 mg/kg (14-day PO pretreatment)	Prophylactic†	Increased ferric-reducing antioxidant power assay antioxidant capacity; decreased cardiac malondialdehyde; modest histological protection.	[99]

CAT indicates catalase; DIC, doxorubicin-induced cardiotoxicity; GSH, Reduced glutathione; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NOS, nitric oxide synthase; RL, human B-cell lymphoma cell lineand SOD, superoxide dismutase.
*Cotreatment (concurrent): doxorubicin and vitamin C administered at the same time.
†Prophylactic: pretreatment with vitamin C followed by doxorubicin.
‡Therapeutic (rescue): doxorubicin administered first, followed by posttreatment with vitamin C.

lining of blood vessels (), which may further support vascular function and mitigate the deleterious effects of reduced NO bioavailability.[94]

Recent animal studies conducted by Dulf et al have provided further insights into the mechanism underlying DIC. Their work reported that GSH was depleted with an increase in glutathione disulfide after 1 week, leading to oxidative imbalance after a single dose of doxorubicin. Additionally, this imbalance is compounded by significant reductions in key protective antioxidant enzymes, such as CAT and SOD, observed between 3 to 7 days following doxorubicin administration. Furthermore, the study noted elevation in malondialdehyde, the final product of polyunsaturated fatty acids peroxidation in the cells. An increase in free radicals causes overproduction of malondialdehyde, making it a marker of oxidative stress and the antioxidant status in cancer patients.[23] In addition to the findings by Dulf et al, emerging evidence suggests that doxorubicin increases ROS production facilitates increased iron uptake and accumulation into cardiomyocytes, a process that induces ferroptosis, an iron dependent form of regulated cell death. This effect was named doxorubicin-induced ferroptosis, representing a novel mechanistic insight into the multifaceted nature of DIC.[23]

Muscle and Myocardial Toxicity

DIC significantly influences patient prognosis and survival. Myocardial injury may begin immediately after drug administration; although the acute clinical stage is frequently asymptomatic and quietly initiates a cascade of cellular damage that compromises cardiomyocyte integrity.[5,89] By producing free radicals, doxorubicin results in oxidative stress, disrupts mitochondrial function, impairs energy production, and causes DNA damage that lead to initiation of a cascade of events that activate apoptotic pathways, further compromising the function of the heart and muscles. doxorubicin increases the levels of cardiac cytokines TNF-α, IL-1β, and IL-6 that are important in the proinflammatory cascade. One of the common effects of doxorubicin toxicity is the reduction of the expression of vitamin C transporter proteins, specifically the sodium-ascorbate cotransporter 2 and certain glucose transporters, impairing vitamin C uptake.[94]

Prophylactic and coadministration strategies of vitamin C alongside doxorubicin may prevent these deleterious changes and improve patient survival ().[5,42,73,74,87,95–99] Vitamin C ameliorates by reducing oxidative and nitrosative stress, inflammation, and apoptosis, as well as restoring the expression of vitamin C transporter proteins. Furthermore, vitamin C also improved doxorubicin-mediated systolic and diastolic dysfunctions and structural myocardial damage.[94] For

instance, Ludke et al, reported improvements in cardiac dysfunction and structural integrity through the mitigation of oxidative stress-mediated apoptotic pathways.[87] Investigation of the synergistic effect of vitamin C in combination with another antioxidant, polydatin, to alleviate DIC was reported by Wang et al, revealing enhanced myocardial protective effects by antioxidation mechanism.[100]

Furthermore, vitamin C prevents DIC by lowering inflammatory cytokines, altering NOS activity, and modulating NO and reactive nitrogen species concentrations. Together, these data imply that vitamin C might be a useful supplementary treatment for DIC effects.[96,101] Moreover, doxorubicin has been reported to have complex and dose dependent effect on the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway, which is a key regulator of cellular antioxidant and cytoprotective responses.[102] Although vitamin C is generally referred to as a direct radical scavenger, it also acts as a redox switch for the KEAP1 (Kelch-like ECH-associated protein 1)-Nrf2-antioxidant response element axis. Under physiological conditions, KEAP1 is attached to and prevents the degradation of Nrf.[103] Specifically, KEAP1 functions as an adapter for the CUL3 (Cullin-3) E3 ubiquitin ligase complex, that targets and tags Nrf2 for ubiquitin-mediated degradation. However, under oxidative conditions KEAP1 changes conformation and dissociates from Nrf2.[104] When vitamin C becomes oxidized to dehydroascorbic acid (DHA) it produces brief hydrogen peroxide pulse that oxidize redoxsensitive Cys151 and Cys273 residues on KEAP1, disrupting the KEAP1-CUL3 ligase.[103,105] This results in stabilized Nrf2 that translocates to the nucleus and binds with antioxidant-response elements to regulate the expression of antioxidant enzyme genes (ie, NQO1 [NAD(P)H:quinone oxidoreductase 1] and HO-1 [heme oxygenase-1]).[103] This nuclear accumulation of Nrf2 leads to dimerization with small Maf proteins, driving antioxidant response element-dependent transcription of phaseII detoxifiers (ie, NQO1), glutathionesynthetic enzymes (ie, GCLC [glutamate-cysteine ligase catalytic subunit], GCLM [glutamate-cysteine ligase modifier subunit]), ROS metabolizing systems (ie, SOD1/2, catalase) and thiolrepair proteins (ie, GPx [glutathione peroxidase], TrxR [thioredoxin reductase]). Collectively, this coordinated Nrf2-driven transcriptional response increases overall cellular antioxidant defenses beyond the direct antioxidant action of vitamin C itself.[104] The overall mechanism is relevant to DIC because doxorubicin sends mixed signals to Nrf2 that partially activate and suppress it through p38 MAPK and TRIM21mediated KEAP1 stabilization-.[81] Notably, vitamin C has been shown to play a role in overriding these conflicting signals, reliably priming Nrf2 activation and downstream defenses.[72,81] However, excessive and prolonged Nrf2/HO-1 activity can raise free iron and trigger cellular damage (ferroptosis).[102] Therefore, maintaining vitamin C within physiologic plasma ranges (~50–250 μmol/L) minimizes the risk of pro-oxidant spillover while still providing antioxidant boost.[106]

Nevertheless, vitamin C appears to positively influence the Nrf2 pathway, leading to the upregulation of antioxidant and detoxification genes that contribute to the cellular defense against oxidative stress and support overall cellular health.[103–105] summarizes the in vitro and in vivo results from the literature describing the protective effects of vitamin C against DIC.[5,42,73,74,87,95–99]

Comparison Between Vitamin C and Food and Drug Administration-Approved Therapies for Doxorubicin-Induced Cardiotoxicity

Numerous preclinical studies have shown that vitamin C can reduce biomarkers of cardiac damage, suppress proinflammatory cytokines, and restore antioxidant enzyme levels. However, the clinical application of vitamin C as a cardioprotective remains unapproved and has been limited by inconsistent outcomes in clinical settings, often attributed to variable pharmacokinetics and dosing strategies. Compared with Food and Drug Administration-approved agents (ie, dexrazoxane), vitamin C is more affordable, accessible, and has a more favorable safety profile.

Dexrazoxane

Dexrazoxane, derived from EDTA, has emerged as a potent cardioprotective agent primarily due to its iron chelating properties. By binding iron, dexrazoxane reduces the formation of superoxide radicals that are formed when doxorubicininteracts with metal ions. Dexrazoxane's dual mechanism of action can be summarized as an iron chelator that reduces the production of the oxygen free radicals within cardiomyocytes and interferes with the formation of doxorubicin-topoisomerase IIb–anthracycline-mediated, preventing the resultant double-stranded DNA breaks that contribute to cellular injury.[107]

Clinically, dexrazoxane has been used since the 1980s in oncology patients, with US Food and Drug Administration approval in May 1995 under the brand name Zinecard. This approval specifically targeted its use for the prevention of cardiomyopathy associated with doxorubicin in women with metastatic breast cancer who have received a cumulative dose of 300 mg/m^2.[107] Dexrazoxane has gained the clinical interest that eventually prompted the Medicines and Healthcare Products Regulatory Agency in the United Kingdom to request the Committee for Medicinal Products for

Human Use to review the use of dexrazoxane as a cardioprotectant in 2010.[108] This was followed by a revised recommendation for the use of dexrazoxane in both adults and children with cancer, as published in 2011 by the Committee for Medicinal Products for Human Use.[108]

Liposomal Doxorubicin

Liposomal doxorubicin, marketed under the tradenames Doxil and Caelyx, was initially approved by the Food and Drug Administration in November 1995 for the treatment for AIDS-related Kaposi's sarcoma, ovarian cancer, and multiple myeloma (when used in combination with bortezomib).[109] It has been further developed to decrease the anthracycline-associated cardiotoxicity without affecting the antitumor efficiency.[110] Liposomal doxorubicin has been shown in several studies to be effective as a monotherapy or in combination with other medications for the treatment of patients.[111,112] Notably, several clinical trials have reported reduced cardiotoxicity, while maintaining comparable antitumor responses relative to conventional doxorubicin.[113] The meta-analysis conducted by Xing et al supports the clinical utility of liposomal doxorubicin, indicating a significant improvement in overall response rates coupled with a marked reduction in cardiotoxicity risk.[114]

Long-Term Safety and Oncologic Efficacy Considerations

The cardioprotective potential of vitamin C must be considered alongside possible impacts on oncologic efficacy and long-term cardiovascular outcomes. Preclinical studies have shown that vitamin C can mitigate oxidative/nitrosative stress and inflammation in DIC, however translating these findings to human populations has remained challenging. The variability in clinical data and dearth of large-scale, long-term studies have impeded the ability to assess the combined safety and efficacy of vitamin C supplementation. Accordingly, and although vitamin C holds promise as a cardioprotective agent during chemotherapy, the potential impact of vitamin C on chemotherapy efficacy and enduring cardiovascular health will require careful consideration and further clinical investigation.

Further, concerns still surround the potential interference of vitamin C with the pro-oxidant mechanisms that contribute to doxorubicin's anticancer efficacy. Heaney et al demonstrated that vitamin C, in a dose-dependent manner, reduced the cytotoxic effects of several antineoplastic drugs, including doxorubicin, in leukemia and lymphoma cell lines.[42] A systematic review by Block et al reached a similar conclusion, stating that antioxidant administration during chemotherapy can protect tumor cells from oxidative injury and diminish treatment benefit.[42,115] In contrast, other studies have reported that vitamin C supplementation does not reduce the antitumor effects of chemotherapy.[116–118] These disparate reports combined with the lack of large-scale, long-term clinical investigation emphasize the need for further research to better assess and validate the role of vitamin C in cancer therapy.

Sources of Clinical Heterogeneity

Although the cardioprotective research on vitamin C has revealed promise, clinical trials in humans have shown inconsistent results compared with preclinical research. Such heterogeneity between preclinical and clinical outcomes has been attributed to dosing (oral, intravenous, and pharmacologic, as well as dietary levels), administration timing (before, during, or after chemotherapy) and patient-specific factors (baseline antioxidant levels, tumor type, metabolic environment, and genetics).

Vitamin C pharmacokinetics differ sharply between administration routes, creating substantial clinical variability. Oral dosing relies on specialized gut transporter proteins (ie, SVCT-1 [sodium-dependent vitamin C transporter 1]) and once saturated, no additional vitamin C crosses, irrespective of the dosage. Thus, even large oral dosing strategies of 3 g have been shown to modestly raise blood vitamin C levels to approximately 70 to 80 μmol/L before plateauing.[119] By contrast, intravenous administration bypasses the gut, delivering vitamin C directly into the bloodstream and achieving plasma concentrations in the millimolar range, nearly 50-fold higher than oral approaches.

Many laboratory models require superphysiological dosages to see the pro-oxidant or cytotoxic effects on cancer cells, which cannot be achieved via oral supplementation due to intestinal and renal regulation. Heaney et al showed in vitro that preloading cancer cells (K562 and human B-cell lymphoma cell line) with DHA at pharmacologic levels led to rapid, dose-dependent intracellular accumulation of vitamin C, providing protection against chemotherapeutic cytotoxicity.[42] These in vitro results revealed that cancer cells take up DHA via GLUT1 (glucose transporter 1) transporters and convert DHA to ascorbate intracellularly. This uptake revealed resistance to multiple chemotherapies by preserving mitochondrial membrane potential and reducing apoptosis. In the same study, a severe combined immunodeficiency mouse human B-cell lymphoma cell line xenograft model confirmed that these intracellular protective mechanisms reduced chemotherapy efficacy. Administration of DHA intravenously 2 hours before doxorubicin treatment showed tumors that were 4 times larger than doxorubicin alone, even though intratumor doxorubicin levels were nearly

identical. This suggests the protection was not due to altered drug pharmacokinetics or delivery but rather a function of intracellular protective effects (ie, mitochondrial membrane potential), as was observed in vitro. Thus, administering vitamin C before, during, or after chemotherapy may shape its influence on treatment response.

In addition to administration dosage, route, and timing, the tumor microenvironment and patient-specific factors represent another cause of outcome heterogeneity. Although some cells transport ascorbic acid directly, most cancer cells rely on GLUT-mediated uptake of DHA. Tumors injected with vitamin C, in Agus et al, showed that vitamin C only accumulated inside the cancer cells after being oxidized in the extracellular space.[120] In these studies, vitamin C encounters ROS generated by stromal cells surrounding the tumor and is oxidized and converted to DHA, which is more hydrophilic and can be transported into cells via GLUT1. Variability in stromal oxidative activity, GLUT expression, baseline antioxidant status, and tumor redox environment likely contributes to differential intracellular vitamin C accumulation across patients. These factors emphasize the need to consider not only pharmacokinetics, but also tumor-specific redox mechanisms, when designing and interpreting clinical trials.[121]

Emerging Combination Therapies

Although immunecheckpoint inhibitors (ICIs) are mechanistically distinct from anthracyclines, many modern oncology protocols give ICIs concurrently or soon after doxorubicin-based chemotherapy. Because doxorubicin primes the myocardium through oxidative stress and ferroptosis, any additional ICI-related cardiac burden can amplify the risk of cumulative cardiotoxicity. Therefore, recent evidence has brought to light the potential benefits of integrating vitamin C with ICIs to enhance antitumor efficacy while conferring cardioprotective effects. High-dose vitamin C has been shown to augment T cell–mediated immune responses and enhance antitumor activity in various malignancies, including non-small-cell lung cancer and hepatocellular carcinoma.[122–126] These dual effects stem from vitamin C-mediated modulation of redox pathways, epigenetic tuning of T-cell function and ferroptosis inhibition. Given that DIC itself is driven by oxidative stress, mitochondrial dysfunction, and ferroptosis, vitamin C's protective mechanisms are directly applicable. For instance, cardiomyocytespecific deletion of SNX3 (sorting nexin 3) mitigates doxorubicin cardiotoxicity by suppressing GPx4 (glutathione peroxidase 4) dependent ferroptosis.[127] Accordingly, combining vitamin C with ICIs may enhance anticancer efficacy and safeguard the heart, which could represent a favorable clinical strategy for patients susceptible to cardiac complications.

CONCLUSIONS AND FUTURE PERSPECTIVES

Vitamin C, known for its antioxidant properties, has shown promise in preclinical studies to reduce DIC by scavenging free radicals, reducing oxidative stress, preserving mitochondrial function, and potentially inhibiting apoptosis in doxorubicin-exposed cardiac cells. The vitamin is typically well tolerated and has been implicated with very few adverse effects, making it an adjunct therapy that does not jeopardize doxorubicin's anticancer effectiveness. Future studies should concentrate on improving the amount, timing, and duration of vitamin C supplementation, as well as investigating alternate delivery methods (oral versus intravenous) and their impact on long-term cardiovascular outcomes. Further research is also warranted to elucidate the precise molecular mechanisms by which vitamin C confers cardioprotection, particularly regarding its modulation of oxidative stress pathways, mitochondrial function, and the regulation of cellular signaling cascades linked to apoptosis and inflammation.

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