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Original
Antioxidant Approach as a Cardioprotective Strategy in Chemotherapy-Induced Cardiotoxicity / Cadeddu Dessalvi, Christian; Deidda, Martino; Noto, Antonio; Madeddu, Clelia; Cugusi, Lucia; Santoro, Ciro; López-Fernández, Teresa; Galderisi, Maurizio; Mercuro, Giuseppe. - In: ANTIOXIDANTS & REDOX SIGNALING. - ISSN 1523-0864. - 34:7(2021), pp. 572-588. [10.1089/ars.2020.8055]

Availability:
This version is available at: 11388/232696 since: 2021-04-01T18:12:16Z

Publisher:

Published
DOI:10.1089/ars.2020.8055

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31 May 2026

Antioxidants and Redox Signaling
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DOI: 10.1089/ars.2020.8055

FORUM REVIEW ARTICLE

Antioxidant approach as a cardioprotective strategy in chemotherapy-induced cardiotoxicity

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Running Head: Antioxidant protection against cardiotoxicity

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Word count: 5448

Reference number: 182

Figures: 6

Color Figures: 4 (online only)

Keywords: Chemotherapy-induced cardiotoxicity; oxidative stress; cardioprotection

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Abstract

Significance. Chemotherapy-induced cardiotoxicity has been associated with redox signaling imbalance. In fact, redox reactions are crucial for normal heart physiology, whereas excessive oxidative stress can cause cardiomyocyte structural damage.

Recent Advances. An antioxidant approach as a cardioprotective strategy in this setting has shown encouraging results in preventing anticancer drug-induced cardiotoxicity.

Critical Issues. In fact, traditional heart failure drugs as well as many other compounds and non-pharmacological strategies, with a partial effect in reducing oxidative stress, have been shown to counterbalance chemotherapy-induced cardiotoxicity in this setting to some extent.

Future Directions. Given the various pathways of toxicity involved in different chemotherapeutic schemes, interactions with redox balance needs to be fine-tuned and a personalized cardioprotective approach seems to be required.

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Introduction

In the last decade, there have been significant advances in the treatment of cancer with a substantial increase in patient survival (25). However, the cardiotoxic effects triggered by anticancer drugs have been affecting many patients, causing myocardial dysfunction, and even heart failure (HF) (168). HF due to cardiotoxicity (CTX) has been recently related to redox signaling imbalance. As signaling molecules, radical oxygen species (ROS) are very important for the normal physiology of an organism, whereas an excess of oxidative stress can activate a series of pathways that can damage the cardiomyocyte membrane, proteins, and DNA (157)(Figure 1).

Counteracting these toxic effects has proven beneficial, thanks to a multifactorial approach for heart protection with specific drugs, dietary compounds, and exercise training programs.

Oxidative and Nitrosative stress in cardiovascular toxicity

Oxidative stress may occur when the production of ROS oversaturates the capacity of cellular antioxidant defenses. These oxidant species are derived from the incomplete reduction of molecular oxygen, thus forming free radical species (R•). These classes of compounds are ions presenting one or more unpaired electrons in their orbitals, which makes them very unstable and highly reactive to electrons of other chemical species. The free radical species include (a) radical anionic superoxide (O_2•-), (b) hydrogen peroxide (H_2O_2), and (c) hydroxyl radical (OH•) (11). The most important intracellular sources of ROS under both physiological and pathological conditions are the mitochondria (118), where ROS production is a direct consequence of electron transfer along the respiratory chain. Here, electrons provided by the oxidation of reduced coenzymes such as NADH and FADH2 are transferred to molecular oxygen, resulting in its reduction to water. Although mitochondria are one of the major sources of ROS, their membrane structure, which is rich in polyunsaturated fatty acids, is prone to lipid peroxidation and renders them vulnerable to ROS attacks. More specifically, ROS induces cardiomyocyte apoptosis by activating the death-pathway through a JNK-dependent mechanism (49). ROS are also capable of degrading the proteins of cardiomyocytes, whose cytoskeleton oxidation causes amino

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acid fragmentation. This in turn leads to altered protein activity, thereby potentially contributing to the development of contractile dysfunction, arrhythmias and possibly altered energetics in HF (50) (Figure 2). Another important cause of CTX related to chemotherapy is the production of radical nitrogen species (RNS). This is a family of nitrogen-related free radicals (NO ●) such as nitric oxide, which are formed from the amino acid L-arginine through the enzyme nitric oxide synthase (NOS)(figure 3). NOS isoforms modulate several cardiac functions, growth, hypertrophy, and cell viability under normal and pathological conditions (50). NOS can be uncoupled under increased oxidative stress, switching from NO production to O2- production, thus acting as amplifiers of cardiac ROS. If the levels of superoxide and H_2O_2 are high at the cellular level, these molecules can react with nitric oxide and form peroxynitrite (OONO-), a compound with high cytotoxicity whose oxidizing power is greater than that of the superoxide anion and hydrogen peroxide (105). Peroxynitrite has the ability to react with different molecules such as CO_2. Depending on the conditions, peroxynitrite can give rise to other highly reactive compounds. Currently, the use of antioxidant compounds has been hypothesized to be useful against cardiotoxic events. In particular, vitamin A, C, E, N-acetylcysteine, amifostin, and flavonoids have been tested. However, despite encouraging results, the direct translatability of such treatments into clinical practice has failed to demonstrate clinical benefits (60; 71; 142; 165).

Redox-related biomarkers of cardiotoxicity

The pathways involved in CTX induction through oxidative stress by antineoplastic drugs, particularly by anthracycline (ANT), are well known. However, identification of reliable redox markers that can possibly correlate with the clinical symptoms of cardiovascular (CV) events is yet under investigation. A “biomarker” is defined as “a characteristic that can be objectively measured as an indicator of physiological and pathogenic processes, or biological responses to a therapeutic intervention”. An ideal biomarker should be sensitive and simultaneously simple to measure, non-invasive, widely available, and low-cost.

Preclinical models of doxorubicin (DOX)-induced CTX have shown that oxidative stress characterized by high levels of ROS and reduced levels of NADPH:quinone oxidoreductase

activity, is an early indicator of myofibrillar and mitochondrial energetic changes associated with heart damage (86)(figure 4).

In a population of breast cancer patients in a clinical setting, a significant increase in ROS along with a decrease in the antioxidant enzyme glutathione peroxidase was consistently associated with an early reduction of left ventricular (LV) longitudinal systolic function, assessed by tissue Doppler imaging, after administration of a cumulative dose of 200 mg/m^2 of Epirubicin (112). The increase in ROS and IL-6 levels was inversely correlated with the deterioration of systolic parameters. Notably, the ROS level was the only independent predictive variable for the decrease in strain rate (112). The reliability of oxidative stress for CTX monitoring was also demonstrated in a cardioprotective setting, in which an ATII receptor blocker was used during epirubicin treatment: improvement of myocardial function was associated with a reduction of ROS levels (47).

However, ROS and RNS are very unstable and short lived, which may represent a major obstacle to their detection. Moreover, clear guidelines on the sensitivity, specificity, and accuracy of specific tests for free radical measurement are not available yet, and many challenges such as optimal timing, schedule, and cut-off value for their clinical evaluation are yet unresolved (123).

Another redox biomarker that is widely tested in clinical studies is myeloperoxidase (MPO) (figure 4). MPO is an enzyme secreted by neutrophils during periods of inflammation and exerts pro-oxidant effects due to scavenging of nitric oxide, inhibition of nitric oxide synthase, and lipid peroxidation. Such association of MPO with oxidative stress suggests that elevated MPO could be related to LV dysfunction. A recent study showed that early increases in MPO levels were associated with subsequent CTX in patients treated with trastuzumab and ANT-based combination therapy (84). The same study showed that an increase in MPO beyond 3 months of chemotherapy in the same cohort of patients is still predictive of increased CTX over the course of treatment. Therefore, MPO could be used as diagnostic biomarker in the risk assessment for antineoplastic drug-induced CTX, but further studies are needed to validate this marker in clinical use (139).

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Other biomarkers of oxidative stress such as oxidized DNA, protein, and lipid damage adducts have been tested in clinical practice. These include 8-hydroxy-deoxyguanosine (8-Oxo-dG) and markers of lipid peroxidation such as 4-hydroxy-2'-nonenal (4HNE) and malondialdehyde (MDA) (80, 175, 181).

Among redox biomarkers, protein carbonylation represents an irreversible oxidative modification induced by ROS in proteins (39) (Figure 1 and 4). Progress in mass spectrometry-based technology and proteomics has improved the ability to identify the oxidative changes such as carbonylation in specific proteins. In particular, proteomics-based techniques have been tested to assess the oxidative changes of specific proteins following cardiac damage by DOX, confirming that carbonylation of human apolipoprotein A1 occurs in mice treated with high-dose DOX (6, 22). In an experimental model, changes in total protein levels of peroxiredoxin-1, HSPb6, GRP75, VDAC2, and methylmalonate semialdehyde dehydrogenase have also been observed after DOX exposure (83; 46).

Another indicator of early oxidative cell damage is represented by autophagy, which can be induced by DOX, as shown in preclinical animal models (52). Indeed, different grades of autophagy have been detected by western blotting and electron microscopy in animal models treated with DOX (51)

However, the clinical data are very few to date. One study carried out in a population of triple-negative breast cancer patients investigated the CTX of chemotherapy and found that an autophagy-related single nucleotide polymorphism was associated with chemotherapy-induced CTX (93). Notably, the modern "omics" approach seems very useful and valid in assessing CTX (45), especially considering that the mechanisms mediating it are multiple and complex (27, 43). Indeed, metabolomic analysis can assess some alternative redox biomarkers such as acetate, succinate, and others (7). Some metabolomic studies in experimental models of CTX have found increased levels of hydroxyl radical metabolites such as 4-hydroxybutyrate, 5-hydroxylysine, 2-hydroxybutyrate, and 3-hydroxybutyrate in DOX-treated groups (133). Moreover, a decrease in total glutathione levels and GSH/GSSG ratio after DOX exposure compared to the control group was found. A significantly persistent decrease in the serum levels of the

antioxidant cysteine and its precursor methionine was also observed, suggesting progressive oxidative stress related to DOX-induced CTX. The DOX-treated group also had decreased levels of arginine and citrulline, two amino acids involved in the urea cycle. In particular, arginine represents a byproduct of nitric oxide formation that is known to play a role in DOX-induced CTX. Consistently with these preclinical data, Finkelman et al. found that early alterations in arginine-NO metabolite levels occurred in breast cancer patients undergoing DOX therapy, and that the early changes in these biomarkers were associated with a higher cardiac dysfunction rate (57).

Specific drug-related oxidative toxicity

Chemotherapeutic agents promote CV damage through different mechanisms, but mostly act by enhancing ROS and RNS concentration, as a consequence of direct production or through inactivation of the redox process. At physiological concentrations, ROS/RNS compounds regulate CV functions such as coronary vasodilation (125). However, unbalanced levels of ROS/RNS compounds induce irreparable cell damage, particularly membrane lipid peroxidation, causing impaired adaptation and eventual cell death. Macroscopically, ROS/RNS damage results in vacuolization and replacement with fibrous tissue leading to irreversible cardiac damage (85, 108, 109). ROS production can be induced by a different mechanism within (NAD(P)H oxidase, xanthine oxidase) and outside (peroxisome, NO synthase) the mitochondria. The CV system is vulnerable to ROS/RNS damage because it is rich in mitochondria (they occupy 36%-40% of myocytes) and has lower antioxidant defenses compared to other tissues (108, 110). Moreover, oxidative stress and inflammation are the two main causes of CV damage in anticancer drug therapy. In the next paragraphs the effect of different anticancer drugs on redox processes will be analyzed, focusing on CV damage.

Anthracyclines

Anthracyclines (ANTs) are anticancer agents commonly used in different oncologic conditions (e.g. breast cancer, sarcoma, non-Hodgkin lymphoma) (111). ANTs induce dose-dependent CTX (106), causing evident ultrastructural myocardial abnormalities (162), which appear to be gender-specific (18). Female subjects, especially before puberty and

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adolescence, or after menopause, seem to be at increased risk of ANTs-induced CTX, suggesting that sex differences could arise from the lack of protective effects of sex hormones against anthracycline-initiated damage in cardiac cells, or from differential mitochondria-related oxidative gene expression (119). ANT induced CTX is caused by a series of cellular (mainly affecting mitochondrial function) and molecular mechanisms that cause myocardial damage and overt LV dysfunction underlying "the multiple-hit hypothesis." This hypothesis may explain the individual variability in CTX (56).

Mitochondrial damage plays a pivotal role in ANT-derived CTX. ANTs are metabolized to an unstable compound which reacts with O_2, producing ROS. ROS generated by ANTs affect the mitochondrial enzymes, NAD(P) H oxidase and catalase. Direct peroxidation of ANTs on phospholipid cardiolipin directly stimulates ROS/RNS production and suppresses oxidative phosphorylation with consequent reduction of energy production and cell dysfunction. Membrane lipid peroxidation by ANT-induced ROS causes irreversible damage and myocyte replacement with connective tissue (158, 180). ANTs seem to be also responsible for mitochondrial calcium accumulation, mitochondrial DNA damage, and cellular apoptosis involving mitochondrial membrane elements such as cytochrome C and caspase (128) Moreover, ANTs seem to have a direct detrimental effect on cardiac progenitor cells, and reduce the regeneration ability of cardiac tissues after myocardial damage (124).

Additionally, two types of topoisomerase 2 (TOP2) are targeted by ANTs: TOP2 α, expressed in rapidly dividing cells, and TOP2β, highly expressed in cardiomyocytes. A direct link with topoisomerase (TOP2) creates a complex between ANT, TOP2, and DNA, which causes a double-strand break and transcriptome modification that in turn, induces apoptosis (94) (Figure 1). Moreover, ANTs may affect P53 activities. P53 is a pivotal protein in the DNA repair process and is responsible for autophagy and the recycling of dysfunctional mitochondria that eventually accumulate in the cardiomyocyte. Therefore, ANT-induced metabolic alteration (145) causes ROS/RNS production and ultimately cell death. ANT metabolites interfere with iron-dependent and iron-independent mechanisms leading to intracellular Ca^{2+} overload, cellular disarray, and sarcomere disruption. Consequent iron accumulation has also been proved to induce ROS generation (68). Detrimental effects of ANTs have also been demonstrated on inflammatory cells. ANTs

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induce cells to release high mobility group box 1 (HMGBI) that triggers toll-like receptor (TLR) 2 and 4 (96, 179) with the release of proinflammatory cytokines (i.e., IL-6, IL-1β, TNF-α).

Antimetabolites

Antimetabolite drugs are mostly used to treat gastrointestinal, breast, head and neck and pancreatic cancers. These drugs are rapidly converted into their active form. The onset of CTX induced by antimetabolites is usually rapid. Moreover, the enzyme responsible for conversion is mainly expressed in endothelial and cancer cells, explaining why myocardial ischemia represents the most common manifestation of fluoropyrimidine-induced CTX (82). CTX incidence by fluoropyrimidine may be as high as 35% with a mortality rate between 2 and 13%. The mechanisms of CTX induced by 5-fluorouracil (5-FU) and capecitabine are still debated and seem to involve different processes such as inhibition of NO production, increased intracellular levels of ROS/RNS, higher endothelial thrombogenicity, direct DNA and RNA damage, and cell senescence (5, 31, 74, 87). Notably, thymidine phosphorylase is the main enzyme responsible for activating capecitabine to 5-FU. This enzyme is highly expressed in both atherosclerotic plaques and cancer tissues, explaining why patients with previous coronary artery disease (CAD) are at higher risk of developing CTX. At a molecular level, upregulation of endothelin 1 and activation of protein kinase C may induce endothelium-dependent and independent vasoconstriction leading to coronary spasms (155).

Her-2 inhibitors

Trastuzumab is the first humanized monoclonal antibody directed against the extracellular domain of HER-2, a protein receptor expressed on myocytes and overly expressed on 30% of breast cancer cell (152). This antibody is mostly used to treat Erb2+ breast and gastric cancer. Combining trastuzumab with standard chemotherapy significantly improves the progression-free survival in patients with metastatic breast cancer (102, 104). Its toxicity is considered to be reversible and dose-independent (41). However, trastuzumab toxicity may lead to irreversible LV dysfunction in patients with CV risk factors, ischemic heart disease, or previous ANT exposure (163). The risk of CTX following trastuzumab ranges

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from 2% in young women to 40% in patients over 75 years of age, with hypertension or ischemic heart disease (14, 166), and is directly related to the patient´s CV risk and concomitant therapies. Indeed, trastuzumab enhances ANT toxicity; therefore, sequential use of these drugs is recommended. In human cardiomyocytes, HER receptors are involved in redox mechanisms through the neuregulin/Erb2 pathway, thus modulating the response to stress conditions including hypertension (61) and ANT therapy (63). ANT may promote a high concentration of ROS, whereas contemporary blockage of HER-2 can induce dysregulation of redox homeostasis (35). Notably, after ANT treatment, KO-mice for Erb-2 gene tend to develop LV dilation and dysfunction (12), whereas experimental overexpression of Erb-2 in mice decreases the ROS concentration in mitochondria and lowers the rate of cell death (38). Moreover, the HER-2 pathway is involved in cell survival and regeneration (160). Additionally, several studies suggest that catecholamines, whose levels increase in presence of LV dysfunction and ANT administration, can induce cardiomyocyte HER-2 expression, particularly exposing these cells to trastuzumab detrimental effects (9)

Nowadays, new HER-2 inhibitors have been introduced as anticancer options, both as an alternative to or in combination with trastuzumab. Pertuzumab is a new recombinant humanized monoclonal antibody that binds domain II of HER-2 and blocks the signaling pathway. Like trastuzumab, pertuzumab also seems to induce modest left ventricular dysfunction in patients with HER-2 positive breast cancer (62, 149), though in a recent phase II study, no significant CTX was observed when adding pertuzumab during trastuzumab treatment (3, 146).

Vascular Endothelial Growth Factor (VEGF) inhibitors

VEGF plays a fundamental role in endothelial and general cardiovascular homeostasis. It comprises several factors (VEGF-A, VEGF-B, VEGF- C, VEGF-D, and PlGF) that exert their effect of activating specific tyrosine kinase receptors in endothelial cells (95) and endothelial colony forming cells (53). VEGFs are also crucial in several myocardial functions and for the integrity of blood vessels (170, 101), thus producing different forms of CTX, mainly hypertension, thromboembolism, LV dysfunction, and HF (122, 176).

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Moreover, tyrosine kinase inhibitors (TKIs) act by inducing both oxidative and endoplasmic reticulum stress, exploiting oxidative stress as a participating mechanism in their therapeutic effects. (182)

Patient treated with Bevacizumab (anti-VEGF mAb) mostly experience hypertension and cardiac dysfunction in 1–3% (113). Regorafenib, a multi-target TKI, was demonstrated to induce hypertension and less frequently, cardiac ischemia and myocardial infarction (15). Pazopanib and Axitinib (inhibitors of VEGFRs, PDGFRA and B, and KIT) can also cause hypertension (115). Novel anti- angiogenic drugs such as Cediranib, Vatalanib, and Nintedanib also exhibit a potential risk of hypertension and HF (64, 173, 137).

Sunitinib and Sorafenib are not selective TKIs, inhibiting several kinases other than VEGFR, thus increasing the risk of cardiac dysfunction (164). The CTX induced by sunitinib also occurs due to interference with ribosomal S6 kinase (171) that then triggers apoptosis (77). Sunitinib also affects myocardial mitochondrial pressure overload (30), paralleled by a decline in intracellular Ca2+ and increase in ROS production, producing a dose-dependent negative inotropic effect (134).

In conclusion, VEGF inhibitors and TKIs affect cardiac function mainly through alterations of mitochondrial function and energy production with an increase in ROS generation (117). Hypertension appears to be the most frequent complication related to the inactivation of endothelial NO synthase and production of vasoconstrictors such as endothelin-1, thus increasing the peripheral vascular resistance (122, 66). However, reduction of NO synthesis associated with endothelial dysfunction during treatment with TKIs was shown to induce plaque instability, significantly increasing the risk of arterial and venous thrombosis.

Antioxidant role of classic cardiovascular drugs

The first approach proposed in treating chemotherapy-related CTX is the use of drugs with antioxidant properties, which can prevent the CTX induced by an increase in ROS (16, 20, 90, 156).

The first drug approved by the FDA in this setting is Dexrazoxane, an iron-chelating drug that has been tested as a cardioprotective agent for ANT-induced CTX.

Dexrazoxane is a pro-drug that is metabolized into its active form in cardiomyocyte cytosol, and inhibits the formation of ANT-iron complexes and ROS production (151).

Its efficacy as a cardioprotective agent has been validated in clinical trials with different tumors and in two pooled analyses (92, 150, 159). Since other iron chelators failed to be effective as cardioprotective agents, it has been suggested that the efficacy of dexrazoxane is related to an additional protective mechanism (151), and the ability to interfere with Top2b configuration preventing the formation of Top2-DNA complexes (89, 94) (Figure 5). This interaction with Top2-b seems to be the main reason for its cardioprotective activity, rather than its iron-chelating properties (157). Given their high costs and reduced availability, traditional HF drugs were also examined in preventing chemotherapy-related CTX (72). This approach proved to be effective considering that their extensive properties to improve myocardial function through several mechanisms are not all completely understood (72). However, an interesting positive effect in counteracting ROS damage has been shown for most of these drugs (13).

Renin-Angiotensin-Aldosterone System (RAAS). In the setting of ANT-induced CTX, the RAAS was proved to have a central role in reducing the progression of myocardial dysfunction and preventing the development of HF in high-risk patients (132). The efficacy of RAAS blockade has been tested in animal models, as angiotensin converting enzyme inhibitors (ACE-Is) counterbalance ANT-induced CTX (1, 13). The effect of ACEIs as cardioprotective agents includes reduced ROS damage, intracellular calcium overload and interstitial fibrosis, and enhanced mitochondrial respiration, and cardiomyocyte metabolism (1, 13) (Figure 5). In animal models, captopril, enalapril, and lisinopril appeared to be effective in acute and chronic ANT-induced CTX (1). More recently, in a small human placebo-controlled trial, enalapril, administered for cardioprotection during ANT treatment was confirmed to reduce the rate of development of symptomatic LV dysfunction (24).

Similarly, angiotensin II receptor blockers (ARBs) candesartan, telmisartan, and valsartan were shown to modulate CTX induced by ANTs in experimental models (69, 120, 153). AT1 seems to mediate the Ang II signaling pathway, playing an important role in DOX-induced

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LV dysfunction. This suggests that an AT1 antagonist can be used to prevent DOX-induced cardiomyopathy (172). In an experimental model, after DOX was administered, cardiomyopathic hearts showed a significant increase in myocardial fibrosis, apoptosis, and the myocyte diameter/body weight ratio, but candesartan treatment was able to reverse these changes (153). Likewise, telmisartan was shown to protect myocardial cells from acute DOX-induced myocardial injury in rats, affecting NO bioavailability and inhibiting the production of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (178). Treatment with telmisartan elicited a significant decrease in the activities of LDH and catalase; in animals pre-treated with telmisartan, a decrease in lipid peroxidation and an increase in GSH content were observed (69) (Figure 5).

In a small prospective study, telmisartan moderated the subclinical cardiotoxic effects of epirubicin (EPI) in humans (20). Early EPI-induced myocardial dysfunction appeared to be reversed by telmisartan and the normal LV systolic function was stabilized during the 18-months of follow-up (47, 48). Finally, valsartan also appeared to be important for preventing acute toxicity, exerting a cardioprotective effect in patients treated with ANTs (120). More recently, several clinical trials have evaluated the role of ACE-Is and ARBs as cardioprotective agents in patients undergoing chemotherapy (91, 115). Prophylactic administration of ACE-Is and ARBs in patients treated with ANTs was shown to be effective in reducing the risk of developing CTX compared with the placebo in a large meta-analysis (74).

Beta-blockers. These represent a basic treatment for HF patients with reduced EF (132), and have been translated to ANT-related CTX settings with encouraging results (19, 37). Their possible use has been hypothesized after the evidence of early impairment of beta-adrenergic receptor (beta-AR) signaling in LV dysfunction caused by ANTs (59). Moreover, in experimental models, a positive effect of beta-AR blockage was observed by the reduction of oxidative stress and myocardial calcium overload (121). However, the majority of last generation beta-blockers (e.g., carvedilol and nebivolol) have mostly been tested in relation with their likely cardioprotective setting. Carvedilol proved to be more effective than atenolol as a cardioprotective strategy in ANT induced LV-dysfunction. This

effect has been attributed to its antioxidant properties rather than to the beta-AR blocking action (103) (Figure 5).

Carvedilol could inhibit ANT-induced ROS release, cardiomyocyte apoptosis (156), and mitochondrial damage (144) in experimental models. Moreover, in the clinical setting, despite the limited sample size of enrolled patients, the incidence of LV dysfunction was reduced when carvedilol was administered before the beginning of ANT treatment (75).

Similarly, in an experimental model of ANT-induced CTX, Nebivolol, a cardioselective beta-blocker with partial vasodilating properties was shown to enhance NO levels and lower oxidative stress, while improving myocardial function (42). More recently, its use as a cardioprotective agent was demonstrated to reduce the incidence of LV systolic dysfunction in patients undergoing ANT-based treatments alone or in association with trastuzumab, when compared with a placebo group (76, 148).

On the contrary, bisoprolol and metoprolol did not prove to be effective as cardioprotective agents (130), suggesting that blockade of beta1 alone without a specific effect in lowering oxidative stress is not sufficient to guarantee effective cardioprotection (65, 160).

Finally, experimental and clinical studies should be planned to evaluate the safety and efficacy of the combination of ACE-Is and beta-blockers in preventing TKI-induced CTX. The need for specific studies in various settings of cancer treatment is mandatory, given the high prevalence of drug interaction and specific treatment effects. For instance, in patients with anti-angiogenic drug-induced hypertension, evidence shows that non-dihydropyridine calcium channel blockers are not indicated due to the pharmacokinetic interaction of sorafenib and sunitinib with CYP3A4 (19, 98).

Experimental antioxidant drugs in cardioprotection

Various drugs whose main indications are remarkably variable, have been deemed efficacious in preventing anticancer drug induced CTX. Various studies have shown that ranolazine (RAN) has cardioprotective effects against LV dysfunction induced by ANTs (33, 34, 136, 141). RAN seems to reduce oxidative stress, thus preserving cardiac function in a mouse model of ANT-induced CTX (23, 169) (Figure 5). Moreover, it can limit calcium

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overload and suppress ROS production (81). The INTERACT study confirmed the cardioprotective effects of RAN in preventing DOX-induced CTX: however, additional studies are needed (114). Furthermore, RAN seems to be efficacious in preventing Trastuzumab-induced heart dysfunction by lowering ROS production. In fact, in a mouse model of trastuzumab CTX, RAN could preserve endocardial fractional shortening and ejection fraction and avoid the increase in natriuretic peptides and matrix metalloproteinase 2 mRNAs (138). However, due to cytochrome interaction, RAN cannot be used during trastuzumab administration (138).

Trimetazidine, another anti-anginal drug that also acts as a scavenger of oxygen-derived free radicals (129), was shown to significantly attenuate DOX-induced CTX as assessed by the tissue distribution of DOX, histological examination, and scintigraphy-derived LVEF. (143) A small randomized clinical trial conducted on 61 patients compared the effect of trimetazidine (TMZ) and dexrazoxane (DEX) in preventing the LV diastolic dysfunction induced by ANT treatment, without significant differences in cardioprotective effects between TMZ and DEX against subacute and chronic subclinical CTX with no significant results after a 1-year follow-up (161).

Phosphodiesterase-5 inhibitors sildenafil and tadalafil seem to have cardioprotective effects against ANT-induced cardiac dysfunction. The former can preserve mitochondrial membrane potential and myofibrillar integrity and can prevent cardiomyocyte apoptosis due to its ability of opening mitochondrial K_{ATP} channels (58); the latter can mitigate LV dysfunction induced by ANT-treatment through NO-mediated pathways (73, 82) (Figure 5). However, a recent small randomized clinical trial failed to demonstrate sildenafil-induced cardioprotection following DOX treatment (131).

In mice, cardiac-specific endothelin-1 overexpression can determine ANT-induced-like cardiomyopathy; furthermore, it DOX was shown to induce an increase in endothelin-1 plasma levels in men. On these grounds, Bien et al evaluated whether pretreatment with the endothelin receptor antagonist bosentan could inhibit the development of ANT-induced CTX in a mouse model. The authors found that bosentan preserved the indices of contractility, reduced the tumor necrosis factor-alpha content, lipid peroxidation, and Bax expression, as well as increased GATA-4 expression (10). More recently, bosentan (most

effective), sitaxentan, and BQ788 (endothelin receptor blocker) were shown to improve the hemodynamic performance in mice treated with DOX through modulation of cardiac gene expression involved in signal transduction, fibrosis, energy production, and oxidative stress (147).

The hormone erythropoietin (EPO) has been demonstrated to be effective in preventing DOX-induced CTX. EPO was found to upregulate silent mating type information regulation 2 homolog 1 (SIRT1) activity, reverse the DOX-induced acetylation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and suppress PGC-1α-activated genes involved in mitochondrial function and biogenesis, including superoxide dismutase 2; accordingly, EPO seems capable of reversing DOX-induced mitochondrial superoxide accumulation. The findings of the study suggested that EPO may activate SIRT1 to enhance mitochondrial function, thus protecting against DOX-induced CTX (36). EPO could also modulate the imbalance of matrix metalloproteinase-2 and its tissue inhibitor (28) and could activate phosphatidylinositol 3-kinase-dependent cell survival pathways (78). EPO was also effective as a cardioprotective compound against CTX induced by mitomycin C (140).

Redox agents such as hydrogen sulfide (H_2S) have already shown protective effects in the setting of ischemia/reperfusion injury (IRI) (32). Given the similarity between IRI and ANT-induced CTX, it has been hypothesized that H_2S can also exert its cardioprotective effect in case of CTX-induced by anticancer drugs.(54, 174) Cystathionine gamma-lyase, a crucial enzyme in the H_2S pathway, is involved in ANT-induced CTX in cardiomyocytes and exogenous H_2S has been shown to protect against CTX (19, 107, 126).

Another compound proposed as a cardioprotective agent is VEGF-B. It plays a crucial role in coronary arteriogenesis, physiological cardiac hypertrophy, and resistance to ischemia (17, 79). The preliminary data collected in a mouse model of DOX-induced CTX seem to suggest that VEGF-B, can a) inhibit cardiac atrophy and body wasting, b) prevent loss of capillaries in the heart thus improving endothelial function, c) avoid apoptosis of endothelial cells (*in vitro* data), and d) determine positive cardiac remodeling and improve mitochondrial respiration in cardiomyocytes (135). These data were indirectly confirmed

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by a recent study showing that resveratrol, a nonflavonoid polyphenol extracted from a variety of plants, can mitigate DOX-induced CTX by upregulation of VEGF-B (167).

Taurine, a conditionally essential amino acid, was demonstrated to induce cardioprotection from DOX as well, reducing the mortality rate in both acute and sub-acute CTX. Its protective effect seems to be due to the inhibition of DOX-induced oxidative stress; moreover, taurine modulates heart gene expression during DOX treatment (70). Similar effects have also been found in the setting of cisplatin-based chemotherapy (29).

Antioxidant role of non-pharmacological strategies in cardioprotection

With the increased survival rates of cancer patients, appraisal of novel and promising forms of treatments aims to mitigate cancer drug-related side effects has become a priority in clinical research and practice (44, 97). Indeed, in addition to the cardioprotective effects of drug-based therapies, other non-pharmacological treatments such as nutritional supplementation and exercise training programs have been associated with potential beneficial effects (55).

Thanks to their properties, nutritional supplements such as omega-3 fatty acids and coenzyme Q10 represent relatively novel yet established options to significantly reduce the sensitivity of oxidative stress damage in cardiomyocytes. Their effects occur via various mechanisms, ranging from the enhancement of antioxidant defense, to changes in membrane fluidity, and reversion of DOX-induced myocyte apoptosis and fibrosis (26, 40) (Figure 5). In the last decade, dietary supplements with antioxidative proprieties such as phytochemicals and Chinese herbal medicines, been investigated in animal studies, and have showed efficacy in contrasting DOX-induced CTX (2). They limit DOX-mediated oxidative stress mechanisms by a) decreasing ROS generation and reducing lipid peroxidation (*e.g.*, *Boswellia ovalifoliolata* ethanolic extract, Astragalus polysaccharide, Grape extract, *Aerva lanata*, Ellagic acid, Yam extracts, Folic acid, indole-3-carbinol, Resveratrol), b) by increasing the production of antioxidants in cells (*e.g.*, Allicin, Quercetin, Spinochrome D, Scutellarin, Pristimerin), c) by regulating the expression of Nrf2 and increasing the antioxidative stress products NQO1, HO-1, and GST (*e.g.*, Sulforaphane,

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Baicalein, Asiatic Acid, *Ganoderma lucidum* polysaccharides, Dioscin, p-Coumaric acid, Tanshinone IIA, Pristimerin, Spinochrome D) (154).

The key role of regular exercise in the prevention of oncological disease and in the attenuation of cancer treatment-related side effects has been the focus of a number of clinical investigations over the past 15 years (127, 21).

Data from animal models showed cardioprotective effects for different aerobic exercise programs (*e.g.,* acute, short-term, and long-term interventions) prior to, during and, most recently, after multiple cycles of DOX treatment, thus mitigating DOX-induced cardiac injuries and dysfunctions (67, 88, 100, 177). Specifically, these studies have revealed that exercise-induced cardioprotection against DOX-exposure could be associated both with improvement in antioxidant capacity such as manganese superoxide dismutase (SOD), copper-zinc SOD, and glutathione peroxidase (GPX), and exercise-induced NOX2 modulation (4, 8, 88)(Figure 5). In addition, exercise-induced autophagy/mitophagy promotion has been associated with prevention of DOX-induced oxidative injury and cell death, due to the antioxidative effect of exercise linked to NOX2 suppression rather than other major enhanced antioxidant enzymes (88)(Figure 6).

Currently, several animal studies support the role of aerobic exercise as a preventive and adjuvant approach to manage the side effects of cancer drugs. Future investigations in patients are needed to identify the appropriate intensity, frequency, duration, and length of exercise training for the primary and secondary prevention of CTX associated with different currently available chemotherapeutic drugs.

CONCLUSIONS

Given the increasing rate of cancer survival, counteracting the CTX of both old and recent cancer therapies has become an issue of primary importance. Numerous strategies were tested to reduce CTX from antineoplastic agents, although they were only partially satisfactory given the complexity of the oncological setting associated with an elevated number of side effects.

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Moreover, a high percentage of patients with subclinical CTX develop significant myocardial dysfunction only years after therapy completion, making it difficult to assess the efficacy of the cardioprotective approach.

However, several pharmacological and non-pharmacological approaches have proved to reduce oxidative stress and consequently CTX in experimental models, but we are still far from being able to translate these results into clinical practice.

Probably, a better understanding of biochemical and molecular mechanisms by which anticancer agents affect cardiomyocytes will facilitate determination of the best strategy for implementing cardioprotection, which should be personalized and targeted to individual patients.

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List of Abbreviations

4HNE	4-Hydroxy-2'-NonEnal
5-FU	5-FluoroUracil
8-Oxo-dG	8-Hydroxy-deoxyguanosine
ACE-Is	Angiotensin Converting Enzyme Inhibitors
ANT	Anthracycline
ARBs	Angiotensin II Receptor Blockers
AT1	Angiotensin II receptor subtype 1
Bax	BCL2 Associated X
beta-AR	beta-Adrenergic Receptor
Ca^{2+}	Calcium
CAD	Coronary Artery Disease
CTX	Cardiotoxicity
CV	Cardiovascular
DEX	DEXrazoxane
DNA	DeoxyriboNucleic Acid
DOX	Doxorubicin
EF	Ejection Fraction
EPI	Epirubicin
EPO	Erythropoietin
GATA-4	Transcription factor GATA-4
GPX	Glutathione Peroxidase
GRP75	Glucose-Regulated Protein 75
GSH	Glutathione
GSSG	Glutathione disulfide
GST	Glutathione S-Transferases
FADH2	Flavin adenine dinucleotide
H_2O_2	Hydrogen Peroxide
H_2S	Hydrogen Sulfide
HER-2	Human Epidermal growth factor Receptor 2

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HO-1	Heme Oxygenase 1
Erb2	Receptor tyrosine-protein kinase erbB-2
HF	Heart Failure
HMGBI	High Mobility Group Box 1
HSPb6	Heat Shock Protein beta-6
IL	Interleukin
KIT	Tyrosine-Protein Kinase KIT
LDH	Lactate DeHydrogenase
LV	Left ventricular
MDA	MaloniAldehyde
MPO	MyeloPerOxidase
mRNAs	Messenger RNA
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide Phosphate
Nrf2	Nuclear factor erythroid 2-like 2
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NOX2	NADPH oxidase 2
NQO1	NAD (P)H:Quinone Oxidoreductase
O_2•-	Radical Anionic Superoxide
OH•	Hydroxyl Radical
OONO-	Peroxynitrite
P53	Protein 53
PDGFR	Platelet-erived Growth Factor Receptor
PGC-1α	Peroxisome proliferator-activated receptor gamma Coactivator 1-alpha
PlGF	Placental Growth Factor
RAAS	Renin-Angiotensin-Aldosterone System
RAN	Ranolazine
RNA	RiboNucleic Acid
RNS	Radical Nitrogen Species

ROS	Radical Oxygen Species
SIRT1	Silent mating type information regulation 2 homolog 1
SOD	SuperOxide Dismutase
TKIs	Tyrosine Kinase Inhibitors
TLR	Toll-Like Receptor
TMZ	TriMetaZidine
TNF	Tumor Necrosis Factor
TOP2	Topoisomerase 2
VDAC2	Voltage-ependent Anion-selective Channel protein 2
VEGF	Vascular Endothelial Growth Factor
VEGFRs	Vascular Endothelial Growth Factor Receptor

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Figure Legend

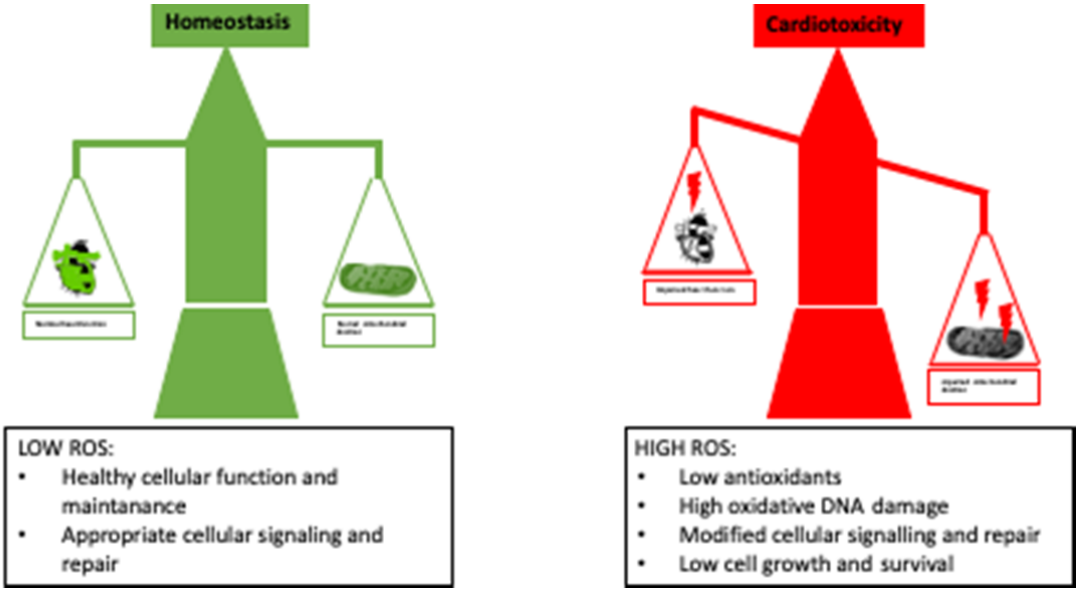

Figure 1

Cardiac imbalance due to cancer treatment

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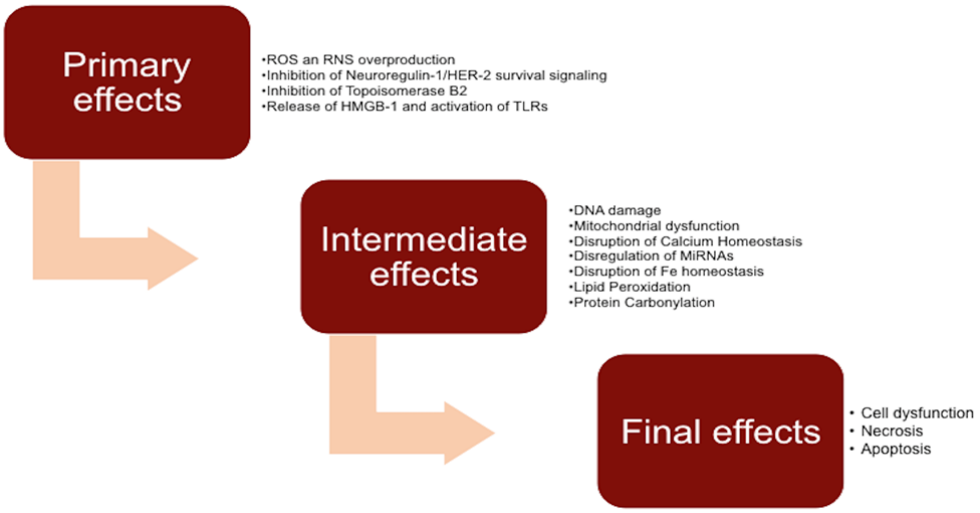

Figure 2

Effect of cancer therapy on myocardial cells

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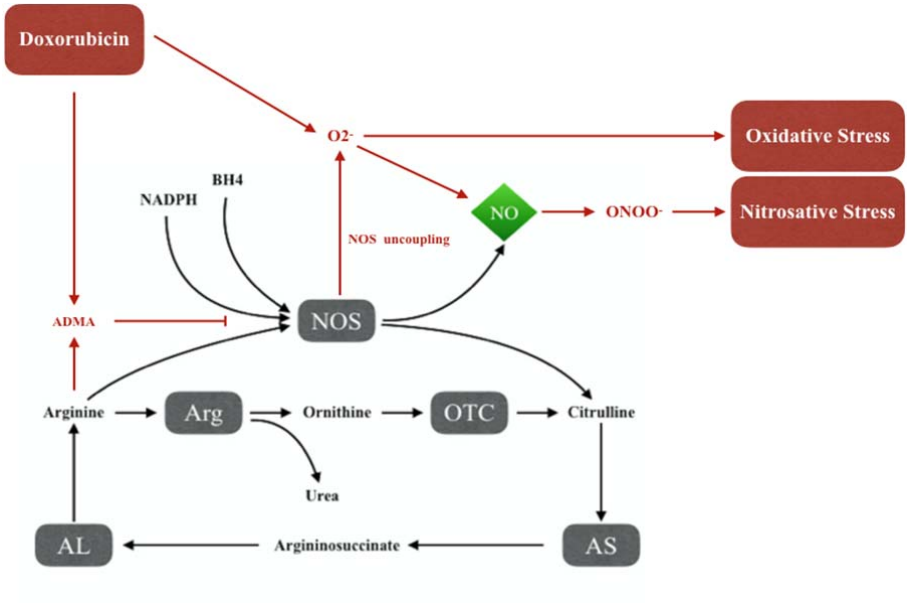

Figure 3

DOX related effects on oxidative/nitrosative stress

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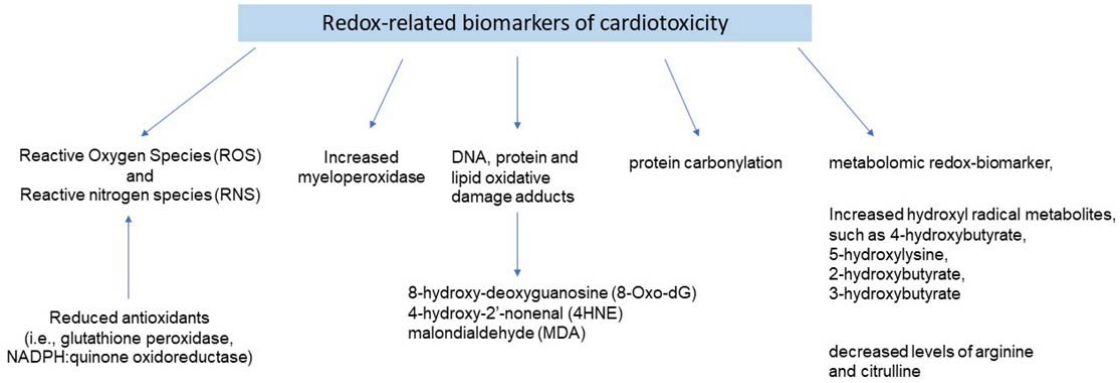

Figure 4

Main redox-related biomarkers of cardiotoxicity

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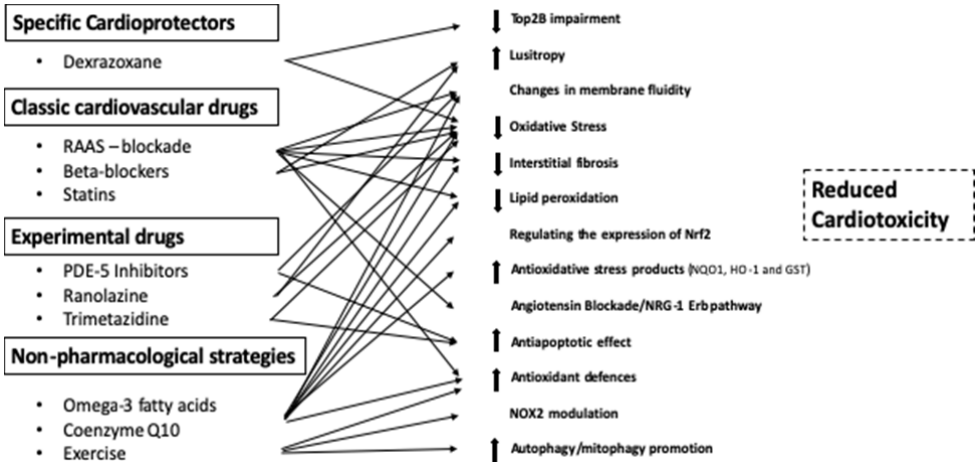

Figure 5

Strategies related effects for CTX cardioprotection

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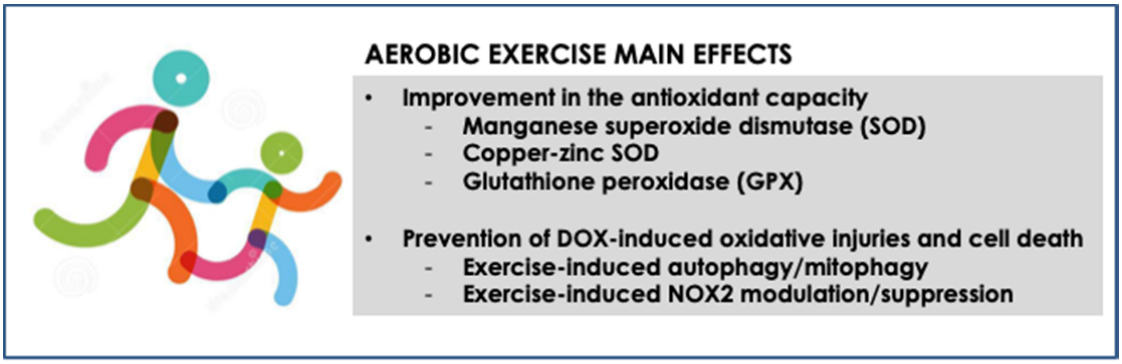

Figure 6. Cardioprotective effects of aerobic exercise

Figure 6

Cardioprotective effects of aerobic exercise

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