Food and Chemical Toxicology 134 (2019) 110834

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

An update on the mechanisms related to cell death and toxicity of doxorubicin and the protective role of nutrients

Alfonso Varela-López[a], Maurizio Battino[b,c,d], María D. Navarro-Hortal[a], Francesca Giampieri[b], Tamara Y. Forbes-Hernández[c], José M. Romero-Márquez[a], Ricardo Collado[e], José L. Quiles[a,*]

[a] Department of Physiology, Institute of Nutrition and Food Technology "José Mataix", Biomedical Research Centre, University of Granada, 18071, Granada, Spain
[b] Dipartimento di Scienze Cliniche Specialistiche Ed Odontostomatologiche (DISCO)-Sez, Biochimica, Facoltà di Medicina, Università Politecnica Delle Marche, 60131, Ancona, Italy
[c] Nutrition and Food Science Group. Department of Analytical and Food Chemistry, CITACA, CACTI, University of Vigo, Vigo, Spain
[d] International Research Center for Food Nutrition and Safety, Jiangsu University, Zhenjiang, China
[e] Complejo Hospitalario Universitario de Cáceres, Cáceres, Spain

ARTICLE INFO

Keywords:
Adriamycin
n-3 PUFA
Selenium
Vitamin A
Vitamin C
Vitamin E

ABSTRACT

Doxorubicin (DOX), is a very effective chemotherapeutic agent against cancer whose clinical use is limited by toxicity. Different strategies have been proposed to attenuate toxicity, including combined therapy with bioactive compounds. This review update mechanisms of action and toxicity of doxorubicin and the role of nutrients like vitamins (A, C, E), minerals (selenium) and n-3 polyunsaturated fatty acids. Protective activities against DOX toxicity in liver, kidney, skin, bone marrow, testicles or brain have been reported, but these have not been evaluated for all of the reviewed nutrients. In most cases oxidation-related effects were present either, by reducing ROS levels and/or increasing antioxidant defenses. Antiapoptotic and anti-inflammatory mechanisms are also commonly reported. In some cases, interferences with autophagy and calcium homeostasis also have shown to be affected. Notwithstanding, there is a wide variety in duration and doses of treatment tested for both, compounds and DOX, which make difficult to compare the results of the studies. In spite of the reduction of DOX cardiotoxicity in health models, DOX anti-cancer activity in cancer cell lines or xenograft models usually did not result compromised when this has been evaluated. Importantly, clinical studies are needed to confirm all the observed effects.

1. Introduction

Doxorubicin (DOX) or adriamycin (ADR) is an antibiotic initially isolated from *Streptomyces peacetius,* although currently it can be chemically synthesized. This substance belongs to anthracyclines, a class of chemotherapeutic drugs with a large spectrum of activity. Namely, DOX is a non-selective class I anthracycline that possess two differentiated moieties, an aglyconic moiety that consists in a tetracyclic ring with quinine–hydroquinone adjacent groups and a methoxy substituent short side chain followed by the carbonyl group. The second one, known as daunosamine, comprises a 3-amino-2,3, 4-trideoxy-L-fucosyl moiety. This sugar is attached to one of the rings by a glycosidic bond (Hilmer et al., 2004).

DOX, alone or in combination with other drugs, has been employed for more than 40 years to fight against cancer, showing great efficacy in cell killing in both hematological liquid and solid tumors (Weiss, 1992). Actually, it can be considered as one of the most potent of all 132 Food and Drug Administration (FDA)-approved chemotherapeutic drugs (Carvalho et al., 2009). In particular, DOX is essential in treating breast and esophageal carcinomas, solid tumors in childhood, osteosarcomas, Kaposi's sarcoma, soft tissue sarcomas, and Hodgkin and non-Hodgkin lymphomas (Minotti et al., 2004; Quiles et al., 2002, 2006).

DOX combats rapidly-dividing-cells and delays the progression of the disease, characteristics that have led to its reputation as a very important chemotherapeutic agent. However, drug resistance and side effects are important limitations to its clinical use. Side effects related to intravenous (iv) injection of DOX are mainly a consequence of its toxicity on non-cancerous cells, which is particularly notably at the heart level. Toxicity occurs both in acute and chronic modes, affecting the overall outcome of the patients (Bonadonna et al., 1969; Cardinale et al., 2010; Praga et al., 1979; Steinherz et al., 1991). Acute toxicity includes nausea, vomits, myelosuppression and arrhythmia, and appear

* Corresponding author.
E-mail address: jlquiles@ugr.es (J.L. Quiles).

https://doi.org/10.1016/j.fct.2019.110834
Received 19 July 2019; Received in revised form 10 September 2019; Accepted 21 September 2019
Available online 29 September 2019
0278-6915/

Abbreviations

OH	hydroxyl radical
ADR	adriamycin
AMPK	AMP-activated protein kinase
ATM	ataxia-telangiectasia mutated protein
bw	body weight
CPK	creatine phosphokinase
cTnI	cardiac troponin I
DHA	docosahexanoic acid
DOX	doxorubicin
dsDNA	double strand DNA
eNOS	endothelial nitric oxide synthase
EPA	eicosapentanoic acid
ER	endoplasmic reticulum
ERK	extracellular signal–regulated kinases
FDA	Food and Drug Administration
GPX	glutathione peroxidase
GSH	reduced glutathione
H_2O_2	hydrogen peroxide
ig	intragastric
IL	interleukin
INF-γ	interferon -γ
iNOS	inducible nitric oxide synthase
ip	intraperitoneal
iv	intravenous
JNK	c-Jun-N-terminal kinase
LAMP-2A	lysosome-associated membrane protein 2
LDH	lactate dehydrogenase
LKB1	liver kinase B1
MAPK	mitogen-activated protein kinase
MDR	multidrug resistance
MMP	matrix metalloproteinase
mPTP	mitochondrial permeability transition pore
mtETC	mitochondrial electron transport chain
mTOR	mammalian target of rapamycin
MUFA	monounsaturated fatty acids
NF-κB	nuclear factor κB
NOX	NAD(P)H-oxidases
$O_2^{\cdot}$	superoxide anion
$ONOO^-$	peroxynitrite
P-gp	P-glycoprotein
PKB	protein kinase B
Po	perioral
PPARγ	proliferator–activated receptor γ
PUFA	polyunsaturated fatty acids
RNS	reactive nitrogen species
ROS	reactive oxygen species
SOD	superoxide dismutase
TFEB	transcription factor EB
TNF-α	tumor necrosis factor α
UCP2	uncoupling protein 2

within minutes after infusion. On the other hand, chronic toxicity may be developed several weeks or even months after the recurrent administration of the drug, leading to heart, liver, and brain or kidney injury. Cardiotoxicity is the most prominent side effect and involves cardiomyocyte damage as well as apoptotic and necrotic cell death (Wang et al., 2012). Since cardiomyocytes are post-mitotic cells, a great proportion of the damage is irreversible, affecting thus to cardiac function and leading to a dose-dependent cardiomyopathy and congestive heart failure (Chen et al., 2007; Quiles et al., 2002, 2006). The long-term effects are such that even years after stopping treatment, left ventricular dysfunction, dilated cardiomyopathy and heart failure may appear (Colombo et al., 2013; Lipshultz et al., 2012, 2010). Neurons and brain function may also be affected, with the possibility of persistent changes at the cognitive level. These cognitive changes include memory and concentration losses as well as difficulty completing multiple tasks (Chen et al., 2007). However, the repercussions at the cardiac level are more prevalent and important than those observed in the rest of organs, and since the survival of cancer patients continues to increase, the clinical significance of DOX-related cardiotoxicity must be considered in depth (DeSantis et al., 2014).

2. Mechanisms related to cell death and toxicity

The mechanisms of action of doxorubicin are common both to the cancer cells that the clinical treatment aims to attack and to the healthy cells that are affected as a side effect of this treatment. In the following sections the known mechanisms of action for the drug will be presented, without specifying whether such mechanisms are responsible for the efficacy of the treatment or its toxicity.

2.1. DNA alterations associated to the presence of doxorubicin in the nucleus

DOX enters the cell by diffusion. Once in the cytoplasm it binds to the 20S subunit of the proteasome thanks to its high affinity, forming a DOX–proteasome complex (Carvalho et al., 2009). This complex is able to diffuse into the nucleus through the nuclear pores where interact with nuclear proteins and DNA. This is possible because of the dissociation of DOX from the proteasome due to variations in affinity (Kiyomiya et al., 2001). DOX interactions at the nucleus lead to DNA alterations, which finally result in cell damage and death. Unfortunately, these cellular damages not only occur in cancer cells, but also in healthy cells, which at least in part explains some of the toxic effects of adriamycin. The possible mechanism involved in alterations in DNA caused by the presence of adriamycin in the nucleus are described below.

2.1.1. Actions on topoisomerase II

It has been hypothesized that DOX functions as a trap for topoisomerase II at cleavage sites, stabilizes the cleavage complex and avoids the resealing of DNA, thus leading to more double strand DNA (dsDNA) breaks (Nitiss, 2009). At the moment, this has been reported for etoposide, an anthracycline related to DOX (Nitiss, 2009). Cells would attempt to repair DNA breaks, but if this fails, apoptosis pathway would be triggered and cellular growth would be inhibited at phases G1 and G2 (Broeyer et al., 2014). Response against DOX-induced DNA damage involves Ataxia-Telangiectasia Mutated protein (ATM) that results activated by binding to DNA break sites activating, in turn, the tumor suppressor protein p53 (Yoshida et al., 1990). It has been reported that p53 suppresses the cardioprotective transcription factor GATA-4 when is up-regulated as consequence of DOX treatment (Park et al., 2011). Nevertheless, activation of some p53-independent pathways in relation to DOX presence in cardiomyocytes has been reported (Feridooni et al., 2011). Importantly, p53 is mutated in many human cancers and both ATM and p53 have been implicated in the response of tumors to DOX therapy (Jackson et al., 2012; Jiang et al., 2009), which could be related resistance to this drug. Overall, it seems that the role of p53 in mediating the multiple DOX-induced deleterious effects is context dependent, and likely depends on the experimental model used and the timing of the assessment. Emphasizing the importance of this mechanism, it has been shown that topoisomerase II levels determine the effectiveness of DOX treatment in a mouse model of lymphoma (Burgess et al., 2008). However, based on existing evidence, it is unlikely that this is the only mechanism through which anthracycline

drugs kill cancer cells (Sørensen et al., 1992; Swift et al., 2006). In addition, chromatin-associated processes as replication and transcription could be dramatically affected by DOX due to this role as topoisomerase inhibitor (Liu and Wang, 1987). Other findings also suggest that trapping topoisomerase IIβ (the predominant form of topoisomerase II in non-dividing cells) by DOX in non-dividing heart cells underlies DOX-induced cardiotoxicity (Vavrova et al., 2013; Zhang et al., 2012). Following the same reasoning, the potential capacity of adriamycin to modify histones could have effects not yet discovered that would be independent of its actions related to chromatin.

2.1.2. Formation of doxorubicin-DNA adducts

It has been reported that the formation of DOX-DNA adducts might contribute to increased effectiveness of the drug in DOX-sensitive tumor cells. In fact, DOX has the ability to intercalate itself into the DNA base pairs (Vincent et al., 2013). This allows the formation of covalent DOX-DNA adducts during chemotherapy, as has been evidenced (Coldwell et al., 2008). This DNA intercalation has been also associated with dsDNA breaks and progressive mitotic catastrophe since it inhibits the DNA and RNA polymerases, ultimately ceasing DNA replication and RNA transcription (Tacar et al., 2013). DOX-DNA adducts have been shown to activate DNA damage responses and to induce cell death in a topoisomerase II trap-independent manner (Forrest et al., 2012; Swift et al., 2006). Despite the evidence that DNA adducts form during DOX treatment, DNA adduct formation is unlikely to be the main mechanism of DOX action, because the amount of adducts formed represents just a small fraction of total DOX (Swift et al., 2006). It seems that adducts are formed by hydrogen-bond between DOX and guanine, which would explain why DOX prefers an intercalation site with adjacent GC base pairs (Chaires et al., 1987, 1990; Chen et al., 1986a). Interestingly, the interaction between DOX and DNA can be stabilized by a covalent bond mediated by cellular formaldehyde, which can be originated in free radical reactions from carbon sources such as lipids and spermine (Taatjes et al., 1997, 1996).

2.1.3. Alterations in the topology of DNA and nucleosome destabilization

Intercalation of ADR within the DNA induces its unwinding which, in turn, could destabilize the nucleosomes due to the positive torsional stress originated. A comparison between nucleosome turnover profiles in mouse squamous carcinoma cells before and after DOX treatment showed that DOX enhanced nucleosome turnover around active gene promoters, despite it had a minor effect on gene expression level. This enhancement was independent of the DNA damage response proteins p53 and ATM, which is particularly important since p53 is mutated in many human cancers (Jackson et al., 2012; Jiang et al., 2009).

Moreover, some anthracyclines including DOX are able to evict histones from regions of accessible chromatin leading to impairment of DNA repair and apoptosis as it has been reported in both, acute myeloid leukemia blasts isolated from patients, and human melanoma cell lines (Pang et al., 2013). In addition, results found in topoisomerase IIα-depleted cells suggest that such enzyme is not required for DOX-induced histone eviction (Pang et al., 2013). Additionally, topoisomerase II inhibition could exacerbate the torsional stress caused by these drugs, leading to enhancement of nucleosome turnover downstream of promoters. Supporting this finding, increased positive torsion and nucleosome turnover in gene bodies and *vice versa* have been reported in intergenic regions of *Drosophila* cells treated with inhibitors of topoisomerases I and II (Teves and Henikoff, 2014). Therefore, DOX treatments may have dramatic effects on chromatin-associated processes, including replication and transcription, as consequence of its inhibitory activity on Topoisomerase II. In addition, nucleosome destabilization during RNA polymerase transit would increase DNA exposure to insults such as reactive oxygen species (ROS), causing DNA breaks, and ultimately cell death.

Another potential mechanism for DOX-induced nucleosomes unwrapping lays on DOX effect on replication and transcription processes. The positive torsion generated ahead of RNA polymerase (Liu and Wang, 1987) can potentially unwrap nucleosomes, which are negatively supercoiled, and destabilize them (Lee and Garrard, 1991). DOX intercalation into promoters and genes might act by interfering with the balance between maintaining promoters free of nucleosomes while preventing loss of nucleosomes during transcription. However, there is no clear evidence confirming this model yet.

2.2. Ceramide overproduction

Ceramide is a lipid molecule implicated in growth arrest, apoptosis, and senescence (Senchenkov et al., 2001). Different studies have reported that DOX treatment increases ceramide levels (Delpy et al., 1999; Kawase et al., 2002; Lucci et al., 1999). Also, ceramide production has been related to DOX resistance in studies comparing MCF-7 cells versus the resistant MCF-7-AdrR cells (Liu et al., 2008, 2001; Uchida et al., 2004). However, more studies are needed to explain how DOX ultimately modulates ceramide formation.

2.3. Production of free radicals and ROS

Adriamycin has the ability to increase the production of free radicals and ROS through various mechanisms. ROS overproduction and antioxidant depletion may cause oxidative stress, leading to DNA, proteins and lipids damage, which altogether contributes to major cellular damage and death (Miura et al., 1995). Among damaged proteins, there are enzymes which may, directly or indirectly, perform key roles in cell protection. Among other consequences, it is possible that oxidative modifications of certain enzymes leads to alterations on chromatin and DNA damage.

ROS have been already recognized as signaling molecules participating in many cellular processes including stress response. Further, subcellular compartmentalization of ROS may contribute to it (Brown and Griendling, 2015). Key enzymatic activities also could be modulated by this way. This would explain AMP-activated protein kinase (AMPK) activation reported in embryonic ventricular myocardial H9c2 rat cells in response to ROS (Chen et al., 2011). Increased levels of ROS induced by DOX treatment would activates dependent liver kinase B1 (LKB1), an upstream signal necessary for AMPK activation. This process ultimately leads to p53 phosphorylation and apoptosis. In any case, this implies that the development of strategies to reduce morbidity and mortality associated with oxidative stress must focus on subcellular ROS or down-stream molecular signals. Rather than eliminate ROS, it seems that modifying cellular responses to excessive levels is a more effective strategy.

2.3.1. Formation of semiquinone radicals by NAD(P)H-oxidoreductases

NAD(P)H-oxidoreductases such as the mitochondrial electron transport chain (mtETC) complex I and plasma membrane NADPH-oxidases (NOX) are able to oxidize the quinone structure of DOX through addition of one electron producing a semiquinone radical (Berlin and Haseltine, 1981; Minotti et al., 2004). Semiquinone radicals react with O_2 to generate superoxide anion ($O_2^{\cdot-}$), which subsequently give rise to other ROS and reactive nitrogen species (RNS) such as hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}OH$) or peroxynitrite ($ONOO^-$). Consequently, DOX is reconverted into quinone, leading to a quinone-semiquinone cycle able to generate large amounts of $O_2^{\cdot-}$, and subsequently ROS and RNS species (Chen et al., 2007; Quiles et al., 2006).

2.3.2. Activation of NAD(P)H-oxidoreductases

DOX activates NOXs, which give rise to free radicals that participate in activating the apoptotic pathway in cardiac cells (Gilleron et al., 2009). NOX activation may generate $ONOO^-$ through the mitochondrial production of ROS as $O_2^{\cdot-}$ and the reaction with nitric oxide (NO) (Kimura et al., 2005). $ONOO^-$ also activates matrix metalloproteinases

(MMPs); these proteases have been implicated as a major mechanism of the $ONOO^-$-dependent cardiotoxicity of DOX (Bai et al., 2004).

2.3.3. Alterations of nitric oxide synthases

In vitro, DOX has shown to be able to bind reductase domain of endothelial nitric oxide synthase (eNOS) generating $O_2^{\cdot-}$ (Vásquez-Vivar et al., 1997). Moreover, it is known that renal NO is an important controller of urinary sodium excretion. Thus, altering NO system at the kidney could also cause salt-sensitive hypertension.

2.3.4. Mitochondrial dysfunction

Alternatively, DOX might be metabolized into a lipophilic aglycone capable of diffusing through the mitochondrial membrane and accumulating within it. This aglycone is the starting point for several reactions that release electrons, producing ROS and disturbing the functional integrity of the respiratory chain (Chen et al., 2007). Inner mitochondrial membrane is very susceptible to lipid peroxidation since DOX has a high affinity for negatively-charged membranes (Nohl, 1988; Tacar et al., 2013). In particular, cardiolipin peroxidation uncouples mitochondrial respiratory chain complexes resulting in mitochondrial dysfunction, and thus in reduced ATP and increased ROS production (Cheung et al., 2015; de Wolf, 1991; Parker et al., 2001; Robinson, 1993). In cardiomyocytes, mitochondrial production of ATP primarily is required for contractile function. Still, other important processes such as some ER protein quality control mechanisms, cytoskeletal reassembly, protein synthesis, or autophagy also needs ATP (Biswas et al., 2008; Hahn-Windgassen et al., 2005). However, mitochondrial dysfunction induced by DOX treatment would led to ATP deficient cardiomyocytes (Lv et al., 2012) that also exhibit increased proteotoxic load (Li et al., 2014). This last suggest that DOX treatment comprises protein degradation, overwhelming the endoplasmic reticulum (ER) and mitochondria and contributing to cardiac injury (Li et al., 2014). Notwithstanding, these can be a consequence of additional DOX effects different from those on ATP production.

On the other hand, formation of mitochondrial permeability transition pore (mPTP), that facilitates the release of the intrinsic apoptosis pathway inducer cytochrome C, is promoted as consequence of DOX-induced peroxidation of mitochondria. Interestingly, necrotic cell death also is associated with mPTP (Galluzzi et al., 2012).

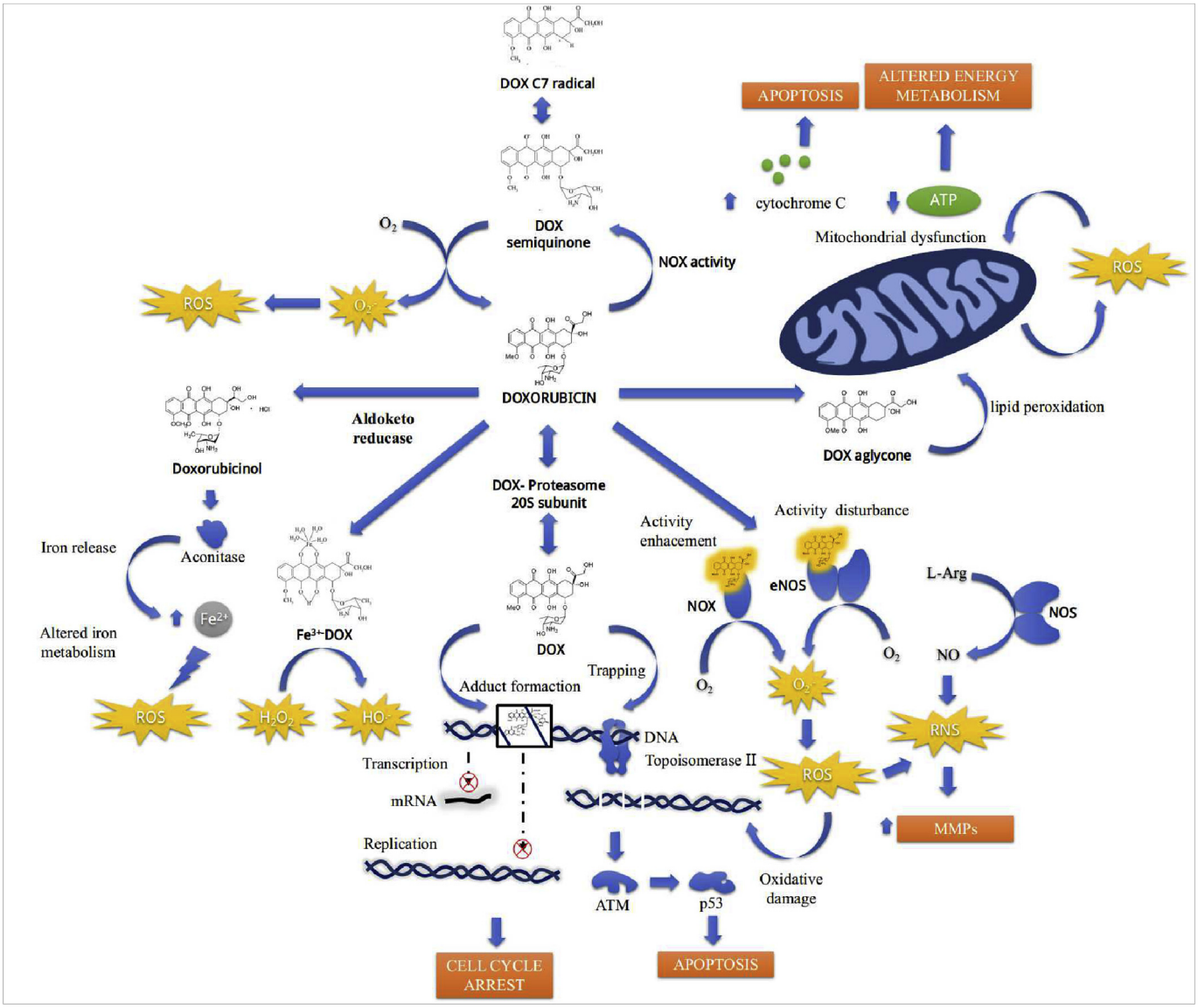

Fig. 1. Main molecular mechanisms of doxorubicin toxicity. Abbreviations: ATM: ataxia telangiectasia mutated protein, DOX: doxorubicin, MMP; Matrix metalloproteinase, ROS: reactive oxygen species, NOX: NAD(P)H oxidase, NOS: Nitric oxide synthase, eNOS: endothelial nitric oxide synthase, RNS: reactive nitrogen species, L-Arg: L-Arginine.

2.3.5. Iron-coupling and production of hydroxyl radicals

DOX treatment could affect to iron metabolism and its cell levels by different mechanisms. On the one hand, aldoketo reductases are able to convert the side chain carbonyl group of the carbon 13 of DOX into an OH group, giving rise to doxorubicinol, a secondary alcohol. Then, this chemical form can release iron from cytoplasmic aconitase, disturbing the iron metabolism and subsequently leading to oxidative stress. In addition, DOX interferes with non-enzymatic metabolic reactions which implies a ROS production facilitated by iron. Likewise, the DOX semiquinone form, as well as ROS such as $O_2^{\cdot-}$, and H_2O_2, can promote the release of iron from ferritin and cytoplasmic aconitase altering iron metabolism. DOX also acts as an iron chelator forming a complex that catalyzes the conversion of H_2O_2 to ·OH that is highly reactive (Myers, 1998).

2.3.6. Disturbances in calcium homeostasis

The treatment with DOX increases intracellular Ca^{2+} at the ventricular myocardium, including that found at the mitochondrial level. Moreover, calcium transport is also affected as consequence of changes at ionic channels of the sarcoplasmic ER (Quiles et al., 2006). These alterations might help to explain some aspects associated to DOX-related cardiomyopathies. Variations in the intracellular levels of Ca^{2+} associated to adriamycin treatment also affect the muscle function by altering the balance in the response of the myotubes, disrupting skeletal muscle relaxation and producing a restriction in the contraction (van Norren et al., 2009). Down-regulation of the calcium/calmodulin-dependent protein kinase II gene expression has been observed in cardiomyopathies associated to chronic administration of DOX. This finding correlated with a reduced expression of sarcomeric proteins, cardiac function depletion and a greater injury (Little et al., 2009).

Moreover, the endocannabinoid system might have a role in DOX-induced cardiotoxicity, since the use of cannabinoid-1-receptor antagonists can reverse the cardiodepressive effects of endocannabinoids (Mukhopadhyay et al., 2007). Similarly, some alterations possibly related with the unbalance in the cellular levels of calcium have been also reported at the brain. Cardoso et al. (2008) have reported that DOX treatment (2 mg/kg) increases the susceptibility of brain mitochondria to Ca^{2+}-induced mPTP opening and oxidative stress in rats, which in this case predisposed brain cells to degeneration and death. Part of the events linked to DOX-induced cardiotoxicity (probably triggered by the elevated ROS levels) might explain the reported disturbances in Ca^{2+} homeostasis. Among others, such events include the direct inhibition of key transporters involved in ion homeostasis and cellular iron and calcium metabolism alterations. In addition mitochondrial dysfunction and the disruption of the sarcoplasmic ER function should be considered (Berthiaume and Wallace, 2007). In particular, the reduced DOX metabolite, doxorubicinol, is able to interfere with the calcium pump of the sarcoplasmic reticulum, ATP2A2, and the Na^+/K^+ pump of sarcolemma, RYR2 (Minotti et al., 1998; Mordente et al., 2009). Fig. 1 presents main molecular mechanisms treated in the preceding section.

2.4. DOX interactions with autophagy

Alterations in proteolytic processes have been consistently found in cardiomyocytes exposed to DOX. Actually, the treatment with this anthracycline leads to an increased proteotoxic load in cardiomyocytes (Li et al., 2014). This suggests that protein degradation pathways are compromised, overwhelming the ER and mitochondria. This has been associated with a decrease in ATP production, but also can result from DOX-induced alteration of autophagic machinery that contributes to the quality control of cell components. Indeed, numerous studies have demonstrated that DOX-induced cardiac injury is associated with dysregulation in autophagic function (Bartlett et al., 2016; Ge et al., 2016; Kawaguchi et al., 2012; Li et al., 2016; Sun et al., 2014; Wang et al., 2014; Wu et al., 2014). Different up-stream regulatory signals that govern autophagy, including mammalian target of rapamycin (mTOR) and AMPK (ATP and ROS might also be considered among them), have shown to be deregulated by DOX, leading to a robust initiation of autophagy and stimulation of autophagosome formation (Terman and Brunk, 2005). Importantly, strategies aimed at reversing DOX's effect on autophagy initiation and autophagosome formation have shown to attenuate cell death (Sishi et al., 2013).

The autophagic process must be completed through autophagosome clearance to take advantage of its protective effect. Recent studies suggest that DOX-mediated cardiac dysfunction could be determined by inhibiting autophagic flux at the lysosome rendering lysosomes incapable of processing proteotoxic load in spite of their actions on macroautophagy upstream processes (i.e. regulation of autophagy initiation) (Li et al., 2016; Pizarro et al., 2016). For instance, robust accumulation of non-degraded and dysfunctional autolysosomes have been reported in cardiomyocytes exposed to DOX (Li et al., 2016). Up to date, inhibition of lysosomal biogenesis and/or lysosomal function seem the most feasible mechanism for this effect of DOX (Bartlett et al., 2016; Kawaguchi et al., 2012; Li et al., 2016; Xu et al., 2013). It remains to be established if DOX targets lysosomal signaling proteins to modulate autophagic function in cardiomyocytes. In this sense, it is also plausible that DOX might interrupt chaperone mediated autophagy with the concomitant inhibition of lysosomal function. Such effect, attributed to its action on mitochondrial function, would starves cardiomyocytes by ATP deprivation. However, little is known on the implications of chaperone-mediated autophagy in DOX cardiotoxicity at the present. Notwithstanding, treatment with daunorubicin, a DOX-related compound, led to increased expression of the chaperone Hsc70 in a rabbit model (Stěrba et al., 2011). More recently, it has been reported that lysosome-associated membrane protein 2 (LAMP-2A) is suppressed in H9c2 cardiomyoblasts after chronic treatment with DOX (Bartlett et al., 2016).

It is possible that defects at the transcriptional level might be responsible of autophagy-related effects of DOX in cardiac cells, which could result in proteotoxic stress and cell death. It is also plausible that the potential effects of DOX on the different steps of the process would be related to the loss of the transcription factor EB (TFEB) expression, signaling and action after DOX exposure. Supporting this hypotheses, DOX-treated cardiomyocytes showed depleted TFEB levels, which correlated with impaired autophagic flux, decreased expression of LAMP-2A, reduced lysosomal content and lysosomal dysfunction (Bartlett et al., 2016). On the other hand, TFEB restoration or activation attenuated DOX-mediated suppression of the activity of the lysosomal protein cathepsin B, reduced overproduction of ROS and increased cell viability in cardiomyocytes (Bartlett et al., 2016). Anyway, to clarify the direct consequences of DOX treatment on lysosomal TFEB and its impact on autophagy in the heart, research utilizing models of cardiomyocyte with specific TFEB alterations is needed.

Results from a murine genetic modified model of lysosomal environmental changes has shown that baseline levels of mitophagy are high at the heart in comparison with other organs (Sun et al., 2015). Mitophagy plays a fundamental role in cardiomyocyte survival under various cellular stresses. This is because this process targets defective mitochondria for autophagic elimination contributing to a mitochondrial quality control. Thus, cardiomyocytes ensure clearance of dysfunctional mitochondria in the lysosome via mitophagy, a process that has also shown to be sensitive to DOX (Dirks-Naylor et al., 2014; Gharanei et al., 2013). In adult female rats, DOX treatment resulted in an increase in PINK1 and a decrease in p62 in intermyofribilar mitochondria, while Parkin content did not vary. These results suggest that DOX induced mitophagy are mediated by Parkin upregulation (Kavazis et al., 2017). However, other authors proposed that DOX mediates inhibition of Parkin translocation to the mitochondria with impaired subsequent p62 translocation as has also been described (Hoshino et al., 2013). Still, contribution of each mitophagy specific receptor to baseline and DOX-associated mitophagy needs to be

determined. Moreover, the increased levels of ROS and apoptotic initiating proteins released after DOX treatment have also been associated with inhibited clearance of damaged mitochondria (Bin-Umer et al., 2014; Kubli and Gustafsson, 2012). This modulation of mitophagy seems to depend on Parkin p53-dependent inhibition (Hoshino et al., 2013). Moreover, some associations between alteration of mitochondrial functioning induced by DOX and resultant disruptions in autophagy have been revealed by additional studies (Ge et al., 2016; Sun et al., 2014). Overall, these studies suggest that DOX treatment leads to mitophagy disruption via dysregulation of various cytosolic and mitochondrial signaling axes. Subsequent dysfunctional mitochondria accumulation would cause ROS overproduction and ATP starvation.

Interestingly, several studies have reported that stimulation of autophagy prior to the administration of DOX can protect from its harmful effects. For instance, administration of the mTOR inhibitor rapamycin prevents DOX-induced cardiomyopathy in mice (Xu et al., 2013). Similar results have been found for the combination of resveratrol with moderate caloric restriction that activates AMPK (Dutta et al., 2014). It is hypothesized that a modest activation of autophagy would eliminate dysfunctional mitochondria and remove toxic aggregates which boost cellular health prior DOX insult. Fig. 2 summarizes the interactions between autophagy and DOX.

3. Nutrients with preventive and therapeutical properties against doxorubicin toxicity

According to the information presented above, it is clear that DOX can exert toxic effects by multiple mechanisms affecting cancer, but also non-cancer cells. In turn, DOX toxicity to non-cancer cells would ultimately lead to acute and chronic alterations at different organs and tissues (Bonadonna et al., 1969; Cardinale et al., 2010; Praga et al., 1979). Consequently, future well-being and lifespan of persons treated with DOX can result seriously compromised, which is an important limitation to its clinical use. This background makes essential to find strategies to reduce DOX toxicity and there are several ways to achieve this. The first option is optimizing the dosage (Chen et al., 2007), but even a continuous infusion of low doses of DOX reaching a cumulative dosage under of 450–550 mg/mL can elevate the risk of cardiotoxicity

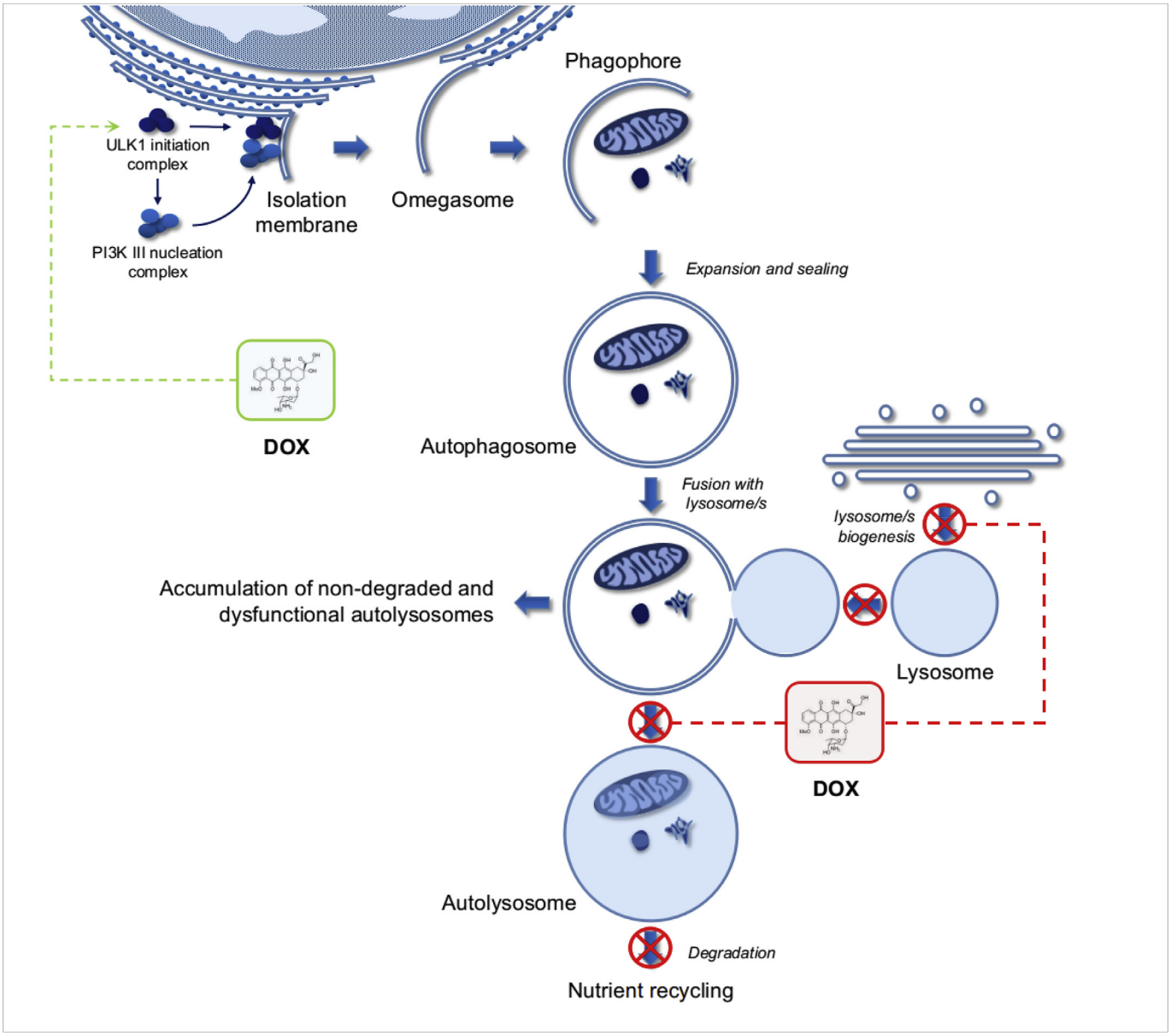

Fig. 2. Doxorubicin interaction with macroautophagic proccess. AMPK, AMP-activated protein kinase; DOX, doxorubicin; PI3K, phosphatidylinositol 3-kinase.

(Verma et al., 2008). Another strategy is to synthesize and use DOX analogues with equivalent activity but less toxicity. Finally, a third possibility is to use substances, either combined with DOX, or administered prior to the treatment, that protect against or prevent from DOX toxic effects. This last strategy has received a considerable interest (Granados-Principal et al., 2010; Quiles et al., 2002).

Dexrazoxane is a drug that has been used with this aim since it is able to chelate the free iron ions released by DOX (Chen et al., 2007; Della Torre et al., 1999a, 1999b; Minotti et al., 2004; Xiang et al., 2009). Still, multiple compounds present in the diet have been proposed to protect against DOX toxicity (Granados-Principal et al., 2010; Quiles et al., 2002). Its use has been usually intended to reduce levels of DOX-induced free radicals. This could be the consequence of free-radical scavenging activities presented by such compounds, but many of them also have shown to interact with components of different cellular regulatory pathways including mitogen-activated protein kinases (MAPKs), peroxisome proliferator–activated receptor γ (PPARγ), serine/threonine protein kinase Akt/protein kinase B (PKB) and/or nuclear factor κB (NF-κB). There is certain controversy about the use of substances able to reduce DOX toxicity. For instance, it has been postulated that different antioxidant compounds can diminish the antitumor activity of DOX by eliminating the oxidative component connected with the toxic side-effects but also with the anti-neoplastic actions. Nevertheless, there are a growing number of studies reporting that many of these bioactive compounds does not diminish the efficacy of DOX, but rather they would prevent some of its toxic side effects. In many cases, they even would act in synergy with DOX anti-neoplasitc activity despite reducing its toxicity (Ozben, 2007).

Because of their clinical and social relevance, this review summarizes recent findings about the use of various nutrients to protect against DOX toxicity and the possible mechanisms explaining such effects. For this, an initial search was done in PubMed to identify main compounds of interest. Then, an individualized search was performed for each compound to collect the highest number of published studies for each compound on this topic as possible.

3.1. Vitamin E

Vitamin E is a nutritional term referring to a family of eight molecules with “similar biological activities” (Lobo et al., 2010; Srividya et al., 2010). Vitamin E (Wong and Radhakrishnan, 2012) is a well-known lipid-soluble antioxidant (Traber and Atkinson, 2007) that prevents lipid and lipoprotein peroxidation into cellular membranes protecting cells and tissues from oxidative damage (Packer et al., 2001; Quiles et al., 2002, 2006; Roy et al., 2002). This property was taken into account for many researchers to carry out investigations on vitamin E potential for preventing DOX-based chemotherapy side effects. Despite an old study reported that vitamin E potentiated DOX toxicity (Alberts et al., 1978), most of earlier preclinical studies in rodents have shown that oral vitamin E tends to protects against acute and chronic toxic effects of DOX, specially at heart, without interfering with its effectiveness as chemotherapeutic agent (Geetha et al., 1990; Herman and Ferrans, 1983; Krivit, 1979; Milei et al., 1986; Myers et al., 1976). Additionally, some old preclinical studies have also observed that oral vitamin E even tended to increase anti-tumor actions (Quiles et al., 2006; Ripoll et al., 1986; Tanigawa et al., 1986). Still, other authors had reported no effect of certain treatments with vitamin E on DOX toxicity (Breed et al., 1980; Legha et al., 1982; Van Vleet and Ferrans, 1980).

During the last decades, some new studies confirming vitamin E protective or preventive actions against DOX toxicity have been carried out, many of them administrating this compound intraperitoneally. A single dose of vitamin E (100 mg/kg of body weight [bw], intraperiotoneal [ip]) prior to a DOX injection (4 mg/kg of bw, ip), has shown to reduce the electrocardiographic changes, as well as the DOX-caused increase in serum levels of the biochemical markers of cardiac injury creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) in Wistar male rats (Puri et al., 2005). Similarly, a study in the same similar model showed that an 8-day treatment with vitamin E (100 mg/kg of bw per day, ip) inhibited hepatotoxic effects of a higher dose of DOX (20 mg/kg of bw, ip) (Gokcimen et al., 2007). Likewise, other authors reported that vitamin E (200 IU/kg of bw per week, ip), reduced hepatotoxicity associated to a 6-week treatment with DOX (5 mg/kg of bw per week, intravenous [iv]) in male Sprague–Dawley rats (Kalender et al., 2005). Interestingly, in guinea pigs, vitamin E administration (500 mg/kg of bw, ip) even reversed some degenerative changes at the ultrastructural level derived from a DOX injection (5 mg/kg of bw, ip) when it was administrated during 5 days from the day of injection (Görgün et al., 1999). Some positive effects have been also reported when vitamin E was orally administrated. Washio et al. (1994) reported an improvement of focal glomerulosclerosis condition with progressive renal failure induced by two injections of DOX (2 mg/kg of bw) administered in a 20-days period by a 5-days pretreatment with α-tocopherol (500 IU/Kg of bw per day, intragastric [ig]) in male Lewis rats. In contrast, consumption of a diet supplemented with D-α-tocopheryl succinate for one week prior to begin a 7-week DOX-based chemotherapeutic treatment (2 mg/kg of bw in 7 weekly subcutaneous [sc] injections) was unable to prevent histopathological alterations at male rat heart induced by the drug (Berthiaume et al., 2005). However the supplemented amount (2 g/kg of diet) was very low in comparison with the previous study. In contrast, oral vitamin E (100 IU/kg of bw, perioral [po]) was also ineffective in reducing cardiotoxicity induced by a single dose of DOX (10 mg/kg of bw) (Berthiaume et al., 2005). Notwithstanding, in this case the drug was intravenously administrated, and of vitamin E was orally administrated in a single dose (100 IU/kg of bw, po) as post-treatment, so DOX toxicity could be higher and/or the tested vitamin E treatment could be very weak. All these findings suggest that this type of acute interventions with vitamin E can be interesting to modulate DOX acute toxicity, although results supporting validity of these type of compounds as protective agents against DOX toxicity if they are administrated by oral via only have been reported at kidney. Likewise, a single dose of vitamin E (200, 400 or 800 mg/kg of bw, ig) reduced the total number of chromosomal aberrations at bone marrow cells induced by a single and high dose of DOX (90 mg/kg of bw, ip) in rats, obtaining the best result with the lowest one (Antunes and Takahashi, 1998). A diet supplemented with vitamin E at different doses (45, or 200 mg/kg per day) 2 weeks prior to initiate a DOX treatment (5 mg/kg of bw in 3 daily injections to reach a cumulative dose of 15 mg/kg of bw, ip) also prevented decreases in blood cells in mice inoculated with L1220 leukemia cells (Thabrew et al., 1999). However, vitamin E-supplemented diet consumption was unable to mitigate DOX-induced leucopenia in Fisher 344 rats at low (50 mg/kg of diet) or high (750 mg/kg of diet) doses, although this means a lower daily dose of vitamin E respect than the previous study taking into account that rats daily intake was 15 g of diet (Branda et al., 2006). Lastly, topical application of vitamin E (10%) in hydrophilic gels alone or in combination with other antioxidants, two days before and five after intradermal administration of DOX (0.05 mg), reduced ulcers size and accelerated epidermal regeneration respect than rats only receiving DOX (Lucero et al., 1996). Similar protective effects against DOX-induced skin lesions for α-tocopherol in combination with dimethyl sulfoxide have been already reported in early studies, an ability proposed to be used for prevention against local consequences of DOX extravasation during iv infusion in humans (Svingen et al., 1981a, 1981b).

Those experiments reporting Vitamin E beneficial effects against DOX toxicity usually related the improvement of antioxidant defenses and reduction of ROS generation and oxidative damage, particularly lipid peroxidation (Dominguez-Rodriguez et al., 2001; Kalender et al., 2005; Quiles et al., 2006; Thabrew et al., 1999; Wahab et al., 2000). Notwithstanding, it has been reported that dietary vitamin E was unable to prevent the heart mitochondrial dysfunction caused by DOX in rats in spite of a decrease in DOX-induced oxidative damage was

detected (Berthiaume et al., 2005). Here, the effect could be not enough as consequence of the low amount of vitamin provided. Likewise, in mice, DOX-induced oxidative damage at the liver was shown to be prevented by a single dose (10 and 50 mg/kg of bw) of d-α-tocopheryl N,N-dimethyl aminoacetate hydrochloride, a water-soluble vitamin E derivative, 2 h prior to a single injection of DOX (15 mg/kg of bw, ip) (Nagata et al., 1999). Pretreatment with oral vitamin E supplementation also decreased DOX-induced oxidative damage at blood cells in mice inoculated with L1220 leukemia cells which correlated to increases in superoxide dismutase (SOD) activity (Thabrew et al., 1999). Importantly, some authors (Nagata et al., 1999; Thabrew et al., 1999) have also reported no reduction of efficacy in mice inoculated with L1220 leukemia cells or even an increase in chemotherapy efficacy by vitamin E treatments despite it showed positive effect on health cells. In this sense, a 2-weeks vitamin E treatment (250 mg/kg of bw per day, po) in parallel with administration of DOX (4 mg/kg of bw per week, ip) led to an increase in the average lifespan of the animals and the number of long-term survivors in Ehrlich ascites carcinoma-bearing mice (Wahab et al., 2000).

In sharp contrast, clinical studies up to date suggest that vitamin E does not protect against DOX chronic cardiotoxicity, and provides only slight protection against acute cardiotoxicity (Conklin, 2000; Quiles et al., 2002, 2006). Still, there are interesting results concerning DOX treatment consequences in skin and some mucosa. A preliminary study by Ludwig et al. (1987) in DOX-treated patients found positive effects of topically applied vitamin E in prevention of skin ulcers by weakening ulcer aggressiveness and accelerating skin regeneration. However, oral topical application of 2 ml of vitamin E (800 mg of DL α-tocopheryl acetate diluted with corn oil) 24 h after DOX administration, once daily for 2 weeks, did not reduce oral mucositis in children under chemotherapy (2–6 DOX-containing chemotherapy cycles) (Sung et al., 2007). Table 1 presents a summary of the effects of vitamin E on DOX toxicity.

3.2. Vitamin C

Vitamin C or L-ascorbic acid is a water-soluble antioxidant (Padh, 1991) scavenging ROS from cell aqueous fraction before these molecules can give rise to lipid peroxidation (Conklin, 2000). For this reason, several studies have been conducted to investigate possible effects of the administration of vitamin C on DOX toxicity. In 1991, Shimpo et al. reported that daily delivered ascorbic acid (2 g/kg of bw, sc) increased lifespan in BD2FI mice receiving repeated administration of DOX at a dose of 5 mg/kg of bw, but not when a dose of 1 mg/kg of bw (ip) was administered. Similarly, daily ascorbate (835 mg/kg of kg) prolonged the life of guinea pigs after injecting a single dose of DOX (2 mg/kg of bw) without any effect on median lifespan. However, ascorbate did not protect against body weight loss in of these experiments. Earliest myocardial ultrastructural alterations in cardiac tissues from guinea pigs obtained on day 17 after 4 injections of DOX (0.5 mg/kg of bw) were not observed when they were co-administered with ascorbate (Shimpo et al., 1991). Co-treatment with vitamin C (100 mg/kg of diet per week, ip) mitigated increases in serum biomarkers of cardiac injury and some histological alterations as infiltration, myofibrillar loss and edema induced by a 3-weeks treatment with DOX (1.5 mg/kg per week, ip) in rats with 1,2-dimethyl-hydrazine-induced colorectal cancer (Injac et al., 2009). However, protective effect against DOX hepatotoxicity was almost absent (Injac et al., 2009).

Importantly, oral intake of vitamin C has been also tested in animals with promising results. Prevention of increases in biochemical markers of cardiac injury and histopathological findings found after a 15-days treatment with DOX (2.5 mg/kg of bw six equal injections, ip) were reduced by a 15-days pre-treatment with ascorbic acid (20 mg/kg of bw, po) in Wistar rats (Viswanatha Swamy et al., 2011). In this last study, ascorbic acid was also used as post-treatment after DOX injection, reducing the severity of cellular damage at the myocardium as confirmed by histopathology, but without effect on the rest of markers, suggesting that post-treatment had weaker protective effects (Viswanatha Swamy et al., 2011). Prophylactic and concurrent daily treatment with vitamin C (50 mg/kg of bw, ig) improved cardiac structure and function in rats treated with DOX (2.5 mg/kg of bw, ip to reach a cumulative 114 dose of 15 mg/kg of bw) over 3 weeks, improving survival (Akolkar et al., 2017). In addition, oral vitamin C administration counteracted clastogenic consequences of DOX (90 mg/kg of bw, ip) in Wistar rat bone marrow cells using high doses of vitamin C (200, 400 or 800 mg/kg of bw) (Antunes and Takahashi, 1999; Tavares et al., 1998). However, no differences concerning mitotic index values were found, suggesting that vitamin C does not affects the proliferation of the osteoclast progenitor cells. Interestingly, the lowest dose seemed to be more efficient in decreasing the total number of chromosomal aberrations at bone marrow in animals treated with DOX. The authors tried to explain their finding as a consequence of the antioxidant properties of vitamin C at low doses and its pro-oxidant effects with higher doses. The protective effect of vitamin C at low doses (10 μM) on leukocytes was also supported by a previous study reporting an effective reduction of micronuclei in DOX-treated (1.5 or 10.2 μM) human lymphocytes without cytotoxicity sings (Amara-Mokrane et al., 1996).

At the heart, oxidative damage markers measured in different studies (Akolkar et al., 2017; Shimpo et al., 1991; Viswanatha Swamy

Table 1
Vitamin E effects on DOX toxicity.

Model	Organ/tissue/cell affected (administration via)	Effects *vs.* DOX toxicity[1]	Effect on cell signaling and/or DOX efficiency[2]
Rodents	Heart (oral)	▼ ECG alterations	
		▲ Antioxidant defenses	
		▼ ROS generation	
		▼ Oxidative damage	
	Liver (ip)	▲ Histopathological alterations	
		▲ Antioxidant defenses	
		▼ Oxidative damage	
	Kidney	▼ Biochemical markers of injury	
		▼ Alterations in TEM	
	Skin (topical)	▲ Regeneration	
		▼ Ulcers	
	Bone marrow (ip)	▼ Mutagenity	
	Red blood cells (oral)	▲ Antioxidant defenses	
		▼ Oxidative damage	
Cell lines	HEK cells	▼ ROS production	▼ p53 activation

Abbreviations: ECG, electrocardiogram; ip, intraperitoneal; ROS, reactive oxygen species; TEM, transmission electron microscopy. [1]A green arrow indicates positive effect. The direction of the arrow indicates that the effect or process on which it applies is increased or decreased. [2]A black arrow indicates that the corresponding cellular signaling process is activated (upwards) or inactivated (downwards).

et al., 2011) suggest that vitamin C reduces oxidative stress associated to DOX. This has been associated with increases in the concentration of reduced glutathione (GSH) as well as in the activity of SOD, and catalase until arrive to normal values (Injac et al., 2009; Viswanatha Swamy et al., 2011). Therefore, toxicity would be reduced by scavenging ROS as consequence of restoration of the endogenous antioxidant system depicted by vitamin C (Viswanatha Swamy et al., 2011). In addition, oral vitamin C has been shown to reduce DOX-induced-increases in the apoptosis markers Bnip-3, Bak, and caspase-3 (Akolkar et al., 2017) and pro-inflamatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-6 (Akolkar et al., 2017). An interesting finding from one of this studies was that vitamin C upregulated cardiac vitamin C transporter proteins (sodium-ascorbate cotransporter 2 and glucose transporter 4) which were reduced by DOX treatment alone. This could have a crucial role in improving antioxidant status in this cardiomyopathy by increasing the intracellular concentration of ROS scavenger molecules (Akolkar et al., 2017). Similar conclusion about the protective effect of vitamin C arise from studies in cardiomyocytes isolated from adult (Wold et al., 2005) and neonate (Yamanaka et al., 2003) rats, as well as in cell lines, namely H9c2 cardiomyocytes (Choi et al., 2007; Chularojmontri et al., 2005; Kim et al., 2006). In this sense, a lower production of ROS has been reported in cardiomyocytes isolated from adult Sprague-Dawley rats treated with vitamin C (Ludke et al., 2017). As expected, cardioprotective effects of vitamin C has been associated with prevention of apoptosis in this assay (Ludke et al., 2017), but also with autophagy. Namely, vitamin C pretreatment (25 μM) prevented the activation of stress-induced proteins p53, p38 MAPK and c-Jun N-terminal kinase (JNK) which also has shown to be induced by DOX treatment (10 μM) (Ludke et al., 2017). Anyway, vitamin C effects on autophagy, apoptosis and on signaling was mainly attributed to its antioxidant properties (Ludke et al., 2017). Moreover, ultrastructural features associated to DOX toxicity that were prevented by vitamin C in guinea pigs might be related to prevention autophagy induction and to apoptosis rate decrease (Shimpo et al., 1991). On the other hand, there is an interesting alternative closely related to vitamin C that has also been tested in this context, ascorbyl palmitate, which is a lipid-soluble molecule, instead water-soluble like vitamin C. Ascorbyl palmitate (50 mg/kg of bw, ip) was also tested by Shimpo et al. (1991) reporting that DOX-associated lipid peroxidation in mouse heart was reduced after a treatment with this molecule for 5 days before plus 5 days after a single subcutaneous injection of DOX (15 mg/kg of bw).

On other hand, some preclinical studies carried out in different cancer cell lines have generated certain controversy about vitamin C effects on the anti-tumor activity of DOX. In two human breast cancer lines (MCF-7 and MDA-MB-231) some pretreatments with ascorbic acid (1 and 100 mM) has shown a strong synergistic action on DOX (ranged from 10^4 to 10 mM) (Kurbacher et al., 1996). Interestingly, both non-toxic (1 mM) and moderately cytotoxic concentrations (100 mM) similarly contributed to DOX effect in MCF-7 line, whereas a clear dose-dependency was found in MBA-MB-231 cells. These findings points out the relevance of the type of cell line in the modulation of DOX antineoplastic activity by vitamin C that is likely to be *in vivo* transferable to tumor or cancer type. In contrast, other results indicate that the use of vitamin C to prevent the toxic effects of DOX may not be an effective choice. Wells et al. (1995) reported that a more stable ascorbate derivative, L-ascorbic acid 2-phosphate (2 and 10 mM) enhanced resistance to DOX in a DOX-resistant MCF-7 cell line but has no effect on a DOX-sensitive MCF-7 cell line. In this sense, vitamin C caused a dose-dependent decrease in apoptosis in cancer cell lines of leukemia (K562) and lymphoma (RL) treated with DOX (Heaney et al., 2008). In this last study, it was found only a modest effect on intracellular ROS, suggesting a mechanism of action that is not mediated by ROS. However, vitamin C prevented DOX-induced mitochondrial membrane depolarization, an activity with interesting consequences from a mechanistically standpoint by its role in apoptosis (Heaney et al., 2008). On the other hand, DOX ROS accumulation in human ovarian carcinoma cells 3AO exposed to ultrasounds was decreased by vitamin C, at least at a final concentration of 10 mM (Yu et al., 2003). This could be a consequence of the increase in the expression of the multidrug resistance (MDR) transport protein P-glycoprotein (P-gp) by ascorbic acid as has been reported in NOX-1 over-expressing prostate tumor cells (Wartenberg et al., 2005). Curiously, no up-regulation of P-gp or vitamin C retention was found in the first study mentioned (Heaney et al., 2008). Thus, the reported vitamin C inhibition of the anti-tumor action of DOX could operate by different mechanisms, whose importance could depend on cell line or vitamin C dose. The contradiction respect than vitamin C effect on DOX anti-tumor activity is also present in studies in animals. In the study by Shimpo et al. (1991), daily ascorbic acid (2 g/kg) had no effects on DOX (5 mg/kg of bw, ip) anti-tumor action in mice inoculated with leukemia L1210 or Erlich ascites carcinoma (three injections of 0.5 mg/kg of bw, ip). In contrast, a study on mice with lymphoma cell-derived xenogeneic tumors shows that iv dehydroascorbic acid (250 mg/kg of bw, iv) reduced the therapeutic efficacy of DOX. Pro-oxidant effect of vitamin C at high doses have been suggested as responsible for this controversial findings (Conklin, 2000; Quiles et al., 2002, 2006). Despite the controversy, vitamin C is commonly used to compare the protective activity of other compounds against the toxic effects of DOX. Table 2 presents a summary of the effects of vitamin C on DOX toxicity.

3.3. Vitamin A and carotenoids

Retinoids, as vitamin A, and carotenoids, are lipid-soluble pigments derived from plants, but also from animal sources. Vitamin A comprises

Table 2
Vitamin C effect on DOX toxicity.

Model	Organ/tissue/cell affected (administration via)	Effects *vs.* DOX toxicity[1]	Effect on Cell signaling and/or DOX efficiency[2]
Rodents	Heart (oral)	▼ Histopathological alterations ▼ Biochemical markers of injury ▼ Alterations in TEM ▲ Antioxidant defenses ▼ Oxidative damage	▼ p53 activation ▼ JNK activation ▼ p38 MAPK activation Efficiency: ↑/↓
	Bone marrow (ip)	▼ Oxidative damage (at low doses)	
Isolated cells	Rat cardiomyocytes	▼ ROS levels ▼ Apoptosis ▼ Autophagy initiation	▼ p53 activation ▼ JNK activation ▼ p38 MAPK activation
	Human lymphocytes	▼ Micronuclei	
Cell lines	H9c2 cells	▼ Cell death	
	Cancer cells (MCF-7 and MDA-MB-231, K562, RL)		Efficiency: ↑/↓

Abbreviations: MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; TEM, transmission electronic microscopy; ip, intraperitoneal. [1]A green arrow indicates positive effect. The direction of the arrow indicates that the effect or process on which it applies is increased or decreased. [2]A black arrow indicates that the corresponding cellular signaling process is activated (upwards) or inactivated (downwards).

2 possible chemical forms: retinol, termed "vitamin A_1", and dehydroretinol, called "vitamin A_2". Carotenoids are closely related to retinoids because many of them are vitamin A precursors (Holden et al., 1999). An important antioxidant activity has been reported for these dietary compounds (Krinsky and Johnson, 2005; Livrea et al., 1961). Overall, both vitamin A and carotenoids have been administered during or before DOX administration aimed to diminish its toxicity. Retinol and its metabolite retinol palmitate administered at similar doses (3.3 mg/kg of bw, ip) in mice have shown to reduce lipid peroxidation in heart, brain membranes, liver microsomes and kidney, but they does not facilitate the anti-tumor action of DOX (Quiles et al., 2006). Similarly, a daily pretreatment with a natural derivative of vitamin A, all-trans-retinoic acid (0.5 mg/kg of bw, ip) preserved mice cardiac histology and prevented increases in serum biochemical biomarkers of cardiac injury after DOX treatment (2.5 mg/kg of bw, ip, twice weekly) for 3 weeks (Khafaga and El-Sayed, 2018). In addition, the assessment of TNF-α and IL-6 levels and cardiac caspase 3 and p53 levels suggested, respectively, that this compound had an anti-inflammatory actions and that prevented mitochondrial apoptotic pathway activation (Khafaga and El-Sayed, 2018). The effects of vitamin A on the consequences of DOX-based chemotherapy have also been evaluated in bone. Thus, Gülkaç et al. (2004) reported a protective dose-dependent effect against the DOX-induced chromosomal aberrations in rat-isolated bone marrow cells with 15 μg/kg as the most effective dose. However, a higher dosage (30 μg/kg) was found to be clastogenic. This could be due to the existence of a dose-dependent dual role for vitamin A, as it has been described for vitamin C, at least in this model. However, whether this is due to pro-oxidant and antioxidant activities or to other mechanisms remains unclear. Additionally, retinol increased the efficiency of DOX in mice with P388 leukemia, although this enhancement has not been reported in all cases, e.g. in mice bearing ascites sarcoma 180 (Nakagawa et al., 1985).

Several studies have been conducted on the effects of oil extracted from pequi (*Caryocar brasiliense*), very rich in carotenoids, in the prevention of DOX-induced toxicity and action. Thus, it has been reported the reduction in oxidative stress in normal cells from an Ehrlich solid tumor-bearing mice model when it is applied both, before tumor inoculation and in continuous and concurrent administration with DOX (Miranda-Vilela et al., 2014). Pequi oil also resulted effective in containing tumor growth by increasing internal necrosis and reducing cell proliferation, besides increasing lymphocyte-dependent immunity (Miranda-Vilela et al., 2014). Notwithstanding, other studies focused on specific carotenoids support some of the mentioned effects. Lycopene has received a special attention since it presents a powerful antioxidant activity. A unique dose of this intraperiotoneally administrated lycopene (1.7 or 3.5 mg/kg of bw, ip) following by a single injection of DOX (15 mg/kg of bw, ip) has shown to be enough to ameliorate cardiac cell injury in mice (Karimi et al., 2005). Still, other studies confirmed the protective effect of this compound when orally administrated. Thus, a daily treatment (4 mg/kg of bw in corn oil, ig) for 10 days before a DOX

Table 3
Carotenoids and retinoids effect on DOX toxicity.

Model	Organ/tissue/cell affected (administration)	Effects *vs.* DOX toxicity[1]	Effect on Cell signaling and/or DOX efficiency[2]
Vitamin A			
Rodents	Heart (ip)	▼ Oxidative damage	
	Liver (ip)	▼ Oxidative damage	
	Kidney (ip)	▼ Oxidative damage	
	Brain (ip)	▼ Oxidative damage	
	Bone marrow (ip)	▼ Mutagenity	
		▲ Clastogenesis (at high doses)	
All-trans retinoic acid			
Rodents	Heart (ip)	▼ Histopathological alterations	▼ p53 levels
		▼ Biochemical markers of injury	
		▼ TNF-α and IL-6 levels	
		▼ Apoptosis	
β-carotene			
Rodents	Heart (oral)	▼ Histopathological alterations	Efficiency: ↑
		▼ Biochemical markers of injury	
		▲ Antioxidant defenses	
		▼ Oxidative damage	
	Liver (oral)	▼ Oxidative damage	
Lycopene			
Rodents	Heart (oral)	▼ Histopathological alterations	
		▼ Biochemical markers of injury	
		▲ Antioxidant defenses	
		▼ Oxidative damage	
	Kidney (oral)	▼ Histopathological alterations	
		▼ Biochemical markers of injury	
		▲ Antioxidant defenses	
		▼ Oxidative damage	
	Testicles (spermatogenesis) (oral)	▼ Histopathological alterations	
		▼ Biochemical markers of injury	
		▲ Antioxidant defenses	
		▼ Oxidative damage	
Astaxanthin			
Rodents	Brain (oral)	▼ Hippocampal alterations	Efficiency: ↑
		▼ Cognitive impairment	
		▼ Oxidative damage	
		▼ Inflammatory biomarkers	
		▼ Apoptosis	
Bixin			
In vitro	HL60 cells	▲ Apoptosis	Efficiency: ↑

Abbreviations: ip, intraperitoneal. [1]A green arrow indicates positive effect. A red arrow means a negative effect. The direction of the arrow indicates that the effect or process on which it applies is increased or decreased. [2]A black arrow indicates that the corresponding cellular signaling process is activated (upwards) or inactivated (downwards).

injection (10 mg/kg of bw, ip) has shown to prevent histopatological alterations in heart and kidney tissues (Yilmaz et al., 2006). In the same study, another experimental group received a similar treatment but only for 2 days prior to and 3 days after the administration of DOX. This group also presented normalized levels of plasma creatinine and urea, confirming the role of lycopene in kidney protection (Yilmaz et al., 2006). These results also suggested that the oral administration of this carotenoid for a short period also is useful in reducing DOX toxicity, at least in such organs. Lycopene effect on cardiotoxicity has been corroborated by additional studies. Oral supplementation with a lower dose (5 mg/kg per day) for seven weeks has demonstrated a cardioprotective effect of myocytes of male rats chronically treated with DOX (four equal injections containing 4 mg/kg of bw at week 3, 4, 5 and 6, ip), although it did not prevent cardiac dysfunction (Anjos Ferreira et al., 2007). At the testis, it has been reported that pretreatment with intragastric lycopene (4 mg/kg of bw) reversed the histopathologic changes in rats treated with DOX (10 mg/kg of bw, ip). The treatment prevented deleterious consequences of DOX treatment less explored in this context attributed to spermatogonia and primary spermatocytes apoptosis (Zanetti et al., 2007). Protection affected also germ cell disorganization and separation and gradual loss of spermatogenic cells in association with a marked reduction in testicular size and weight (Ateşşahin et al., 2006). In any case, effects on toxicity of lycopene were related to prevention of DOX-induced oxidative damage again, particularly to lipid peroxidation (Ateşşahin et al., 2006; Yilmaz et al., 2006). This probably occurred as consequence of an increase in some antioxidant defenses, but reduction of ROS production also could be implicated. Interestingly, decreased GSH levels at the heart, kidney (Yilmaz et al., 2006) and testis (Ateşşahin et al., 2006) and a normalized catalase activity were found in heart and kidney tissues of animals treated with lycopene (Yilmaz et al., 2006). Similarly, it has been reported that supplementation with a tomato oleoresin containing mostly lycopene (95%) reduced DOX-induced oxidative DNA damage of cardiomyocytes in rats (Ferreira et al., 2007a). The same authors reported that the treatment maintained lycopene levels raising antioxidant capacity in rat myocardial tissue despite DOX treatment (Ferreira et al., 2007b). Notwithstanding, it is important to note that all-trans-β-carotene (5%), and 13-cis-β-carotene (1%) were also present in the tested product (Ferreira et al., 2007a) which could have contributed to the reported effects.

Another carotenoid particularly important, since it has a great antioxidant activity and is the main vitamin A precursor, is β-carotene. This compound has been evaluated as a protective agent against DOX hepatotoxicity. An early study in rats (Vile and Winterbourn, 1988) showed that treatment with β-carotene inhibited lipid peroxidation in microsomes of liver. Then, Aissa et al. (2012) reported that administration of β-carotene (5.0 mg/kg of bw, ig) for 14 days protected against liver DNA damage produced after an injection of DOX (16 mg/kg of bw, ip). The effect of a lower dosage (2.5 mg/kg) was also tested but it was not effective in reducing genotoxicity. Additionally, β-carotene effects of a microencapsulated form were also tested in the same study. Differences found suggested that the biodisponibility offered by this delivering system could be modified maintaining the protective properties (Aissa et al., 2012).

Other carotenoids that have shown to protect against DOX deleterious effects and that have deserved less attention are bixin and astaxanthin. Astaxanthin treatment (25 mg/kg) protected against DOX-induced memory impairment and restored hippocampal histopathological architecture. This would indicate that this carotenoid might reduce DOX neurotoxicity that usually would lead to decline in cognitive functions, another side effect of DOX-based chemotherapy (El-Agamy et al., 2018). On the other hand, bixin reduced the DNA damage induced by DOX in HL60 cells. In addition, it has been shown an agonistic effect on DOX-induced apoptosis as revealed the apoptotic cells percentage (Santos et al., 2016).

Importantly, different carotenoids including β-carotene, lutein, astaxanthin or fucoxanthin (< 5 μM) have shown to increase DOX efficacy in breast cancer cells in a combined treatment context. Several markers pointed to a synergistic effect of carotenoid and DOX treatment promoting oxidative stress-mediated apoptosis as main cause. Interestingly, normal breast epithelial cells (MCF10A) exposed to similar treatments resulted in non-significant cytotoxicity. Curiously, in breast cancer cells, a low-dose of DOX significantly enhanced cytotoxicity in carotenoid (< 5 μM)-treated cells compared to a high-dose of DOX (> 1 μM) or carotenoid (20 μM) treatment alone (Vijay et al., 2018). If this relationship is maintained *in vivo*, a combined therapy would allow to reduce DOX dose decreasing side effects on health cells. In particular, the synergy between DOX and β-carotene in relation to its antitumor activity has been also noted in two murine solid tumors, the FsaII fibrosarcoma and the SCCVII carcinoma. As suggested, the co-treatment with the carotenoid increased the tumor growth delay (Teicher et al., 1994). Table 3 presents a summary of the effects of carotenoids and retinoids on DOX toxicity.

3.4. Selenium

Selenium is a trace element that forms part of the antioxidant enzyme gluthathione peroxidase (GPX). In fact, it has been widely demonstrated that alterations in selenium levels directly affect the concentration and activity of GPX (Halliwell and Gutteridge, 2015). Given the established relationship between DOX toxicity and oxidative stress, there are an important number of studies investigating possible beneficial roles of selenium against DOX side effects. Earlier studies indicated that oral supplementation with selenium diminished heart injury caused by DOX in animals and fortified the antioxidant defenses of cardiac cells. Curiously, the oldest studies in preclinical models used great animals. In a study in pigs by Van Vleet et al. (1981), dietary supplementation with selenium led to a prolonged survival and delayed onset of leukopenia after a 13-week treatment with DOX (1.6 mg/kg of bw per week, ip). However, the same authors previously reported that pretreatment with intraperitoneally-administrated selenium (0.06 mg/kg of bw) failed to generate cardioprotection in dogs under a 20-week DOX treatment (1 mg/kg of bw to reach a cumulative dose of 400 mg/kg of bw, ip) (Van Vleet et al., 1980). The reason for this lack of effect could reside in the low amount administrated, since co-administration with DOX (2.4 mg/kg of bw, ip, once a week) of a similar dose for 17 weeks resulted in a better survival rate and improved cardiomyopathic symptoms in rabbits (Van Vleet and Ferrans, 1980). Other subsequent studies on dietary selenium reported benefits only in some cases. In mice, no protection against toxicity caused by a single injection of DOX at different doses (15 and 30 mg/kg, ip) was found for a supplementation with selenium (27 mg/kg per day) during 2 weeks before and 5 weeks after the injection (Hermansen and Wassermann, 1986). In contrast, the increase in the degree of structural alterations to sarcomeres caused by a 3-weeks DOX treatment (2.5 mg/kg of bw, ip, twice weekly) has shown to be abolished in rats fed a selenium-supplemented diet (2500 μg/kg of diet) for 8 weeks (Boucher et al., 1995). Importantly, there was a great difference in the amount of DOX administrated, which could explain the absence of effects seen in the first study. Other recent studies have also found protective activity, but weak, of selenium (15 mg/kg of bw, ip) against DOX (20 mg/kg of bw, iv) nephrotoxicity (Bulucu et al., 2008) and hepatotoxicity (Bulucu et al., 2009) in male rats. In turn, there are also some studies carried out in rats investigating the consequences of selenium deficiency on DOX toxicity. Most authors (Chen et al., 1986b; Coudray et al., 1992; Matsuda et al., 1997; Nakano et al., 1989), but not all (Fischer et al., 1992; Sokolove et al., 1993), have reported that selenium deficiency led to an enhancement of DOX cardiotoxicity in rats.

Prophylactic effect of dietary selenium on DOX toxicity seems to be mediated, at least in part, by reductions of oxidative damage in health cells (Boucher et al., 1995). A moderate dietary supplementation with selenium (0.1 mg/kg) increased the total antioxidant activity and GSH

concentration (Danesi et al., 2006) as well as GPX (Boucher et al., 1995; Danesi et al., 2006) and catalase activities (Danesi et al., 2006) in heart of rats treated with DOX in different studies. Likewise, overall, higher DOX-cardiotoxic insults found in the selenium deficient rats were related to a greater formation of ROS with subsequent damage at the levels of lipids, DNA, as well as to mitochondrial dysfunction (Quiles et al., 2002). The administration of selenium increased catalase activity in contrast to chemotherapy alone that led to a decrease in the activity of this enzyme (Popovic et al., 2007). Such effect on catalase activity could be also relevant for preventing damage caused by chemotherapy with DOX alone.

On the other hand, selenium has demonstrated to have synergic effects on DOX toxicity in several malignant cells lines (breast, colon, prostate, lung, small intestine and liver cancer). Thus, when this compound was simultaneously added to the culture medium, apoptosis rate was increased or DNA synthesis was decreased (Li et al., 2007a, 2007b; Vadgama et al., 2000). In MCF-7 breast cancer cells, the increased sensitivity to DOX-induced apoptosis after selenium treatment has been reported to be related to DOX-induced Akt activation repression of selenium (Li et al., 2007b), and Fas death pathway induction (Li et al., 2007a). It also induced massive apoptosis in a DOX resistant cell line derived from human small cell lung carcinoma in a caspase-3 independent manner (Jönsson-Videsäter et al., 2004). Interestingly, this element induced protective responses in normal human mononuclear cells but cytotoxic effects in malignant cells (THP1 monocytic leukemia cells), alone and in conjunction with chemotherapy in the same study that it was administered in the chemical form of methylseleninic acid (Lobb et al., 2018). According to these effects, combined therapies with selenium and DOX can significantly reduce DOX dose-limiting toxicities and potentially improve their anti-cancer efficacy. Importantly, higher methylseleninic acid concentrations were generally more effective in combination with cancer treatments in malignant cells. However, in normal cells higher concentrations of methylseleninic acid were toxic and increased the cytotoxicity of radiation but not chemotherapy (Lobb et al., 2018). These results suggest that selenium should be limited in the applied dosage.

The use of selenium nanoparticles (NPs) have received attention in recent years, reporting synergic effects with DOX on human hepatic cancer cells Bel7402 (Tan et al., 2009). The advantages of selenium NPs in combination with DOX or alone have been corroborated in a hepatocellular carcinoma model in male rats where the treatment with nanoselenium either alone or in combination with DOX was more effective than treatment with DOX alone. Moreover, the NPs also had protective effects against bone marrow and liver cytogenetic toxicity (Abd El-Moneim et al., 2018). Different DOX-coated NPs with selenium polymer (Fang et al., 2018; Kumari et al., 2018; Purohit et al., 2017; Xia et al., 2018) or nanocomposites with additional elements (Deng et al., 2018; Kumari et al., 2018; Luesakul et al., 2018; Purohit et al., 2017; Wang et al., 2018) have been studied. These nanoparticles can be modified with targeting moieties for specific binding to components overexpressed in certain cancer cells to and accumulate in the tumor site (Kumari et al., 2018; Xia et al., 2018). These preparations have shown an interesting potential as cancer therapeutic agents and emerging drug delivery carriers. This would be consequence of pharmacokinetic properties improvement, but also of the synergic effect on different mechanisms under DOX anti-cancer effect (Deng et al., 2018; Fang et al., 2018; Luesakul et al., 2018; Purohit et al., 2017) and alleviating the overall MDR (Kumari et al., 2018). Moreover, some of these studies tested and confirmed the absence of adverse effects (Deng et al., 2018) and reduction of DOX toxicity for some of these NPs (Deng et al., 2018; Fang et al., 2018). Modification of form and structure also is very relevant for its activity since they could have effects on selenium NPs stability. For instance, chemical structures of pullulan selenium NPs decorated with cysteine and folic acid showed more potent activity against cancer cells while showing less toxicity against normal cells (Nonsuwan et al., 2018). In this sense, DOX-coated selenium liposomes have shown to enhance the antitumor efficacy of DOX in tumor-bearing mice (Xie et al., 2018). Overall, all these studies would allow to design specific novel and promising candidates for DOX-based therapies against different cancers. In addition to increase anti-tumor effects of DOX, cancer-specific drug delivery also represents an attractive approach to prevent undesirable side effects increasing the accumulation of the drug in tumors. However, the optimal selenium compound and dose has not yet been fully established. Table 4 presents a summary of the effects of selenium on DOX toxicity.

3.5. N- 3 polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFA) belonging to n-3 series (n-3 PUFA) are the most common fatty acids found in fish, although other foods as nuts or egg yolk also present important amounts. From a nutritional standpoint, n-3 PUFA are essential nutrients since human cells are not able to synthesize them. The amount of these fatty acid presents in cell membranes have important consequences for health, particularly in modulation of inflammatory processes and susceptibility to lipid peroxidation. Overall, preclinical studies in rodents have provided promising results for n-3 PUFA supplementation in relation to DOX side effects. Pretreatment with daily fish n-3 PUFA (400 mg/kg of bw, ig) for 28 days prior and 2 days after receiving a single DOX injection (30 mg/kg of bw, ip) improved different histological features of myocardial acute injury including muscle fibers disorganization, myofibrillar loss, and myocardial fibers with cytoplasmic vacuoles appeared 48 h after DOX treatment (Tulubas et al., 2015; Uygur et al., 2014a). Cardioprotective role of n-3 PUFA also has been supported by a study in dogs with lymphoblastic lymphoma receiving a diet supplemented with menhaden fish oil (140 g of eicosapentanoic acid [EPA] per kg fish oil, 120 g of docosahexanoic acid [DHA] per kg fish oil) and arginine (5.5 4% dry matter basis). In this study supplements were provided before and after a chemotherapeutic treatment with DOX (up to five dosages of 30 mg/m2 every 3 weeks, iv) that finished with tumor remission. Results included the improvement of different metabolic parameters for dogs with Stage III lymphoma in comparison with those treated on a diet supplemented with soybean oil (Ogilvie et al., 2000). Likewise, testis tissues from rats pretreated with n-3 PUFA in the same conditions as the previously mentioned study showed an improvement in histological parameters, a reduced cell death and a higher cell proliferation

Table 4
Selenium effects on DOX toxicity.

Model	Organ/tissue/cell affected (administration)	Effects *vs.* DOX toxicity[1]	Effect on Cell signaling and/or DOX efficiency[2]
Pigs	Leucocytes (ip)	▼ Leucopenia onset	
Dogs	Heart (ip)	No effect	
Rodents	Heart (oral)	▲ Antioxidant defenses ▼ Oxidative damage	
	Heart (ip)	▼ Cardiomyopathic symptoms	
Cell lines	Cancer cells (MCF-7, Bel7402, SKBR-3, RH2, HCF8, Caco-2, & HepG2 cells)	▲ Apoptosis	Efficiency: ↑

Abbreviations: ip: intraperitoneal. [1]A green arrow indicates positive effect. The direction of the arrow indicates that the effect or process on which it applies is increased or decreased. [2]A black arrow indicates that the corresponding cellular signaling process is activated (upwards) or inactivated (downwards).

Table 5
n-3 PUFA effects on DOX toxicity.

Model	Organ/tissue/cell affected (administration via)	Effects *vs.* DOX toxicity[1]	Effect on Cell signaling &/or DOX efficiency[2]
Rodents	Heart (oral)	▼ Histopathological alterations ▼ Biochemical markers of injury ▲ Antioxidant defenses ▼ Oxidative damage	Efficiency: ↑
	Testicles (spermatogenesis) (oral)	▼ Histopathological alterations ▼ Cell death	
	Brain (oral)	▼ neuroinflammation marker	
Cell lines	H9c2 cells	▲ Antioxidant defenses ▼ Oxidative damage ▼ Inflammatory cytokines ▲ UCP2 ▼ Mitochondrial depolarization ▲ Mitochondria	▼ NF-κB/iNOS/NO
	EHEB, MEC-2, JVM-2, L1210, A-172, U-87 MG and A-427 cancer cells	▲ Cell death	Efficiency: ↑

Abrreviations: UCP2, uncoupling protein 2; NF-κB; nuclear factor κB, iNOS, inducible nitric oxide synthse; NO, nitric oxide. [1]A green arrow indicates positive effect. The direction of the arrow indicates that the effect or process on which it applies is increased or decreased. [2]A black arrow indicates that the corresponding cellular signaling process is activated (upwards) or inactivated (downwards).

compared with animals only treated with DOX (Uygur et al., 2014b). Moreover, a daily n-3 PUFA supplement at higher doses (0.6% of bw, ig) during a 8-week DOX-treatment (2 mg/kg of bw, ip, once weekly) attenuated DOX-derived myocardial injury in rats according echocardiographic and histological parameters (Teng et al., 2010). These results suggest that supplementation with n-3 PUFA could have a prophylactic but also therapeutical use for reducing acute and chronic cardiac injuries associated to DOX-based chemotherapy. In the same way, these dietary interventions could be also useful for palliating acute testicular damages caused by DOX.

The usefulness of n-3 PUFA against DOX toxicity has also been evaluated in female rats treated with DOX and cyclophosphamide. In this study n-3 PUFA (375 mg/100 g per day) attenuated chemotherapy-induced bone marrow cell depletion and marrow adiposity. This intervention also attenuated trabecular bone separation, normalized cell size and the number of osteoclasts formed *ex vivo* from bone marrow cells isolated from chemoterapy-treated rats (Fan et al., 2018). Likewise, a low sucrose diet (9% of Kcal) supplemented with EPA and DHA (2% of Kcal) for four to six weeks attenuated synaptic damage at the cortex, but not at the hippocampus. In this study, chemotherapy consisted in a combined therapy of DOX (9 mg/kg of bw, ip) and cyclophosphamide (90 mg/kg of bw, ip) administered two and four weeks after starting the dietary treatment in ovariectomized C57BL/6 mice (Orchard et al., 2018). Therefore, it is possible that protective effects of dietary n-3 PUFA could be extended to DOX toxicity in bone, nervous system and even in blood cells, at least in part. In another study, Merino sheep received repeated intracoronary infusions of DOX (to reach a total dosage of 3.6 mg/kg of bw). Oral treatment with fish oil (10 mL fish oil comprising 3 g of n-3 PUFA per day) 3 weeks before and 12 weeks after DOX exposure did not reported positive effects. Even the opposite, n-3 PUFA exacerbated DOX-induced cardiotoxicity (Carbone et al., 2012). Notwithstanding, in the last study, olive oil was used as placebo. This might suggest a potential for monounsaturated fatty acids (MUFA) in the prevention of DOX toxicity.

Additional findings support that n-3 PUFA benefits on DOX toxicity would be a consequence of reductions in oxidative stress. This recommends the assessment of oxidative damage markers. In this sense several studies have confirmed the improvement of the antioxidant enzymes SOD and GPX activities after the co-treatment with n-3 PUFA (Tulubas et al., 2015; Uygur et al., 2014a, 2014b). This antioxidant role has been supported by *in vitro* assays in H9c2 cells showing a reduction of ROS production after DOX treatments by 24-h pretreatments with these nutrients (EPA 100 μM or DHA 50 μM) in parallel with increases in cell viability (Hsu et al., 2014; Wang et al., 2016). Sardine oil microencapsulated in vanillic acid-grafted chitosan (Va-g-Ch) also revealed an effective cytoprotective and antiapoptotic effect at concentration of 12.5 μg/mL with decreased ROS production in H9c2 cardiomyocytes (Vishnu et al., 2018). The reduction in ROS production could be related to the prevention of mitochondrial potential losses and the maintenance of mitochondrial function observed in H9C2 cells pretreated with n-3 PUFA and subsequently treated with DOX (1 μM, 24 h) (Hsu et al., 2014). The mentioned mitochondrial alterations could be also responsible of cell events leading to apoptosis associated with exposition to DOX and avoided by n-3 PUFA (Hsu et al., 2014). The reported maintenance of mitochondrial potential and function by n-3 PUFA could be consequence of the prevention of oxidative damage. Also the reduction in the decrease of uncoupling protein 2 (UCP2) mRNA and protein levels as consequence of the pretreatment could be involved (Hsu et al., 2014). According to that, the presence of higher levels of UCP2 could dissipate mitochondrial ROS production, reducing by this way oxidative damage and consequently preventing membrane potential changes. Interestingly, the effect on UCP-2 gene expression were not seen when cells were exposed simultaneously to the n-3 PUFA and DOX (Hsu et al., 2014). It has been also evidenced an anti-inflammatory effect as an additional protective mechanism of n-3 PUFA against DOX toxicity. This has been demonstrated to happen at least at heart and could explain the recovery from DOX-induced pro-inflammatory cytokine network imbalance by DHA found in some *in vitro* studies (Teng et al., 2010; Wang et al., 2016). This anti-inflammatory role seems to be mediated, at least in part, by inducible nitric oxide synthase (iNOS) reduction as consequence of the transcriptional control exerted by DHA via NF-κB/iNOS/NO signaling pathway (Wang et al., 2016). Sardine oil microencapsulated at concentration of 12.5 μg/mL also down-regulated NF-κB expression in H9c2 cardiomyocytes (Vishnu et al., 2018). A decrease in the inflammation markers α-1 acid glycoprotein, TNFα and IL-6 was also noted in dogs with lymphoblastic lymphoma receiving a diet supplemented with menhaden fish oil (Ogilvie et al., 2000) supporting the *in vitro* n-3 PUFA anti-inflammatory effects found in cardiomyocytes (Wang et al., 2016). At brain, it was shown a reduced expression of the synaptic marker Shank 3 protein that has been related with a reduction in neuroinflammation. That was found in ovariectomized C57BL/6 mice fed a low sucrose diet (9% of Kcal) supplemented with EPA and DHA treated with a combined chemotherapy containing DOX and cyclophosphamide (Orchard et al., 2018). A third mechanism by which DHA might exert their effects on DOX-associated toxicity would involve interference with ER Ca^{2+} release channel (Ondrias et al., 1990). In that sense, a 20 min-treatment with DHA (10 μM) prevented acute modifications of calcium homeostasis in adult rat ventricular cardiomyocytes perfused with $CaCl_2$ Krebs solution and treated with DOX (100 μM) (Vitelli et al., 2002).

Other preclinical studies have also explored the potential of n-3 PUFA for improving DOX chemotherapy effectiveness. In this context, it was reported that co-administration of different n-3 PUFA in diet (Hardman et al., 2001; Newell et al., 2019) or parenteral (Xue et al., 2016) improved the anti-cancer efficacy of chemotherapeutic treatment in cancer xenograft rodent models without increase in DOX toxicity (Hardman et al., 2001; Newell et al., 2019; Xue et al., 2016). Supporting these findings from animal studies, different *in vitro* assays carried out in cell lines including the B-leukemic cell lines EHEB, MEC-2, JVM-2 and L1210 (Guffy et al., 1984), the glioblastoma cell lines A-172 and U-87 MG (Rudra and Krokan, 2001), as well as the bronchial carcinoma cell lines A-427, reported an increase in sensitivity to DOX cytotoxic effects (Guffy et al., 1984; Rudra and Krokan, 2001) affecting viability, cell growth, or both (Guffy et al., 1984). Moreover, in some assays, a dose-dependent effect was found (Guffy et al., 1984). However, some cell lines (like the bronchial carcinoma cell line SK-LU-1) were not affected in this way, suggesting that this effect could be cell line dependent (Rudra and Krokan, 2001). Moreover, comparisons between DOX-resistant and sensitive cell lines have also indicated that pretreatment with n-3 PUFA increase sensitivity to DOX cytotoxicity in DOX resistant cells such as mouse leukemia cell subline P388/DOX (Liu and Tan, 2000) or resistant small-cell lung carcinoma cells (Zijlstra et al., 1987). More recently, DHA has been co-loaded with DOX in Tc-99m-labeled nanostructured lipid carrier formulation improving substantial tumor growth inhibition (Fernandes et al., 2018). Moreover, in this study favorable toxicity profiles were found when compared to equivalent doses of free administered drug, reducing heart and liver damage compared with equivalent doses of free administered DOX.

It has been reported that cells in culture adapted membrane lipids to the composition of the medium (Guffy et al., 1984; Zijlstra et al., 1987). In an study of n-3 PUFA supplementation it was found that for the same supplementation, the content of n-3 PUFA was 2-3-fold higher in DOX-sensitive compared with DOX-resistant rat glioblastoma cells. Authors suggested that the uptake of fatty acids by resistant cells was twice of that in sensitive cells (Vrignaud et al., 1986; Vrignaud and Robert, 1987). This difference could explain why in some assays n-3 PUFA only increased DOX cytotoxicity in resistant cell lines, but not in sensitive cells since the change in membrane composition would occur in a higher degree with the same treatment (Zijlstra et al., 1987). A higher content of PUFA in cell membranes might facilitate the formation of cytotoxic lipid peroxidation products as consequence of the known susceptibility of membranes rich in PUFA to lipid peroxidation. Nevertheless in EHEB and JVM-2 cells, n-3 PUFA enhanced chemosensitivity without showing a clear effect on lipid peroxidation and ROS generation (Fahrmann and Hardman, 2013). Likewise, it has been reported that GPX activity increased after DOX exposure and even more after addition of Na-selenite in DHA-treated cells, but this did not reduce the cytotoxicity of DOX (Rudra and Krokan, 2001). These results demonstrated that the mechanisms of cytotoxicity enhancement by n-3 PUFA are complex and probably cell-specific and do not require increased lipid peroxidation or ROS. On the other hand, the alteration of the lipid domain of the cell membrane results in a higher intracellular drug level, circumventing drug resistance and increasing deleterious effects in the cell. Among these effects oxidative damage accumulation (Hardman et al., 2001; Xue et al., 2016) and the subsequent induction of cell cycle arrest and apoptosis (Newell et al., 2019) should be considered. This has been observed *in vivo* in xenograft models (Hardman et al., 2001; Newell et al., 2019; Xue et al., 2016) and different cell lines (Newell et al., 2019). In support of this, cellular accumulation of DOX was greater in the DHA-enriched L1210 murine leukemia cell line as compared to those cells enriched with the MUFA oleate (Burns and North, 1986). Similarly, the increase in sensitivity to DOX cytotoxicity as consequence of a pretreatment with n-3 PUFA in mouse leukemia cell subline P388/DOX has been associated with DOX accumulation, an effect not associated with p-gp expression changes (Liu and Tan, 2000). Moreover, the accumulation of DOX has been directly correlated with the average number of double bonds in cells's membrane fatty acids. The observed effect for n-3 PUFA could also be the same for n-6 PUFA in relation to DOX uptake (Burns and North, 1986). In fact, the content of both, n-3 and n-6 PUFA, was higher in DOX-resistant cells compared to DOX-sensitive rat glioblastoma cells (Vrignaud and Robert, 1987). Table 5 presents a summary of the effects of n-3 PUFA on DOX toxicity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was been partially supported by Visiting Scholar Program from the University of Granada. María D. Navarro-Hortal and José M. Romero-Márquez are FPU fellow from the Spanish Ministry of Educación y Formación Profesional.

References

Abd El-Moneim, O.M., Abd El-Rahim, A.H., Hafiz, N.A., 2018. Evaluation of selenium nanoparticles and doxorubicin effect against hepatocellular carcinoma rat model cytogenetic toxicity and DNA damage. Toxicol. Rep. 5, 771–776. https://doi.org/10.1016/j.toxrep.2018.07.003.

Aissa, A.F., Bianchi, M.L.P., Ribeiro, J.C., Hernandes, L.C., de Faria, A.F., Mercadante, A.Z., Antunes, L.M.G., 2012. Comparative study of β-carotene and microencapsulated β-carotene: evaluation of their genotoxic and antigenotoxic effects. Food Chem. Toxicol. 50, 1418–1424. https://doi.org/10.1016/j.fct.2012.02.030.

Akolkar, G., da Silva Dias, D., Ayyappan, P., Bagchi, A.K., Jassal, D.S., Salemi, V.M.C., Irigoyen, M.C., De Angelis, K., Singal, P.K., 2017. Vitamin C mitigates oxidative/nitrosative stress and inflammation in doxorubicin-induced cardiomyopathy. Am. J. Physiol. Heart Circ. Physiol. 313, H795–H809. https://doi.org/10.1152/ajpheart.00253.2017.

Alberts, D.S., Peng, Y.M., Moon, T.E., 1978. alpha-Tocopherol pretreatment increases adriamycin bone marrow toxicity. Biomedicine 29, 189–191.

Amara-Mokrane, Y.A., Lehucher-Michel, M.P., Balansard, G., Duménil, G., Botta, A., 1996. Protective effects of alpha-hederin, chlorophyllin and ascorbic acid towards the induction of micronuclei by doxorubicin in cultured human lymphocytes. Mutagenesis 11, 161–167.

Anjos Ferreira, A.L., Russell, R.M., Rocha, N., Placido Ladeira, M.S., Favero Salvadori, D.M., Oliveira Nascimento, M.C.M., Matsui, M., Carvalho, F.A., Tang, G., Matsubara, L.S., Matsubara, B.B., 2007. Effect of lycopene on doxorubicin-induced cardiotoxicity: an echocardiographic, histological and morphometrical assessment. Basic Clin. Pharmacol. Toxicol. 101, 16–24. https://doi.org/10.1111/j.1742-7843.2007.00070.x.

Antunes, L.M., Takahashi, C.S., 1999. Protection and induction of chromosomal damage by vitamin C in human lymphocyte cultures. Teratog. Carcinog. Mutagen. 19, 53–59.

Antunes, L.M., Takahashi, C.S., 1998. Effects of high doses of vitamins C and E against doxorubicin-induced chromosomal damage in Wistar rat bone marrow cells. Mutat. Res. 419, 137–143.

Ateşşahin, A., Türk, G., Karahan, I., Yilmaz, S., Ceribaşi, A.O., Bulmuş, O., 2006. Lycopene prevents adriamycin-induced testicular toxicity in rats. Fertil. Steril. 85 (Suppl. 1), 1216–1222. https://doi.org/10.1016/j.fertnstert.2005.11.035.

Bai, P., Mabley, J.G., Liaudet, L., Virág, L., Szabó, C., Pacher, P., 2004. Matrix metalloproteinase activation is an early event in doxorubicin-induced cardiotoxicity. Oncol. Rep. 11, 505–508.

Bartlett, J.J., Trivedi, P.C., Yeung, P., Kienesberger, P.C., Pulinilkunnil, T., 2016. Doxorubicin impairs cardiomyocyte viability by suppressing transcription factor EB expression and disrupting autophagy. Biochem. J. 473, 3769–3789. https://doi.org/10.1042/BCJ20160385.

Berlin, V., Haseltine, W.A., 1981. Reduction of adriamycin to a semiquinone-free radical by NADPH cytochrome P-450 reductase produces DNA cleavage in a reaction mediated by molecular oxygen. J. Biol. Chem. 256, 4747–4756.

Berthiaume, J.M., Oliveira, P.J., Fariss, M.W., Wallace, K.B., 2005. Dietary vitamin E decreases doxorubicin-induced oxidative stress without preventing mitochondrial dysfunction. Cardiovasc. Toxicol. 5, 257–267.

Berthiaume, J.M., Wallace, K.B., 2007. Adriamycin-induced oxidative mitochondrial cardiotoxicity. Cell Biol. Toxicol. 23, 15–25. https://doi.org/10.1007/s10565-006-0140-y.

Bin-Umer, M.A., McLaughlin, J.E., Butterly, M.S., McCormick, S., Tumer, N.E., 2014. Elimination of damaged mitochondria through mitophagy reduces mitochondrial oxidative stress and increases tolerance to trichothecenes. Proc. Natl. Acad. Sci. U.S.A. 111, 11798–11803. https://doi.org/10.1073/pnas.1403145111.

Biswas, D., Qureshi, O.S., Lee, W.-Y., Croudace, J.E., Mura, M., Lammas, D.A., 2008. ATP-induced autophagy is associated with rapid killing of intracellular mycobacteria within human monocytes/macrophages. BMC Immunol. 9, 35. https://doi.org/10.1186/1471-2172-9-35.

Bonadonna, G., Monfardini, S., De Lena, M., Fossati-Bellani, F., 1969. Clinical evaluation of adriamycin, a new antitumour antibiotic. Br. Med. J. 3, 503–506.
Boucher, F., Coudray, C., Tirard, V., Barandier, C., Tresallet, N., Favier, A., de Leiris, J., 1995. Oral selenium supplementation in rats reduces cardiac toxicity of adriamycin during ischemia and reperfusion. Nutrition 11, 708–711.
Branda, R.F., Powden, C., Brooks, E.M., Yildirim, Z., Naud, S.J., McCormack, J.J., 2006. Vitamin E but not St. John's wort mitigates leukopenia caused by cancer chemotherapy in rats. Transl. Res. 148, 315–324. https://doi.org/10.1016/j.trsl.2006.05.007.
Breed, J.G., Zimmerman, A.N., Dormans, J.A., Pinedo, H.M., 1980. Failure of the antioxidant vitamin E to protect against adriamycin-induced cardiotoxicity in the rabbit. Cancer Res. 40, 2033–2038.
Broeyer, F.J.F., Osanto, S., Suzuki, J., de Jongh, F., van Slooten, H., Tanis, B.C., Bruning, T., Bax, J.J., Ritsema van Eck, H.J., de Kam, M.L., Cohen, A.F., Mituzhima, Y., Burggraaf, J., 2014. Evaluation of lecithinized human recombinant super oxide dismutase as cardioprotectant in anthracycline-treated breast cancer patients. Br. J. Clin. Pharmacol. 78, 950–960. https://doi.org/10.1111/bcp.12429.
Brown, D.I., Griendling, K.K., 2015. Regulation of signal transduction by reactive oxygen species in the cardiovascular system. Circ. Res. 116, 531–549. https://doi.org/10.1161/CIRCRESAHA.116.303584.
Bulucu, F., Ocal, R., Karadurmus, N., Sahin, M., Kenar, L., Aydin, A., Oktenli, C., Koc, B., Inal, V., Yamanel, L., Yaman, H., 2009. Effects of N-acetylcysteine, deferoxamine and selenium on doxorubicin-induced hepatotoxicity. Biol. Trace Elem. Res. 132, 184–196. https://doi.org/10.1007/s12011-009-8377-y.
Bulucu, F., Oktenli, C., Kenar, L., Ocal, R., Koc, B., Inal, V., Yamanel, L., Yaman, H., Sanisoglu, Y.S., Aydin, A., 2008. Efficacy of deferoxamine, N-acetylcysteine and selenium treatments in rats with Adriamycin-induced nephrotic syndrome. J. Nephrol. 21, 576–583.
Burgess, D.J., Doles, J., Zender, L., Xue, W., Ma, B., McCombie, W.R., Hannon, G.J., Lowe, S.W., Hemann, M.T., 2008. Topoisomerase levels determine chemotherapy response in vitro and in vivo. Proc. Natl. Acad. Sci. U.S.A. 105, 9053–9058. https://doi.org/10.1073/pnas.0803513105.
Burns, C.P., North, J.A., 1986. Adriamycin transport and sensitivity in fatty acid-modified leukemia cells. Biochim. Biophys. Acta 888, 10–17.
Carbone, A., Psaltis, P.J., Nelson, A.J., Metcalf, R., Richardson, J.D., Weightman, M., Thomas, A., Finnie, J.W., Young, G.D., Worthley, S.G., 2012. Dietary omega-3 supplementation exacerbates left ventricular dysfunction in an ovine model of anthracycline-induced cardiotoxicity. J. Card. Fail. 18, 502–511. https://doi.org/10.1016/j.cardfail.2012.03.005.
Cardinale, D., Colombo, A., Lamantia, G., Colombo, N., Civelli, M., De Giacomi, G., Rubino, M., Veglia, F., Fiorentini, C., Cipolla, C.M., 2010. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J. Am. Coll. Cardiol. 55, 213–220. https://doi.org/10.1016/j.jacc.2009.03.095.
Cardoso, S., Santos, R.X., Carvalho, C., Correia, S., Pereira, G.C., Pereira, S.S., Oliveira, P.J., Santos, M.S., Proença, T., Moreira, P.I., 2008. Doxorubicin increases the susceptibility of brain mitochondria to Ca(2+)-induced permeability transition and oxidative damage. Free Radic. Biol. Med. 45, 1395–1402. https://doi.org/10.1016/j.freeradbiomed.2008.08.008.
Carvalho, C., Santos, R.X., Cardoso, S., Correia, S., Oliveira, P.J., Santos, M.S., Moreira, P.I., 2009. Doxorubicin: the good, the bad and the ugly effect. Curr. Med. Chem. 16, 3267–3285.
Chaires, J.B., Fox, K.R., Herrera, J.E., Britt, M., Waring, M.J., 1987. Site and sequence specificity of the daunomycin-DNA interaction. Biochemistry 26, 8227–8236.
Chaires, J.B., Herrera, J.E., Waring, M.J., 1990. Preferential binding of daunomycin to 5'ATCG and 5'ATGC sequences revealed by footprinting titration experiments. Biochemistry 29, 6145–6153.
Chen, K.S., Gresh, N., Pullman, B., 1986a. A theoretical investigation on the sequence selective binding of adriamycin to double-stranded polynucleotides. Nucleic Acids Res. 14, 2251–2267.
Chen, M.-B., Wu, X.-Y., Gu, J.-H., Guo, Q.-T., Shen, W.-X., Lu, P.-H., 2011. Activation of AMP-activated protein kinase contributes to doxorubicin-induced cell death and apoptosis in cultured myocardial H9c2 cells. Cell Biochem. Biophys. 60, 311–322. https://doi.org/10.1007/s12013-011-9153-0.
Chen, X.S., Xue, A., Morris, V.C., Ferrans, V.J., Herman, E.H., el-Hage, A., Levander, O.A., 1986b. Effect of selenium deficiency on the chronic toxicity of adriamycin in rats. J. Nutr. 116, 2453–2465. https://doi.org/10.1093/jn/116.12.2453.
Chen, Y., Jungsuwadee, P., Vore, M., Butterfield, D.A., St Clair, D.K., 2007. Collateral damage in cancer chemotherapy: oxidative stress in nontargeted tissues. Mol. Interv. 7, 147–156. https://doi.org/10.1124/mi.7.3.6.
Cheung, K.G., Cole, L.K., Xiang, B., Chen, K., Ma, X., Myal, Y., Hatch, G.M., Tong, Q., Dolinsky, V.W., 2015. Sirtuin-3 (SIRT3) protein attenuates doxorubicin-induced oxidative stress and improves mitochondrial respiration in H9c2 cardiomyocytes. J. Biol. Chem. 290, 10981–10993. https://doi.org/10.1074/jbc.M114.607960.
Choi, E.H., Chang, H.-J., Cho, J.Y., Chun, H.S., 2007. Cytoprotective effect of anthocyanins against doxorubicin-induced toxicity in H9c2 cardiomyocytes in relation to their antioxidant activities. Food Chem. Toxicol. 45, 1873–1881. https://doi.org/10.1016/j.fct.2007.04.003.
Chularojmontri, L., Wattanapitayakul, S.K., Herunsalee, A., Charuchongkolwongse, S., Niumsakul, S., Srichairat, S., 2005. Antioxidative and cardioprotective effects of Phyllanthus urinaria L. on doxorubicin-induced cardiotoxicity. Biol. Pharm. Bull. 28, 1165–1171.
Coldwell, K.E., Cutts, S.M., Ognibene, T.J., Henderson, P.T., Phillips, D.R., 2008. Detection of Adriamycin-DNA adducts by accelerator mass spectrometry at clinically relevant Adriamycin concentrations. Nucleic Acids Res. 36, e100. https://doi.org/10.1093/nar/gkn439.
Colombo, A., Meroni, C.A., Cipolla, C.M., Cardinale, D., 2013. Managing cardiotoxicity of chemotherapy. Curr. Treat. Options Cardiovasc. Med. 15, 410–424. https://doi.org/10.1007/s11936-013-0248-3.
Conklin, K.A., 2000. Dietary antioxidants during cancer chemotherapy: impact on chemotherapeutic effectiveness and development of side effects. Nutr. Cancer 37, 1–18. https://doi.org/10.1207/S15327914NC3701_1.
Coudray, C., Mouhieddine, S., Richard, M.J., Arnaud, J., De Leiris, J., Favier, A., 1992. Effects of adriamycin on chronic cardiotoxicity in selenium-deficient rats. Basic Res. Cardiol. 87, 173–183.
Danesi, F., Malaguti, M., Di Nunzio, M., Maranesi, M., Biagi, P.L., Bordoni, A., 2006. Counteraction of adriamycin-induced oxidative damage in rat heart by selenium dietary supplementation. J. Agric. Food Chem. 54, 1203–1208. https://doi.org/10.1021/jf0518002.
de Wolf, F.A., 1991. Binding of doxorubicin to cardiolipin as compared to other anionic phospholipids–an evaluation of electrostatic effects. Biosci. Rep. 11, 275–284.
Della Torre, P., Imondi, A.R., Bernardi, C., Podestà, A., Moneta, D., Riflettuto, M., Mazué, G., 1999a. Cardioprotection by dexrazoxane in rats treated with doxorubicin and paclitaxel. Cancer Chemother. Pharmacol. 44, 138–142. https://doi.org/10.1007/s002800050958.
Della Torre, P., Mazué, G., Podestà, A., Moneta, D., Sammartini, U., Imondi, A.R., 1999b. Protection against doxorubicin-induced cardiotoxicity in weanling rats by dexrazoxane. Cancer Chemother. Pharmacol. 43, 151–156. https://doi.org/10.1007/s002800050876.
Delpy, E., Hatem, S.N., Andrieu, N., de Vaumas, C., Henaff, M., Rücker-Martin, C., Jaffrézou, J.P., Laurent, G., Levade, T., Mercadier, J.J., 1999. Doxorubicin induces slow ceramide accumulation and late apoptosis in cultured adult rat ventricular myocytes. Cardiovasc. Res. 43, 398–407.
Deng, G., Chen, C., Zhang, J., Zhai, Y., Zhao, J., Ji, A., Kang, Y., Liu, X., Dou, K., Wang, Q., 2018. Se@SiO2 nanocomposites attenuate doxorubicin-induced cardiotoxicity through combatting oxidative damage. Artif. Cells Nanomed. Biotechnol. 1–10. https://doi.org/10.1080/21691401.2018.1452250.
DeSantis, C.E., Lin, C.C., Mariotto, A.B., Siegel, R.L., Stein, K.D., Kramer, J.L., Alteri, R., Robbins, A.S., Jemal, A., 2014. Cancer treatment and survivorship statistics, 2014. CA A Cancer J. Clin. 64, 252–271. https://doi.org/10.3322/caac.21235.
Dirks-Naylor, A.J., Kouzi, S.A., Bero, J.D., Phan, D.T., Taylor, H.N., Whitt, S.D., Mabolo, R., 2014. Doxorubicin alters the mitochondrial dynamics machinery and mitophagy in the liver of treated animals. Fundam. Clin. Pharmacol. 28, 633–642. https://doi.org/10.1111/fcp.12073.
Dominguez-Rodriguez, J.R., Gomez-Contreras, P.C., Hernandez-Flores, G., Lerma-Diaz, J.M., Carranco, A., Cervantes-Munguia, R., Orbach-Arbouys, S., Bravo-Cuella, A., 2001. In vivo inhibition by antioxidants of adriamycin-induced apoptosis in murine peritoneal macrophages. Anticancer Res. 21, 1869–1872.
Dutta, Debapriya, Dutta, Debariya, Xu, J., Dirain, M.L.S., Leeuwenburgh, C., 2014. Calorie restriction combined with resveratrol induces autophagy and protects 26-month-old rat hearts from doxorubicin-induced toxicity. Free Radic. Biol. Med. 74, 252–262. https://doi.org/10.1016/j.freeradbiomed.2014.06.011.
El-Agamy, S.E., Abdel-Aziz, A.K., Wahdan, S., Esmat, A., Azab, S.S., 2018. Astaxanthin ameliorates doxorubicin-induced cognitive impairment (chemobrain) in experimental rat model: impact on oxidative, inflammatory, and apoptotic machineries. Mol. Neurobiol. 55, 5727–5740. https://doi.org/10.1007/s12035-017-0797-7.
Fahrmann, J.F., Hardman, W.E., 2013. Omega 3 fatty acids increase the chemo-sensitivity of B-CLL-derived cell lines EHEB and MEC-2 and of B-PLL-derived cell line JVM-2 to anti-cancer drugs doxorubicin, vincristine and fludarabine. Lipids Health Dis. 12, 36. https://doi.org/10.1186/1476-511X-12-36.
Fan, C.-M., Su, Y.-W., Howe, P.R., Xian, C.J., 2018. Long chain omega-3 polyunsaturated fatty acid supplementation protects against adriamycin and cyclophosphamide chemotherapy-induced bone marrow damage in female rats. Int. J. Mol. Sci. 19. https://doi.org/10.3390/ijms19020484.
Fang, X., Li, C., Zheng, L., Yang, F., Chen, T., 2018. Dual-Targeted selenium nanoparticles for synergistic photothermal therapy and chemotherapy of tumors. Chem. Asian J. 13, 996–1004. https://doi.org/10.1002/asia.201800048.
Feridooni, T., Hotchkiss, A., Remley-Carr, S., Saga, Y., Pasumarthi, K.B.S., 2011. Cardiomyocyte specific ablation of p53 is not sufficient to block doxorubicin induced cardiac fibrosis and associated cytoskeletal changes. PLoS One 6 e22801. https://doi.org/10.1371/journal.pone.0022801.
Fernandes, R.S., Silva, J.O., Mussi, S.V., Lopes, S.C.A., Leite, E.A., Cassali, G.D., Cardoso, V.N., Townsend, D.M., Colletti, P.M., Ferreira, L.A.M., Rubello, D., de Barros, A.L.B., 2018. Nanostructured lipid carrier Co-loaded with doxorubicin and docosahexaenoic acid as a theranostic agent: evaluation of biodistribution and antitumor activity in experimental model. Mol. Imaging Biol. 20, 437–447. https://doi.org/10.1007/s11307-017-1133-3.
Ferreira, A.L.A., Salvadori, D.M.F., Nascimento, M.C.M.O., Rocha, N.S., Correa, C.R., Pereira, E.J., Matsubara, L.S., Matsubara, B.B., Ladeira, M.S.P., 2007a. Tomato-oleoresin supplement prevents doxorubicin-induced cardiac myocyte oxidative DNA damage in rats. Mutat. Res. 631, 26–35. https://doi.org/10.1016/j.mrgentox.2007.04.003.
Ferreira, A.L.A., Yeum, K.-J., Matsubara, L.S., Matsubara, B.B., Correa, C.R., Pereira, E.J., Russell, R.M., Krinsky, N.I., Tang, G., 2007b. Doxorubicin as an antioxidant: maintenance of myocardial levels of lycopene under doxorubicin treatment. Free Radic. Biol. Med. 43, 740–751. https://doi.org/10.1016/j.freeradbiomed.2007.05.002.
Fischer, J.G., Tackett, R.L., Howerth, E.W., Johnson, M.A., 1992. Copper and selenium deficiencies do not enhance the cardiotoxicity in rats due to chronic doxorubicin treatment. J. Nutr. 122, 2128–2137. https://doi.org/10.1093/jn/122.11.2128.
Forrest, R.A., Swift, L.P., Rephaeli, A., Nudelman, A., Kimura, K.-I., Phillips, D.R., Cutts, S.M., 2012. Activation of DNA damage response pathways as a consequence of anthracycline-DNA adduct formation. Biochem. Pharmacol. 83, 1602–1612. https://doi.org/10.1016/j.bcp.2012.02.026.

Galluzzi, L., Kepp, O., Trojel-Hansen, C., Kroemer, G., 2012. Mitochondrial control of cellular life, stress, and death. Circ. Res. 111, 1198–1207. https://doi.org/10.1161/CIRCRESAHA.112.268946.

Ge, W., Yuan, M., Ceylan, A.F., Wang, X., Ren, J., 2016. Mitochondrial aldehyde dehydrogenase protects against doxorubicin cardiotoxicity through a transient receptor potential channel vanilloid 1-mediated mechanism. Biochim. Biophys. Acta 1862, 622–634. https://doi.org/10.1016/j.bbadis.2015.12.014.

Geetha, A., Sankar, R., Marar, T., Devi, C.S., 1990. Alpha-tocopherol reduces doxorubicin-induced toxicity in rats–histological and biochemical evidences. Indian J. Physiol. Pharmacol. 34, 94–100.

Gharanei, M., Hussain, A., Janneh, O., Maddock, H., 2013. Attenuation of doxorubicin-induced cardiotoxicity by mdivi-1: a mitochondrial division/mitophagy inhibitor. PLoS One 8 e77713. https://doi.org/10.1371/journal.pone.0077713.

Gilleron, M., Marechal, X., Montaigne, D., Franczak, J., Neviere, R., Lancel, S., 2009. NADPH oxidases participate to doxorubicin-induced cardiac myocyte apoptosis. Biochem. Biophys. Res. Commun. 388, 727–731. https://doi.org/10.1016/j.bbrc.2009.08.085.

Gokcimen, A., Cim, A., Tola, H.T., Bayram, D., Kocak, A., Ozgüner, F., Ayata, A., 2007. Protective effect of N-acetylcysteine, caffeic acid and vitamin E on doxorubicin hepatotoxicity. Hum. Exp. Toxicol. 26, 519–525. https://doi.org/10.1177/0960327107076885.

Görgün, M., Erdogan, D., Abban, G., Türközkan, N., Elbeg, S., 1999. Effect of vitamin E on adriamycin- induced nephrotoxicity at the ultrastructural level in Guinea pigs. Nephron 82, 155–163. https://doi.org/10.1159/000045392.

Granados-Principal, S., Quiles, J.L., Ramirez-Tortosa, C.L., Sanchez-Rovira, P., Ramirez-Tortosa, M.C., 2010. New advances in molecular mechanisms and the prevention of adriamycin toxicity by antioxidant nutrients. Food Chem. Toxicol. 48, 1425–1438. https://doi.org/10.1016/j.fct.2010.04.007.

Guffy, M.M., North, J.A., Burns, C.P., 1984. Effect of cellular fatty acid alteration on adriamycin sensitivity in cultured L1210 murine leukemia cells. Cancer Res. 44, 1863–1866.

Gülkaç, M.D., Akpinar, G., Ustün, H., Ozön Kanli, A., 2004. Effects of vitamin A on doxorubicin-induced chromosomal aberrations in bone marrow cells of rats. Mutagenesis 19, 231–236.

Hahn-Windgassen, A., Nogueira, V., Chen, C.-C., Skeen, J.E., Sonenberg, N., Hay, N., 2005. Akt activates the mammalian target of rapamycin by regulating cellular ATP level and AMPK activity. J. Biol. Chem. 280, 32081–32089. https://doi.org/10.1074/jbc.M502876200.

Halliwell, B., Gutteridge, J.M.C., 2015. Free Radicals in Biology and Medicine. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780198717478.001.0001.

Hardman, W.E., Avula, C.P., Fernandes, G., Cameron, I.L., 2001. Three percent dietary fish oil concentrate increased efficacy of doxorubicin against MDA-MB 231 breast cancer xenografts. Clin. Cancer Res. 7, 2041–2049.

Heaney, M.L., Gardner, J.R., Karasavvas, N., Golde, D.W., Scheinberg, D.A., Smith, E.A., O'Connor, O.A., 2008. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. Cancer Res. 68, 8031–8038. https://doi.org/10.1158/0008-5472.CAN-08-1490.

Herman, E.H., Ferrans, V.J., 1983. Influence of vitamin E and ICRF-187 on chronic doxorubicin cardiotoxicity in miniature swine. Lab. Investig. 49, 69–77.

Hermansen, K., Wassermann, K., 1986. The effect of vitamin E and selenium on doxorubicin (Adriamycin) induced delayed toxicity in mice. Acta Pharmacol. Toxicol. 58, 31–37.

Hilmer, S.N., Cogger, V.C., Muller, M., Le Couteur, D.G., 2004. The hepatic pharmacokinetics of doxorubicin and liposomal doxorubicin. Drug Metab. Dispos. 32, 794–799.

Holden, J.M., Eldridge, A.L., Beecher, G.R., Marilyn Buzzard, I., Bhagwat, S., Davis, C.S., Douglass, L.W., Gebhardt, S., Haytowitz, D., Schakel, S., 1999. Carotenoid content of U.S. Foods: an update of the database. J. Food Compos. Anal. 12, 169–196. https://doi.org/10.1006/jfca.1999.0827.

Hoshino, A., Mita, Y., Okawa, Y., Ariyoshi, M., Iwai-Kanai, E., Ueyama, T., Ikeda, K., Ogata, T., Matoba, S., 2013. Cytosolic p53 inhibits Parkin-mediated mitophagy and promotes mitochondrial dysfunction in the mouse heart. Nat. Commun. 4, 2308. https://doi.org/10.1038/ncomms3308.

Hsu, H.-C., Chen, C.-Y., Chen, M.-F., 2014. N-3 polyunsaturated fatty acids decrease levels of doxorubicin-induced reactive oxygen species in cardiomyocytes – involvement of uncoupling protein UCP2. J. Biomed. Sci. 21, 101. https://doi.org/10.1186/s12929-014-0101-3.

Injac, R., Perse, M., Cerne, M., Potocnik, N., Radic, N., Govedarica, B., Djordjevic, A., Cerar, A., Strukelj, B., 2009. Protective effects of fullerenol C60(OH)24 against doxorubicin-induced cardiotoxicity and hepatotoxicity in rats with colorectal cancer. Biomaterials 30, 1184–1196. https://doi.org/10.1016/j.biomaterials.2008.10.060.

Jackson, J.G., Pant, V., Li, Q., Chang, L.L., Quintás-Cardama, A., Garza, D., Tavana, O., Yang, P., Manshouri, T., Li, Y., El-Naggar, A.K., Lozano, G., 2012. p53-mediated senescence impairs the apoptotic response to chemotherapy and clinical outcome in breast cancer. Cancer Cell 21, 793–806. https://doi.org/10.1016/j.ccr.2012.04.027.

Jiang, H., Reinhardt, H.C., Bartkova, J., Tommiska, J., Blomqvist, C., Nevanlinna, H., Bartek, J., Yaffe, M.B., Hemann, M.T., 2009. The combined status of ATM and p53 link tumor development with therapeutic response. Genes Dev. 23, 1895–1909. https://doi.org/10.1101/gad.1815309.

Jönsson-Videsäter, K., Björkhem-Bergman, L., Hossain, A., Söderberg, A., Eriksson, L.C., Paul, C., Rosén, A., Björnstedt, M., 2004. Selenite-induced apoptosis in doxorubicin-resistant cells and effects on the thioredoxin system. Biochem. Pharmacol. 67, 513–522. https://doi.org/10.1016/j.bcp.2003.09.021.

Kalender, Y., Yel, M., Kalender, S., 2005. Doxorubicin hepatotoxicity and hepatic free radical metabolism in rats. The effects of vitamin E and catechin. Toxicology 209, 39–45. https://doi.org/10.1016/j.tox.2004.12.003.

Karimi, G., Ramezani, M., Abdi, A., 2005. Protective effects of lycopene and tomato extract against doxorubicin-induced cardiotoxicity. Phytother Res. 19, 912–914. https://doi.org/10.1002/ptr.1746.

Kavazis, A.N., Morton, A.B., Hall, S.E., Smuder, A.J., 2017. Effects of doxorubicin on cardiac muscle subsarcolemmal and intermyofibrillar mitochondria. Mitochondrion 34, 9–19. https://doi.org/10.1016/j.mito.2016.10.008.

Kawaguchi, T., Takemura, G., Kanamori, H., Takeyama, T., Watanabe, T., Morishita, K., Ogino, A., Tsujimoto, A., Goto, K., Maruyama, R., Kawasaki, M., Mikami, A., Fujiwara, T., Fujiwara, H., Minatoguchi, S., 2012. Prior starvation mitigates acute doxorubicin cardiotoxicity through restoration of autophagy in affected cardiomyocytes. Cardiovasc. Res. 96, 456–465. https://doi.org/10.1093/cvr/cvs282.

Kawase, M., Watanabe, M., Kondo, T., Yabu, T., Taguchi, Y., Umehara, H., Uchiyama, T., Mizuno, K., Okazaki, T., 2002. Increase of ceramide in adriamycin-induced HL-60 cell apoptosis: detection by a novel anti-ceramide antibody. Biochim. Biophys. Acta 1584, 104–114.

Khafaga, A.F., El-Sayed, Y.S., 2018. All-trans-retinoic acid ameliorates doxorubicin-induced cardiotoxicity: in vivo potential involvement of oxidative stress, inflammation, and apoptosis via caspase-3 and p53 down-expression. Naunyn Schmiedebergs Arch. Pharmacol. 391, 59–70. https://doi.org/10.1007/s00210-017-1437-5.

Kim, D.-S., Kim, H.-R., Woo, E.-R., Kwon, D.-Y., Kim, M.-S., Chae, S.-W., Chae, H.-J., 2006. Protective effect of calceolarioside on adriamycin-induced cardiomyocyte toxicity. Eur. J. Pharmacol. 541, 24–32. https://doi.org/10.1016/j.ejphar.2006.04.045.

Kimura, S., Zhang, G.-X., Nishiyama, A., Shokoji, T., Yao, L., Fan, Y.-Y., Rahman, M., Suzuki, T., Maeta, H., Abe, Y., 2005. Role of NAD(P)H oxidase- and mitochondria-derived reactive oxygen species in cardioprotection of ischemic reperfusion injury by angiotensin II. Hypertension 45, 860–866. https://doi.org/10.1161/01.HYP.0000163462.98381.7f.

Kiyomiya, K., Matsuo, S., Kurebe, M., 2001. Mechanism of specific nuclear transport of adriamycin: the mode of nuclear translocation of adriamycin-proteasome complex. Cancer Res. 61, 2467–2471.

Krinsky, N.I., Johnson, E.J., 2005. Carotenoid actions and their relation to health and disease. Mol. Asp. Med. 26, 459–516. https://doi.org/10.1016/j.mam.2005.10.001.

Krivit, W., 1979. Adriamycin cardiotoxicity amelioration by alpha-tocopherol. Am. J. Pediatr. Hematol. Oncol. 1, 151–153.

Kubli, D.A., Gustafsson, Å.B., 2012. Mitochondria and mitophagy: the yin and yang of cell death control. Circ. Res. 111, 1208–1221. https://doi.org/10.1161/CIRCRESAHA.112.265819.

Kumari, M., Purohit, M.P., Patnaik, S., Shukla, Y., Kumar, P., Gupta, K.C., 2018. Curcumin loaded selenium nanoparticles synergize the anticancer potential of doxorubicin contained in self-assembled, cell receptor targeted nanoparticles. Eur. J. Pharm. Biopharm. 130, 185–199. https://doi.org/10.1016/j.ejpb.2018.06.030.

Kurbacher, C.M., Wagner, U., Kolster, B., Andreotti, P.E., Krebs, D., Bruckner, H.W., 1996. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. Cancer Lett. 103, 183–189.

Lee, M.S., Garrard, W.T., 1991. Transcription-induced nucleosome "splitting": an underlying structure for DNase I sensitive chromatin. EMBO J. 10, 607–615.

Legha, S.S., Wang, Y.M., Mackay, B., Ewer, M., Hortobagyi, G.N., Benjamin, R.S., Ali, M.K., 1982. Clinical and pharmacologic investigation of the effects of alpha-tocopherol on adriamycin cardiotoxicity. Ann. N. Y. Acad. Sci. 393, 411–418.

Li, D.L., Wang, Z.V., Ding, G., Tan, W., Luo, X., Criollo, A., Xie, M., Jiang, N., May, H., Kyrychenko, V., Schneider, J.W., Gillette, T.G., Hill, J.A., 2016. Doxorubicin blocks cardiomyocyte autophagic flux by inhibiting lysosome acidification. Circulation 133, 1668–1687. https://doi.org/10.1161/CIRCULATIONAHA.115.017443.

Li, S., Wang, W., Niu, T., Wang, H., Li, B., Shao, L., Lai, Y., Li, H., Janicki, J.S., Wang, X.L., Tang, D., Cui, T., 2014. Nrf2 deficiency exaggerates doxorubicin-induced cardiotoxicity and cardiac dysfunction. Oxid. Med. Cell Longev. 748524. 2014. https://doi.org/10.1155/2014/748524.

Li, S., Zhou, Y., Dong, Y., Ip, C., 2007a. Doxorubicin and selenium cooperatively induce fas signaling in the absence of Fas/Fas ligand interaction. Anticancer Res. 27, 3075–3082.

Li, S., Zhou, Y., Wang, R., Zhang, H., Dong, Y., Ip, C., 2007b. Selenium sensitizes MCF-7 breast cancer cells to doxorubicin-induced apoptosis through modulation of phospho-Akt and its downstream substrates. Mol. Cancer Ther. 6, 1031–1038. https://doi.org/10.1158/1535-7163.MCT-06-0643.

Lipshultz, S.E., Miller, T.L., Scully, R.E., Lipsitz, S.R., Rifai, N., Silverman, L.B., Colan, S.D., Neuberg, D.S., Dahlberg, S.E., Henkel, J.M., Asselin, B.L., Athale, U.H., Clavell, L.A., Laverdière, C., Michon, B., Schorin, M.A., Sallan, S.E., 2012. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. J. Clin. Oncol. 30, 1042–1049. https://doi.org/10.1200/JCO.2010.30.3404.

Lipshultz, S.E., Scully, R.E., Lipsitz, S.R., Sallan, S.E., Silverman, L.B., Miller, T.L., Barry, E.V., Asselin, B.L., Athale, U., Clavell, L.A., Larsen, E., Moghrabi, A., Samson, Y., Michon, B., Schorin, M.A., Cohen, H.J., Neuberg, D.S., Orav, E.J., Colan, S.D., 2010. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol. 11, 950–961. https://doi.org/10.1016/S1470-2045(10)70204-7.

Little, G.H., Saw, A., Bai, Y., Dow, J., Marjoram, P., Simkhovich, B., Leeka, J., Kedes, L., Kloner, R.A., Poizat, C., 2009. Critical role of nuclear calcium/calmodulin-dependent protein kinase IIdeltaB in cardiomyocyte survival in cardiomyopathy. J. Biol. Chem. 284, 24857–24868. https://doi.org/10.1074/jbc.M109.003186.

Liu, L.F., Wang, J.C., 1987. Supercoiling of the DNA template during transcription. Proc. Natl. Acad. Sci. U.S.A. 84, 7024–7027. https://doi.org/10.1073/pnas.84.20.7024.

Liu, Q.Y., Tan, B.K., 2000. Effects of cis-unsaturated fatty acids on doxorubicin sensitivity in P388/DOX resistant and P388 parental cell lines. Life Sci. 67, 1207–1218. https://

doi.org/10.1016/s0024-3205(00)00714-1.
Liu, Y.Y., Han, T.Y., Giuliano, A.E., Cabot, M.C., 2001. Ceramide glycosylation potentiates cellular multidrug resistance. FASEB J. 15, 719–730. https://doi.org/10.1096/fj.00-0223com.
Liu, Y.-Y., Yu, J.Y., Yin, D., Patwardhan, G.A., Gupta, V., Hirabayashi, Y., Holleran, W.M., Giuliano, A.E., Jazwinski, S.M., Gouaze-Andersson, V., Consoli, D.P., Cabot, M.C., 2008. A role for ceramide in driving cancer cell resistance to doxorubicin. FASEB J. 22, 2541–2551. https://doi.org/10.1096/fj.07-092981.
Livrea, M.A., Tesoriere, L., Freisleben, H.J., 1961. Vitamin A as an antioxidant. In: Cadenas, E., Packer, L. (Eds.), Handbook of Antioxidants. Marcel Dekker, Inc, New York, NY, pp. 371–405.
Lobb, R.J., Jacobson, G.M., Cursons, R.T., Jameson, M.B., 2018. The interaction of selenium with chemotherapy and radiation on normal and malignant human mononuclear blood cells. Int. J. Mol. Sci. 19. https://doi.org/10.3390/ijms19103167.
Lobo, V., Patil, A., Phatak, A., Chandra, N., 2010. Free radicals, antioxidants and functional foods: impact on human health. Pharmacogn. Rev. 4, 118–126. https://doi.org/10.4103/0973-7847.70902.
Lucci, A., Han, T.Y., Liu, Y.Y., Giuliano, A.E., Cabot, M.C., 1999. Multidrug resistance modulators and doxorubicin synergize to elevate ceramide levels and elicit apoptosis in drug-resistant cancer cells. Cancer 86, 300–311.
Lucero, M.J., Vigo, J., León, M.J., Martin, F., Sánchez, J.A., 1996. Therapeutic efficacy of hydrophilic gels of α-tocopherol and tretinoin in skin ulcers induced by adriamycin hydrochloride. Int. J. Pharm. 127, 73–83. https://doi.org/10.1016/0378-5173(95)04132-X.
Ludke, A., Akolkar, G., Ayyappan, P., Sharma, A.K., Singal, P.K., 2017. Time course of changes in oxidative stress and stress-induced proteins in cardiomyocytes exposed to doxorubicin and prevention by vitamin C. PLoS One 12 e0179452. https://doi.org/10.1371/journal.pone.0179452.
Ludwig, C.U., Stoll, H.R., Obrist, R., Obrecht, J.P., 1987. Prevention of cytotoxic drug induced skin ulcers with dimethyl sulfoxide (DMSO) and alpha-tocopherole. Eur. J. Cancer Clin. Oncol. 23, 327–329.
Luesakul, U., Puthong, S., Neamati, N., Muangsin, N., 2018. pH-responsive selenium nanoparticles stabilized by folate-chitosan delivering doxorubicin for overcoming drug-resistant cancer cells. Carbohydr. Polym. 181, 841–850. https://doi.org/10.1016/j.carbpol.2017.11.068.
Lv, X., Yu, X., Wang, Yiyang, Wang, F., Li, H., Wang, Yanping, Lu, D., Qi, R., Wang, H., 2012. Berberine inhibits doxorubicin-triggered cardiomyocyte apoptosis via attenuating mitochondrial dysfunction and increasing Bcl-2 expression. PLoS One 7 e47351. https://doi.org/10.1371/journal.pone.0047351.
Matsuda, A., Kimura, M., Itokawa, Y., 1997. Influence of selenium deficiency on the acute cardiotoxicity of adriamycin in rats. Biol. Trace Elem. Res. 57, 157–167. https://doi.org/10.1007/BF02778199.
Milei, J., Boveris, A., Llesuy, S., Molina, H.A., Storino, R., Ortega, D., Milei, S.E., 1986. Amelioration of adriamycin-induced cardiotoxicity in rabbits by prenylamine and vitamins A and E. Am. Heart J. 111, 95–102.
Minotti, G., Menna, P., Salvatorelli, E., Cairo, G., Gianni, L., 2004. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol. Rev. 56, 185–229. https://doi.org/10.1124/pr.56.2.6.
Minotti, G., Recalcati, S., Mordente, A., Liberi, G., Calafiore, A.M., Mancuso, C., Preziosi, P., Cairo, G., 1998. The secondary alcohol metabolite of doxorubicin irreversibly inactivates aconitase/iron regulatory protein-1 in cytosolic fractions from human myocardium. FASEB J. 12, 541–552.
Miranda-Vilela, A.L., Grisolia, C.K., Longo, J.P.F., Peixoto, R.C.A., de Almeida, M.C., Barbosa, L.C.P., Roll, M.M., Portilho, F.A., Estevanato, L.L.C., Bocca, A.L., Báo, S.N., Lacava, Z.G.M., 2014. Oil rich in carotenoids instead of vitamins C and E as a better option to reduce doxorubicin-induced damage to normal cells of Ehrlich tumor-bearing mice: hematological, toxicological and histopathological evaluations. J. Nutr. Biochem. 25, 1161–1176. https://doi.org/10.1016/j.jnutbio.2014.06.005.
Miura, T., Muraoka, S., Ogiso, T., 1995. Adriamycin-Fe3+-induced mitochondrial protein damage with lipid peroxidation. Biol. Pharm. Bull. 18, 514–517.
Mordente, A., Meucci, E., Silvestrini, A., Martorana, G.E., Giardina, B., 2009. New developments in anthracycline-induced cardiotoxicity. Curr. Med. Chem. 16, 1656–1672.
Mukhopadhyay, P., Bátkai, S., Rajesh, M., Czifra, N., Harvey-White, J., Haskó, G., Zsengeller, Z., Gerard, N.P., Liaudet, L., Kunos, G., Pacher, P., 2007. Pharmacological inhibition of CB1 cannabinoid receptor protects against doxorubicin-induced cardiotoxicity. J. Am. Coll. Cardiol. 50, 528–536. https://doi.org/10.1016/j.jacc.2007.03.057.
Myers, C., 1998. The role of iron in doxorubicin-induced cardiomyopathy. Semin. Oncol. 25, 10–14.
Myers, C.E., McGuire, W., Young, R., 1976. Adriamycin: amelioration of toxicity by alpha-tocopherol. Cancer Treat Rep. 60, 961–962.
Nagata, Y., Takata, J., Karube, Y., Matsushima, Y., 1999. Effects of a water-soluble prodrug of vitamin E on doxorubicin-induced toxicity in mice. Biol. Pharm. Bull. 22, 698–702.
Nakagawa, M., Yamaguchi, T., Ueda, H., Shiraishi, N., Komiyama, S., Akiyama, S., Ogata, J., Kuwano, M., 1985. Potentiation by vitamin A of the action of anticancer agents against murine tumors. Jpn. J. Cancer Res. 76, 887–894.
Nakano, E., Takeshige, K., Toshima, Y., Tokunaga, K., Minakami, S., 1989. Oxidative damage in selenium deficient hearts on perfusion with adriamycin: protective role of glutathione peroxidase system. Cardiovasc. Res. 23, 498–504.
Newell, M., Brun, M., Field, C.J., 2019. Treatment with DHA modifies the response of MDA-MB-231 breast cancer cells and tumors from nu/nu mice to doxorubicin through apoptosis and cell cycle arrest. J. Nutr. https://doi.org/10.1093/jn/nxy224.
Nitiss, J.L., 2009. Targeting DNA topoisomerase II in cancer chemotherapy. Nat. Rev. Cancer 9, 338–350. https://doi.org/10.1038/nrc2607.
Nohl, H., 1988. Identification of the site of adriamycin-activation in the heart cell. Biochem. Pharmacol. 37, 2633–2637.
Nonsuwan, P., Puthong, S., Palaga, T., Muangsin, N., 2018. Novel organic/inorganic hybrid flower-like structure of selenium nanoparticles stabilized by pullulan derivatives. Carbohydr. Polym. 184, 9–19. https://doi.org/10.1016/j.carbpol.2017.12.029.
Ogilvie, G.K., Fettman, M.J., Mallinckrodt, C.H., Walton, J.A., Hansen, R.A., Davenport, D.J., Gross, K.L., Richardson, K.L., Rogers, Q., Hand, M.S., 2000. Effect of fish oil, arginine, and doxorubicin chemotherapy on remission and survival time for dogs with lymphoma: a double-blind, randomized placebo-controlled study. Cancer 88, 1916–1928.
Ondrias, K., Borgatta, L., Kim, D.H., Ehrlich, B.E., 1990. Biphasic effects of doxorubicin on the calcium release channel from sarcoplasmic reticulum of cardiac muscle. Circ. Res. 67, 1167–1174.
Orchard, T.S., Gaudier-Diaz, M.M., Phuwamongkolwiwat-Chu, P., Andridge, R., Lustberg, M.B., Bomser, J., Cole, R.M., Belury, M.A., DeVries, A.C., 2018. Low sucrose, omega-3 enriched diet has region-specific effects on neuroinflammation and synaptic function markers in a mouse model of doxorubicin-based chemotherapy. Nutrients 10. https://doi.org/10.3390/nu10122004.
Ozben, T., 2007. Oxidative stress and apoptosis: impact on cancer therapy. J. Pharm. Sci. 96, 2181–2196. https://doi.org/10.1002/jps.20874.
Packer, L., Weber, S.U., Rimbach, G., 2001. Molecular aspects of alpha-tocotrienol antioxidant action and cell signalling. J. Nutr. 131, 369S–373S. https://doi.org/10.1093/jn/131.2.369S.
Padh, H., 1991. Vitamin C: newer insights into its biochemical functions. Nutr. Rev. 49, 65–70.
Pang, B., Qiao, X., Janssen, L., Velds, A., Groothuis, T., Kerkhoven, R., Nieuwland, M., Ovaa, H., Rottenberg, S., van Tellingen, O., Janssen, J., Huijgens, P., Zwart, W., Neefjes, J., 2013. Drug-induced histone eviction from open chromatin contributes to the chemotherapeutic effects of doxorubicin. Nat. Commun. 4, 1908. https://doi.org/10.1038/ncomms2921.
Park, A.-M., Nagase, H., Liu, L., Vinod Kumar, S., Szwergold, N., Wong, C.-M., Suzuki, Y.J., 2011. Mechanism of anthracycline-mediated down-regulation of GATA4 in the heart. Cardiovasc. Res. 90, 97–104. https://doi.org/10.1093/cvr/cvq361.
Parker, M.A., King, V., Howard, K.P., 2001. Nuclear magnetic resonance study of doxorubicin binding to cardiolipin containing magnetically oriented phospholipid bilayers. Biochim. Biophys. Acta 1514, 206–216.
Pizarro, M., Troncoso, R., Martínez, G.J., Chiong, M., Castro, P.F., Lavandero, S., 2016. Basal autophagy protects cardiomyocytes from doxorubicin-induced toxicity. Toxicology 370, 41–48. https://doi.org/10.1016/j.tox.2016.09.011.
Popovic, M., Kolarovic, J., Mikov, M., Trivic, S., Kaurinovic, B., 2007. Anthracycline-based combined chemotherapy in the mouse model. Eur. J. Drug Metab. Pharmacokinet. 32, 101–108. https://doi.org/10.1007/BF03190998.
Praga, C., Beretta, G., Vigo, P.L., Lenaz, G.R., Pollini, C., Bonadonna, G., Canetta, R., Castellani, R., Villa, E., Gallagher, C.G., von Melchner, H., Hayat, M., Ribaud, P., De Wasch, G., Mattsson, W., Heinz, R., Waldner, R., Kolaric, K., Buehner, R., Ten Bokkel-Huyninck, W., Perevodchikova, N.I., Manziuk, L.A., Senn, H.J., Mayr, A.C., 1979. Adriamycin cardiotoxicity: a survey of 1273 patients. Cancer Treat Rep. 63, 827–834.
Puri, A., Maulik, S.K., Ray, R., Bhatnagar, V., 2005. Electrocardiographic and biochemical evidence for the cardioprotective effect of vitamin E in doxorubicin-induced acute cardiotoxicity in rats. Eur. J. Pediatr. Surg. 15, 387–391. https://doi.org/10.1055/s-2005-872923.
Purohit, M.P., Verma, N.K., Kar, A.K., Singh, A., Ghosh, D., Patnaik, S., 2017. Inhibition of thioredoxin reductase by targeted selenopolymeric nanocarriers synergizes the therapeutic efficacy of doxorubicin in MCF7 human breast cancer cells. ACS Appl. Mater. Interfaces 9, 36493–36512. https://doi.org/10.1021/acsami.7b07056.
Quiles, J.L., Huertas, J.R., Battino, M., Mataix, J., Ramírez-Tortosa, M.C., 2002. Antioxidant nutrients and adriamycin toxicity. Toxicology 180, 79–95.
Quiles, José L., Ochoa, J.J., Huertas, J.R., López-Frias, M., Mataix, J., 2006. Olive oil and mitochondrial oxidative stress: studies on adriamycin toxicity, physical exercise and ageing. In: Quiles, J.L., Ramírez-Tortosa, M.C., Yaqoob, P. (Eds.), Olive Oil and Health. CABI, Wallingford, pp. 119–151.
Ripoll, E.A., Rama, B.N., Webber, M.M., 1986. Vitamin E enhances the chemotherapeutic effects of adriamycin on human prostatic carcinoma cells in vitro. J. Urol. 136, 529–531.
Robinson, N.C., 1993. Functional binding of cardiolipin to cytochrome c oxidase. J. Bioenerg. Biomembr. 25, 153–163.
Roy, S., Lado, B.H., Khanna, S., Sen, C.K., 2002. Vitamin E sensitive genes in the developing rat fetal brain: a high-density oligonucleotide microarray analysis. FEBS Lett. 530, 17–23.
Rudra, P.K., Krokan, H.E., 2001. Cell-specific enhancement of doxorubicin toxicity in human tumour cells by docosahexaenoic acid. Anticancer Res. 21, 29–38.
Santos, G.C., Almeida, M.R., Antunes, L., Bianchi, M., 2016. Effect of bixin on DNA damage and cell death induced by doxorubicin in HL60 cell line. Hum. Exp. Toxicol. 35, 1319–1327. https://doi.org/10.1177/0960327116630352.
Senchenkov, A., Litvak, D.A., Cabot, M.C., 2001. Targeting ceramide metabolism–a strategy for overcoming drug resistance. J. Natl. Cancer Inst. 93, 347–357.
Shimpo, K., Nagatsu, T., Yamada, K., Sato, T., Niimi, H., Shamoto, M., Takeuchi, T., Umezawa, H., Fujita, K., 1991. Ascorbic acid and adriamycin toxicity. Am. J. Clin. Nutr. 54, 1298S–1301S. https://doi.org/10.1093/ajcn/54.6.1298s.
Sishi, B.J.N., Loos, B., van Rooyen, J., Engelbrecht, A.-M., 2013. Autophagy upregulation promotes survival and attenuates doxorubicin-induced cardiotoxicity. Biochem. Pharmacol. 85, 124–134. https://doi.org/10.1016/j.bcp.2012.10.005.
Sokolove, P.M., Kester, M.B., Haynes, J., 1993. Interaction of adriamycin aglycones with isolated mitochondria. Effect of selenium deficiency. Biochem. Pharmacol. 46, 691–697.
Sørensen, B.S., Sinding, J., Andersen, A.H., Alsner, J., Jensen, P.B., Westergaard, O.,

1992. Mode of action of topoisomerase II-targeting agents at a specific DNA sequence. Uncoupling the DNA binding, cleavage and religation events. J. Mol. Biol. 228, 778–786.
Srividya, A.R., Venkatesh, N., Vishnuvarthan, V.J., 2010. Nutraceutical as medicine. Int. J. Adv. Pharm. Sci. 1, 132–133.
Steinherz, L.J., Steinherz, P.G., Tan, C.T., Heller, G., Murphy, M.L., 1991. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. J. Am. Med. Assoc. 266, 1672–1677.
Stěrba, M., Popelová, O., Lenčo, J., Fučíková, A., Brčáková, E., Mazurová, Y., Jirkovský, E., Simůnek, T., Adamcová, M., Mičuda, S., Stulík, J., Geršl, V., 2011. Proteomic insights into chronic anthracycline cardiotoxicity. J. Mol. Cell. Cardiol. 50, 849–862. https://doi.org/10.1016/j.yjmcc.2011.01.018.
Sun, A., Cheng, Y., Zhang, Y., Zhang, Q., Wang, S., Tian, S., Zou, Y., Hu, K., Ren, J., Ge, J., 2014. Aldehyde dehydrogenase 2 ameliorates doxorubicin-induced myocardial dysfunction through detoxification of 4-HNE and suppression of autophagy. J. Mol. Cell. Cardiol. 71, 92–104. https://doi.org/10.1016/j.yjmcc.2014.01.002.
Sun, N., Yun, J., Liu, J., Malide, D., Liu, C., Rovira, I.I., Holmström, K.M., Fergusson, M.M., Yoo, Y.H., Combs, C.A., Finkel, T., 2015. Measuring in vivo mitophagy. Mol. Cell 60, 685–696. https://doi.org/10.1016/j.molcel.2015.10.009.
Sung, L., Tomlinson, G.A., Greenberg, M.L., Koren, G., Judd, P., Ota, S., Feldman, B.M., 2007. Serial controlled N-of-1 trials of topical vitamin E as prophylaxis for chemotherapy-induced oral mucositis in paediatric patients. Eur. J. Cancer 43, 1269–1275. https://doi.org/10.1016/j.ejca.2007.02.001.
Svingen, B.A., Powis, G., Appel, P.L., Scott, M., 1981a. Protection by alpha-tocopherol and dimethylsulfoxide (DMSO) against adriamycin induced skin ulcers in the rat. Res. Commun. Chem. Pathol. Pharmacol. 32, 189–192.
Svingen, B.A., Powis, G., Appel, P.L., Scott, M., 1981b. Protection against adriamycin-induced skin necrosis in the rat by dimethyl sulfoxide and alpha-tocopherol. Cancer Res. 41, 3395–3399.
Swift, L.P., Rephaeli, A., Nudelman, A., Phillips, D.R., Cutts, S.M., 2006. Doxorubicin-DNA adducts induce a non-topoisomerase II-mediated form of cell death. Cancer Res. 66, 4863–4871. https://doi.org/10.1158/0008-5472.CAN-05-3410.
Taatjes, D.J., Gaudiano, G., Resing, K., Koch, T.H., 1997. Redox pathway leading to the alkylation of DNA by the anthracycline, antitumor drugs adriamycin and daunomycin. J. Med. Chem. 40, 1276–1286. https://doi.org/10.1021/jm960835d.
Taatjes, D.J., Gaudiano, G., Resing, K., Koch, T.H., 1996. Alkylation of DNA by the anthracycline, antitumor drugs adriamycin and daunomycin. J. Med. Chem. 39, 4135–4138. https://doi.org/10.1021/jm960519z.
Tacar, O., Sriamornsak, P., Dass, C.R., 2013. Doxorubicin: an update on anticancer molecular action, toxicity and novel drug delivery systems. J. Pharm. Pharmacol. 65, 157–170. https://doi.org/10.1111/j.2042-7158.2012.01567.x.
Tan, L., Jia, X., Jiang, X., Zhang, Y., Tang, H., Yao, S., Xie, Q., 2009. In vitro study on the individual and synergistic cytotoxicity of adriamycin and selenium nanoparticles against Bel7402 cells with a quartz crystal microbalance. Biosens. Bioelectron. 24, 2268–2272. https://doi.org/10.1016/j.bios.2008.10.030.
Tanigawa, N., Katoh, H., Kan, N., Mizuno, Y., Tanimura, H., Satomura, K., Hikasa, Y., 1986. Effect of vitamin E on toxicity and antitumor activity of adriamycin in mice. Jpn. J. Cancer Res. 77, 1249–1255.
Tavares, D.C., Cecchi, A.O., Antunes, L.M., Takahashi, C.S., 1998. Protective effects of the amino acid glutamine and of ascorbic acid against chromosomal damage induced by doxorubicin in mammalian cells. Teratog. Carcinog. Mutagen. 18, 153–161.
Teicher, B.A., Schwartz, J.L., Holden, S.A., Ara, G., Northey, D., 1994. In vivo modulation of several anticancer agents by beta-carotene. Cancer Chemother. Pharmacol. 34, 235–241.
Teng, L.L., Shao, L., Zhao, Y.T., Yu, X., Zhang, D.F., Zhang, H., 2010. The beneficial effect of n-3 polyunsaturated fatty acids on doxorubicin-induced chronic heart failure in rats. J. Int. Med. Res. 38, 940–948. https://doi.org/10.1177/147323001003800320.
Terman, A., Brunk, U.T., 2005. Autophagy in cardiac myocyte homeostasis, aging, and pathology. Cardiovasc. Res. 68, 355–365. https://doi.org/10.1016/j.cardiores.2005.08.014.
Teves, S.S., Henikoff, S., 2014. Transcription-generated torsional stress destabilizes nucleosomes. Nat. Struct. Mol. Biol. 21, 88–94. https://doi.org/10.1038/nsmb.2723.
Thabrew, M.I., Samarawickrema, N., Chandrasena, L.G., Jayasekera, S., 1999. Effect of oral supplementation with vitamin E on the oxido-reductive status of red blood cells in normal mice and mice subject to oxidative stress by chronic administration of adriamycin. Ann. Clin. Biochem. 36 (Pt 2), 216–220. https://doi.org/10.1177/000456329903600214.
Traber, M.G., Atkinson, J., 2007. Vitamin E, antioxidant and nothing more. Free Radic. Biol. Med. 43, 4–15. https://doi.org/10.1016/j.freeradbiomed.2007.03.024.
Tulubas, F., Gurel, A., Oran, M., Topcu, B., Caglar, V., Uygur, E., 2015. The protective effects of ω-3 fatty acids on doxorubicin-induced hepatotoxicity and nephrotoxicity in rats. Toxicol. Ind. Health 31, 638–644. https://doi.org/10.1177/0748233713483203.
Uchida, Y., Itoh, M., Taguchi, Y., Yamaoka, S., Umehara, H., Ichikawa, S.-I., Hirabayashi, Y., Holleran, W.M., Okazaki, T., 2004. Ceramide reduction and transcriptional up-regulation of glucosylceramide synthase through doxorubicin-activated Sp1 in drug-resistant HL-60/ADR cells. Cancer Res. 64, 6271–6279. https://doi.org/10.1158/0008-5472.CAN-03-1476.
Uygur, R., Aktas, C., Tulubas, F., Alpsoy, S., Topcu, B., Ozen, O.A., 2014a. Cardioprotective effects of fish omega-3 fatty acids on doxorubicin-induced cardiotoxicity in rats. Hum. Exp. Toxicol. 33, 435–445. https://doi.org/10.1177/0960327113493304.
Uygur, R., Aktas, C., Tulubas, F., Uygur, E., Kanter, M., Erboga, M., Caglar, V., Topcu, B., Ozen, O.A., 2014b. Protective effects of fish omega-3 fatty acids on doxorubicin-induced testicular apoptosis and oxidative damage in rats. Andrologia 46, 917–926. https://doi.org/10.1111/and.12173.
Vadgama, J.V., Wu, Y., Shen, D., Hsia, S., Block, J., 2000. Effect of selenium in combination with Adriamycin or Taxol on several different cancer cells. Anticancer Res. 20, 1391–1414.
van Norren, K., van Helvoort, A., Argilés, J.M., van Tuijl, S., Arts, K., Gorselink, M., Laviano, A., Kegler, D., Haagsman, H.P., van der Beek, E.M., 2009. Direct effects of doxorubicin on skeletal muscle contribute to fatigue. Br. J. Canc. 100, 311–314. https://doi.org/10.1038/sj.bjc.6604858.
Van Vleet, J.F., Ferrans, V.J., 1980. Evaluation of vitamin E and selenium protection against chronic adriamycin toxicity in rabbits. Cancer Treat Rep. 64, 315–317.
Van Vleet, J.F., Ferrans, V.J., Weirich, W.E., 1980. Cardiac disease induced by chronic adriamycin administration in dogs and an evaluation of vitamin E and selenium as cardioprotectants. Am. J. Pathol. 99, 13–42.
Van Vleet, J.F., Greenwood, L.A., Rebar, A.H., 1981. Effect of selenium-vitamin E on hematologic alterations of adriamycin toxicosis in young pigs. Am. J. Vet. Res. 42, 1153–1159.
Vásquez-Vivar, J., Martasek, P., Hogg, N., Masters, B.S., Pritchard, K.A., Kalyanaraman, B., 1997. Endothelial nitric oxide synthase-dependent superoxide generation from adriamycin. Biochemistry 36, 11293–11297. https://doi.org/10.1021/bi971475e.
Vavrova, A., Jansova, H., Mackova, E., Machacek, M., Haskova, P., Tichotova, L., Sterba, M., Simunek, T., 2013. Catalytic inhibitors of topoisomerase II differently modulate the toxicity of anthracyclines in cardiac and cancer cells. PLoS One 8 e76676. https://doi.org/10.1371/journal.pone.0076676.
Verma, S., Dent, S., Chow, B.J.W., Rayson, D., Safra, T., 2008. Metastatic breast cancer: the role of pegylated liposomal doxorubicin after conventional anthracyclines. Cancer Treat Rev. 34, 391–406. https://doi.org/10.1016/j.ctrv.2008.01.008.
Vijay, K., Sowmya, P.R.-R., Arathi, B.P., Shilpa, S., Shwetha, H.J., Raju, M., Baskaran, V., Lakshminarayana, R., 2018. Low-dose doxorubicin with carotenoids selectively alters redox status and upregulates oxidative stress-mediated apoptosis in breast cancer cells. Food Chem. Toxicol. 118, 675–690. https://doi.org/10.1016/j.fct.2018.06.027.
Vile, G.F., Winterbourn, C.C., 1988. Inhibition of adriamycin-promoted microsomal lipid peroxidation by beta-carotene, alpha-tocopherol and retinol at high and low oxygen partial pressures. FEBS Lett. 238, 353–356.
Vincent, D.T., Ibrahim, Y.F., Espey, M.G., Suzuki, Y.J., 2013. The role of antioxidants in the era of cardio-oncology. Cancer Chemother. Pharmacol. 72, 1157–1168. https://doi.org/10.1007/s00280-013-2260-4.
Vishnu, K.V., Ajeesh Kumar, K.K., Chatterjee, N.S., Lekshmi, R.G.K., Sreerekha, P.R., Mathew, S., Ravishankar, C.N., 2018. Sardine oil loaded vanillic acid grafted chitosan microparticles, a new functional food ingredient: attenuates myocardial oxidative stress and apoptosis in cardiomyoblast cell lines (H9c2). Cell Stress Chaperones 23, 213–222. https://doi.org/10.1007/s12192-017-0834-5.
Viswanatha Swamy, A.H.M., Wangikar, U., Koti, B.C., Thippeswamy, A.H.M., Ronad, P.M., Manjula, D.V., 2011. Cardioprotective effect of ascorbic acid on doxorubicin-induced myocardial toxicity in rats. Indian J. Pharmacol. 43, 507–511. https://doi.org/10.4103/0253-7613.84952.
Vitelli, M., Filippelli, A., Rinaldi, B., Rossi, S., Palazzo, E., Rossi, F., Berrino, L., 2002. Effects of docosahexaenoic acid on [Ca(2+)](i) increase induced by doxorubicin in ventricular rat cardiomyocytes. Life Sci. 71, 1905–1916.
Vrignaud, P., Montaudon, D., Londos-Gagliardi, D., Robert, J., 1986. Fatty acid composition transport and metabolism in doxorubicin-sensitive and-resistant rat glioblastoma cells. Cancer Res. 46, 3258–3261.
Vrignaud, P., Robert, J., 1987. Free fatty acid uptake is increased in doxorubicin-resistant rat glioblastoma cells. Biochim. Biophys. Acta 902, 149–153.
Wahab, M.H., Akoul, E.S., Abdel-Aziz, A.A., 2000. Modulatory effects of melatonin and vitamin E on doxorubicin-induced cardiotoxicity in Ehrlich ascites carcinoma-bearing mice. Tumori 86, 157–162.
Wang, E.Y., Biala, A.K., Gordon, J.W., Kirshenbaum, L.A., 2012. Autophagy in the heart: too much of a good thing? J. Cardiovasc. Pharmacol. 60, 110–117. https://doi.org/10.1097/FJC.0b013e31824cc427.
Wang, Q., Yang, L., Hua, Y., Nair, S., Xu, X., Ren, J., 2014. AMP-activated protein kinase deficiency rescues paraquat-induced cardiac contractile dysfunction through an autophagy-dependent mechanism. Toxicol. Sci. 142, 6–20. https://doi.org/10.1093/toxsci/kfu158.
Wang, Y., Liu, X., Deng, G., Sun, J., Yuan, H., Li, Q., Wang, Q., Lu, J., 2018. Se@SiO2-FA-CuS nanocomposites for targeted delivery of DOX and nano selenium in synergistic combination of chemo-photothermal therapy. Nanoscale 10, 2866–2875. https://doi.org/10.1039/c7nr09237g.
Wang, Z.-Q., Chen, M.-T., Zhang, R., Zhang, Y., Li, W., Li, Y.-G., 2016. Docosahexaenoic acid attenuates doxorubicin-induced cytotoxicity and inflammation by suppressing NF-κB/iNOS/NO signaling pathway activation in H9C2 cardiac cells. J. Cardiovasc. Pharmacol. 67, 283–289. https://doi.org/10.1097/FJC.0000000000000350.
Wartenberg, M., Hoffmann, E., Schwindt, H., Grünheck, F., Petros, J., Arnold, J.R.S., Hescheler, J., Sauer, H., 2005. Reactive oxygen species-linked regulation of the multidrug resistance transporter P-glycoprotein in Nox-1 overexpressing prostate tumor spheroids. FEBS Lett. 579, 4541–4549. https://doi.org/10.1016/j.febslet.2005.06.078.
Washio, M., Nanishi, F., Okuda, S., Onoyama, K., Fujishima, M., 1994. Alpha tocopherol improves focal glomerulosclerosis in rats with adriamycin-induced progressive renal failure. Nephron 68, 347–352. https://doi.org/10.1159/000188398.
Weiss, R.B., 1992. The anthracyclines: will we ever find a better doxorubicin? Semin. Oncol. 19, 670–686.
Wells, W.W., Rocque, P.A., Xu, D.P., Meyer, E.B., Charamella, L.J., Dimitrov, N.V., 1995. Ascorbic acid and cell survival of adriamycin resistant and sensitive MCF-7 breast tumor cells. Free Radic. Biol. Med. 18, 699–708.
Wold, L.E., Aberle, N.S., Ren, J., 2005. Doxorubicin induces cardiomyocyte dysfunction via a p38 MAP kinase-dependent oxidative stress mechanism. Cancer Detect. Prev. 29, 294–299. https://doi.org/10.1016/j.cdp.2004.07.008.

Wong, R.S.Y., Radhakrishnan, A.K., 2012. Tocotrienol research: past into present. Nutr. Rev. 70, 483–490. https://doi.org/10.1111/j.1753-4887.2012.00512.x.

Wu, H., Xue, D., Chen, G., Han, Z., Huang, L., Zhu, C., Wang, X., Jin, H., Wang, J., Zhu, Y., Liu, L., Chen, Q., 2014. The BCL2L1 and PGAM5 axis defines hypoxia-induced receptor-mediated mitophagy. Autophagy 10, 1712–1725. https://doi.org/10.4161/auto.29568.

Xia, Y., Chen, Y., Hua, L., Zhao, M., Xu, T., Wang, C., Li, Y., Zhu, B., 2018. Functionalized selenium nanoparticles for targeted delivery of doxorubicin to improve non-small-cell lung cancer therapy. Int. J. Nanomed. 13, 6929–6939. https://doi.org/10.2147/IJN.S174909.

Xiang, P., Deng, H.Y., Li, K., Huang, G.-Y., Chen, Y., Tu, L., Ng, P.C., Pong, N.H., Zhao, H., Zhang, L., Sung, R.Y.T., 2009. Dexrazoxane protects against doxorubicin-induced cardiomyopathy: upregulation of Akt and Erk phosphorylation in a rat model. Cancer Chemother. Pharmacol. 63, 343–349. https://doi.org/10.1007/s00280-008-0744-4.

Xie, Q., Deng, W., Yuan, X., Wang, H., Ma, Z., Wu, B., Zhang, X., 2018. Selenium-functionalized liposomes for systemic delivery of doxorubicin with enhanced pharmacokinetics and anticancer effect. Eur. J. Pharm. Biopharm. 122, 87–95. https://doi.org/10.1016/j.ejpb.2017.10.010.

Xu, X., Bucala, R., Ren, J., 2013. Macrophage migration inhibitory factor deficiency augments doxorubicin-induced cardiomyopathy. J. Am. Heart Assoc. 2 e000439. https://doi.org/10.1161/JAHA.113.000439.

Xue, H., Ren, W., Denkinger, M., Schlotzer, E., Wischmeyer, P.E., 2016. Nutrition modulation of cardiotoxicity and anticancer efficacy related to doxorubicin chemotherapy by glutamine and ω-3 polyunsaturated fatty acids. JPEN - J. Parenter. Enter. Nutr. 40, 52–66. https://doi.org/10.1177/0148607115581838.

Yamanaka, S., Tatsumi, T., Shiraishi, J., Mano, A., Keira, N., Matoba, S., Asayama, J., Fushiki, S., Fliss, H., Nakagawa, M., 2003. Amlodipine inhibits doxorubicin-induced apoptosis in neonatal rat cardiac myocytes. J. Am. Coll. Cardiol. 41, 870–878.

Yilmaz, S., Atessahin, A., Sahna, E., Karahan, I., Ozer, S., 2006. Protective effect of lycopene on adriamycin-induced cardiotoxicity and nephrotoxicity. Toxicology 218, 164–171. https://doi.org/10.1016/j.tox.2005.10.015.

Yoshida, H., Hayashi, S., Kunisada, T., Ogawa, M., Nishikawa, S., Okamura, H., Sudo, T., Shultz, L.D., Nishikawa, S., 1990. The murine mutation osteopetrosis is in the coding region of the macrophage colony stimulating factor gene. Nature 345, 442–444. https://doi.org/10.1038/345442a0.

Yu, T., Bai, J., Hu, K., Wang, Z., 2003. The effect of free radical scavenger and antioxidant on the increase in intracellular adriamycin accumulation induced by ultrasound. Ultrason. Sonochem. 10, 33–35.

Zanetti, S.R., Maldonado, E.N., Aveldaño, M.I., 2007. Doxorubicin affects testicular lipids with long-chain (C18-C22) and very long-chain (C24-C32) polyunsaturated fatty acids. Cancer Res. 67, 6973–6980. https://doi.org/10.1158/0008-5472.CAN-07-0376.

Zhang, S., Liu, X., Bawa-Khalfe, T., Lu, L.-S., Lyu, Y.L., Liu, L.F., Yeh, E.T.H., 2012. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat. Med. 18, 1639–1642. https://doi.org/10.1038/nm.2919.

Zijlstra, J.G., de Vries, E.G., Muskiet, F.A., Martini, I.A., Timmer-Bosscha, H., Mulder, N.H., 1987. Influence of docosahexaenoic acid in vitro on intracellular adriamycin concentration in lymphocytes and human adriamycin-sensitive and -resistant small-cell lung cancer cell lines, and on cytotoxicity in the tumor cell lines. Int. J. Cancer 40, 850–856.