Archives of Razi Institute Journal
"Arch. Razi Inst."

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Review Paper

Reducing Doxorubicin Cardiotoxicity With Dapsone, Febuxostat, Telmisartan

Najmaldin Saki[1], Richard Eric Kast[2], Seyed Sobhan Bahreiny[3], Mojtaba Aghaei[1, 3*]

1. Thalassemia & Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
2. IIAIGC Study Center, Burlington, United States.
3. Student Research Committee, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran.

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How to cite this article Saki N, Kast RE, Bahreiny SS, Aghaei M. Reducing Doxorubicin Cardiotoxicity With Dapsone, Febuxostat, Telmisartan. Archives of Razi Institute Journal. 2026; 81(1):21-30. https://doi.org/10.32598/ARI.81.1.3165

https://doi.org/10.32598/ARI.81.1.3165

Article info:
Received: 12 Oct 2025
Accepted: 10 Dec 2025
Published: 01 Jan 2026

Keywords:
Cardiotoxicity, Dapsone, Doxorubicin, Febuxostat, Telmisartan

ABSTRACT

Doxorubicin is a chemotherapeutic agent widely recognized for its efficacy in cancer treatment but also associated with a significant risk of inducing cardiomyopathy, both acutely and over the long term. The underlying mechanisms of myocardial damage involve the generation of reactive oxygen species (ROS), myocardial infiltration by neutrophils, elevated levels of myeloperoxidase (MPO) and tumor necrosis factor-alpha (TNF-α), as well as an increase in cardiac xanthine oxidase (XO) activity. This review presents and evaluates the burgeoning field of interventions aimed at reducing the cardiotoxicity associated with doxorubicin, a potent chemotherapeutic agent. To mitigate doxorubicin-induced cardiotoxicity, we introduce a novel therapeutic approach termed the dapsone, febuxostat, telmisartan (DFT) therapy. This regimen involves the administration of dapsone, febuxostat, and telmisartan—compounds known for their cardioprotective effects. This review synthesizes findings from the literature, detailing how each component of the DFT regimen contributes to cardioprotection through mechanisms such as the attenuating oxidative stress and inflammation, and modulating cardiac enzyme activities. Research on the DFT regimen has yielded encouraging outcomes in attenuating doxorubicin-induced cardiotoxicity. Dapsone, febuxostat, and telmisartan, both individually and in combination, have demonstrated a capacity to protect the heart by inhibiting ROS production, diminishing neutrophil infiltration, reducing levels of MPO and TNF-α, and suppressing XO activity. Furthermore, these agents are implicated in preserving cardiac function, preventing myocardial injury, and averting adverse remodeling. The DFT therapy presents a promising approach to reducing the cardiotoxic effects associated with doxorubicin in cancer patients. The collective evidence suggests that the DFT regimen not only attenuates doxorubicin-induced cardiotoxic effects but also preserves cardiac function, prevents myocardial injury, and averts adverse remodeling, underscoring its potential as an adjunctive therapy. Nonetheless, further preclinical and clinical studies are essential to confirm the cardioprotective efficacy of this regimen and to refine its application in oncology.

*** Corresponding Author:**
Mojtaba Aghaei
Address: *Thalassemia & Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*
Tel: *+98 (937) 0201396*
E-mail: *mojtabaaghaei745@gmail.com*

1. Context

Introduced into clinical oncology practice in the late 1960s, doxorubicin remains in the 2023s one of the most effective and widely used cancer chemotherapeutic drugs. Shortly after its clinical introduction in the 1970s, cardiomyopathy was recognized as one of its potential adverse effects [1, 2]. The risk of cardiomyopathy rises with increasing dose and duration of use. Recent insights into the mechanisms by which doxorubicin induces cardiomyopathy allow us to match these mechanisms with several current non-oncology drugs from general medical practice. These drugs have documented abilities to inhibit or block some of these doxorubicin-related cardiotoxicities without interfering with doxorubicin's anticancer efficacy. Accordingly, this paper shows how the dapsone, febuxostat, telmisartan (DFT) regimen- which combines three drugs from general medical practice: the antibiotic dapsone, the antihypertension drug telmisartan, and the xanthine oxidase (XO) inhibitor febuxostat (used to treat gout)- febuxostat, works by having each component individually inhibit or block a specific cardiotoxic mechanism of doxorubicin. This is summarized in Table 1 and discussed in the Results section.

The drugs of the DFT regimen are all inexpensive, generic, widely available, and are associated with low risk of side effects when used in their respective clinical application. We have no reason to believe that the DFT agents will be any less tolerable or more problematic when given with doxorubicin, although we cannot exclude the possibility of unforeseen adverse effects.

This paper builds upon previous ideas and studies that examined the potential of approved drugs to ameliorate doxorubicin cardiotoxicity [3]. Among the many pharmaceutical and herbal preparations explored in the peer-reviewed literature for mitigating doxorubicin cardiomyopathy, the DFT regimen comprises agents with the strongest established physiological rationale and safety profile.

Doxorubicin induces cardiac muscle damage via:

- The generation of reactive oxygen species (ROS);
- Neutrophil infiltration into the myocardium;
- Elevation of myeloperoxidase (MPO) and tumor necrosis factor-alpha (TNF-α) among other factors, and
- Increased cardiac XO activity.

2. Evidence Acquisition

Doxorubicin-induced cardiotoxicity is an important problem in cancer treatment, and its mitigation is crucial. To gather relevant information, a comprehensive search was conducted in scientific databases such as PubMed, Scopus, Web of Science, and the Cochrane Library, using keywords such as "doxorubicin cardiotoxicity," "dapsone and cardiotoxicity," "febuxostat and cardiotoxicity," "telmisartan and cardiotoxicity," "dft regimen," "cardioprotection in chemotherapy," "antioxidants and cardioprotection," "urate-lowering Therapy and heart," and "angiotensin receptor blockers and cardiotoxicity." In addition to these search results, several cross-references were also reviewed to ensure a comprehensive understanding. The research team carefully screened the articles for relevance before inclusion in the manuscript. Articles addressing the individual and combined effects of dapsone, febuxostat, and telmisartan on doxorubicin-induced cardiotoxicity were included in the final review, covering preclinical and clinical studies, mechanistic findings, and outcome measures such as left ventricular ejection fraction, cardiac biomarkers, and incidence of heart failure. All relevant articles from the databases listed were included regardless of their year of publication.

3. Results

3.1. Doxorubicin

Doxorubicin's anticancer effects are primarily due to its ability to intercalate between DNA base pairs and inhibit topoisomerase II, resulting in DNA double-stranded breaks. It also tTriggers oxidative stress-induced damage by generating superoxide (O^{-}_{2}), hydroxyl radicals (•OH), and hydrogen peroxide (H_2O_2) [4, 5]. Other mechanisms have also been recognized as potentially operative [1, 6]. Doxorubicin's cardiotoxicity derives primarily from its generation of ROS, with consequent multilevel cellular and mitochondrial damage [7, 8]. See Table 2 for definitions of several ROS and Murotomi et al. for a review of ROS states [9].

Side effects, emergence of resistance, and cardiomyopathy limit doxorubicin's usefulness [10]. Cardiomyopathy risk increases as the cumulative dose of doxorubicin exceeds 250 mg/m^2 BSA. Pegylated, liposomal, micellar, nano, and other formulations have been developed in an attempt to limit doxorubicin's cardiomyopathy risk [11, 12]. These modified doxorubicin formulations have improved biocompatibility, reduced immunogenicity, reduced dermatological side effects, and enhanced solubility, distribution control, targeting, and release kinetics [11]. See the brief glossary in Table 2.

Table 1. A brief summary of the effects of dapsone, febuxostat, and telmisartan on doxorubicin-induced cardiotoxicity

Drug	General Medicine Use	Targets with Doxorubicin
Telmisartan	Hypertension	ARB, PPAR-gamma, ROS reduction
Febuxostat	Gout (podagra)	XO, ROS reduction
Dapsone	Toxoplasmosis, malaria	IL-8, neutrophils, ROS reduction

Despite these newer formulations, cardiomyopathy-related morbidity and mortality remain significant risks. ROS generated by doxorubicin's interaction with Fe^{2+} (vide infra) cause irreversible mitochondrial damage, which is believed to be one of the principal causes of this cardiomyopathy [7, 13]. An iron chelating drug, dexrazoxane, administered immediately prior to doxorubicin, has been shown to reduce cardiomyopathy, However, because doxorubicin-related cardiac damage is multifactorial, morbidity and mortality remain significant problems [14]. Multiple myocyte damaging consequences derive from this ROS generation, such as endothelium damage, mitochondrial dysfunction, cytokine release, NLRP3 inflammasome generation, and platelet and monocyte activations [15].

Since doxorubicin generates reactive nitrogen species as well as ROS through similar and related pathways, and both species damage vital cell structures, the two will be considered here collectively as ROS.

Doxorubicin belongs to the anthracycline-class of cancer chemotherapy drugs. Other members of this class include daunorubicin, epirubicin, idarubicin, and mitoxantrone. The primary mechanism of action against cancer for all anthracycline-class drugs is similar: intercalation between DNA base pairs, which causes DNA uncoiling and inhibition of topoisomerase II, leading to double-strand breaks.

3.1.1. MPO

MPO is a heme-containing peroxidase that, through intermediates, catalyses the following reactions:

$$C_l^- + H_2O_2 \rightarrow HOCl \text{ (hypochlorous acid)}$$

$$SCN^- + H_2O_2 \rightarrow HOSCN \text{ (hypothiocyanous acid)}.$$

These MPO end products are strong oxidants and are core elements mediating cardiac damage after doxorubicin exposure. These MPO end products and other related peroxidase reaction products participate in defense against bacteria, fungi, and protozoa [16]. MPO is a disulfide-linked dimer that comprises about 5% of the dry mass of neutrophils and is contained predominantly within azurophilic granules. MPO is required for neutrophil extracellular trap (NET) formation [17, 18]. MPO also exerts proinflammatory properties independent of its catalytic activity (Figure 1) [19].

Table 2. Brief glossary of some terms used in this paper

Term	Definition
Hydroxyl	•OH, a neutral, highly reactive ROS
Hypochlorous acid	HClO, a neutral ROS
Liposome	A spherical lamellar phospholipid bilayer with hydrophilic outer layer surrounding a hydrophilic core 5 to 500 nm diameter
Micelle	A spherical amphiphilic lipid polymer with hydrophilic shell and lipophilic core, 15-80 nm diameter, able to carry water insoluble or poorly soluble drugs
NET	Neutrophil extracellular trap, a <50 nm agglomeration of DNA, MPO and other proteins released from dead neutrophils
O_2	Oxygen, ground state triplet oxygen molecule $^3O_2$, stable
Pegylation	Polyethylene glycol added to a molecule, increasing its mass
Peroxynitrite	O=N-O-O^-, an ROS with negative charge of −1
Singlet oxygen	Singlet oxygen molecule $^1O_2$, half-life of microseconds, an ROS
Superoxide	$O2^-$, an oxygen molecule with an added electron, negative charge −1, with one unpaired outer shell electron, an ROS

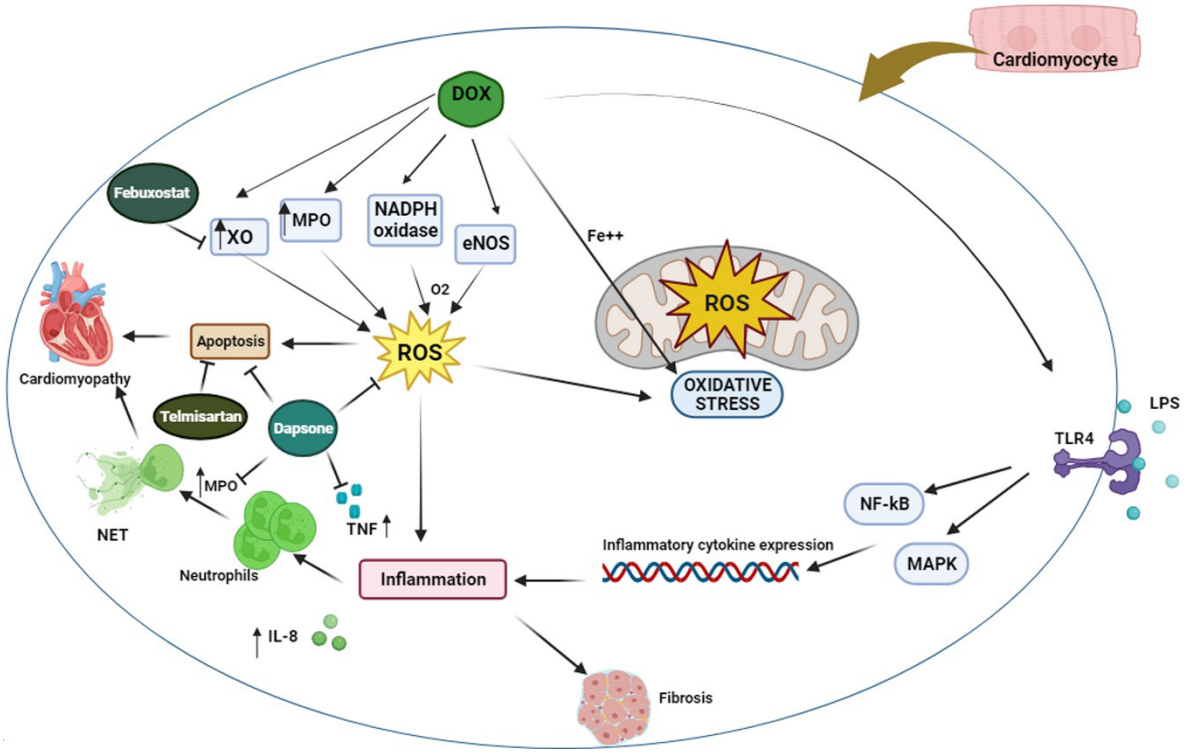

Figure 1. The role of doxorubicin in the risk of cardiomyopathy and the interaction of DFT in reducing the cardiotoxicity of doxorubicin

Doxorubicin increased circulating neutrophil counts and soluble circulating MPO levels, with an increase in neutrophil invasion of cardiac muscle compared to saline control mice, and an experimental, non-marketed MPO inhibitor reduced the doxorubicin cardiotoxicity in this murine model [20]. MPO is also produced by CNS microglia and astrocytes.

Large population studies have shown a strong correlation between plasma MPO and cardiovascular disease and a poorer cardiovascular prognosis [21].

3.1.2. Neutrophils

Much of the DFT regimen is centered on reducing neutrophil contributions to doxorubicin-provoked cardiomyocyte damage.

The finding of extensive neutrophil infiltration into heart muscle is a core feature of and major pathophysiologic contributor to generating doxorubicin's cardiotoxicity [20]. A murine study showed that neutrophils accumulated along cardiac small vessel walls, damaging them, which led to muscle damage, while neutrophil depletion reduced doxorubicin-induced structural and functional myocardial damage [22].

In the attempt to diminish doxorubicin-provoked neutrophil-mediated cardiomyopathy, Zhu et al. (2023) subjected doxorubicin-treated mice to transthoracic pericardial ultrasound (1.0 MHz, duty cycle 20%, 110 mW/cm^2) for 15 min. This reduced the doxorubicin-induced cardiac infiltration of neutrophils, lessened the ejection fraction decrease, and lowered cardiomyocyte terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling (TUNEL) staining indicative of apoptosis [23].

Fourteen days after doxorubicin treatment, breast cancer patients with reduced ejection fraction had strongly increased plasma MPO, while those who had a normal ejection fraction showed no or minimal MPO increases [24]. Similar increases in soluble circulating MPO occur in human breast cancer patients treated with doxorubicin, with cardiomyopathy incidence proportional to MPO increases (Figure 1) [25].

NETs are filamentous extracellular agglomerations of decondensed chromatin DNA, histones, MPO, matrix metalloproteinases, and neutrophil elastase released by stimulated, dying, or dead neutrophils. Interleukin-8 (IL-8), lipopolysaccharide (LPS), microbial triggers, and tumor cell-secreted cytokines activate neutrophils to form membrane protuberances that release or become NETs [26]. NETs are primarily an element of antibacterial and

antifungal defense but are derailed to promote metastases and primary tumor growth by multiple complex elements [27, 28].

Superoxide dismutase (SOD) and catalase (CAT) in the heart of mice were increased by the intraperitoneal administration of doxorubicin [29].

3.2. DFT, the repurposed drugs

All the DFT drugs, dapsone, febuxostat, and telmisartan, have well-established safety profiles, are inexpensive, and are generically available worldwide.

3.2.1. Dapsone

Dapsone empirically diminished the severity of doxorubicin-induced myocardial damage in rats. Commensurate with that, doxorubicin-induced cardiac contraction dysfunction was reduced by dapsone. This effect was not large, but it was clear and significant [30]. MPO-related tissue damage reduction by dapsone is probably an indirect effect of its inhibition of the characteristic neutrophil respiratory burst, rather than a direct inhibition of MPO itself [30].

3.2.2. Dapsone, neutrophils, and MPO

Dapsone reduces MPO activity in a variety of settings, including dihydrofolic acid synthesis, ROS generation, IL-8, and TNF synthesis. Dihydrofolic acid synthesis inhibition is the basis of its antibacterial action, while its anti-inflammatory properties derive from reducing the effect of eosinophil peroxidase on mast cells and down-regulating IL-8, TNF, and neutrophil-mediated inflammatory responses (Figure 1) [31].

Strong neutrophil related HOCl was observed at the lesion site in experimental spinal cord injury in mice, which is not present in similarly injured MPO knockout mice [32, 33]. Inhibiting MPO activity with dapsone enhanced motor recovery after experimental spinal cord injury in rats [34].

Compared to control spinal cord-injured mice, those given dapsone 5 hours after injury had less dramatic increases in cell death or injury markers. Reductions were seen in caspase-8 by 44%, caspase-9 by 37%, and caspase-3 by 38% [35]. Counts of Annexin V- and TUNEL-positive cells were correspondingly decreased by dapsone. Similarly, this study showed a doubling of myocardial TNF after doxorubicin, an increase that was reduced by dapsone.

3.2.3. Doxorubicin, dapsone, and TNF

TNF upregulation by dapsone is a secondary mediator of myocardial damage. Many currently approved and marketed non-oncology drugs, other than the DFT drugs, have been shown to reduce the doxorubicin-mediated increased TNF and associated myocardial tissue damage: the beta blocker nebivolol [36, 37], the melatonergic antidepressant agomelatine [38], the ARB losartan (related to telmisartan) [39], the ARB valsartan (related to telmisartan) [40], the ARB olmesartan (related to telmisartan) [41], the anti-diabetes PPAR-gamma agonist pioglitazone [42], and the nootropic piracetam [43], are recent examples, in addition to dapsone. The DFT drugs were selected as those with the lowest side effect risk and strongest preclinical evidence for cardioprotection during doxorubicin use.

Dapsone reduces TNF increases triggered by various stimuli other than doxorubicin, in animal models [35], in vitro [44], and clinically in humans [45].

3.2.4. Febuxostat

Febuxostat is an XO inhibitor used clinically to treat gout (podagra) [46]. XO catalyses the reactions below that generate powerful, vessel-damaging oxidants [47]:

$$Hypoxanthine + H_2O + O_2 \rightarrow xanthine + H_2O_2$$

$$Xanthine + H_2O + O_2 \rightarrow uric\ acid + H_2O_2$$

$$RH + H_2O + 2O_2 \rightarrow ROH + 2O_2^- + 2\,H^+$$

$$S\text{-}nitrosothiols \rightarrow NO$$

Then without XO, reactions proceed:

$$NO + 2O_2^- \rightarrow O{=}N\text{-}O\text{-}O^-\ (peroxynitrite)$$

Febuxostat reduced doxorubicin-induced creatinine kinase MB and TNF increases, and decreased the doxorubicin-related cardiomyocyte mitochondrial damage [48]. Doxorubicin increased ROS in multiple myeloma cells in vitro, and febuxostat reduced that ROS increase without reducing doxorubicin's cytotoxicity [49, 50]. XO catalyses doxorubicin's reduction, generating tissue-damaging ROS and peroxynitrite within the myocardium [51]. Peroxynitrite damages the myocardium by oxidizing cellular lipids and proteins, thereby interfering with their essential functions [52].

In general, in non-cancer populations, higher constitutive levels of XO are associated with greater cardiac mortality [53, 54].

In mice with acetic acid-induced colitis, febuxostat decreased XO, NO, MPO, and TNF [55]. In tracheally instilled, dilute HCl-induced lung injury, febuxostat reduced tissue destruction, MPO, and neutrophil infiltration [56]. In diabetic mice, febuxostat reduced glomerular injury and reduced mRNA for IL-1 beta and IL-6, but not that of TNF, which remained elevated [57]. In mice, rectal instillation of 5% acetic acid (table vinegar) induced colon inflammation, with increased XO, nitric oxide, MPO, TNF, IL-6, IL-1 beta, and IL-6 levels of colon tissue — all increases were significantly reduced but remained elevated after febuxostat [58].

Ferroptosis (iron-dependent ROS- and lipid peroxidation-related cell death)

3.2.5. Telmisartan

Telmisartan is a drug of the angiotensin receptor blocker (ARB) class used to treat hypertension. It selectively inhibits the interaction of angiotensin II with the angiotensin II receptor type 1 receptor and is increasingly being used to treat disorders of inflammation by virtue of its stimulation of PPAR-gamma [59]. A dozen recent studies, predominantly of phyto-derived PPAR-gamma agonists, have been shown to reduce doxorubicin-related cardiomyopathy [40]. Multiple studies have shown that PPAR-gamma agonists enhance doxorubicin cytotoxicity against the malignancy in a variety of cancers [60].

A 2010 rat study showed reduced apoptosis and better cardiac output after doxorubicin when telmisartan was also given (Figure 1) [61]. Telmisartan halved the doxorubicin-provoked increase in creatinine kinase-MB and reduced the provoked increase in troponin I levels by 30% in a similar rat model of doxorubicin cardiomyopathy. In a hepatic ischaemia-reperfusion injury model, telmisartan lowered the provoked MPO activity and caspase-3 immunoexpression [62].

As an example of several similar studies, Yuan et al [63] and Mahdizade et al [64] showed that chronic intermittent hypoxia resulted in myocardial cell damage, apoptosis, and increased blood IL-6. All these parameters were reduced by telmisartan [63, 64].

Epirubicin is a doxorubicin epimer with a similar cardiomyopathy risk and similar myocardial damage risk to doxorubicin. A human trial showed significantly less contractile dysfunction when telmisartan was given along with epirubicin [65]. A similar protective effect was not seen with a related ARB, candesartan, during doxorubicin or epirubicin treatment [66]. This suggests that it might be the PPAR-gamma agonist function of telmisartan that mediates cardioprotection, not the ARB action. However, another larger study of candesartan did show cardioprotection during doxorubicin [67].

4. Discussion

By understanding the core elements of how doxorubicin damages the myocardium, then matching these pathophysiological processes with attributes of drugs in the current FDA/EMA pharmacopeia, it becomes apparent that three drugs from general medical practice can undermine, circumvent, or inhibit these core cardio-damaging effects of doxorubicin. This paper reviews that data. The three drugs, dapsone, febuxostat, and telmisartan, are well known to general practitioners worldwide, are cheap generic drugs, and carry very low side effect risks. Several other drugs from general medicine have shown potential to be repurposed to mitigate doxorubicin cardiac damage. The DFT regimen drugs were chosen based on 1) foremost on their safety, 2) secondly on the strength of preclinical animal model evidence to reduce doxorubicin-generated cardiac damage - hence dapsone [30], febuxostat [48], and telmisartan [61], and 3) thirdly on the soundness of the known physiology of how cardioprotection occurs. Given the benignity of the DFT drugs and the strength of the evidence, it is time to run a pilot clinical study.

Specifically, the collected data above show: 1) that neutrophil infiltration into the myocardium and related blood vessels is an important element of doxorubicin-related heart damage; 2) this neutrophil-related cardiac damage is due both to elevated MPO and to the release of other neutrophil products; 3) this data set also shows that doxorubicin elevates cardiac tissue ROS in both neutrophil-related and neutrophil-unrelated pathways.

A caveat: DFT is designed to block elements of doxorubicin-related ROS and neutrophil cardio-damaging elements. It cannot be excluded that some of these elements may contribute to doxorubicin's cancer cell killing. Data reviewed in this paper did not show such a reduction, and doxorubicin's primary action in malignant cell cytotoxicity is DNA intercalation and topoisomerase-2 inhibition secondary to that. Also, reviewed data indicate that PPAR-gamma agonism by febuxostat both reduces ROS and enhances doxorubicin cytotoxicity in malignancies.

5. Conclusion

This paper showed how three drugs from general medical practice have potential to reduce doxorubicin's damaging effects on the heart muscle. Given i) the lethality of doxorubicin-induced cardiomyopathy and ii) the benign nature of the DFT drugs and their documented physiological potential to prevent elements of doxorubicin cardiomyopathy, plus iii) our ongoing need for doxorubicin to treat some cancers, this altogether leads to the conclusion that a pilot study of DFT-augmented doxorubicin in a doxorubicin-sensitive cancer is warranted.

Acknowledgements

This was unfunded research carried out under the aegis of the IIAIGC Study Center. The IIAIGC had no influence on any matter related to this work. We wish to thank all our colleagues at Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Compliance with ethical guidelines

We hereby declare that all ethical standards have been respected in the preparation of the submitted article.

Data availability

All data have been presented in the published paper.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization, study design: Seyed Sobhan Bahreiny; Data analysis and visualization: Mojtaba Aghaei; Writing the original draft: Najmaldin Saki and Richard Eric Kast; Review and editing: Mojtaba Aghaei; Supervision: Seyed Sobhan Bahreiny and Mojtaba Aghaei; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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