Review (Word count: 2894)

DFT regimen: Reducing doxorubicin cardiotoxicity by using dapsone, febuxostat, telmisartan

Running title: DFT Regimen: Alleviating Doxorubicin Cardiotoxicity

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), as well as an increase in cardiac xanthine oxidase (XO) activity. This review article evaluates the burgeoning field of interventions aimed at reducing the cardiotoxicity associated with doxorubicin, a potent chemotherapeutic agent. In an effort to mitigate doxorubicin-induced cardiotoxicity, we introduce a novel therapeutic approach termed DFT therapy. This regimen involves the administration of dapsone, febuxostat, and telmisartan—compounds known for their cardioprotective effects. This review synthesizes findings from related articles, detailing how each component of the DFT regimen contributes to cardioprotection through mechanisms such as the reduction of oxidative stress, inflammation, and modulation of cardiac enzyme activities. Research on the DFT regimen has yielded encouraging outcomes in attenuating doxorubicin-induced cardiotoxicity. Dapsone, febuxostat, and telmisartan, both individually and collectively, have demonstrated a capacity to protect the heart by inhibiting ROS production, diminishing neutrophil infiltration, reducing levels of MPO and TNF, and suppressing XO activity. Furthermore, these agents are implicated in preserving cardiac function, preventing myocardial injury, and averting adverse remodeling. 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 prevents adverse remodeling, underscoring its potential as an adjunctive therapy. Nonetheless, further preclinical and clinical studies are essential to confirm the cardioprotective efficacy of DFT therapy and to refine its application in oncology.

Keywords: Doxorubicin, Cardiotoxicity, Dapsone, Febuxostat, Telmisartan

Abbreviations: Interleukin-8, IL-8; myeloperoxidase, MPO; neutrophil extracellular traps, NET; reactive oxygen species, ROS; tumor necrosis factor alpha, TNF; xanthine oxidase, XO;

1. Context

Introduced into clinical oncology practice in the late 1960's, doxorubicin remains in 2023 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 the potential consequences of its use (1, 2).Cardiomyopathy risk rises with increasing dose and duration of use. Recent insights into the mechanisms of doxorubicin's generation of cardiomyopathy allow us to match these mechanisms to several current non-oncology drugs from general medical practice that have documented abilities to inhibit or block some of these doxorubicin related cardiotoxicities without interfering with doxorubicin's anticancer effect. Accordingly, this paper shows how the DFT regimen, using four drugs from general medical practice -and the antibiotic dapsone, the antihypertension drug telmisartan, xanthine oxidase (XO) inhibitor used to treat gout, febuxostat, individually inhibit or block a respective cardiodamaging aspects of doxorubicin. This is summarized in Table 1 and discussed in Section 3 below.

The drugs of the DFT regimen are all inexpensive, generic, widely available, and have low side effect risks when used in their respective general medical application. We have no reason to think that the DFT drugs will be any less tolerable or problematic when given with doxorubicin, although we cannot exclude surprises in this regard.

This paper now adds to previous ideas and studies that looked at attributes of existing pharmaceutical approved drugs that have potential to ameliorate doxorubicin cardiotoxicity (3). From among the many drugs and herbal preparations that have been explored and reported in the peer-reviewed literature for mitigation of doxorubicin cardiomyopathy reduction, the DFT regimen drugs are those with the strongest established physiological rationale and strongest safety profile.

- doxorubicin generates cardiac muscle damage via reactive oxygen species (ROS) and

- neutrophil infiltration into myocardium and
- elevation of myeloperoxidase (MPO), tumor necrosis alpha (TNF) i.a. and
- Increased cardiac xanthine oxidase (XO)

Table 1. A brief of the effect of dapsone, febuxostat, telmisartan on doxorubicin

drug	general medicine use	targets with doxorubicin
telmisartan	hypertension	ARB, PPAR-gamma, ROS reduction
febuxostat	gout (podagra)	xanthine oxidase, ROS reduction
dapsone	toxoplasmosis, malaria	IL-8, neutrophils, ROS reduction

2. Evidence Acquisition

Cardiotoxicity of doxorubicin is an important problem in cancer treatment and mitigation of this adverse effect is crucial. To gather relevant information, a comprehensive search was conducted in scientific databases such as PubMed, Scopus, Web of Science and 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 they were included 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 year of publication.

Results

3. Doxorubicin

Doxorubicin's anticancer effects are primarily due to its intercalating between DNA base-pairs and inhibition topoisomerase 2, resulting in DNA double-stranded breaks. Triggers oxidative stress-induced damage by generating superoxide O^{-}_{2}, hydroxyl radicals, •OH, and hydrogen peroxide, H2O2 (4, 5). Other mechanisms also have been recognized as potentially operative (1, 6). Doxorubicin's cardiotoxicity derives primarily by its generation of reactive oxygen species (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/m2 BSA. Pegylation, liposomal, micelle, and nano- and other formulations have been developed in the attempt to limit doxorubicin's cardiomyopathy risk (11, 12). These doxorubicin formulations have improved biocompatibility, lowered immunogenicity, lowered dermatological side effects, and enhanced doxorubicin's solubility, controlled distribution, and allowed better targeting and kinetics of release (11). See brief glossary, Table 2.

But despite these newer formulations, cardiomyopathy morbidity and mortality remain risks. ROS generated by doxorubicin's interaction with Fe^{++} (vide infra) irreversibly damage mitochondria, believed to be one of the causes of this cardiomyopathy (7, 13). An iron chelating drug, dexrazoxane, delivered immediately prior to doxorubicin has lowered cardiomyopathy but because doxorubicin related cardiac damage is multifactorial, morbidity and mortality remain problems (14). Multiple myocyte damaging consequences derive from the ROS, such

as endothelium damage, mitochondrial dysfunction, cytokine releases, NLRP3 inflammasome generation, platelet and monocyte activations, and other contributors (15).

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

Doxorubicin belongs to the anthracycline class of cancer chemotherapy drugs. Other members of this class are daunorubicin, epirubicin, idarubicin, mitoxantrone. The primary mode of action in treating cancer for all anthracycline class drugs remains the same, by intercalating between DNA base pairs, causing uncoiling and inhibition of topoisomerase II with ensuing double-strand breaks.

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
O2	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

3.1. Myeloperoxidase (MPO)

MPO is a heme containing peroxidase that, through intermediates, catalyses reactions

$Cl^- + H2O2 \longrightarrow HOCl$ (hypochlorous acid)

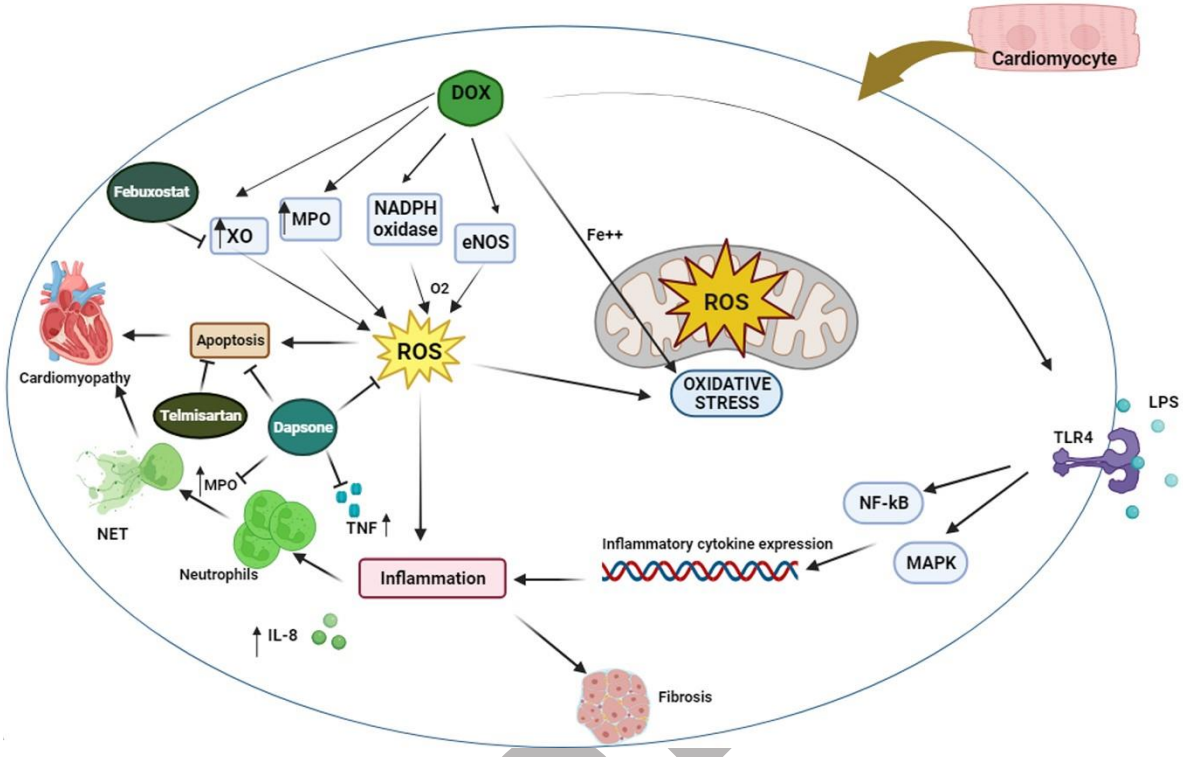
$SCN^- + H2O2 \longrightarrow HOSCN$ (hypothiocyanous acid).

These MPO end products are strong oxidants and a core element 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 the azurophilic granules. MPO is required for neutrophil extracellular trap (NET) formation (17, 18). MPO also exerts proinflammatory properties independent of its catalytic activity (**Fig. 1**) (19).

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

Large population studies have shown strong correlation between plasma MPO and cardiovascular disease and poorer cardiovascular prognosis (21).

Fig. 1. The role of doxorubicin in the risk of cardiomyopathy and the interaction of dapsone, febuxostat and telmisartan in reducing the cardiotoxicity of doxorubicin.



3.2. 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 generating doxorubicin's cardiotoxicity (20). A murine study showed that neutrophils collected along cardiac small vessel walls, damaging them, leading 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 subjected doxorubicin treated mice to transthoracic pericardial ultrasound, 1.0 MHz, duty cycle 20%, 110 mW/cm2, 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 normal ejection fraction showed no or minimal MPO increases (24). Similar increases in soluble circulating MPO occurs in human breast cancer patients treated with doxorubicin with cardiomyopathy incidence proportional to MPO increases (**Fig. 1**) (25).

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

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

4. DFT, the repurposed drugs

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

4.1. Dapsone

Dapsone empirically diminished 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 direct inhibition of MPO itself (30).

4.1.1. Dapsone, neutrophils, and MPO

Dapsone reduces MPO activity in a variety of settings, 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 its reducing the effect of eosinophil peroxidase on mast cells and downregulating IL-8, TNF, and neutrophil-mediated inflammatory responses (**Fig. 1**) (31).

Strong neutrophil related HOCl was observed at the lesion site in experimental cord injury in mice that is not present in similarly injured MPO knock-out 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 of caspase-8 by 44%, caspase-9 by 37%, and caspase-3 a decrease of 38% (35). Counts of Annexin V and TUNEL positive cells were correspondingly decreased by dapsone. Similarly, this same study showed a doubling of myocardial TNF after doxorubicin, an increase that was reduced by dapsone.

4.1.2. Doxorubicin, dapsone and TNF

TNF upregulation by dapsone is a secondary mediator of myocardium 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), the nootropic piracetam (43), are recent examples, in addition to dapsone. The DFT drugs were selected as those with 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), in clinically in humans (45).

4.2. 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):

$$\text{hypoxanthine} + H_2O + O_2 \rightleftharpoons \text{xanthine} + H_2O_2$$

$$\text{xanthine} + H_2O + O_2 \rightleftharpoons \text{uric acid} + H_2O_2$$

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

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

then without XO, reactions proceed,

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

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

In general, 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 tracheal 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 that remained elevated (57). In mice, rectal instillation of 5% acetic acid (table vinegar) induced a colon inflammation, with increased XO, nitric oxide, MPO, TNF, IL-6, IL-1 beta, and IL-6 of colon tissue - all increases were significantly reduced but remained elevated after febuxostat (58).

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

4.3. Telmisartan

Telmisartan is a drug of the angiotensin receptor blocker class (ARB) used to treat hypertension. It selectively inhibits the interaction of angiotensin II on 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 phytoderived PPAR-gamma agonists have been shown to reduce doxorubicin-related cardiomyopathy (60). Multiple studies have shown PPAR-gamma agonists enhance doxorubicin cytotoxicity to the malignancy in a variety of cancers (61).

A 2010 rat study showed reduced apoptosis and better cardiac output after doxorubicin when telmisartan was also given (**Fig. 1**) (62). Telmisartan halved the doxorubicin-provoked increase in creatinine kinase-MB and reduced provoked increase in troponin 1 levels by 30% in a similar rat model of doxorubicin cardiomyopathy. In a hepatic ischaemia-reperfusion injury model, telmisartan lowered the provoked myeloperoxidase activity and caspase 3 immunoexpression (63).

As example of several similar studies, Yuan et al showed chronic intermittent hypoxia results in myocardial cell damage, apoptosis, and increased blood IL-6. All these parameters were reduced by telmisartan (64, 65).

Epirubicin is a doxorubicin epimer with a similar cardiomyopathy risk and similar myocardial damage risk as for doxorubicin. A human trial showed significantly less contractile dysfunction when telmisartan was given along with epirubicin (66). A similar protective effect was not seen with a related ARB, candesartan during doxorubicin or epirubicin treatment (67). 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 dis show cardioprotection during doxorubicin (68).

5. Discussion

By understanding the core elements of how doxorubicin damages myocardium, then matching these pathophysiological processes with attributes of drugs in the current FDA/EMA pharmacopeia, it becomes apparent that four drugs from general medical practice can undermine, circumvent, or inhibit these core cardiodamaging effects of doxorubicin. This paper reviews that data. The four 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 cardiodamage. The DFT regimen drugs were chosen based 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 (62)

and 3) thirdly on the soundness of the known physiology of how cardioprotection occurs. Given the benignity of the DFT drugs and strength of evidence, it is time to run a pilot clinical study.

Specifically, collected data above shows: 1) that neutrophil infiltration into myocardium and related blood vessels is an important element of doxorubicin-related heart damage. 2] This neutrophil-related cardiac damage is both due to elevated MPO and by release of other neutrophil products. 3] This data set also showed 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 cardiodamaging 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 reduction and doxorubicin's primary action in malignant cell cytotoxicity is DNA intercalation and topoisomerase-2 inhibition secondary to that. Also reviewed data indicates that PPAR-gamma agonism by febuxostat both reduces ROS and enhances doxorubicin cytotoxicity in malignancy.

6. Conclusion

This paper showed how four drugs from general medical practice have potential to reduce doxorubicin's damaging effects on 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, altogether lead to the conclusion that a pilot study of DFT augmented doxorubicin in a doxorubicin sensitive cancer is warranted.

Declarations

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Ethics

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

AUTHOR CONTRIBUTIONS

In this study, Najmaldin Saki and Richard Eric Kast wrote the first draft of the manuscript. The study was formulated, designed and supervised by Seyed Sobhan Bahreiny. Mojtaba Aghaei also conducted the data analysis, visualized the results and contributed to the critical revision and editing of the manuscript. Mojtaba Aghaei supervised and reviewed the project. Finally, all authors reviewed and approved the final version of the manuscript before submission.

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All data has been presented in the published paper.

Conflicts of Interest

The author declares no conflict of interest.

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