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Original Research Article

Fumarate ameliorated doxorubicin-induced nephrotoxicity: The role of pro-inflammatory cytokines and endothelial nitric oxide synthase signaling pathway

Aladuna Joseph Omo-Erhabor[1] and Osaze Edosuyi*[2],

[1]*Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Nigeria*
[2]*Department of Pharmacology & Toxicology, Faculty of Pharmacy, University of Benin PMB 1154, Benin City, Nigeria*

*For correspondence: Email: Osaze.edosuyi@uniben.edu ; Tel. +2348025228545

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Abstract

Purpose: Nephrotoxicity is a deleterious effect of doxorubicin (dox). This study investigated the renoprotective property of the tricarboxylic acid cycle metabolite, fumarate, in dox-induced nephrotoxicity.
Methods: Male Wistar rats were randomly divided into four groups containing eight animals each; I: distilled water (10 ml/kg, po), II: dox (10 mg/kg stat. ip), III: dox (10 mg/kg, ip) + fumarate (50 mg/kg, po) and IV: dox (10 mg/kg, ip) + fumarate (100 mg/kg, po). The animals were treated for 10 days and euthanised on the last day. The kidneys were excised and immediately frozen for molecular analysis. A kidney section was fixed in formalin + saline solution for the histological assay.
Results: Fumarate at 50 mg/kg caused a 23. 2 %, $p<0.01$ reduction in kidney injury molecule (KIM) expression in dox-treated rats. There was a reduction in the expression of interleukin (IL)-1β expression in nephrotoxic rats at 100 mg/kg of fumarate, (32.4±0.6 vs 28.5±0.0, $p<0.05$). Similarly, IL-6 expression was decreased in a dose-dependent manner in dox-treated rats. The initial fall in superoxide dismutase (SOD) activity at 50 mg/kg of fumarate was reversed at 100 mg/kg (27.7±0.9 vs 28.6±0.4, $p>0.05$) in rats treated with dox. Endothelial nitric oxide synthase (eNOS) expression was significantly reduced in fumarate-treated dox rats at 50 mg/kg only, (27.1±0.7 vs 23.2±0.7, $p<0.05$). Histological sectioning of the kidney revealed distortions in the glomerulus of dox-treated rats and fumarate reversed these changes.
Conclusion: Data from this study show that fumarate ameliorated dox-induced nephrotoxicity by reducing eNOS and cytokine signaling.

Keywords: Cytokine, doxorubicin, endothelial nitric oxide synthase, fumarate, nephrotoxicity, tricarboxylic acid cycle.

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INTRODUCTION

The adverse effects of chemotherapeutic agents remain a barrier to therapy. [1] In addition to nausea and vomiting, most chemotherapeutic agents cause a specific end-organ injury that affects the patient's quality of life. For instance, the use of doxorubicin is associated with cardiotoxic and nephrotoxic adverse effects. [2] Despite its broad spectrum of activity, this action on the cardiorenal system complicates its use as a chemotherapeutic agent. Therefore, orthodox agents are usually co-administered during dox therapy.[3] Although some of these orthodox agents are effective, they burden the patient with additional side effects.[4] Hence, there is a continuous search for new agents with minimal side effects.[5]

Dox-associated toxicity has been closely related to up-regulation of mitochondrial-induced oxidative stress and the consequent generation of reactive radicals.[2, 4] The accumulation of dox in renal tissues particularly subjects the kidneys to these effects. Dox causes indirect kidney injury through a cardiotoxic effect that eventually results in a reduction in heart pump efficiency, leading to reduced perfusion to the kidneys. A culmination of these mechanisms can lead to chronic renal failure.[6, 7]

Fumarate, an intermediary in the tricarboxylic acid (TCA) cycle, has been reported to exert cardio and renoprotective effects. [8, 9] Fumarate has been shown to upregulate the expression of protective genes such as nuclear erythroid factor (Nrf2) that improve the redox state of the kidneys and possibly ameliorate reactive radical-induced injury. [10, 11] Furthermore, fumarate is reported to increase renal perfusion through nitric oxide-induced vasodilatory action, improving renal function. Since fumarate directly influences most of the mechanisms involved in dox-induced renal injury, fumarate can mitigate these mechanism(s) and exert a nephroprotective action. This study investigated the effect of fumarate on dox-induced nephrotoxicity in experimental animals.

MATERIAL AND METHOD

Animals

Male Wistar rats (5-11 weeks; 118–220 g) were kept in the animal facility of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin. The animals were placed on pelletized rat food (Growers Mash, Feed Mills Co. Ltd, Nigeria) with free access to clean water. A 12-hour lightning/dark cycle was observed under controlled conditions (28 ± 2℃; humidity, 58 ± 10%). The protocols for this study were approved by the Institutional Ethics Committee of the Faculty of Pharmacy, University of Benin, Benin City (EC/FP/024/07).

Experimental Procedure

Male Wistar rats (118g – 220g) were assigned to four (4) groups containing eight (8) animals; group I; control (distilled water; 10 ml/kg); group II; doxorubicin (10 mg/kg i/p, single dose); group III; doxorubicin (10 mg/kg, i/p, single dose) + fumarate (50 mg/kg po.), and group IV; doxorubicin (10 mg/kg, i/p, single dose) + fumarate (100 mg/kg po.). Animal weights were recorded on days 0 and 10. Animals were sacrificed (ketamine + xylazine; 100 mg/kg, i/p) on the last day. The kidney (100 mg) was excised and immediately transferred to a triazole solution for superoxide dismutase (SOD), kidney injury molecule (KIM-1), interleukin 1β and 6, and endothelial nitric oxide synthase (eNOS) expression assay. A section of the kidney was fixed in formalin + saline for histopathological assay.

Polymerase chain reaction assay.

Total RNA was isolated from kidney samples using the protocols in the Quick-RNA Miniprep™ Kit (Zymo Research). The DNA contaminant was removed with DNase I (NEB, Cat: M0303S). The DNA-free RNA was quantified using a spectrophotometer (A&E Lab, UK).

Deoxyribonucleic acid (cDNA) conversion

One (1 µg) of DNA-free RNA was converted to cDNA by reverse transcriptase using the cDNA synthesis kit (New England BioLabs).[12]

The target gene was amplified with the OneTaqR2X master mix using the following primers (Inqaba Biotec, Hatfield, South Africa), endothelial nitric oxide synthase (eNOS), forward primer: TGGAGCGAGTTGTGGATTG reverse primer: CTACTGGGTCAAAGACAAGAGG, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), forward primer CTGGCAGCTCTTCTCAAAGC, reverse primer CCAGGTCATAGAGAGGCTCAA.

Amplification was performed in a total of 0.025 ml of reaction mixture containing cDNA, primer (forward and reverse) and ready mix Taq PCR master mix. There was an initial denaturation at 95 ◦C for 5 minutes, followed by 30 cycles of amplification (denaturation at 95 C for 30 s, hardening for 30 s, and extension at 72 ◦C for 60 s) and ending with a final extension at 72 ◦C for 10

minutes. The amplified genes were resolved on 1.0 % agarose gel. The GAPDH gene served as a 'housekeeping gene' and was used for the relative expression of each gene. The bands were quantified using the J® image software.[13] The same procedure was repeated for superoxide dismutase (SOD), kidney injury molecule (KIM-1) and interleukin 1β and 6 using the primers.
KIM-1: forward: GGATGAGGATGGGTTTCTTAGG and reverse: CCTGCTCTCTCTCCTTTCTTTC.
SOD forward: AGGGCCTGTCCCATGATGTC and reverse: AGAAACCCGTTTGCCTCTACTGAA.

Histological sectioning of the kidneys

The excised kidney was immediately preserved in 10 % formalin + saline. The preserved kidney was enclosed in paraffin, sectioned, and stained with hematoxylin & eosin. Sections were examined under a light microscope (Motic, Canada) [14].

Statistical analysis

Data are presented as mean ± SEM. Data were subjected to a one-way analysis of variance (ANOVA), followed by Dunnett's post hoc test. Data analyses were carried out using Graph pad Prism® 6 software and $p<0.05$ was considered significant.

RESULT AND DISCUSSION

Fumarate did not cause any significant changes in kidney weight in dox-treated animals

Table 1 shows an 11 % increase in kidney weight in nephrotoxic rats compared to the control **(**$p>0.05$, n=8**).** Fumarate, at both doses, tended to reduce kidney weights by 15 % in dox-treated rats, ($p>0.05$, n=8).

Table 1: Organ weights in nephrotoxic Wistar rats treated with fumarate for 10 days.

Groups	Dose	Kidney
Control	10 ml/kg	0.0034±0.0001
Doxorubicin	10 mg/kg	0.0038±0.0002
Fumarate	50 mg/kg	0.0032±0.0003
Fumarate	100 mg/kg	0.0032±0.0002

Control (distilled water).

Fumarate significantly reduced the expression of the kidney injury molecule (KIM-1) in nephrotoxic rats

As illustrated in Figure 1, KIM-1 expression was significantly increased in dox-treated animals compared to control (38.5±0.4 vs 46.9±0.6, $p<0.001$). Administration of fumarate at 50 mg/kg significantly decreased the expression of KIM-1 from 46.9±0.6 to 36.4±0.5, $p<0.001$. Similarly, fumarate reduced KIM-1 expression at 100 mg/kg in dox-treated rats (46.9±0.6 vs 44.4±0.6, $p<0.05$). The results of our study have shown that the nephrotoxic effect of dox is acute and early-onset as represented by the expression of KIM-1. KIM-1 is a unique and specific marker of peritubular damage with a high predictive index. [15, 16] Fumarate reversed these changes and reduced KIM-1 expression at both doses. This observation is in congruence with data from our previous study, which showed that fumarate reduced KIM-1 expression in hypertensive rats. [11]

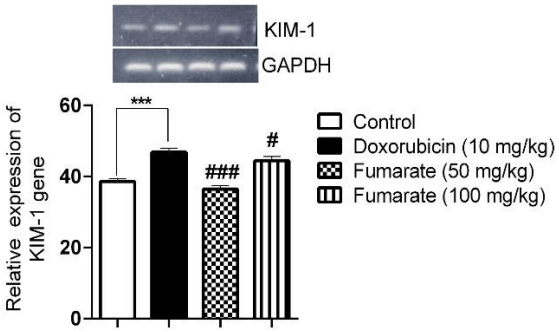

Figure 1: Effect of fumarate on the expression of the kidney injury molecule (KIM) 1 in doxorubicin-induced nephrotoxic rats. ***$p<0.001$ compared to the control (distilled water; 3 ml / kg). ###$p<0.001$, #$p<0.05$, compared to rats treated with doxorubicin. GAPDH=Glyceraldehyde-3-phosphate dehydrogenase

Fumarate exacerbated interleukin-1β levels but reduced the expression of interleukin-6

Figure 2A shows that IL-1β expression increased from 26.9±0.6 in the control group to 32.4±0.6 in dox-treated rats, ($p<0.001$, n=8). Although fumarate initially exacerbated the increase in IL-1β levels at 50 mg/kg (32.4±0.6 vs 36.8±0.9, $p<0.01$), there was a decrease in 1L-1β levels at 100 mg/kg, (32.4±0.6 vs 28.5±0.0, $p<0.05$) in rats treated with dox. IL-6 expression was significantly increased

above control levels in animals treated with dox (18.0±0.8 vs 62.8±1.4, p<0.001) (Figure 2B). Fumarate evoked a dose-dependent reduction in IL-6 expression in dox-treated rats (41.7±1.1 at 50 mg/kg and 38.5±0.5 at 100 mg/kg, p<0.001). Inflammatory cytokines are critical to mediation of dox-induced nephrotoxicity.[6, 17] The proliferation of immune cells associated with dox therapy leads to the direct secretion of pro-inflammatory cytokines such as IL-1β and IL-6, eventually promoting apoptosis. The release of these inflammatory cytokines underlies the extensive upregulation of the redox state in renal cells resulting in oxidative stress; a central pathology in dox-induced nephrotoxicity. [6] The data from this study corroborate these observations as IL-1β and IL-6 was significantly increased in rats treated with dox. These cytokines promote the release of toxic radicals that result in tubular injury and fibrosis. Fumarate exerted an 'anti-cytokine' effect, reducing the expression of IL-1β and IL-6 in rats treated with dox. Hence, fumarate reduced the inflammation associated with dox-induced nephrotoxicity. In addition to its role in inflammation, IL-1β stimulates the production of local mediators such as endothelin-1, a powerful vasoconstrictor that increases renal perfusion pressure., [18] Therefore, fumarate indirectly improved renal perfusion through its reduction in IL-1β expression. By extension, this effect would reduce oxidative stress and protect renal cells from reactive radical damage.

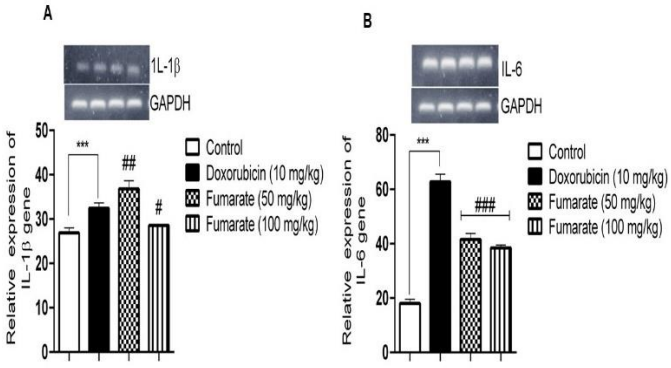

Figure 2: Interleukin 1β and 6 in renal tissues of doxorubicin-induced nephrotoxic rats treated with fumarate. ***p<0.001 compared to the control (distilled water; 3 ml / kg). ###p<0.001, ##p<0.01, #p<0.05, compared to the doxorubicin group. IL=interleukins, GAPDH=Glyceraldehyde-3-phosphate dehydrogenase

The expression of the superoxide dismutase (SOD) gene was reduced at the lower dose of fumarate

Figure 3 illustrates that there was an increase in SOD expression in rats compared to control (18.5±0.5 vs 27.7±0.9, p<0.001). However, there was a significant reduction in SOD expression in nephrotoxic rats treated with 50 mg/kg of fumarate (27.7±0.9 vs 24.9±0.4, p<0.05). In contrast, fumarate tended to reverse this drop in SOD in dox-treated rats (27.7±0.9 vs 28.6±0.4, p>0.05) at 100 mg/kg. SOD is a first line of defence against hydrogen peroxide (H_2O_2) radical. [19] The dismutation of H_2O_2 by SOD is the rate-limiting step in the detoxification of H_2O_2, a radical with profound actions. [20] An increase in SOD activity reduces H_2O_2 production. Fumarate thus acted as an antioxidant and partly exerted its renoprotective effect by increasing SOD activity.

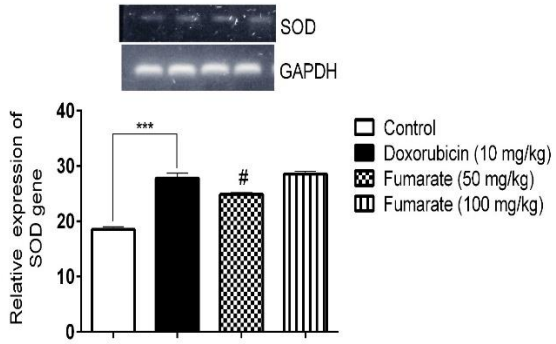

Figure 3: Renal superoxide dismutase (SOD) activity in doxorubicin-induced nephrotoxic rats treated with fumarate for 10 days. ***p<0.001 compared to the control (distilled water; 3 ml / kg). #p<0.05, compared to the doxorubicin group. GAPDH = glycoldehyde-3-phosphate dehydrogenase

Fumarate reduced the expression of endothelial nitric oxide synthase (eNOS)

The activity of endothelial nitric oxide synthase (eNOS) was significantly increased (Figure 4) in dox-treated rats compared to the control (21.9±0.3 vs 27.1±0.7, p<0.001). Fumarate reduced the activity of eNOS in dox-treated rats at 50 mg/kg only (27.1±0.7 vs 23.2±0.7, p<0.05). Endothelial nitric oxide synthase plays an intricate role in vascular homeostasis. [21, 22] By generating nitric oxide (NO), a potent vasodilator with proliferative natriuretic and cell actions, eNOS activity is crucial to renal function. However, as occurs in dox therapy, the eNOS enzyme can become

"uncoupled" in extensive oxidative stress states. [23, 24] Thus, the action of eNOS is redirected to the production of reactive radicals in a feedforward mechanism that exacerbates oxidative stress. Similarly, the product of the action of eNOS, nitric oxide, reacts with the superoxide anion to form a very devastating radical, called peroxynitrite, which can directly stimulate apoptosis and fibrosis. [25, 26] The observed increase in the expression of eNOS in dox-nephrotoxic rats is in congruence with the uncoupling of dox-induced eNOS, which exacerbates oxidative stress and renal injury. In furtherance of its renoprotective actions, fumarate reduced the expression of eNOS, although at the lowest dose. This presents a deviation from the actions of fumarate on NO. Although previous reports have linked the renoprotective action of fumarate in hypertensive rats with NO production., [9] fumarate exerted an opposite action by reducing eNOS expression, which eventually reduces NO activity. Thus, it indicates that fumarate acts as a 'modulator' of NO signaling and the prevailing pathology determines the nature of this pleiotropic action.

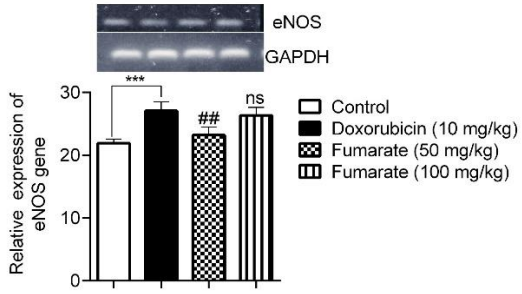

Figure 4: Effect of fumarate on renal endothelial nitric oxide synthase (eNOS) activity in nephrotoxic rats placed on fumarate for 10 days. ***p<0.001 compared to the control (distilled water; 3 ml / kg). ##p<0.05, compared to the doxorubicin group. ns=not significant. GAPDH= Glyceraldehyde-3-phosphate dehydrogenase

Histological sectioning of the kidney revealed an acute tubular injury in dox-treated rats

Histological sectioning of the kidney of the control group (Figure 5) revealed a defined Bowmans capsule containing a normal glomerulus (green arrow), mesangium, blood vessels, and epithelium. The tubules (blue arrow) are oval-shaped and lined with a cuboidal epithelium, with some tubules containing pale eosinophilic material. Treatment with doxorubicin resulted in a thinned epithelium with reduced lining and a distorted glomerulus (green arrow), indicative of acute glomerular injury and tubular necrosis (blue arrow). These observations corroborate the increase in the expression of KIM-1in dox-treated rats. There was damage to the epithelium, causing cellular infiltration and distortions in the Bowman's capsule. In fumarate-treated dox rats, the tubules (blue arrow) were oval-shaped and lined by cuboidal epithelium with some tubules containing pale eosinophilic material. Bowman capsules (green arrow) were defined, indicating that fumarate reversed these distortions. However, there were slight distortions at 100 mg/kg of fumarate. It is important to note that the data from this study have opened a new vista regarding the actions of fumarate. In addition to its action as a renoprotective and cardioprotective agent, fumarate could mitigate the harmful actions of exogenous ligands such as dox. It adds to the ever-expanding role of the intermediaries of the tricarboxylic acid cycle, which now act as modulators capable of ameliorating renal injury through molecular mechanisms with extensive beneficial effects. [27]

CONCLUSION

This study has shown that fumarate improved acute, early-onset nephrotoxicity associated with dox through an anti-cytokine action that reduced oxidative stress. Fumarate exerted a renoprotective action by modulating the activity of eNOS and upregulating the expression of SOD, a protective gene, further reducing radical-induced damage. These actions may attenuate the dox-induced nephrotoxicity, improving renal function and reducing the nephrotoxic action of dox. Further studies to elucidate the endogenous role of the TCA cycle and its intermediaries in the adverse actions of exogenous ligands would highlight new vistas into the future mechanistic targets of prospective ligands.

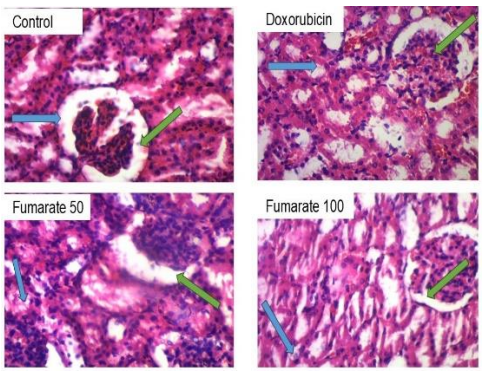

Figure 5: Photomicrographs of renal sections (H&E staining; x400) in rats treated with a single dose of doxorubicin, doxorubicin + fumarate (50 and 100 mg/kg). The control group shows a normal Bowman capsule (blue arrow) with an intact glomerulus (green arrow). The doxorubicin groups revealed degenerative malformation with capsule distortion (green arrow). Fumarate treatment revealed protective changes in the absence of any significant malformations.

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Conflict of interest

The authors declare no conflict of interest.

Authors Declaration

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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