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Effect of Fumarate on Nuclear Factor Erythroid 2 and Transforming Growth Factorβ1 Signaling in Doxorubicin-Induced Cardiorenal Injury.

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Abstract

Nuclear factor erythroid 2-related factor 2 (NRF2) and transforming growth factor (TGFβ1) signalling have been recently implicated in doxorubicin (dox)-induced cardiorenal injury. This study investigated the role of NRF2 and TGFβ1 in mediating the actions of fumarate, a tricarboxylic acid cycle metabolite, in dox-induced cardiorenal injury. Male Wistar rats were grouped into I: control (distilled water, 3 ml/kg, po), II: dox (10 mg/kg, ip), III: dox (10 mg/kg, ip) + fumarate (50 mg/kg, po) and IV: dox (10 mg/kg, ip) + fumarate (100 mg/kg). Treatments lasted for seven days, followed by euthanasia. Blood was withdrawn and the heart and kidneys were excised for biochemical and molecular assays. NRF2 expression in the heart was increased in the dox group (145.8±1.3 vs 150.8±0.4. $P < 0.05$) vs control. Fumarate exerted peak reduction at 50 mg/kg (150.8±0.4 vs 115.6±1.9, $P < 0.001$), in dox-treated animals. Fumarate increased the expression of TGFβ1 in the kidneys of dox-treated animals at 50 mg/kg (78.6±0.5 vs 82.2±0.42, $P < 0.001$) but reversed the decrease in the expression of NRF2 (29.7±0.2 vs 33.0±0.2, $P < 0.001$) at 50 mg/kg and (29.7±0.2 vs 31.3±0.3, $P < 0.05$) at 100 mg/kg. Aspartate transaminase (AST) and alanine transaminase (ALT) levels were increased, and fumarate reduced the expression of these enzymes in dox-treated animals. There was an adverse increase in chloride and lipoprotein levels at 100 mg/kg of fumarate ($P < 0.05$) in dox-treated animals. Data showed that fumarate evoked a cardio-renoprotective effect via selective modulation of NRF2 and TGFβ1 signaling in dox-induced injury.

Keywords: Nuclear factor erythroid 2-related factor 2, transforming growth factorβ1, cardiorenal, doxorubicin, cardiorenal injury.

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Introduction

There is recent evidence showing that fibrosis is a critical mechanism by which doxorubicin (dox) induces cardiorenal toxicity (Patricelli *et al.* 2023). Dox, an anthracycline chemotherapeutic agent, typically suppresses the growth of cancerous cells by targeting the DNA supercoiling and mitochondria function (Christidi and Brunham 2021). This inhibition of mitochondrial function triggers a cascade of inflammatory events that eventually cause apoptosis. Similarly, there is a corresponding increase in the activity of reactive radicals which exacerbate cellular dysfunction. These beneficial actions of dox become deleterious when they extend to normal, non-cancerous cells, leading to organopathies.(Wallace *et al*. 2020) .

A major consequence of the off-target actions of dox, is the increase in the expression of fibroblasts. Fibroblasts are primarily responsible for regulating the proliferation of constituents of the extracellular matrix (ECM) such as collagens (Linders *et al*. 2024). An overexpression and accumulation of components such as collagen and fibronectin can lead to "thickening" of the ECM (fibrosis), which leads to "scarring" and organ dysfunction and Patricelli *et al*. 2023).

Transforming growth factor (TGF)β, is a cytokine that regulates fibrosis, and its actions are closely related to nuclear erythroid factor (NRF2) (Lin *et al*. 2023), another regulator of antioxidant genes. Studies have shown that downregulating the activity of NRF2 exacerbates renal disease. The activities of these markers have also been implicated in cardiorenal injury induced by dox (Hassanein *et al*. 2023). The cardiac and renal systems are susceptible to dox-injury due to their high mitochondrial content. The ECM components of these organs have been reported to become "fibrotic" in dox-treated animals (Renu *et al*. 2018). Furthermore, an overexpression of myofibroblasts has been reported to cause cardiorenal dysfunction (Rawat *et al*. 2021). This portends that the actions of the regulators of the signaling pathways involved in fibrosis and redox homeostasis may be critical in mediating the deleterious actions of dox. The recent actions of fumarate, a natural and endogenous ligand in the tricarboxylic acid (TCA) cycle-acting on the cardiorenal system has become a subject of interest (Zheng and Tian 2022; Edosuyi *et al.* 2023). Fumarate has been documented to possess cardiorenal actions that were protective. It has been reported to exert antihypertensive, anti-radical, vasodilatory and natriuretic effects among others (Ashrafian *et al.* 2012; Edosuyi *et al*. 2021; Omo-Erhabor and Edosuyi 2024). These actions of fumarate have been mediated via downstream pathways such as NRF2 and TGFβ1, which are involved in dox-induced injury. This study evaluated the role of TGFβ1 and NRF2 in mediating the effects of fumarate in dox-induced cardiorenal injury.

Materials and Methods

Animals

Male Wistar rats (150- 190 g), sourced from the Animal's Facility of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, were kept under standard experimental conditions (12-hour light cycle, 60±0.2 humidity). The animals were given free access to clean water and pelletized feed until the last day of the experiment. All study protocols were evaluated and approved the Institutional Ethics Committee of Faculty of Pharmacy, University of Benin. Benin City (EC/FP/024/07).

Experimental Protocols

The animals were randomly allotted to four (4) groups containing eight (8) animals each. Group 1 was treated with distilled water (3 ml/kg, po), while group 2 was given dox (10 mg/kg, ip). Groups 3 and 4 received dox and fumarate at 50 and 100 mg/kg, orally respectively. Dox was administered as a single dose on day 1 (Omo-Erhabor and Edosuyi 2024). All animals were treated with fumarate for seven (7) days and sacrificed under chloroform anesthesia on the last day. The heart and kidney were removed and stored for molecular assays.

Haematological assay

After euthanasia, a midline abdominal laparotomy was performed, and blood was withdrawn via cardiac puncture into plain and EDTA bottles. The blood in the plain bottle was allowed to stand for 1 hour and centrifuged at 5000 rpm for 20 minutes. The supernatant (serum) was withdrawn into clean bottles for biochemical analysis. The assays which included alkaline phosphatase (ALP) and aspartate transaminase (AST). alanine transaminase (ALT), total bilirubin (TB), conjugated bilirubin (CB), globulin (GLO), urea, creatinine, total cholesterol (TCHOL), and lipoproteins such as triglyceride (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were carried out according to the instructions in the Randox® kits using a spectrophotometer. The flame photometer was used to analyze serum sodium (Na^+), potassium (K^+), chloride (CL^-), and bicarbonate (HCO^{3-}) (Edosuyi et al. 2024; Edosuyi and Omo-Erhabor 2024).

Gene expression assays

The excised heart and kidneys were subjected to DNA isolation from the heart and kidney were carried out using the using the Quick-RNA Miniprep™ Kit (Zymo Research). Denaturation, amplification and gel electrophoresis of the isolated DNA were as previously stated (Elekofehinti *et al.* 2020; Omo-Erhabor and Edosuyi 2024). The primers for TGFβ and NRF2 were;

TGFβ1: Forward:
CGAGGTGACCTGGGCACCATCCATGAC
Reverse: CTGCTCCACCTTGGGCTTGCGACCCAC
NRF2: Forward CACATCCAGACAGACACCAGT
Reverse CTACAAATGGGAATGTCTCTGC

Statistical analysis

Data were subjected to one way analysis of variance (ANOVA). The differences between the group means were ascertained via Duncans post hoc test. P<0.05 was chosen as the level of significance. All data in the tables and figures are presented as mean ± SEM.

Results

Effect of 7 days of fumarate treatment on haematological parameters in Wistar rats intoxicated with doxorubicin.

There was a non-significant 58% decrease in WBC count in dox treated animals compared to control (P > 0.05). Fumarate at 50 mg/kg, caused a 3-fold increase in WBC in dox-treated animals (P < 0.05). Similarly, granulocyte levels reduced 4-fold in dox-treated animals and fumarate (50 mg/kg), elicited a 57 % increase in granulocyte levels in dox treated animals (P < 0.05) (Table 1). Red cell concentration, haemoglobin and haematocrit concentration were all reduced by 26.2, 16.9, and 18.9 % in dox treated animals compared to control (P > 0.05). fumarate evoked dose-related increase in RBC (23.7 % at 50 mg/kg and 28.6 % at 100 mg/kg), reversing the decrease in RBC to control levels in dox treated animals (P > 0.05). There was a peak 36.4 % increase in HGB concentration at 50 mg/kg (P > 0.05). Both doses of fumarate caused a 36.1 % increase in haematocrit concentration in rats treated with dox (P > 0.05) (Table 1).

Effect of fumarate on hepatic and renal function parameters of dox-intoxicated animals

As shown in table 2, Aspartate transaminase level was increased from 77.3±12.7 U/L in control to 104.5±1.3 U/L in dox-treated animals (P < 0.05) (Table 2). Administration of fumarate reduced AST levels at both doses (50 mg/kg (18.6 %) and 100 mg/kg (17.7 %) in dox-treated animals (P > 0.05). Alanine transaminase was significantly increased in dox-treated animals compared to control (44.7±6.9 U/L vs 60.7±1.2 U/L, P < 0.05). there was a significant decrease in ALT levels in intoxicated rats treated with 50 mg/kg fumarate only (60.7±1.2 U/L vs 44.3±3.8 U/L, P < 0.05). Aside from chloride which was significantly reduced by fumarate (100 mg/kg) in dox-treated animals (P < 0.05), there were no adverse alterations in serum electrolytes (Table 2).

Effect of fumarate administration on lipoprotein transport in dox-treated rats

Fumarate exerted dose-related elevations in total cholesterol (TCHOL), triglycerides (TG) and low-density lipoprotein (LDL) levels in dox-treated animals. Fumarate (100 mg/kg) significantly increased, TCHOL, TG and LDL significantly increased by 29.3, 20.5, and 41.8 %, (P < 0.05), (Table 3).
in haematocrit concentration in rats treated with dox (P > 0.05) (Table 1).

Table 1: Effect of seven (7) days administration of graded doses of fumarate on haematological parameters in rats dox-treated rats

	Treatments			
Parameters	Control	Dox (10 mg/kg)	Fumarate (50 mg/kg)	Fumarate (100 mg/kg)
WBC 10^3 µL	5.0±0.5	2.1±0.4	6.9±2.1#	2.8±0.6
LYM%	88.1±1.3	86.9±1.2	88.1±2.3	90.0±2.0
GRAN%	8.1±0.4	3.5±0.8***	5.5±0.4**#	3.9±0.4***
RBC 10^6 µL	6.1±0.1	4.5±1.1	5.9±0.6	6.3±0.2
HGB g/dL	10.9±0.4	7.7±2.2	12.1±0.9	11.9±1.1
HCT%	33.7±0.7	27.3±4.2	36.1±2.3	36.1±1.9
MCV fL	55.3±0.6	54.5±0.5	55.3±1.2	54.6±1.7
MCH pg	18.1±0.5	18.0±0.2	18.5±0.8	18.6±1.0
MCHC g/dL	30.9±1.9	33.1±0.5	33.4±0.6	34.1±0.8
RDW-CV%	14.8±0.3	14.1±0.3	14.5±0.9	15.2±0.8
PLT 10^3 µL	581.7±94.3	370.7±77.8	353.3±52.2	404.8±82.4

WBC, white blood cell, LYM, lymphocytes; GRAN, granulocyes: Hb = Hemoglobin; HCT = Hematocrit; RBC = red blood cells; PLT = platelets; MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration; MCH = mean corpuscular hemoglobin; MCHC; mean corpuscular haemoglobin concentration, RDWC = red cell distribution width; PDW = platelet distribution width. **P < 0.01, ***P < 0.001 vs control (distilled water, 3 mL/kg, po). #P < 0.05 vs doxorubicin (dox).

Table 2: Effect of fumarate on liver and renal function parameters in dox-intoxicated rats

	Treatments			
Parameters	Control	Dox (10 mg/kg)	Fumarate (50 mg/kg)	Fumarate (100 mg/kg)
ALP (U/L)	41.0±4.6	45.0±7.5	33.8±1.5	34.8±0.5
AST (U/L)	77.3±12.7	104.5±1.3*	84.5±5.3*	85.5±3.9
ALT (U/L)	44.7±6.9	60.7±1.2*	44.3±3.8*#	49.5±1.9*
TB (g/dL)	0.20±0.0	0.22±0.0	0.1±0.0	0.2±0.0
CB (g/dL)	0.1±0.0	0.1±0.0	0.1±0.0	0.1±0.0
TP (g/dL)	5.9±0.2	5.6±0.3	5.3±0.1	5.45±0.3
ALB (g/dL)	3.9±0.1	3.6±0.2	3.6±0.2	3.1±0.4
GLO (g/dL)	1.8±0.1	2.1±0.1	1.9±0.3	2.1±0.2
Urea (mg/dL)	25.5±1.8	27.8±1.3	39.0±6.2	23.0±2.1
Creatinine (mg/dL)	0.7±0.1	0.8±0.1	1.1±0.2	0.6±0.1
Sodium (mmoI/L)	137.0±0.9	134.3±1.5	136.3±1.1	131.0±2.1
Potassium (mmoI/L)	5.4±0.4	5.2±0.3	5.5±0.4	5.4±0.2
Chloride (mmoI/L)	101.3±0.9	97.8±2.0	101.7±2.3	90.0±2.3#
Bicarbonate (mmoI/L)	18.0±0.0	18.5±0.9	17.0±0.6	17.0±1.0

ALP, Alkaline Phosphatase; AST, Aspartate transaminase; ALT, Alanine transaminase; TB, Total Bilirubin; CB, conjugated Bilirubin; TP, total protein; ALB, albumin; GLO, globulin. *P < 0.05 vs control (distilled water, 3 mL/kg, po). #P < 0.05 vs doxorubicin (dox).

Table 3: Effect of seven (7) days of fumarate administration on lipoprotein transport in dox-induced injury

	Treatments			
Parameter	Control	Dox (10 mg/kg)	Fumarate (50 mg/kg)	Fumarate (100 mg/kg)
TCHOL	97.3±2.9	91.3±2.9	101.8±4.2	129.3±12.3*#
TG	94.7±2.3	126.5±6.6	154.7±23.7	159.3±19.9*
LDL	59.7±3.4	41.5±3.3	41.7±4.1	71.4±14.9#
HDL	19.0±1.3	20.0±1.7	24.3±2.8	24.0±5.4

High-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TCHOL), triglycerides (TG). *P < 0.05 vs control (distilled water, 3 mL/kg). #P < 0.05 vs doxorubicin (dox).

Effect of fumarate on NRF2 expression in the cardiac myocytes of dox-intoxicated rats

NRF2 expression was significantly increased in dox-treated rats compared to control (145.8±1.3 vs 150.8±0.4. P < 0.05). Fumarate significantly reduced NRF2 expression at both doses, eliciting peak reduction at 50 mg/kg (150.8±0.4 vs 115.6±1.9, P < 0.001), in dox-treated animals (Figure 1).

Effect of fumarate on TGFβ1 and NRF2 expression in renal cells of dox treated rats.

Doxorubicin exacerbated the expression of TGFβ1, compared to control (75.8±0.3 vs 78.6±0.5, P < 0.001). Fumarate further worsened the expression of TGFβ1 in dox-treated animals at 50 mg/kg (78.6±0.5 vs 82.2±0.42, P < 0.001) (Figure 2A). NRF2 expression in the kidneys of dox-treated animals were significantly reduced in dox-treated animals compared to control (32.3±0.7 vs 29.2±0.2, P < 0.01). Fumarate reversed the decrease in the expression of NRF2 in dox treated animals at both doses (29.7±0.2 vs 33.0±0.2, P < 0.001) at 50 mg/kg and (29.7±0.2 vs 31.3±0.3, P < 0.05) at 100 mg/kg. (Figure 2)

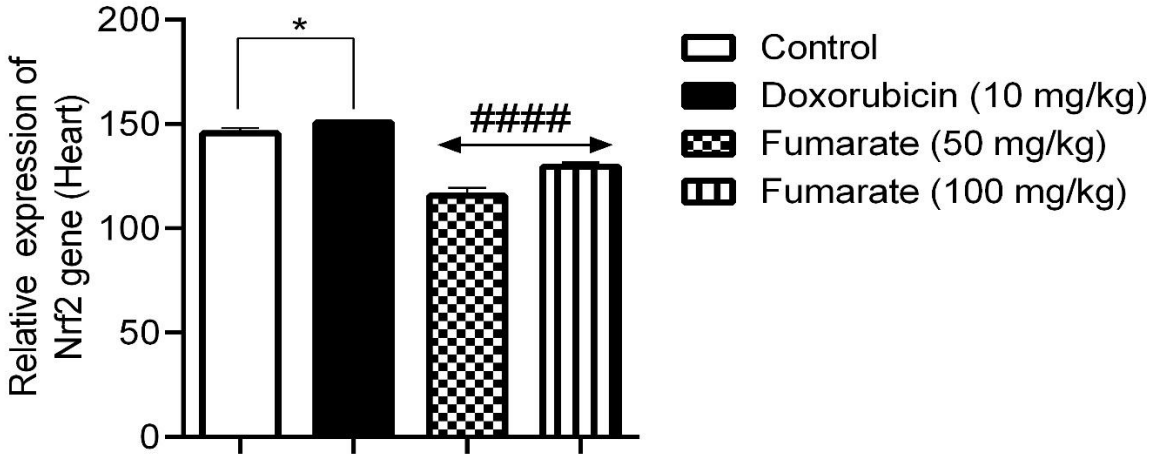

Figure 1: Nuclear erythroid factor (NRF)-2 expression in animals with dox-induced cardiac injury treated with graded doses of fumarate for seven (7) days. *P < 0.05 vs control. ####P < 0.001 vs doxorubicin (dox) group. control (distilled water, 3 mL/kg, po).

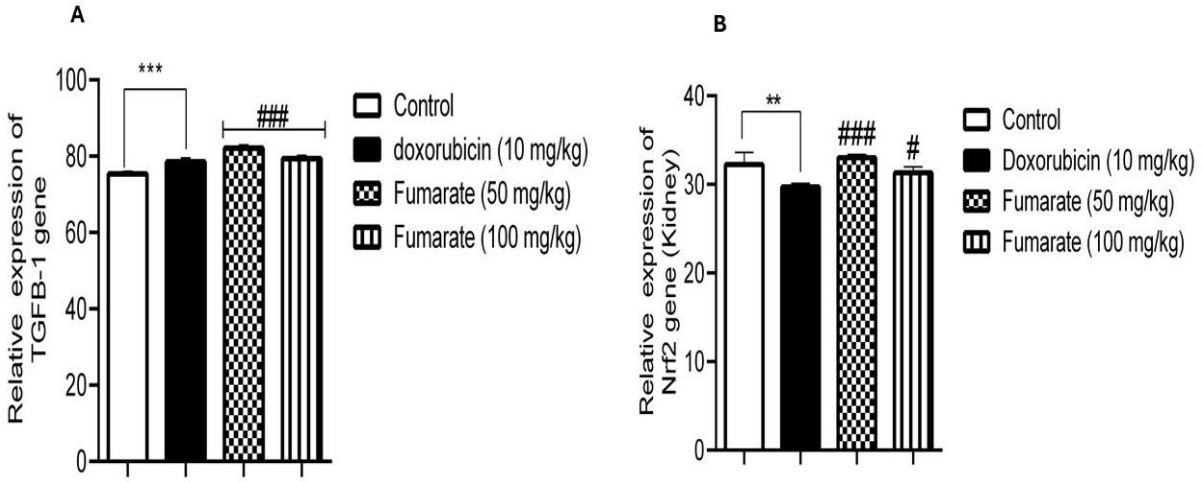

Figure 2: Transforming growth factor (TGF)β1 and nuclear erythroid factor (NRF)-2 expression in animals with renal injury treated with graded doses of fumarate for seven (7) days. **P < 0.05, ***P < 0.01 vs control. #P < 0.05, ####P < 0.001 vs doxorubicin (dox) group. control (distilled water, 3 mL/kg, po).

Discussion

The cardiorenal injury associated with dox therapy is a devastating adverse outcome (Zhang *et al.* 2020; *Rawat et al*. 2021). Previously, it was established that the prevalent mechanisms involved in this pathology were centered around mitochondrial-related dysfunction which exacerbated the production of reactive radicals leading to apoptosis (Qi *et al*. 2020). The realization that epithelial changes that manifest in cardiorenal fibrosis are a prominent and challenging feature in dox-induced injury has set new insights into novel downstream pathways that could serve as therapeutic targets (Patricelli *et al.* 2023).

Epithelial and myofibroblasts changes that underpin the development of fibrosis are regulated by the molecular marker, TGFβ, a pro-fibrotic (Patricelli *et al*. 2023). TGFβ1 acts as a master regulator of fibrosis via the Smad7 pathway, and its expression is stimulated by exogenous ligands such as doxorubicin. The dox-induced cardiac fibrosis has been established to be mediated via the TGFβ1/Smad signalling pathway (Rawat *et al*. 2021). However, fumarate exacerbated the expression of TGFβ1 in dox-treated animals, a paradoxical effect that has been previously reported (Edosuyi *et al*. 2021). It has been shown that there

are beneficial actions related to the expression of TGFβ1. TGFβ1 acting via its Smad7 downstream proteins can regulate the expression of NFκB (Sureshbabu *et al*. 2016), a major inflammatory regulator. Hence, the increase in TGFβ1 observed in fumarate-treated animals may have been partly beneficial in reducing the inflammation in dox-induced cardiac injury. TGFβ1 expression was also aggravated in kidneys of animals that were treated with only dox and fumarate reduced this expression at both doses, indicating an "anti-fibrotic action". This was followed by an increase in nuclear factor erythroid 2-related factor 2 (NRF2) levels.

NRF2 is a master regulator of antioxidant genes and via its action, the activity of the endogenous antioxidant system is regulated (Pall and Levine 2015; Adeyemi *et al*. 2024). NRF2 also increases the expression of cytoprotective and anti-inflammatory genes such as heme oxygenase (Lin *et al.* 2023). This helps mitigate the extensive oxidative stress caused by dox treatment. The upregulation of NRF2 by fumarate is thus "protective" and preserves cardiac and renal function in dox-treated animals. NRF2 has been recently touted to ameliorate renal fibrosis in CKD via the heme oxygenase pathway (Lin *et al*. 2023).

Interestingly, fumarate acted differently in the cardiac cells by reducing the expression of NRF2 in dox-treated animals. This action seems contrary to the expected effect of fumarate which has been reported to be cardioprotective via the NRF2 pathway (Ashrafian *et al*. 2012). It also contradicts the study by Ashrafian *et al*. (2012), which postulated that fumarate increased the expression of NRF2 in reperfusion injury. It is necessary to state that an overexpression of NRF2 induces "reductive stress" due to extensive removal of reactive radicals (Yang *et al*. 2007; Lin *et al*. 2023). This can lead to mitochondrial dysfunction and programmed cell death. Similarly, NRF2 overexpression has been documented to be detrimental to the heart by increasing the release of inflammatory cytokines in cardiac injury (Lin *et al*. 2023). It is thus tenable that the increase in NRF2 expression in dox-treated animals is in congruence with the dox-induced injury and the reduction by fumarate was thus "cardioprotective". This is consistent with the pleiotropic actions of fumarate under different pathological states (Edosuyi *et al.* 2023). It highlights the dual modulatory actions of endogenous ligands like fumarate. NRF2 suppresses fibrosis via its inductive actions on NFκB and HO-1 (Lin *et al.* 2023). Hence, fumarate's actions on NRF2 and TGFβ1 are synergistic.

In this study, the molecular actions of fumarate seemed very prominent compared to its biochemical effects. Fumarate tended to reverse the drop in RBC, HCT and Hb in dox-treated animals. There was a significant increase in granulocytes levels and a restoration in WBC in dox-treated rats. These actions suggest a putative "anti-anemic" and enhanced immunologic activity, and the resultant effects may suggest immunomodulatory effect of fumarate. The same pattern was observed for hepatic and renal function parameters where fumarate only exerted a significant effect on ALT, AST, and chloride levels. The elevations in AST and ALT indicate the presence of hepatic injury and highlights the susceptibility of the hepatic system to the actions of exogenous agents like dox (Ikewuchi *et al*, 2021). The reduction in the levels of these hepatic enzymes by fumarate further highlights a possible hepatoprotective effect. Conversely, lipid transport was significantly impacted by fumarate, albeit at the highest dose, causing exacerbations in cholesterol, triglycerides, and low-density lipoprotein transport. These actions of fumarate on lipid transport seem adverse and could have long-term cardiorenal implications especially as it relates to atherosclerosis (Bolanle *et al,* 2025). However, the dose-related action underscores the need to mediate the dose of fumarate to prevent the occurrence of this adverse outcome. Previous studies in healthy rats showed that fumarate exerted an anti-atherogenic effect and once again, the actions of fumarate seem modulatory, exerting actions that are dependent on the prevailing pathophysiological states (Edosuyi *et al*. 2024, 2025).

The observations in this study underscore the vital predictive actions of molecular markers as therapeutic indicators (Amiteye 2021). Although this study spanned seven days, dox and fumarate elicited significant changes at the genetic level. It also buttresses the early-onset nature of dox-induced cardiorenal toxicity necessitating the need for prophylactic therapy. This study corroborates recent studies from our laboratory that highlighted the renoprotective actions of fumarate in dox-induced renal injury (Omo-Erhabor and Edosuyi 2024). In addition to the reported ameliorative, anti-cytokine and endothelial nitric oxide modulatory actions, fumarate can also selectively modulate the expression of NRF2 and TGFβ1 signaling pathways to exert synergistic anti-fibrotic actions that are cardio- and renoprotective in dox-induced injury.

Conclusion

Fumarate has been shown to selectively modulate the expression of NRF2 and TGFβ1 in the heart and kidneys of animals with dox-induced injury. In addition to its reported ameliorative actions in dox injury, fumarate was also "cytoprotective" via the NRF2 pathway and mitigated renal fibrosis via the TGFβ1 pathway. These actions further buttress the cardio and renoprotective actions of fumarate.

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Conflict of interest

None declared

References

Adeyemi DH., Obembe OO, Hamed MA, Akhigbe RE (2024).

Sodium acetate ameliorates doxorubicin-induced cardiac Injury via upregulation of Nrf2/HO-1 signaling and downregulation of NFkB-mediated apoptotic signaling in Wistar rats', *Naunyn-Schmiedeberg's Archives of Pharmacology* 397(1): 423–435.

Amiteye S (2021). Basic concepts and methodologies of DNA marker systems in plant molecular breeding. *Heliyon* 7(10): e08093.

Ashrafian H., Czibik G, Bellahcene M et al. (2012). Fumarate Is Cardioprotective via Activation of the Nrf2 Antioxidant Pathway. *Cell Metabolism* 15(3): 361–371.

Bolanle IO, Liedekerke Beaufort GC. De Weinberg, PD (2025). Transcytosis of LDL Across Arterial Endothelium: Mechanisms and Therapeutic Targets, *Arteriosclerosis, Thrombosis, Vascular Biology* 45(4): 468–480.

Christidi E, Brunham LR (2021). Regulated cell death pathways in doxorubicin-induced cardiotoxicity. *Cell Death Disease* 12(4):339.

Edosuyi O, Choi M, Igbe I, Oyekan A (2021). Fumarate exerted an antihypertensive effect and reduced kidney injury molecule (KIM)-1 expression in deoxycorticosterone acetate-salt hypertension', *Clinical and Experimental. Hypertension* 43(6):555–564.

Edosuyi O, Igbe I, Oyekan A. (2023). Fumarate and its downstream signalling pathways in the cardiorenal system: Recent insights and novel expositions in the etiology of hypertension', *European Journal of Pharmacology* 961: 176186.

Edosuyi O, Omo-Erhabor AJ (2024). Effects of fumarate on cardiorenal injury markers in normotensive wistar rats, *Journal of Pharmacy and. Allied Sciences* 21(1): 4064–4070.

Edosuyi O, Omo-Erhabor AJ, Osaghae I, Odore S, Igbe I (2024). Acute and Sub-Acute Oral Safety Profile of Fumarate in Normotensive Wistar Rats. *Journal of Pharmacy and. Allied Sciences* 20(2): 3991–4000.

Edosuyi O, Osagiede EB, Eguasa N et al (2025). Fumarate attenuated doxorubicin-induced cardiac injury through modulation of endothelial nitric oxide synthase expression and transforming growth factor-1 signalling. *Prospects in Pharmaceutical Sciences* 12(11):1-8

Elekofehinti OO, Lawal AO, Ejelonu OC et al (2020) Involvement of fat mass and obesity gene (FTO) in the anti-obesity action of Annona muricata Annonaceae: in silico and in vivo studies', *Journal of. Diabetes Metabolic Disease* 19(1): 197–204.

Hassanein EHM, Ibrahim IM, Abd-alhameed EK et al (2023) Nrf2/HO-1 as a therapeutic target in renal fibrosis. *Life Sciences*
3 34: 122209.

Ikewuchi CC, Ifeanacho MO, Ikewuchi JC (2021). Moderation of doxorubicin-induced nephrotoxicity in Wistar rats by aqueous leaf-extracts of *Chromolaena odorata* and *Tridax procumbens. Porto Biomedical Journal* 6(1): 129-142.

Lin DW, Hsu YC, Chang CC., Hsieh CC, Lin CL (2023), Insights into the Molecular Mechanisms of NRF2 in Kidney Injury and Diseases, *International Journal of Molecular Sciences* 24(7): 1-10.

Linders AN, Dias I.B, López Fernández T et al (2024), A review of the pathophysiological mechanisms of doxorubicin-induced cardiotoxicity and aging, *Aging* 10(1): 9-18.

Omo-Erhabor AJ. Edosuyi O (2024). Fumarate ameliorated doxorubicin-induced nephrotoxicity: The role of pro-inflammatory cytokines and endothelial nitric oxide synthase signaling pathway, *Tropical Journal of Drug Research* 1(1): 4-12.

Pall ML, Levine S (2015) Nrf2, a master regulator of detoxification and also antioxidant, anti-inflammatory and other cytoprotective mechanisms, is raised by health promoting factors.', *Acta physiologica Sinica* 67(1): 1–18.

Patricelli C, Lehmann P, Oxford JT. Pu X (2023). Doxorubicin-induced modulation of TGF-β signaling cascade in mouse fibroblasts: insights into cardiotoxicity mechanisms. *Science Reports* 13(1): 14.21.

Qi W, Boliang W, Xiaoxi T et al (2020). Cardamonin protects against doxorubicin-induced cardiotoxicity in mice by restraining oxidative stress and inflammation associated with Nrf2 signaling. *Biomedicine & Pharmacotherapy* 122(2): 13-27.

Rawat PS, Jaiswal A, Khurana A et al (2021). Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management', *Biomedicine and Pharmacotherapy* 122(1): 111-708.

Renu K, Abilash VG, Tirpathi PB, Arunachalam S (2018). Molecular mechanism of doxorubicin-induced cardiomyopathy – An update, *European Journal of Pharmacology* 818: 241–253.

Sureshbabu A, Muhsin SA. Choi ME (2016) TGF-β signaling in the kidney: profibrotic and protective effects. *American. Journal of Physiology-Renal Physiology* 310(7): 596–606.

Wallace KB, Sardão VA. Oliveira PJ (2020). Mitochondrial Determinants of Doxorubicin-Induced Cardiomyopathy. *Circulation. Research* 126(7): 926–941.

Yang Y, Song Y. Loscalzo J (2007). Regulation of the protein disulfide proteome by mitochondria in mammalian cells.*Proceedings of National. Academy of Science* 104(26): 10813–10817.

Zhang J, Sun Z, Lin N et al (2020) Fucoidan from *Fucus vesiculosus* attenuates doxorubicin-induced acute cardiotoxicity by regulating JAK2/STAT3-mediated apoptosis and autophagy', *Biomedicine and Pharmacotherapy* 130(3): 23-40.

Zheng X. Tian Z (2022). Fumarate hydratase as a potential target to ameliorate salt sensitive hypertension, *International Journal of Cardiology and Cardiovascular Disease* 2(13): 24-33.

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