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Research Article

Therapeutic Benefit of Ursodeoxycholic Acid in Tamoxifen-Induced Hepatotoxicity in Rats

Elias Adikwu[1, *], Tobechi Brendan Nnanna[2], Bonsome Bokolo[3]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University, Wilberforce Island, Nigeria
[2]Aston School of Pharmacy, Collage of Health and Life Sciences, Birmingham, United Kingdom
[3]Department of Pharmacology, Faculty of Medicine, College of Health Sciences, Niger Delta University, Wilberforce Island, Nigeria

Abstract

The use of tamoxifen (TAM) for breast cancer treatment may cause hepatotoxicity. Ursodeoxycholic acid (UDCA) is a potential liver protective chemical compound. The protective effect of UDCA on TAM-induced hepatotoxicity in rats was analyzed in this study. Thirty five adult female Wistar rats grouped into 7 of n=5/group were used. The rats were treated for 10 days as follows: Group 1: (Placebo control) Water (10 mL/kg/day/oral), group 2: (Vehicle control) Ethanol 1% (1mL/kg/day) intraperitoneally (i.p), group 3: UDCA (40 mg/kg/day/oral) and group 4: TAM (45 mg/kg/day) i.p. Groups 5-7 were pretreated with UDCA (10, 20 and 40 mg/kg/day/oral) before treatment with TAM (45 mg/kg/day) i.p, respectively. On day 11, blood samples were collected and evaluated for biochemical markers. Liver tissues were analyzed for oxidative stress markers and histology. Results: TAM decreased body weight and increased liver weight significantly ($p<0.01$) when compared to the placebo control. Serum bilirubin, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, aminotransferases, high density lipoprotein cholesterol and liver malondialdehyde levels were significantly ($p<0.001$) elevated by TAM when compared to control. TAM significantly ($p<0.001$) decreased serum triglyceride, very low density lipoprotein cholesterol, total cholesterol, liver glutathione, catalase, superoxide dismutase and glutathione peroxidase levels when compared to the control. TAM caused liver steatosis and necrosis in rats. However, UDCA pretreatment significantly prevented the aforementioned changes caused by TAM in a dose-related fashion. UDCA may be a therapeutic option for TAM associated hepatotoxicity.

Keywords

Tamoxifen, Ursodeoxycholic Acid, Liver, Toxicity, Rat, Protection

1. Introduction

Liver has many functions including the regulation of lipid and glucose levels and energy metabolism. It is also the primary organ for the metabolism of drugs and toxins [1]. The metabolism of drugs and toxins by the liver can predispose it to perturbations [1, 2] such as hepatitis, cirrhosis, steatosis, fibrosis and liver failure [1, 3]. Drug-induced liver perturbation is categorized as hepatitis, cholestatic or mixed. The categorization is based on the duration of perturbation and the histological site of damage [1-3].

*Corresponding author: adikwuelias@gmail.com (Elias Adikwu)

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Tamoxifen (TAM) is used for the treatment of estrogen receptor positive breast cancer in women. It is available as a chemopreventive drug for women at high risk of breast cancer [4]. It competes with estrogen for estrogen receptor in breast carcinomas, thereby decreasing the risk of relapse after the surgical removal of breast cancer [4] Endoxifen and 4-hydroxytamoxifen metabolites of TAM produced through liver action are responsible for its antitumor activity [5]. Despite TAM associated benefits in breast cancer, it can cause some toxicities especially hepatotoxicity [5]. Its hepatotoxicity includes hepatitis, steatosis, cirrhosis, or liver failure [6]. TAM related hepatotoxicity has been attributed to some factors including impaired mitochondrial β-oxidation of fatty acids, inflammation and oxidative stress [6].

Ursodeoxycholic acid (UDCA) is a tertiary dihydroxy hydrophilic bile acid. Initially, it was proposed for the treatment of gall bladder stones, but was later discovered to be effective against cirrhosis, cholestatic disease and hepatitis [7]. It has shown antiapoptotic activity on cholangiocytes and hepatocytes [8]. Preclinical studies showed that it protected against liver mitochondrial damage [9], amoxicillin-clavulanic acid, [7] isoniazid-rifampicin [10] and ceftriaxone [11] induced hepatotoxicity. Over the last two decades studies have associated UDCA with significant antioxidant activity [12, 13] characterized by deceased oxidative liver injury, lipid peroxidation and increased liver antioxidants [14]. In the absence of scientific studies, the protective effect of UDCA was examined against TAM-induced hepatotoxicity in adult Wistar rats.

2. Materials and Methods

2.1. Animals and Drugs

Thirty five adult female Wistar rats (200–250 g) were used for the study. The rats were sourced from the animal unit of the Department of Pharmacology/Toxicology, Faculty of Pharmacy, Niger Delta University, Nigeria. The rats were kept under natural environmental conditions with free access to standard diet and water. TAM (West-Coast, Pharm Works Ltd, India) and UDCA (Win-Medicare PVT Ltd, India) were used. UDCA (10, 20, and 40 mg/kg/day) [7] and TAM (45 mg/kg/day) [15] were used. The Research Ethics Committee of the Department of Pharmacology/Toxicology, Faculty of Pharmacy, Niger Delta University, Nigeria approved the study. The guide for the care and use of laboratory animals, 8th edition was used for the study.

2.2. Experimental Design

The adult female Wistar rats were grouped randomly into 7 of n=5/group and treated daily for 10 days as follows: Group 1: (Placebo control) was treated with water (10 mL/kg/oral) while group 2 (Vehicle control) was treated with ethanol 1% (1mL/kg) intraperitoneally (i.p). Groups 3 and 4 were treated with UDCA (40 mg/kg/oral) and TAM (45 mg/kg) i.p, respectively. Groups 5-7 were pretreated with UDCA (10, 20 and 40 mg/kg/oral), before treatment with TAM (45 mg/kg) i.p, respectively. On day 11, the rats were exposed to diethyl ether and blood samples were collected from the heart. Sera were collected and analyzed for biochemical markers. Liver tissues were collected through dissection and assessed for oxidative stress markers and histology. Liver samples for oxidative stress marker evaluations were rinsed in cold saline and homogenized in a 50 mM phosphate buffer (pH 7.4). The homogenates were centrifuged and the supernatants decanted and evaluated for oxidative stress markers.

2.3. Biochemical Evaluations

2.3.1. Evaluation of Biochemical Markers

Aspartate aminotransferase (AST), total bilirubin (TB), lactate dehydrogenase (LDH), conjugated bilirubin (CB), triglyceride (TG), alkaline phosphatase (ALP), very low density lipoprotein cholesterol (VLDL-C), alanine aminotransferase (ALT), total cholesterol (CHOL) and high density lipoprotein cholesterol levels (HDL-C) were analyzed using an auto analyzer.

2.3.2. Assay of Oxidative Stress Markers

Malondialdehyde (MDA) was assayed using the procedure explained by Buege and Aust 1978 [16]. Catalase (CAT) was analyzed using the method explained by Aebi, 1984 [17]. Glutathione (GSH) was determined as reported by Sedlak and Lindsay, 1968 [18]. Superoxide dismutase (SOD) was measured using the technique explained by Sun and Zigman, 1978 [19]. Glutathione peroxidase (GPX) was assayed using the method explained by Rotruck *et al*.1973 [20].

2.3.3. Histology of the Liver

The excised liver tissues were fixed in saline formalin (10%). The liver tissues were dehydrated in graded alcohol solution, processed and embedded in paraffin wax. Sections (3µcm) were produced using a microtome and stained with hematoxylin and eosin. The stained sections were examined using a microscope.

2.3.4. Statistical Analysis

Data as mean ± SEM (Standard error of mean). Two way analysis of variance (ANOVA) and Tukey's test were used for data analysis. Significance was set at $p < 0.05$, $p < 0.01$ and $p < 0.001$.

3. Results

3.1. Effects of Ursodeoxycholic Acid on the Body and Liver Weights of Tamoxifen -Treated Rats

UDCA (40mg/kg) had no significant ($p>0.05$) effects on the

body and liver weights of the rats when compared to the placebo control. But TAM significantly ($p<0.01$) decreased body weight and significantly ($p<0.01$) increased liver weight of the treated rats when compared to control (Table 1). Interestingly, pretreatment with UDCA restored body and liver weights at 10 mg/kg ($p<0.05$), 20 mg/kg ($p<0.01$) and 40 mg/kg ($p<0.001$) when compared to TAM (Table 1).

3.2. Effect of Ursodeoxycholic Acid on Serum Biochemical Markers of Tamoxifen-Treated Rats

Serum LDH, AST, GGT, TB, ALT, ALP, CB, CHOL, TG, VLDL-C and HDL-C levels did not differ significantly ($p>0.05$) from the placebo control in the rats treated with UDCA (40 mg/kg) (Figures 1-7 and Table 2). TAM significantly ($p<0.001$) increased serum LDH, AST, GGT, TB, ALT, ALP, CB, CHOL, TG, and HDL-C, but decreased VLDL-C levels when compared to the control (Figures 1-7 and Table 2). Nonetheless, pretreatment with UDCA significantly and in a dose-dependent fashion restored serum LDH, AST, GGT, TB, ALT, ALP, CB, CHOL, TG, HDL-C and VLDL-C levels at 10mg/kg ($p<0.05$), 20mg/kg ($p<0.01$) and 40 mg/kg ($p<0.001$) when compared to TAM (Figures 1-7 and Table 2).

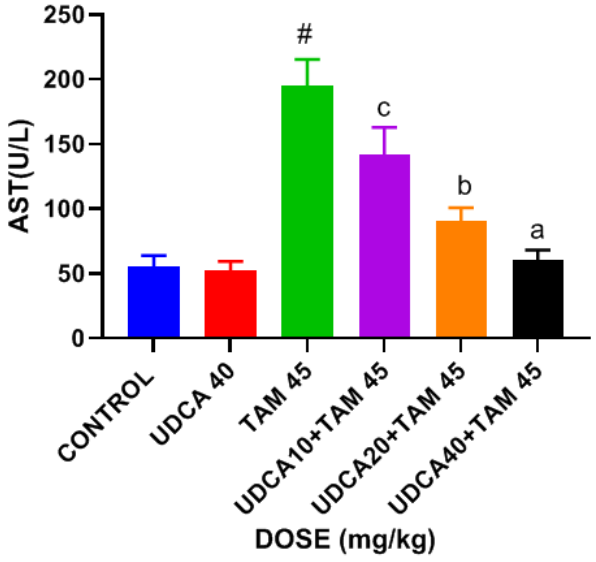


Figure 1. *Effect of ursodeoxycholic acid on serum aspartate aminotranferase of tamoxifen-treated rats. UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, AST: Aspartate aminotransferase, n=5, Data as mean± SEM (Standard error of mean). #p<0.001 Significant difference when compared to control, ap<0.05, bp<0.01 and c p<0.001 Significant difference when compared to TAM.*

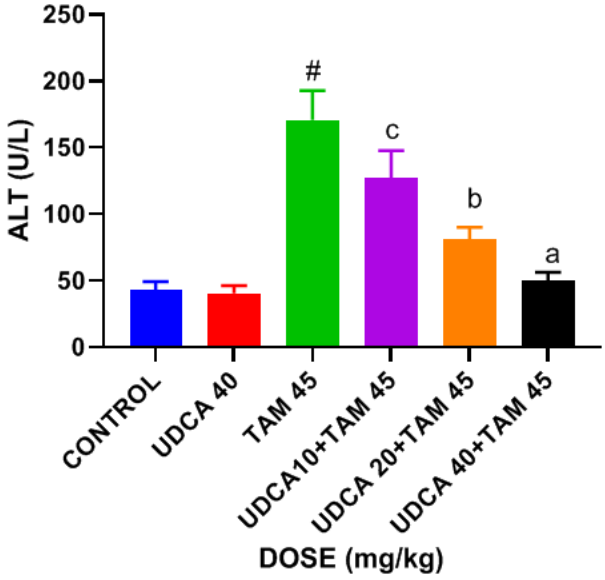


Figure 2. *Effect of ursodeoxycholic acid on serum alanine aminotransferase of tamoxifen-treated rats. UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, ALT: Alanine aminotransferase, n=5, Data as mean± SEM (Standard error of mean). #p<0.001 Significant difference when compared to control, ap<0.05, bp<0.01 and c p<0.001 Significant difference when compared to TAM.*

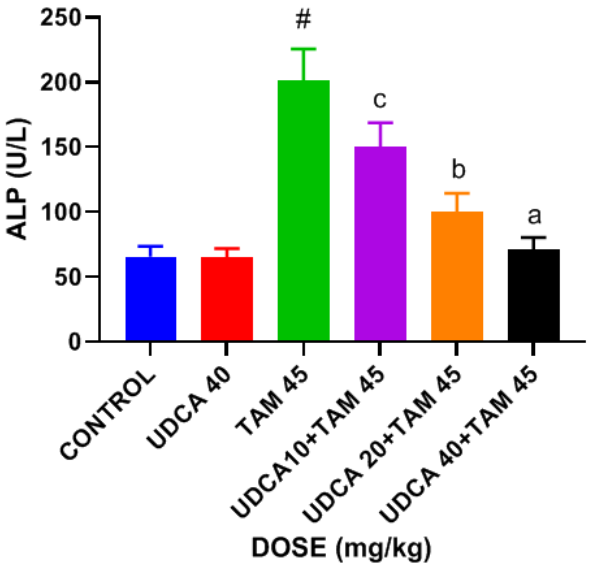


Figure 3. *Effect of ursodeoxycholic acid on serum alkaline phosphatase of tamoxifen-treated rats. UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, ALP: Alkaline phosphatase, n=5, Data as mean± SEM (Standard error of mean). #p<0.001 Significant difference when compared to control, ap<0.05, bp<0.01 and c p<0.001 Significant difference when compared to TAM.*

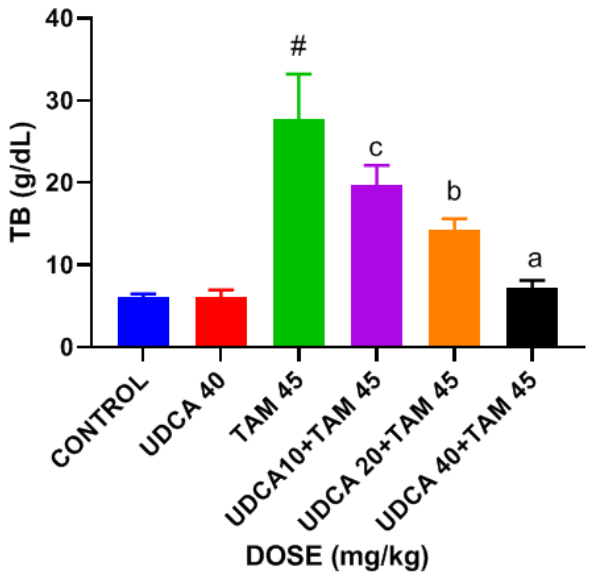


Figure 4. *Effect of ursodeoxycholic acid on serum total bilirubin of tamoxifen-treated rats. UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, TB: Total bilirubin, n=5, Data as mean ± SEM (Standard error of mean).* $^{\#}p<0.001$ *Significant difference when compared to control,* $^{a}p<0.05$, $^{b}p<0.01$ *and* $^{c}p<0.001$ *Significant difference when compared to TAM.*

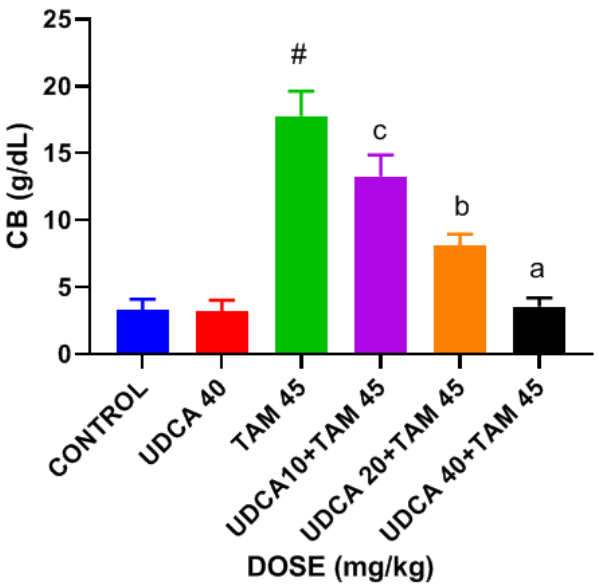


Figure 5. *Effect of ursodeoxycholic acid on serum conjugated bilirubin of tamoxifen-treated rats. UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, CB: Conjugated bilirubin, n=5, Data as mean ± SEM (Standard error of mean).* $^{\#}p<0.001$ *Significant difference when compared to control,* $^{a}p<0.05$, $^{b}p<0.01$ *and* $^{c}p<0.001$ *Significant difference when compared to TAM.*

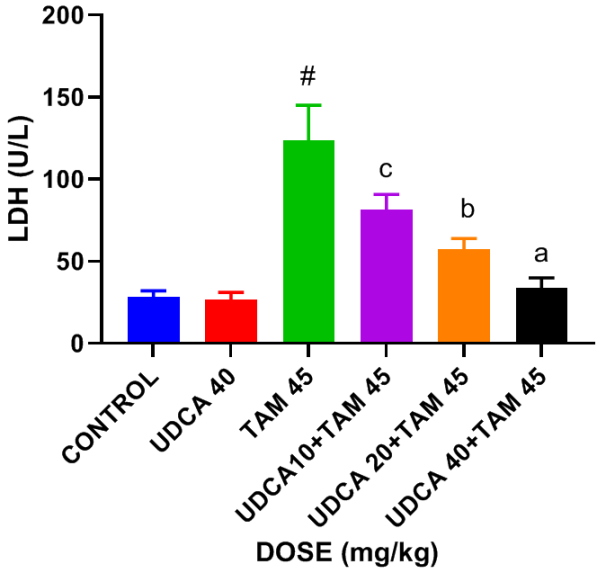


Figure 6. *Effect of ursodeoxycholic acid on serum lactate dehydrogenase of tamoxifen-treated rats. UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, LDH: Lactate dehydrogenase, n=5, Data as mean ± SEM (Standard error of mean).* $^{\#}p<0.001$ *Significant difference when compared to control,* $^{a}p<0.05$, $^{b}p<0.01$ *and* $^{c}p<0.001$ *Significant difference when compared to TAM.*

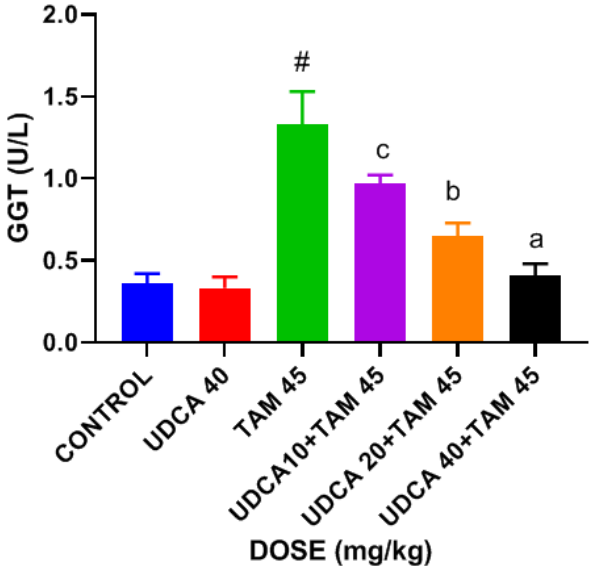


Figure 7. *Effect of ursodeoxycholic acid on serum gamma glutamyl transferase of tamoxifen-treated rats. UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, GGT: Gamma-glutamyl transferase, n=5, Data as mean ± SEM (Standard error of mean).* $^{\#}p<0.001$ *Significant difference when compared to control,* $^{a}p<0.05$, $^{b}p<0.01$ *and* $^{c}p<0.001$ *Significant difference when compared to TAM.*

3.3. Effect of Ursodeoxycholic Acid on Liver Oxidative Stress Markers of Tamoxifen-Treated Rats

Liver GPX, SOD, MDA, GSH and CAT levels were not different ($p>0.05$) from the placebo control in UDCA (40 mg/kg) treated rats (Table 3). In contrast, TAM significantly ($p<0.001$) decreased liver GPX, SOD, GSH and CAT levels and significantly ($p<0.001$) increased liver MDA levels when compared to the control (Table 3). Nevertheless, UDCA pretreatment significantly and in a dose-related fashion restored liver GPX, SOD, MDA, GSH and CAT levels at 10mg/kg ($p<0.05$), 20mg/kg ($p<0.01$) and 40 mg/kg ($p<0.001$) when compared to TAM (Table 3).

3.4. Effect of Ursodeoxycholic Acid on Liver Histology of Tamoxifen-Treated Rats

The liver of the control (Figure 8A) and UDCA (Figure 8B) treated rats showed normal liver histology whereas the liver of TAM (45mg/kg) treated rats showed necrosis, and inflammatory (Figure 8C) and steastosis (Figure 8D). The liver of rats pretreated with UDCA (10 mg/kg) (Figure 8 E), UDCA (20 mg/kg) (Figure 8 F) and UDCA (40 mg/kg) (Figure 8 G) prior to treatment with TAM (45mg/kg) showed normal histology.

Table 1. *Effects of ursodeoxycholic acid on the body and liver weights of tamoxifen -treated rats.*

Dose (mg/kg)	FBW (g)	ALW(g)	RLW (%)
Placebo Control	250.1 ±22.0	6.00 ±0.33	2.40 ±0.09
UDCA 40	240.8 ±20.6	5.63 ±0.27	2.37 ±0.08
TAM 45	120.9 ±17.6#	12.00 ±0.32#	9.93 ±0.78#
UDCA 10 + TAM 45	180.7 ±21.1 [a]	11.14 ±0.71	6.15 ±0.16 [a]
UDCA 20 + TAM 45	210.9 ±18.6 [b]	8.63 ±0.43 [b]	4.09 ±0.33[b]
UDCA 40 + TAM 45	245.0 ±23.7[b]	6.22 ±0.55[c]	2.54 ±0.41[b]

UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, FBW: Final body weight, ALW: Absolute liver weight, RLW: Relative liver weight, Data as mean ± SEM (Standard error of mean), n=5, [#]$p<0.01$ Significant difference when compared to control, [a] $p<0.05$, and [b]$p<0.01$ Significant difference when compared to TAM

Table 2. *Effect of ursodeoxycholic acid on serum lipids of tamoxifen -treated rats.*

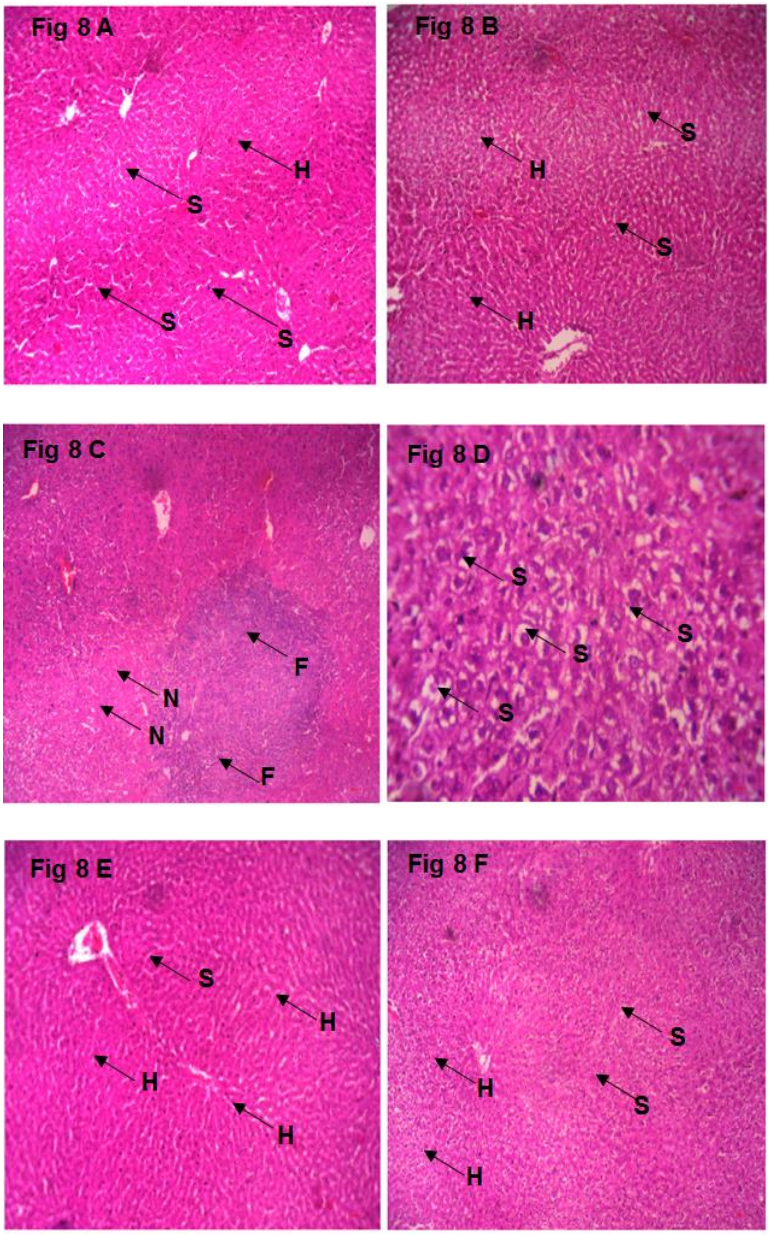
Dose (mg/kg)	TG (mg/dL)	CHOL (mg/dL)	VLDL-C (mg/dL)	HDL-C (mg/dL)
Placebo Control	62.71 ±5.33	84.32 ±7.24	41.57 ±4.22	30.21 ±3.32
UDCA 40	63.03 ±6.21	86.13 ±6.31	43.77 ±3.71	29.75 ±2.11
TAM 45	20.97 ±1.23#	28.21 ±3.42#	10.15 ±0.78#	86.93 ±9.71#
UDCA 10 + TAM 45	31.00 ±2.52 [a]	40.10 ±3.33[a]	16.50 ±1.16 [a]	50.15 ±5.33 [a]
UDCA 20 + TAM 45	45.02 ±3.22 [b]	60.13 ±5.21[b]	20.02 ±2.33[b]	30.10 ±4.71[b]
UDCA 40 + TAM 45	60.22 ±4.44[c]	76.27 ±7.55[c]	31.01 ±2.41[c]	33.21 ±3.67[b]

UDCA: Ursodeoxycholic acid, TAM: Tamoxifen, TG: Triglyceride, CHOL: Total cholesterol, VLDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, Data as mean ± SEM (Standard error of mean), n=5, [#]$p<0.01$ Significant difference when compared to control, [a] $p<0.05$, [b]$p<0.01$ and [c]$p<0.01$ Significant difference when compared to TAM

Table 3. *Effect of ursodeoxycholic acid on liver oxidative stress markers of tamoxifen-treated rats*

Dose (mg/kg)	SOD (u/mg protein)	CAT (u/mg protein)	GSH (µg/mg protein)	GPx (u/mg protein)	MDA (nmol/mg protein)
Placebo Control	47.60 ±4.11	40.21±4.32	25.35 ±3.00	22.27 ±2.55	0.14 ±0.07
UDCA 40	48.54 ±4.35	42.00 ±4.62	25.79 ±3.17	23.00 ±3.21	0.12 ±0.08
TAM 45	21.22 ±2.55$^{\#}$	15.57 ±1.00$^{\#}$	6.68 ±0.20$^{\#}$	8.11 ±0.17$^{\#}$	0.89 ±0.04$^{\#}$
UDCA10 +TAM45	26.35 ±3.06^{a}	20.71 ±3.43^{a}	10.73 ±0.91^{a}	11.24 ±0.93^{a}	0.52 ±0.09^{a}
UDCA 20+TAM 45	34.62 ±3.71^{b}	27.80 ±3.21^{b}	14.83 ±1.11^{b}	14.37 ±1.88^{b}	0.30 ±0.01^{b}
UDCA 40+TAM 45	44.57±4.54^{c}	36.92 ±4.56^{c}	22. 56±3.61^{c}	19.46 ±1.53^{c}	0.22 ±0.04^{c}

UDCA: Ursodeoxycholic Acid, TAM: Tamoxifen, SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, MDA: Malondialdehyde, GPx: Glutathione peroxidase, n=5, Data as mean ±SEM (Standard error of mean), $^{\#}$ p<0.001 Significant difference when compared to control, ^{a} p<0.05, ^{b}p<0.01, and ^{c} p <0.001 Significant difference when compared to TAM.



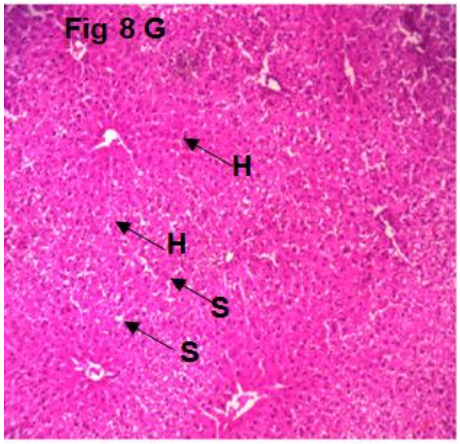


Figure 8. *Fig 8A: Liver of the placebo control rats; Fig 8B: Liver of ursodeoxycholic acid (40 mg/kg) treated rats; Fig 8C and Fig 8D: Liver of tamoxifen (45mg/kg) -treated rats; Fig 8E: Liver of ursodeoxycholic acid (10 mg/kg) pretreated rats; Fig 8F: Liver of ursodeoxycholic acid (20 mg/kg) pretreated rats; Fig 8G: Liver of ursodeoxycholic acid (40mg/kg) pretreated rats; T: Steatosis, H: Normal hepatocytes, N: Hepatocytes necrosis, S: Sinusoids, F: Inflammatory cells. H and E, x 100.*

4. Discussion

TAM may cause hepatotoxicity in women with breast cancer [21]. UDCA is a natural compound that could protect the liver from damage caused by drugs or toxins [7]. The current study assessed the ability of UDCA to prevent TAM-induced hepatotoxicity in adult rats. In this study, TAM perturbations of body and liver weights were marked by decreased body and increased liver weights. Previously, similar decreased body weight was reported in TAM (6 mg/kg/day) treated rats [21]. Also, TAM (45mg/kg/day) notably decreased body weight in rats as reported by Gao *et al.* [22]. The observation in this study correlates with increased liver weight in TAM (45mg/kg)-treated rats reported by Adikwu *et al.* [23]. The decreased body weight may be associated with growth hormone inhibition and decreased fat mass [24, 25] while increased liver weight may be a consequence of inflammation [26]. Nevertheless, UDCA pretreatment restored body and liver weights in a dose-related fashion. This observation may be due to the counter effect of UDCA on the deleterious effects of TAM on growth hormone, fat mass and inflammation. In this study, TAM conspicuously elevated serum LDH, AST, GGT, TB, ALT, CB and ALP levels in rats. Similarly, TAM (45 mg/kg/day) administered to rats for 10 days elevated the aforementioned biochemical markers as reported by Suddek [15]. The elevated serum levels of AST and ALT caused by TAM showed hepatocyte damage probably due to impaired cell membrane integrity and cellular leakage [27]. The increased serum LDH, ALP and GGT levels in TAM-treated rats showed a cholestatic pattern of liver injury [28, 29]. Elevated serum TB level may a consequence of the damage of the bile drainage in the biliary system caused by TAM [4]. Nevertheless, pretreatment with UDCA restored serum LDH, AST, GGT, TB, ALT, CB and ALP levels in a dose-related fashion, which is indicative of its protective activity. This occurrence may be due to the stabilizing effect of UDCA on liver cell membrane, which might have prevented the leakage of the aforementioned biochemical markers. This study observed altered serum lipid levels marked by decreased CHOL, TG, and VLDL-C and increased HDL-C in TAM-treated rats. Similar finding was reported by Gudbrandsen *et al.* [30] in TAM (40 mg/kg) treated rats. Awoade *et al* [31] also showed altered serum lipids caused by TAM (2.07 mg/kg) in mice. However, pretreatment with UDCA restored serum lipids in a dose-related fashion. In the current study, TAM decreased liver antioxidants (GPX, SOD, GSH and CAT) in rats. This finding is in agreement with the observation reported by Famurewa *et al.* [32]. Sakr *et al* [33] also reported similar observation in TAM (20 mg/kg) treated rats. Furthermore, TAM caused liver lipid peroxidation marked by increased MDA activity. This is consistent with the observation reported in rats administered with TAM (45 mg/Kg/day) for 7 days [34]. The decreased liver antioxidants caused by TAM may be due to oxidative stress whereas elevated MDA level connotes the breakdown of liver polyunsaturated fatty acids [35, 36]. Interestingly, liver antioxidants and MDA levels were restored by UDCA pretreatment in a dose-related fashion. TAM might have caused liver oxidative stress through mitochondria damage [26, 37]. Mitochondrial dysfunction can cause ROS production leading to liver oxidative stress and damage [38, 39]. UDCA might have restored liver antioxidants by preventing TAM-induced oxidative stress through its antioxidant activity. UDCA might have inhibited or scavenged TAM generated ROS. UDCA has shown viable antioxidant activity by scavenging superoxide anion, hydrogen peroxide, and hydroxyl radicals [12, 40]. The aforementioned effect of UDCA might have prevented the breakdown of liver polyunsaturated fatty acids thereby inhibiting lipid peroxidation [41]. In addition, TAM caused liver necrosis, steatosis and inflammatory cells infiltration in

rats. Similarly, Mourad *et al.* [4] reported steatosis in TAM (45 mg/kg/day) treated rats whereas Mahboub, [34] documented liver necrosis in TAM-treated rats. TAM induced steatosis has been attributed to impaired mitochondrial fatty acid oxidation triggering lipid peroxidation in the liver [42] while necrosis is a consequence of damage to liver biomolecules (Lipids, proteins and DNA) caused by oxidative stress. However, pretreatment with various doses of UDCA restored liver histology. UDCA might have prevented TAM-induced steatosis by inhibiting liver lipid peroxidation. Also, it prevention of liver necrosis may be due to the inhibition of TAM-induced liver oxidative stress.

5. Conclusion

This research shows that UDCA prevents TAM-induced perturbations in body and liver weights, serum biochemical markers, liver oxidative stress markers and histology. This study suggests that UDCA may be a therapeutic option for TAM associated hepatotoxicity.

Abbreviations

AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANOVA	Analysis of Variance
CAT	Catalase
CB	Conjugated Bilirubin
CHOL	Total Cholesterol
GSH	Glutathione
GPX	Glutathione Peroxidase
HDLC	High Density Lipoprotein Cholesterol
LDH	Lactate Dehydrogenase
MDA	Malondialdehyde
ROS	Reactive Oxygen Species
SEM	Standard Error of Mean
SOD	Superoxide Dismutase
TAM	Tamoxifen
TG	Triglyceride
TB	Total Bilirubin
UDCA	Ursodeoxycholic Acid
VLDLC	Very Low Density Lipoprotein Cholesterol
TB	Total Bilirubin
FBW	Final Body Weight
RLW	Relative Liver Weight
ALW	Absolute Liver Weight

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Author Contributions

Elias Adikwu: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Tobechi Brendan Nnanna: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Bonsome Bokolo: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

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Consent for Publication

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

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