**Alpha-Lipoic Acid Attenuates Cyclophosphamide-Doxorubicin-Induced Hepatic Perturbation in Rats**

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**Abstract**

**Background and Objectives:** The clinical use of cyclophosphamide-doxorubicin (CP-DOX) in breast cancer treatment may cause hepatotoxicity. This study assessed the protective effect of alpha-lipoic acid (ALA) against hepatotoxicity induced by CP-DOX in albino rats. **Materials and Methods:** Thirty-six adult male albino rats were randomized into six groups (A-F) of n = 6. Group A (control) was treated intraperitoneally (ip) with 0.3 mL of normal saline 8 hourly for 48h. Group B was treated with 10 mg/kg of ALA 8 hourly ip for 48 h. Group C was treated with a dose of CP-DOX (150/20 mg/kg) for 24 h. Group D was pre-treated with ALA 8 hourly for 48 h before treatment with a dose of CP-DOX for 24 h. Group E was co-treated with a dose of CP-DOX and ALA ip 8 hourly for 48 h. Group F was treated with a dose of CP-DOX for 24 h before treatment with ALA ip 8 hourly for 48 h. After treatment, rats were euthanized; blood samples were collected and evaluated for serum liver function markers. Liver samples were evaluated for biochemical markers and histology. **Results:** Liver catalase, superoxide dismutase, glutathione (GSH), and GSH peroxidase levels were significantly (P < 0.001) decreased in CP-DOX-treated rats. Aminotransferases, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase, total bilirubin, conjugated bilirubin, and malondialdehyde levels were significantly (P < 0.001) increased in CP-DOX-treated rats. The liver of CP-DOX-treated rats showed hepatocyte necrosis. However, CP-DOX-induced hepatotoxicity was significantly reversed in rats pre-treated (P < 0.001), co-treated (P < 0.01), and post-treated (P < 0.05) with ALA when compared to CP-DOX-treated rats. **Conclusion:** Pre-treatment with ALA produced the best protective effect against CP-DOX-induced hepatotoxicity.

**Keywords:** Anti-cancer, anti-oxidant, liver, rat, toxicity

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**INTRODUCTION**

The liver is the largest gland in the body occupying 2.5% of total body weight and providing a host of functions necessary for maintaining normal physiological homeostasis.[1] It is involved in almost all the biochemical pathways to growth, nutrient supply, energy provision, and syntheses of clotting factors.[1,2] The liver is involved in the biotransformation of drugs which makes it highly vulnerable to toxicity. The manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation in liver enzymes to fulminant hepatic failure. The pathogenesis of drug-induced liver disease usually involves the participation of the parent drug or metabolites that directly affect hepatic cell biochemistry or elicit an immune response.[4]

Cyclophosphamide (CP) has a wide spectrum of clinical uses. It is used for the treatment of cancer and nonmalignant disease states such as rheumatoid arthritis.[3] Doxorubicin (DOX), a quinone-containing anthracycline antibiotic, is an important agent against a wide spectrum of human neoplasms.[6] CP-DOX combination is used for the treatment of breast cancer.[7] It has exhibited high curative rate with appreciable reduction in mortality in cancer patients. Its use is relatively safe, but can be characterised by hepatotoxicity which may limit its use.[7,8] The hepatotoxic effect of CP has been attributed to acrolein one of its metabolites.[9] Acrolein binds to cellular...
Alpha-lipoic acid (ALA) is an antioxidant that can decrease OS response by scavenging reactive oxygen species. It is reduced to dihydrolipoic acid, which is generally regarded as the most bioactive form of ALA and the form responsible for most of the antioxidant effect. Unlike other antioxidants, ALA is both fat and water-soluble; therefore, it can cross biological membranes easily and produce antioxidant action both in the cytosol and in the plasma membranes. In addition to its antioxidant activity, it has been reported to act as a down-modulator of the activities of mediators of inflammation. Also, it has stimulatory effect on some endogenous antioxidants thereby facilitating their activities. It can protect biomolecules such as DNA, lipids and proteins from assaults by free radicals and can inhibit cell apoptosis. This study evaluated the protective effect of ALA against hepatotoxicity induced by CP-DOX in albino rats.

**Materials and Methods**

**Animals**

Thirty-six adult male albino rats were purchased from the animal breeding unit of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University, Nigeria. The rats were kept in cages in a well-ventilated room under natural condition with free access to food and water. The rats were allowed to acclimatize for 1 week before the commencement of the experiment. Rats were handled according to the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Science. This research was approved by the Research Ethics Committee of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University, Nigeria.

**Drugs and chemicals**

ALA (Shijiazhuang AO Pharm Import and Export Co Ltd China). DOX (Ranbaxy Laboratories, Ltd) and CP (Biochem Pharmaceutical Industries Ltd). This study used ALA (10 mg/kg), CP (150 mg/kg) and DOX (20 mg/kg) dissolved in normal saline.

**Animal treatment**

- Group A (control) was treated intraperitoneally (ip) with 0.2 mL of normal saline 8 hourly for 48 h
- Group B was treated with 10 mg/kg of ALA 8 hourly ip for 48 h
- Group C was treated with a dose of CP-DOX (150/20 mg/kg) ip for 24 h
- Group D was pre-treated with 10 mg/kg of ALA 8 hourly for 48 h before treatment with a dose of CP-DOX ip for 24 h
- Group E was co-treated with a dose of CP-DOX and ALA 8 hourly ip for 48 h
- Group F was treated with a dose of CP-DOX ip for 24 h before post-treatment with 10 mg/kg of ALA 8 hourly ip for 48 h.

**Animal sacrifice**

After treatment, rats were fasted overnight and euthanized (ether anaesthesia). Blood samples were collected from the heart in plain sample containers. Blood samples were allowed to clot, centrifuged and serum samples were separated and analysed for liver function markers. Liver samples were excised and homogenized in ice-cold 0.1 M Tris-HCl buffer (pH 7.4). The resultant homogenates were centrifuged at 1200 g, at 20 min and the supernatants were obtained for biochemical analyses.

**Liver function analyses**

Lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin (TB), alanine aminotransferase (ALT), conjugated bilirubin (CB), gamma glutamyl transferase, aspartate aminotransferase (AST) activities were determined using commercial diagnostic test kits (Randox Laboratories Ltd., Crumlin, UK).

**Oxidative stress marker analyses**

Liver protein was determined according to Lowry et al. 1951. GSH was measured as reported by Sedlak and Lindsay, 1968. Superoxide dismutase (SOD) was assayed according to Sun and Zigma, 1978. Catalase (CAT) was measured as described by Aebi, 1984. Glutathione peroxidase (GPx) was determined using the method of Rotruck et al. 1973. Malondialdehyde (MDA) was assayed as reported by Buege and Aust, 1978.

**Histological study**

At the end of treatment, liver samples were excised and sections were fixed in 10% formal saline. Liver tissues were processed and embedded in paraffin block, transverse sections (5 μm) were cut and stained with H and E, and examined for histological changes using a light microscope.

**Statistical analysis**

Data are expressed as mean ± standard error of mean. Values were analyzed using one-way analysis of variance followed by Tukey's test for post hoc comparison using GraphPad Prism 5.0 software (GraphPad Software Inc, La Jolla, CA, USA). P < 0.05; < 0.01 and < 0.001 were selected as the criteria for significance.

**Results**

**Effect on serum liver function markers**

Treatment with ALA did not produce significant (P > 0.05) effects on serum ALT, AST, ALP, LDH, GGT, TB, and CB levels when compared to control [Figures 1-7]. In contrast, the aforementioned parameters were significantly (P < 0.001) increased in rats treated with CP-DOX when compared to control [Figures 1-7]. The increases in the aforementioned
parameters represent 291.7%, 260.7%, 274.8%, 278.1%, 330.4%, 202.4% and 350.5% respectively. Interestingly, serum ALT, AST, ALP, LDH, GGT, TB and CB levels were significantly decreased in rats pre-treated ($P < 0.001$), co-treated ($P < 0.01$) and post-treated ($P < 0.05$) with ALA when compared to rats treated with CP-DOX [Figures 1-7].

**Effect on biochemical parameters in liver tissues**

The liver levels of ALT, AST, ALP, LDH and GGT were normal ($P > 0.05$) in rats treated with ALA when compared to control [Table 1]. On the other hand, liver ALT, AST, ALP, LDH and GGT levels were significantly ($P < 0.001$) increased in rats treated with CP-DOX when compared to control. The increases in liver ALT, AST, ALP, LDH and GGT levels were calculated to be 310.8%, 365.8%, 345.1%, 433.9% and 290.0% respectively [Table 1]. However, liver ALT, AST, ALP, LDH and GGT levels were significantly decreased in rats pre-treated ($P < 0.001$), co-treated ($P < 0.01$) and post-treated ($P < 0.05$) with ALA when compared to rats treated with CP-DOX [Table 1].
Effects on liver oxidative stress markers and histology

Normal (P > 0.05) liver levels of SOD, CAT, GSH, GPx and MDA were obtained in rats treated with ALA when compared to control [Table 2]. However, significant (P < 0.001) decreases in liver SOD, CAT, GSH, and GPx levels with increases in MDA levels were obtained in rats treated with CP-DOX when compared to control [Table 2]. On the other hand, liver SOD, CAT, GSH, and GPx levels were increased whereas MDA levels were decreased significantly in rats pre-treated (P < 0.001), co-treated (P < 0.01) and post-treated (P < 0.05) with ALA when compared to rats treated with CP-DOX [Table 2]. Furthermore, normal histology was observed in the liver of control rat [Figure 8a] whereas hepatocyte necrosis was observed in the liver of rat treated with CP-DOX [Figure 8b]. Also, hepatocyte necroses were

Table 1: Effect of alpha-lipioc acid on biochemical parameters in the liver tissues of cyclophosphamide-doxorubicin-treated rats

| Treatment                        | ALT (U/L) | AST (U/L) | ALP (U/L) | LDH (U/L) | GGT (U/L) |
|----------------------------------|-----------|-----------|-----------|-----------|-----------|
| Control                          | 165.9±10.0| 169.6±13.7| 154.7±11.1| 135.0±12.7| 11.6±1.19 |
| ALA                              | 143.7±15.6| 154.7±16.6| 149.1±14.0| 127.5±12.5| 10.4±0.92 |
| CP                               | 681.5±20.1| 790.0±22.1| 688.5±21.3| 599.2±18.4| 45.2±4.31 |
| ALA + CP-DOX (post-treatment)    | 580.0±16.4| 528.5±19.9| 410.1±14.6| 424.7±13.4| 31.9±3.71 |
| CP DOX + ALA (co-treatment)      | 425.7±18.6| 431.6±17.5| 347.8±12.3| 376.0±12.2| 20.2±2.00 |
| ALA + CP-DOX (pre-treatment)     | 280.3±15.4| 376.5±15.2| 270.7±11.4| 155.6±10.3| 13.6±1.72 |

*P<0.001 when compared to control, *P<0.05 when compared to CP-DOX, **P<0.01 when compared to CP-DOX, ***P<0.001 when compared to CP-DOX.

Data are expressed as mean±SEM, n=6. CP‑DOX: Cyclophosphamide‑Doxorubicin, ALA: Alpha lipoic acid, ALT: Alanine transaminase, AST: Aspartate transaminase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, GGT: Gamma glutamyl transferase

Table 2: Effect of alpha-lipioc acid on liver oxidative stress markers of cyclophosphamide-doxorubicin-treated rats

| Treatment                        | MDA (n mole/ mgprotein) | CAT (U/ mgprotein) | SOD (U/ mgprotein) | GSH (μmole/ mgprotein) | GPx (U/ mgprotein) |
|----------------------------------|-------------------------|--------------------|--------------------|------------------------|-------------------|
| Control                          | 0.16±0.07               | 30.0±3.32          | 22.1±2.32          | 9.50±0.17              | 16.6±1.00         |
| ALA                              | 0.14±0.04               | 32.3±0.11          | 20.7±2.73          | 9.70±0.08              | 17.0±1.22         |
| CP DOX                           | 0.92±0.05               | 10.0±0.20          | 7.52±0.18          | 2.30±0.23              | 5.09±0.75         |
| ALA + CP-DOX (post-treatment)    | 0.71±0.01*              | 15.0±2.21*         | 10.3±0.53*         | 4.40±0.03*             | 7.30±0.72*        |
| CP DOX + ALA (co-treatment)      | 0.51±0.04**             | 20.4±2.23**        | 13.5±1.00**        | 6.43±0.48**            | 10.5±1.43**       |
| ALA + CP-DOX (pre-treatment)     | 0.20±0.02***            | 30.1±2.31***       | 19.5±1.79***       | 8.88±0.28***           | 14.9±1.62***      |

*P<0.001 when compared to control, *P<0.05 when compared to CP-DOX, **P<0.01 when compared to CP-DOX, ***P<0.001 when compared to CP-DOX.

Data are expressed as mean±SEM, n=6. CP‑DOX: Cyclophosphamide‑Doxorubicin, ALA: Alpha lipoic acid, MDA: Malondialdehyde, CAT: Catalase, SOD: Superoxide dismutase, GSH: Glutathione, GPx: Glutathione peroxidase
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obtained in liver of rats pre-treated, co-treated and post-treated with ALA respectively [Figure 8c-e].

**Discussion**

Hepatotoxicity is one of the primary reasons for the withdrawal of drugs from the market. Studies have shown that 5% of all hospital admissions are associated with hepatotoxicity caused by drugs.[27] Experimental studies suggest that OS could be an essential pathologic factor in drug-induced hepatotoxicity.[28] ALA is an antioxidant that has gained considerable attention due to its free radical scavenging activity and the propensity to inhibit OS.[29] This study assessed the protective effect of pre-treatment, co-treatment and post-treatment with ALA against hepatotoxicity induced by CP-DOX in rats. In this study, CP-DOX induced hepatotoxicity was determined by microscopic and biochemical evaluations. Drugs stimulate the production of a variety of serum biochemical and histopathologic indicators of hepatotoxicity. Biochemical markers which include AST, ALP, CB, TB, LDH and GGT have been used to assess the functionally of the liver as a measure of its wellbeing. Also, the aforementioned parameters are usually elevated as a consequence of hepatotoxicity caused by chemical assault.[30] In this study, hepatic assault caused by CP-DOX was confirmed by remarkable increases in the serum levels of ALT, AST, ALP, CB, TB, LDH, and GGT. However, the hepatic assault induced by CP-DOX was reduced in rats pre-treated, co-treated, and post-treated with ALA with most reduction observed in rats pre-treated with ALA. This was evident by observed decreases in serum ALT, AST, ALP, CB, TB, LDH, and GGT levels. Also, the extent of hepatic damage caused by CP-DOX was assessed by measuring ALT, AST, ALP, LDH, and GGT contents of liver tissues. Experimental studies have shown that the hepatic activities of the aforementioned parameters can be up-regulated as a consequence of uncontrollable or untreated hepatic insults by drugs.[31] In this study, ALT, AST, ALP, LDH, and GGT levels were remarkably elevated in the liver tissues of rats treated with CP-DOX which are signs of hepatocyte degeneration and functional incapacitation of the liver.[32] Interestingly, hepatic activities of ALT, AST, ALP, LDH, and GGT were decreased in the liver of rats pre-treated, co-treated, and post-treated with ALA with most decreases observed in rats pre-treated with ALA. The ability of ALA to restore hepatic function in CP-DOX-treated rat is a vivid attestation to its inherent potential to prevent or abrogate hepatotoxicity that can arise from the clinical use of CP-DOX.

Studies suggested that disturbance in oxidant-antioxidant system caused by OS culminating in antioxidant depletion is involved in the pathogenesis of drug-induced hepatotoxicity.[33] In this study, treatment with CP-DOX produced low hepatic antioxidant (SOD, CAT, GSH and GPx) levels. This is an evidence of an over whelming OS which might have surmounted the activities of antioxidants leading to their...
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depletions or suppression of syntheses. Several studies have demonstrated that LPO marked by higher levels of MDA caused by free radicals is frequently associated with hepatotoxicity induced by drugs.\(^{[34]}\) In this study, treatment with CP-DOX caused a remarkable increase in the hepatic activity of MDA. This is an evidence of the breakdown of hepatic poly unsaturated fatty acid via OS caused by reactive oxygen species. Interestingly, the hepatic peroxidative activity of CP-DOX was ameliorated as evidenced by reductions in MDA levels in rats pre-treated, co-treated and post-treated with ALA with most amelioration observed in rats pre-treated with ALA.

In addition to the evaluation of serum biochemical markers, the microscopic assessment of liver histology is also used as a confirmatory investigation for drug-induced hepatotoxicity.\(^{[35]}\) In this study, histological examination of the liver section of rat treated with CP-DOX showed hepatocyte necrosis which supports observed changes in evaluated biochemical parameters. This observation can be attributed to the ability of CP-DOX to produce excess free radicals, and to suppress free radical scavenging capacity of the liver via antioxidant depletion thereby increasing the vulnerability of the liver to more free radical assault leading to OS. This might have resulted to hepatic biomolecular damage creating an enabling environment for necrosis.\(^{[36]}\) Interestingly, hepatocyte necrosis decreased in rats pre-treated, co-treated and post-treated with ALA. The hepatotoxic effect of CP has been primarily attributed to its toxic metabolite (acrolein) which has been associated with the production of free radicals causing OS and biomolecular damage.\(^{[37]}\) Also, studies have associated the hepatotoxic effect of DOX to free radical generation leading to OS, inflammation and cell apoptosis.\(^{[38]}\) The protective effect of ALA observed in this study might be due to its antioxidant effect. The hepatic oxidative activity of CP-DOX might have been down-regulated by the antioxidant action of ALA. Studies have shown that ALA is a unique antioxidant that scavenges free radicals in fat and water-soluble environments in its oxidized and reduced dihydrolipoic acid form.\(^{[39]}\) It is effective in recharging enzymes in the mitochondria “the energy centers” of cells\(^{[40]}\) and can prevent DNA, lipids and proteins from damage caused by OS.\(^{[41]}\) It can increase antioxidant gene expression thereby facilitating antioxidant production and activity.\(^{[42]}\)

**Conclusion**

This study discovered that pre-treatment with ALA produced the best protective effect against CP-induced hepatotoxicity than co-treatment and post-treatment. Pre-treatment with ALA may be clinically used to prevent hepatotoxicity that may arise with the use of CP-DOX.

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**Conflicts of interest**

There are no conflicts of interest.

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