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THE EFFECTS OF COARTEM AND ANTIOXIDANT INTERACTIONS ON SELECTED OXIDATIVE STRESS INDICATORS, LIVER ENZYMES AND BIOMARKERS OF TOXICITY IN ALBINO WISTAR RATS

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Abstract

The effects of Coartem and antioxidant interactions on selected oxidative stress indicators, liver enzymes and biomarkers of toxicity in albino Wistar rats were studied. Fifty-five albino Wistar rats of mixed sexes were selected into eleven study groups of five rats per group. The effect of the various treatments on the weight of the rats, activities of serum enzymes (AST, ALT and ALP), concentrations of albumin and oxidative stress markers (GSH, MDA and SOD) were examined. Coartem treated group showed an increase ($p<0.05$) in the activities of AST, ALT and ALP in relation to control, there was also alterations in the liver architecture which are indicative of hepatotoxicity. Antioxidant groups administered concomitantly at the start of Coartem treatment showed a significant decrease ($p<0.05$) in the activities of serum ALP (for all antioxidant), AST (for Vitamin C and Garlic), ALT (for Garlic), SOD and MDA, a decrease in the activity of GSH, Antioxidant groups given mid-way Coartem treatment showed a decrease ($p<0.05$) in serum ALP (for Vitamin C), AST and ALT (for Vitamin E and Garlic), GSH and SOD (for all antioxidants), MDA (for Vitamin C). Moreover, for antioxidant groups given at the end of Coartem treatment, there were decrease ($p<0.05$) in the activities of serum ALP and AST (for Vitamin E and Garlic), ALT (for Vitamin E), GSH (for all antioxidants), MDA (for Vitamin E), but an increase in SOD activity (for Garlic). Histopathology of the liver tissues showed mild alterations in groups administered with antioxidants. Antioxidants given mid-way and towards the end of Coartem therapy had profound effect on reducing the oxidative stress imposes by Coartem, but the most effective treatment period was at the end. Of the three antioxidants used, Vitamin E and Garlic were more effective, but the most potent was Garlic.

Keywords: Coartem, Toxicity, Antioxidant Interactions, Oxidative Stress, Effect

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INTRODUCTION

Organisms are embedded with an intricate web of antioxidants which are metabolites and catalysts that are synergized to avoid oxidative harm to vital parts of the cell, such as, DNA, proteins and lipids" (Sies, 1997; Vertuani *et al*., 2004). In an oxygenated domain, the most lethal side effects of metabolism are free radicals containing chemically reactive oxygen. "Antioxidants remove these derivatives of oxygen that are reactive in the body, and prevent the oxidation of other molecules. They prevent oxidative damage of cellular components by working on free radicals and chemically active species containing oxygen in the body" (Ukpanukpong 2011). Generally, antioxidant systems work in two ways; they either avert these chemically active species from being produced, or else eliminate them before they cause havoc on fundamental mechanisms of the cells (Rupa *et al*., 2012).

Some factors affect the rate at which antioxidants exert their action - the concentration of the free radical/reactive specie, the type of chemical reaction between the antioxidant and the reactive species, and the capacity of the antioxidants (Vertuani *et al*., 2004). Endogenous antioxidants (those synthesized by the body) and exogenous antioxidants (those obtained from dietary source) exist. An exogenous antioxidant is a component in food that can significantly decrease the harmful effects of reactive oxygen species. Examples include Vitamin C and Vitamin E; carotenoids; minerals such zinc; phytochemicals such as flavonoids; and coenzymes (Ukpanukpong, 2011). The three (3) antioxidants considered in this study are Vitamin E, Garlic and Vitamin C.

Clinical consequences of malaria result primarily from parasitic invasion of erythrocytes. Hemolysis is common in malaria cases and liberates extracellular hemoglobin which triggers specific pathophysiological conditions like inflammation, hepatic failure and anaemia. Hemolysis of infected red cells releases free haem which may be responsible for an external oxidative stress on both infected and non-infected RBCs (Moreira *et al*., 2012); and one of the factors contributing to destruction of normal red cells. Haem plays a predominant role in artemisinin activation; the active molecules bind to multiple parasite proteins and damage and disrupt parasite metabolic pathways and membrane transport channels through free radicals (Wang *et al*., 2015; O'Neil *et al*., 2010). However, activation of artemisinin is from the parasite's haem.

Concerns have therefore been raised about administration of antimalarial drug (like Coartem) alongside antioxidant supplements like ascorbic acid, the later which may antagonize the endoperoxial moiety relevant for antimalarial or parasidal activity of Coartem (which can exert a dose-dependent counter pro-oxidant effect). The effect this may have on behavioral indices of toxicity is not known. Therefore, the objective of this study is to evaluate the effects of Coartem and antioxidants (Vitamin C, Vitamin E and Garlic) interactions on selected oxidative stress indicators, Liver enzymes and Biomarkers of toxicity in albino Wistar rats.

METHODOLOGY

Drugs

Artemether-lumefantrine (Coartem, 80 mg/4800 mg) manufactured by Novartis Pharmaceutical Corporation –Switzerland, Vitamin C (200mg/ml) marketed by May and Baker; Vitamin E (1000IU) product of Puritan's Pride Inc. USA and Garlic capsule (60mg/ml) a product of Softgel Healthcare Private limited, India; were obtained from a registered Pharmacist in Bez Pharmacy Calabar, Nigeria and utilised for the research. The antioxidants were aspirated into a syringe and then reconstituted with measured amount of corn oil prior to daily administration**.**

Experimental animals

Fifty five adult albino Wistar rats, males and females weighing between 80 and 160g were purchased from disease free stock from the Faculty of Basic Medical Sciences animal house facility, University of Calabar. Prior to the experiments, the animals were allowed two weeks of acclimatization and their weights were measured before treatment commenced. The animals were housed in wooden cages of dimension 12m x 12m with wire screen top and sides, 5 animals were kept per cage. They were placed in a well-ventilated animal room at temperature 20 – 25ºC. The feed was obtained from Vital Feed Ltd Lagos, Nigeria. Feed, weighing 80-

150g and tap water were given to the experimental rats, twice a day (morning and evening) without restraint. Each of the animals were given identification marks and observed daily for weight, toxicity signs and behavioural changes. The cages were cleaned every two days.

The Animals were randomly divided into eleven (11) groups of five (n = 5) animals each and administered therapeutic regimen of the drugs; artemether-lumefantrine was administered and antioxidants for 7 days. The dosage given was equivalent to that for a 70kg man and calculated in mg/kg body weights of the experimental animals. The experimental design is as follow;

Group I: Control (placebo)

Group II: Artemether-lumefantrine (8 mg/kg body weight, twice daily) for 7 days

Group III: Co-administration of ACT and Vitamin C (8mg/kgbwt ACT + 5.8mg/kgbwt Vit C, daily).

Group IV: Co-administration of ACT and Vitamin E (8mg/kgbwt ACT + 5.7IU/kgbwt Vit E, daily)

Group V: Co-administration of ACT and Garlic (8mg/kgbwt ACT + 7.2mg/kgbwt Vit E, daily) antioxidants treatment at the start of ACT therapy

Group VI-VIII; Co-administration of ACT, Vit C, E and Garlic daily for 7 days, antioxidants treatment mid-way into ACT therapy.

Group IX-XI Co-administration of ACT, Vit C, E and Garlic daily for 7 days, antioxidants treatment at the end of ACT therapy.

The above schedule was done in three sets, first set antioxidants administered at start of ACT administration, second set midway into ACT administration and third set at completion of ACT dose administration.

Collection and Treatment of Samples

At the end of the experimental period, the animals were subjected to an overnight fast and anaesthetized in chloroform vapour. Blood was gotten via cardiac puncture using "germ-free" needles, from which serum was prepared and used for biochemical analysis. The remaining blood was collected in EDTA sample tubes and used for haematological studies. Relevant tissue liver was excised using a pair of scissors and forceps, trimmed of fat tissue and weighed. The tissues were then preserved in 0.5% formaldehyde for histological investigation.

Determination of Parameters

Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Alanine aminotransferase (ALT) determined using kit based on Reitman and Frankel (1957). Albumin concentration (ALB) was determined based on Bromo cresol-green method of McPherson and Everald (1972) as described in Tietz (1994). Glutathione and Lipid peroxidation (MDA**)** were determined based on Colorimetric Assay Kit while Spectrophotometric assay for superoxide dismutase using assay Kit. The assay procedures described by the kits' leaflet were employed accurately in the assay process.

Statistical Analysis

The data generated from this research were analysed using the one way ANOVA and student's t-test of SPSS (Statistical Package for Social Science) with the aid of Microsoft (MS) Excel Program. All data generated were expressed as mean ± SEM, probability values considered significant was at $p \leq 0.05$.

RESULTS

Mean body weight changes

There was a significant increase ($p<0.05$) in the ten (10) groups when compared to control group. Co-administration of Coartem and Garlic at the end of antimalarial therapy, and co-administration of coartem and Vitamin E at the start of antimalarial therapy caused a weight gain that was more pronounced after day 4.

Table 1 shows the effects of serum enzymes, oxidative stress enzymes activity and albumin concentration in control, coartem and co-administration of coartem and antioxidants administered concomitantly at the start of antimalarial therapy. ALP and AST treated with coartem alone, significantly decreased ($p<0.05$), However, co-administration of Coartem and Vitamin E, there was reduction ($p<0.05$) in ALP activity and a substantial increase ($p<0.05$) in AST and ALT activities when compared with groups administered coartem alone. A decrease ($p<0.05$) in

ALP activity in comparism with control and Coartem alone; but a significant reduction ($p<0.05$) when compared with coartem and Vitamin E concomitantly group, while Albumin (ALB) concentration increased ($p<0.05$) considerably in relation to the control. ALP and AST activity decreased ($p<0.05$) in Coartem and Garlic administered concomitantly with significant increase ($p<0.05$) when compare with Coartem alone. ALT activity decreased significantly ($p<0.05$) with respect to groups given coartem and antioxidants concomitantly. Albumin (ALB) concentration increased ($p<0.05$) compared to the control.

Coartem and Garlic administered concomitantly: Glutathione (GSH) activity decreased significantly ($p<0.05$), while the activities of Malondialdehyde (MDA) and Superoxide dismutase (SOD) increased markedly ($p<0.05$) treated with ACT and Vitamin E. However, MDA and SOD activities showed a significant increase ($p<0.05$) relative to control but decreased substantially ($p<0.05$) compared to group given coartem and Vitamin C concomitantly, while MDA and SOD activities increased significantly ($p<0.05$) when compared with the control and Coartem alone, but decreased remarkably ($p<0.05$) comparative to the group given coartem and Vitamin E concomitantly.

Table 1: Comparative effect on serum enzymes activity and albumin concentration in control, coartem and co-administration of coartem and antioxidants administered concomitantly at the start of antimalarial therapy

Group	GSH (mg/gm)	MDA (u/mol)	SOD (u/L)	ALP (iu/L)	AST (iu/L)	ALT (iu/L)	ALB (g/L)
Normal control	2.24 ±0.01	2.21 ±0.01	0.26 ±0.00	61.00 ±0.96	31.00 ±0.63	14.00 ±1.14	41.48 ±0.92
Coartem	2.24 ±0.01	2.21 ±0.01	0.25 ±0.00	104.48 ±2.07*	69.20 ±2.22*	16.00 ±0.84	38.62 ±0.56
Coartem + Vit. E (Concomitantly)	1.71 ±0.01*,a	2.81 ±0.00*,a	0.67 ±0.00*,a	102.84 ±4.51a	75.00 ±3.89a	32.60 ±1.75*,a	41.76 ±1.31
Coartem + Vit. C (Concomitantly)	1.57 ±0.01*,a,b	2.66 ±0.02*,a,b	0.35 ±0.01*,a,b	89.06 ±1.59*,a,b	68.60 ±2.56a	20.60 ±1.29*,a,b	44.52 ±3.01*
Coartem + Garlic (Concomitantly)	1.64 ±0.01*,a,b,c	2.76 ±0.01*,a,b,c	0.44 ±0.00*,b,c	72.20 ±1.36*,a,b,c	64.00 ±4.04a,b	14.40 ±1.29b,c	44.32 ±0.97*

Values are presented as mean ± SEM of 5 replicates. * Significantly different from control; a from coartem; b from Coartem + Vit. E; c from Coartem + Vit. C.

Table 2 shows the effect of serum enzymes, oxidative stress enzymes activity and albumin concentration in co-administration of coartem and antioxidants mid-way antimalarial therapy. There was an increased ($p<0.05$) in serum ALP and AST activities in the group administered coartem alone. However, co-administration of Coartem and Vitamin E showed increased ($p<0.05$) ALP activity and decreased AST activity ($p<0.05$). AST and ALP also showed an increase ($p<0.05$) when compared to coartem alone. Serum ALT activity were markedly reduced ($p<0.05$) compared to control, group administered coartem alone and other groups given antioxidants mid-way antimalarial therapy. ALP activity increased ($p<0.05$) in Coartem and Vitamin C administered mid-way when compared to control but decreased significantly ($p<0.05$) in comparative to group administered with coartem alone and other

groups of antioxidant. AST and ALT, and Albumin concentration increased significantly ($p<0.05$) when compared to control and all antioxidant group.

ALP and AST activity increased significantly ($p<0.05$) when compared to the control, coartem alone and antioxidants groups mid-way. There was a decreased ($p<0.05$) ALT activity in comparative with groups administered coartem alone and coartem and Vitamin C mid-way. Albumin concentration significantly increased ($p<0.05$) relative to control but reduced significantly ($p<0.05$) relative to group administered coartem alone and coartem and Vit C mid-way antimalarial therapy.

There was an increase ($p<0.05$) in MDA and SOD activity compared to the control and group administered coartem alone in ACT and vitamin E administration, while decrease ($p<0.05$) in the activities GSH and MDA relative to control, Coartem alone and Coartem and Vitamin E administered mid-way. Coartem and Garlic administered mid-way showed decrease ($p<0.05$) in GSH and increased notably ($p<0.05$) in MDA in relation to control and Coartem alone but decrease ($p<0.05$) to another antioxidant group.

Table 2: Comparative effect on serum enzymes activity and albumin concentration in control, coartem and co-administration of coartem and antioxidants mid-way antimalarial therapy

Group	GSH	MDA	SOD	ALP	AST	ALT	ALB
Normal control	2.24 ±0.01	2.21 ±0.01	0.26 ±0.00	61.00 ±0.96	31.00 ±0.63	14.00 ±1.14	41.48 ±0.92
Coartem	2.24 ±0.01	2.21 ±0.01	0.25 ±0.01*	104.48 ±2.07*	69.20 ±2.22*	16.00 ±0.84	38.62 ±0.56
Coartem + Vit. E (Mid-way)	2.17 ±0.18	2.95 ±0.00*, a	0.22 ±0.00*, b	109.92 ±3.49a	58.00 ±2.85*, a	12.60 ±1.02*, a,b	42.78 ±0.91*
Coartem + Vit. C (Mid-way)	1.68 ±0.00*, a,b	1.91 ±0.00*, a,b	0.16 ±0.00	72.50 ±1.27*, b	78.20 ±3.07*, a,b	19.20 ±1.02*, a,b	49.36 ±1.13*, a,b
Coartem + Garlic (Mid-way)	1.79 ±0.00*, a,b	2.57 ±0.00*, a,b,c	0.15 ±0.00b	131.90 ±4.10a, c	55.40 ±2.40*, a,c	14.60 ±0.81c	41.80 ±1.52ac

Values are presented as mean ± SEM of 5 replicates. * Significantly different from control; a from coartem; b from Coartem + Vit. E; c from Coartem + Vit. C.

Table 3 shows the effect of serum enzymes, oxidative stress enzymes activity and albumin concentration in co-administration of coartem and antioxidants at the end of antimalarial therapy. There was an increased ($p<0.05$) in the activities of ALP and AST for groups administered coartem alone compare to control.

Coartem and Vitamin E administered at the end showed a significant increase ($p<0.05$) in the activity of ALP compared to the control and

coartem alone; AST activity also increased ($p<0.05$) when compared with the control while the concentration of Albumin increased ($p<0.05$) compared to coartem alone.

Coartem and Vitamin C group, a significant increase ($p<0.05$) in the activities of ALP and ALT, and ALB relative to control, groups administered coartem alone, but AST activity significantly increased ($p<0.05$) when compared to control.

Coartem and Garlic administered at the end: The activities of ALP, ALT and AST, and ALB increased significantly ($p<0.05$) relatative to all other groups.

Coartem and Vitamin E administered at the end showed a reduction ($p<0.05$) in GSH), MDA and SOD when compared to the control and groups administered coartem alone. The reduction was also shown in GSH and SOD, but MDA activity was significantly increased ($p<0.05$) with group administered Coartem and Vitamin C at the end of antimalarial therapy.

Coartem and Garlic administered at the end showed a significant reduction ($p<0.05$) in the activity of GSH and an increase ($p<0.05$) in SOD relative to control and Coartem alone. Malondialdehye (MDA) reduced substantially ($p<0.05$) compared to the control, Coartem alone and Coartem and Vitamin E at the end; but increased significantly ($p<0.05$) when compare with Coartem and Vitamin C at the end of antimalarial therapy.

Table 3: Comparative effect on serum enzymes activity and albumin concentration in control, coartem and co-administration of coartem and antioxidants administered at the end of antimalarial therapy

Group	GSH	MDA	SOD	ALP	AST	ALT	ALB
Normal control	2.24 ±0.01	2.21 ±0.01	0.26 ±0.00	61.00 ±0.96	31.00 ±0.63	14.00 ±1.14	41.48 ±0.92
Coartem	2.24 ±0.01	2.21 ±0.01	0.25 ±0.00	104.48 ±2.07*	69.20 ±2.22*	16.00 ±0.84	38.62 ±0.56
Coartem + Vit. E (End)	1.65 ±0.00*, a	2.17 ±0.01*, a	0.19 ±0.00*, a	97.82 ±1.66*, a	68.00 ±3.33a	15.60 ±0.68	41.72 ±1.14a
Coartem + Vit. C (End)	1.81 ±0.00*, a,b	3.26 ±0.01*, a,b	0.20 ±0.00*, a,b	124.56 ±0.72*, a,b	72.00 ±1.67a	23.60 ±0.68*, a,b	49.70 ±1.19*, a,b
Coartem + Garlic (End)	2.17 ±0.00*, a,b,c	2.42 ±0.01*, a,b,c	0.65 ±0.00*, a,b,c	81.64 ±3.76*, a,b, c	49.00 ±0.32*, a,b,c	31.00 ±0.95*, a,b, c	45.20 ±1.08*, a,c

Values are presented as mean ± SEM of 5 replicates. * Significantly different from control; a from coartem; b from Coartem + Vit. E; c from Coartem + Vit. C.

DISCUSSION

Studies have shown that exposure to xenobiotics causes a decrease in the body weight despite increases in food and water intakes (Lovati *et al*., 1996). However, in this study, there was an elevation in the mean body weights of all the animals in all the groups. This may be due to the fact that the doses of Coartem administered were not in the toxic range. Besides the use of therapeutic doses, the animals used for the study were normal rats not malaria – induced. Thus, no weight loss or death was recorded.

The present study revealed that administration of Coartem alone shows a rise in the activities of serum AST, ALP and a slight increase in the activity of ALT. This is indicative of hepatotoxicity. Moreover, according to Ofem *et al*. (2014), "when coartem and p-alaxin was administered on albino Wistar rats, the activities of serum ALP, ALT and ASP increased significantly. There was no notable change in the activities of oxidative stress enzymes (GSH, MDA and SOD). The observed changes in the liver architecture for group administered with coartem showed mild toxicity due to oxidative stress evidenced by well - congested central and portal veins, and infiltrates and inflammation. This finding agrees with Ukekwe *et al*. (2013) who reported cellular necrosis and inflammatory liver cells in artemether-lumefantrine treated rats.

In summary, exposure to therapeutic doses of Coartem to normal rats induced toxicity on the liver but not the kidney of rat tissues. Concomitant administration of Coartem with Vitamin C, Vitamin E and Garlic cumulated in reduction in the activities of serum ALP below that of Coartem treated alone. The activity of AST was also reduced for groups concomitantly administered with Vitamin C and Garlic; while the increased activity of ALT found in Coartem treated groups was ameliorated in Garlic treated groups. These collaborates a study by Adegbeson *et al*. (2014) that reported a significant reduction in serum ALP and AST activities in co-administration of Lonart with Vitamin C than that of Lonart alone. Thus, the hepatotoxicity was more reduced in the group administered concomitantly with Garlic. But, the activity of GSH was reduced from that of Coartem treated groups; but increased for MDA and SOD. This might be due to the fact that co-administration of antioxidants with Coartem may have increased oxidative stress thereby causing increased production of free radicals. However, Adegbeson et al (2014) reported a reduction in the activity of MDA and an increase in GSH activity in co-administration of Coartem with Vitamin C compared to the group administered with only Lonart. The introduction of the antioxidants midway into Coartem therapy showed some alterations. The activity of serum ALP decreased only for Vitamin C treatments given midway; while the activities of AST and ALT decreased for Vitamin E and Garlic treatments given midway compared to Coartem treatment alone. It is known that both ALT and AST are very important enzyme markers to ascertain liver cells integrity (Jens & Hanne, 2002). Thus, Vitamin E and Garlic treatments introduced midway into Coartem therapy ameliorated the hepatic damage. There were mild alterations in the kidney function parameters.

Additionally, when the antioxidants were introduced mid-way, the enzyme activities of the antioxidants - GSH and SOD - decreased in all the treatment groups; Thus, Vitamins E and C introduced midway into Coartem therapy reduced the oxidative stress exerted by the drug. When the antioxidants were introduced at the end of Coartem therapy, the hepatic damage was ameliorated; evidenced by reduction in the activities of ALP and AST in Vitamin E and Garlic treatments, and decrease in ALT activity for Vitamin E treated group. Thus, Vitamin E and Garlic treatments given at the end of Coartem therapy had a profound effect on the hepatic damage caused by Coartem therapy. There were mild alterations in kidney function parameters for all the treatment groups. The activity of GSH, SOD and MDA were reduced in all the antioxidant treatment groups relative to ACT alone. The reduction in liver MDA may be due to the antioxidant (Vitamin E) reducing the oxidative stress caused by the antimalarial (Coartem), by

reducing the free radicals produced by the temporal breaking of the endoperoxide bond in the artemisinin structure of Coartem. Thus, Vitamin E and Garlic treated groups given at the end of Coartem therapy had more profound effect in reducing the oxidative stress. Organisms contain an intricate mesh of metabolites and enzymes known as antioxidants that interact to prevent cellular damage. Antimalarial such as Coartem that have the artemisinin structure exhibit their antiplasmodial action by releasing free radicals. These drugs are generally relatively safe, but in recent times there have been reports on its adverse effect such as haemolytic anaemia, oral cancer, hearing loss, neurotoxicity, among others. In an attempt to minimize the side effects, antioxidants are administered along with it on the basis that since both the episode of malaria infection and the antimalarial treatment imposes tremendous oxidative stress on the host, the antimalarial are often prescribed with Vitamin C or similar antioxidant supplements, such that the antioxidants reduce free radical load. However, concomitant administration of artemisinin group of drugs with antioxidant incapacitates its antiprotozoal/antimalarial action.

Free radicals cause oxidative stress on the body particularly the liver which is the major organ of detoxification and biotransformation. The elevation of serum liver enzymes (AST, ALT and ALP) and alteration in the liver architecture is indicative of the hepatotoxicity associated with the intake of Coartem. Thus, results from this study indicated that antioxidants taken concomitantly at the start of Coartem therapy showed a decrease in serum enzymes activity and increase in MDA – which is indicative of oxidative stress. Toxicity was mostly reduced in Garlic treated groups. Similarly, the introduction of antioxidants mid-way into Coartem therapy witnessed a decrease in serum enzymes activity which was more profound in Vitamin E and Garlic treated groups. There was also a decrease in MDA and increase in the activities of SOD and GSH; again Vitamin E had the most effect. Furthermore, when antioxidants were given at the end of Coartem therapy, there was also a decrease in the serum enzymes; decrease in MDA and an increase in SOD activity. The effect was ameliorated in Vitamin E and Garlic treated groups.

CONCLUSION

This study evaluated the effects of Coartem and antioxidant co-administration on oxidative stress markers, liver enzymes, and hepatotoxicity in albino Wistar rats. Coartem treatment significantly increased serum AST, ALT, and ALP activities and caused alterations in liver architecture, indicating oxidative stress and hepatotoxicity. Administration of antioxidants reduced these effects to varying degrees, with improvements observed in oxidative stress markers and liver enzyme activities across treatment groups. Antioxidants administered midway and at the end of Coartem therapy were more effective in reducing oxidative stress and liver toxicity than administration at the start of treatment, with the greatest protective effect observed when antioxidants were given at the end of therapy. Among the antioxidants studied, Vitamin E and Garlic showed stronger protective effects, while Garlic demonstrated the highest overall efficacy in ameliorating Coartem-induced oxidative stress and hepatotoxicity.

DATA AVAILABILITY

The dataset generated and analyzed in this study is available upon request.

AUTHORS CONTRIBUTION

Ugor, M. A: conceived the study, collected data, analyzed the data, and drafted the manuscript. **Eteng, M. U**: supervised the study, contributed to data analysis, and critically revised the manuscript. **Duke, D. N., Ongboche, S.E and Blessing O. Oko**: contributed to data interpretation, manuscript review, and editing. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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