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ASSESSING THE HEPATOTOXIC EFFECTS OF PROLONGED ARTEMETHER-LUMEFANTRINE USE: A HISTOLOGICAL AND BIOCHEMICAL STUDY ON ADULT WISTAR RATS

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ABSTRACT

Background: Artemisinin-based Combination Therapy (ACT) is the current standard treatment for uncomplicated malaria caused by Plasmodium falciparum.

Aim: This study aimed at assessing the histological and biochemical effects of atemether/lumefantrine tablet on the liver of adult Wistar rats.

Methods: This study was conducted on 24 adults male Wistar rats which were randomly assigned into a control group (group A), and three treatment groups (B, C and D) each containing six (6) rats. Group A, received normal rat feed and water. Group B, and C received 0.8 mg/kg and 1.6 mg/kg body weight of the drug respectively three days in a week while group D, received 5 mg of normal saline as a vehicle group. The experimental period was for 6 weeks and the body weight of animals were taken weekly. At the end of the experiment, the rats were sacrificed under chloroform anaesthesia. Blood samples and liver organs were collected from the left ventricle for Liver Function Test and histological processing respectively.

Results: The results of study recorded no significant change ($P>0.05$) in the body weight of experimental groups compared to control. There was also no significant difference ($P>0.05$) in AST and ALT levels in the treatment groups compared to control. Elevated ALP level was observed in both groups that were administered with Amatem Forte but none showed significant increase in ALP levels compared to control. Histological assessment on the Liver showed marked dilatation of portal vein, thinness and rupture of the vasculature, periportal hemorrhage, sinusoidal congestion and activation of Kupffer cells which were worse with the high dose treatment.

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Conclusion: The results showed that high dose use of Amatem Forte could be toxic to the Liver, hence its indiscriminate use should be discouraged, but with strict compliance to doctor's prescription.

Key words: Plasmodium falciparum, Antimalaria, Artemether-Lumenfantrine, Liver toxicity

INTRODUCTION

According to the (World Health Organization, WHO, 2015) there were 149-303 million new cases of malaria worldwide. The African region contributing 88% of total malaria cases, while 10% cases are coming from South-East Asia region and rest cases (2%) are coming from Eastern Mediterranean region. In addition, the 438,000 malaria deaths (range 236 000-635 000) were reported worldwide in 2015. About 90% of these deaths occurred in the African region, while the South-East Asia region contributes 7% and the rest 2% from Eastern Mediterranean region. Mostly the children below 5 years age are more vulnerable to malaria and its devastating consquences1. Malaria is caused by plasmodium parasites. The parasites are spread to people through the bites of infected female Anopheles mosquitoes, called "malaria vectors". There are four major species of plasmodium namely: *Plasmodium falciparum, P. malariae, P. vivax and P. ovale. Plasmodium falciparum* is the deadliest and is responsible for about 80% of all malarial case 2. The parasite spends most of its life cycle in the red blood cells of human. The female anopheles' mosquito transmits the parasite by first ingesting them when feeding on an infected person's blood and then injecting them when biting another person 3. Malaria is the second most common cause of infectious disease-related death in the world after tuberculosis 4. Each attack may last about 5 to 15 days often incapacitating the victim. In highly endemic areas, most cases of severe malaria occur among children aged between six months to five years with the highest mortality in those between one and three years of age. Another risk group in endemic areas is pregnant women who become susceptible to severe infection due to diminished cellular and humoral immunity during pregnancy 5-7. In particular, young children, pregnant women, and non-immune visitors to malarious areas are at greatest risk of severe or fatal illness. Many malaria control strategies exist, but none are appropriate and affordable in all contexts. Malaria control and prevention efforts need to be designed for the specific environment in which they will be used and need to take into account the local epidemiology of malaria and the level of available resources and political will. Antimalarial drug resistance has emerged as one of the greatest challenges facing malaria control today. Drug resistance has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated. Drug resistance has also played a significant role in the occurrence and severity of epidemics in some parts of the world. Population movement has introduced resistant parasites to areas previously free of

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drug resistance. The economics of developing new pharmaceuticals for tropical diseases, including malaria, are such that there is a great disparity between the public health importance of the disease and the amount of resources invested in developing new cures. Plasmodium falciparum malaria is a life-threatening infectious disease that remains a major global health problem. The severe manifestations often present clinically as cerebral malaria, pulmonary oedema, acute kidney injury, hypoglycaemia, lactic acidosis, anaemia and liver involvement. Plasmodium falciparum malaria causes clinical jaundice in 2.5-5.3% of cases in endemic areas. The liver is an important organ involved during the hepatic stage of the malaria parasite's life cycle where malaria sporozoites develop into merozoites. The merozoites are then released into the circulation and enter the erythrocytic stage. In the erythrocytic stage, parasitized red blood cells (PRBCs) become sequestered in small blood vessels. The degraded haemozoin pigment is then engulfed by local tissue macrophages, such as Kupffer cells and alveolar macrophages. Common histopathological findings of the liver in P. falciparum malaria include reactive Kupffer cells, retention of haemozoin pigment and minimal PRBC sequestrationmic areas. The development of drug resistance has caused the evolution of the use of different therapies for the treatment of the ailment. Available evidence show that traditional and herbal medicine have been used for the treatment of the ailment from time immemorial and have continued to play a significant role in the general provision of good health to people over the world 8. Amatem, which is one the several families of approved drugs used in treating and preventing malaria parasite consisting of Artemether-Lumefantrine was the first fixed-dose artemisinin-based combination therapy (ACT) recommended and prequalified by the World Health Organization (WHO) for the treatment of uncomplicated falciparum malaria [9].

MATERIALS AND METHOD

Twenty-four (24) adult Wistar rats with an average weight of 170g were used for this study. The animals were purchased and maintained at the Animal House of the Department of Anatomy, University of Benin. They were kept in cleaned cages, maintained at room temperature with 12hours light and dark cycle and also allowed free access to drinkable water and rat Grower's feed manufactured by Premier Feed Mills co Ltd (a subsidiary of flour mills of Nigeria Plc.) ad libitum. The animals were allowed to acclimatize for a period of two weeks to the laboratory conditions prior to the commencement of experiment at the Animal House of the Department of Anatomy.

Experimental Design

Twenty (24) Adult Wistar rats were randomly selected into a control group (group A) and three experimental groups (B, C and D) each containing six (6) animals (n= 6 per group). The animals in each cage were given Growers' mash, manufactured by

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Premier Feed Mills co Ltd (a subsidiary of flour mills of Nigeria Plc.) and water. The experimental design is shown as follows;

- Group A: Control group, received normal rat feed and water.
- Group B: Low dose group, treated with 0.8mg/kg body weight of Amatem (Artemisinin Based Combination Therapy).
- Group C: High dose group, treated with 1.6mg/kg body weight of Amatem (Artemisinin Based Combination Therapy).
- Group D: Positive control group, treated with 0.5mg/kg body weight of normal saline.

The experimental period was for 6weeks (42days) and the body weight of animals were taken weekly and recorded.

Administration of the Drug

Low and high dose the drug, Amatem containing Artemether/ lumefantrine combination was administered to the animals in Group B and C respectively for three (3) days in a week regularly over a period of 6weeks (42days). Similarly, and the animals in Group D were given normal saline for 6weeks (42days). The route of the administration of both the drug and normal saline was oral, using gavage, also known as orogastric tube. The drug doses were based on therapeutic indices.

Procedure for Estimation of Liver Function

The blood samples collected were centrifuged at 3000 rev/min using a centrifuge for 10 min. Serum alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), Total bilirubin (TB), and conjugated bilirubin (CB), were assayed for spectrometrical analysis using Randox diagnostic kits 10 by calorimetric method and Alkaline phosphatase (ALP) by method of Belfield and Goldberg (year)11, Total protein (TP), Albumin (ALB) and Serum globulin (GLO) were assayed for by Biuret method (year).

Assay for Aspartate Aminotransaminase (AST) – colorimetric method

In the estimation of AST, serum was treated with aspartate and α-leptoglutarate. The new amino acid formed in the reaction (i.e oxaloacetate) is treated with 2,4 dinitrophenylhydrazine. The absorbance of the resulting brown colour due to the dinitrophenylhydrazine is measured under alkaline condition at 546nm. AST is measured by monitoring the concentration of oxaloacetate hydrazine formed with 2,4 dinitrophenylhydrazine.

Assay for Alanine Aminotransaminase (ALT) – colorimetric method

The estimation of ALT, serum is treated with alanine and α-leptoglutarate. The new keto formed in the reaction (i.e pyruvate) is treated

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with 2,4 dinitrophenylhydrazine. The absorbance of the initial brown color due to the dinitrophenylhydrazine is measured using alkaline condition at 546nm. ALT is measured by monitoring the concentration of pyruvate hydrazone formed with 2,4 dinitrophenylhydrazine.

Assay for Alkaline Phosphatase (**ALP**)

ALP activity was determined by measuring the rate of absorbance change at 40nm due to enzymes hydrolysis of p-nitrophenylphosphate in the presence of the enzyme.

Assay Procedure

One hundred (100µL) of each sample was mixed with 1000µL of the reconstituted reagent in a 2ml cuvette at room temperature. The initial absorbance of the mixture was read on the spectrophotometer at 405nm and the timer was started simultaneously. Absorbance was read again after 1, 2, 3 minutes.

Assay for Total Protein (TP)

The total protein concentration in serum was determined using the Biuret (year) method based on interaction of cupric ions with protein in an alkaline medium resulting in the formation of a coloured complex.

Assay for Total Bilirubin (TB)

Principle: Direct (conjugated) bilirubin reacts with the diazotized sulphanilic acid medium to form a blue colored complex. Total bilirubin is determined in the presence of caffeine which releases albumin bound to bilirubin.

Assay for Direct (Conjugated) Bilirubin (CB)

Procedure:

Pipette into tube	Sample blank	Sample
Reagent 1	100µl	100µl
Reagent 2	-	1 drop (0. 05ml)
Normal saline	1ml	1ml
Sample	100µl	100µl

Mix and allow to stand exactly 5min at RT, read at 546 (530 - 560)

Assay for Albumin (**ALB**)

Biuret Method: The globulin in serum is precipitated by the addition of 23% sodium sulfate (salting out). Ethyl-ether is added to help separate the precipitated globulin by centrifugation. The chemical determination of albumin is based on the formation of

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purple colored complex (biuret) between alkaline copper sulfate and the albumin.

Albumin (gm/dl) = A test /A standard x concentration of standard

Assay for Serum Globulin (GLO)

Globulin was calculated by subtracting the measured albumin from the measured total protein.

Globulin = Total Protein - Albumin

Histological Procedures

The tissues were dehydrated in ascending grades of alcohol (ethanol), cleared in xylene and embedded in paraffin wax. The deparaffinised sections were stained routinely with Hematoxylin and Eosin 12.

Photomicrography

The histological sections of the liver tissues were examined under Leica DM750 research microscope with a digital camera Leica ICC50) attached. Digital photomicrographs of the tissue sections were taken at x40 and x100 magnifications.

Statistical Analysis

The data was analyzed using descriptive and inferential statistics. All values were presented as mean ± standard error of mean (SEM) for six rats in each of the four groups. The significant difference in the means of all parameters was determined using one-way analysis of variance (ANOVA; 95% confidence interval). Least square difference, post hoc tests were carried out for all groups with control and comparison of all pairs of groups respectively using Bonferoni multiple comparison. All statistical analysis was carried out using Statistical package for Social Sciences (SPSS).

RESULTS

Table 1: The body weight of the animals in the experimental groups during pre- and post-administration of drug

Group	INITIAL BODY WEIGHT Initial weight of rats (mean ± SEM)	FINAL BODY WEIGHT Weight of rats at 42 days (mean ± SEM)	WEIGHT CHANGE Change in mean weight ± SEM	*P*-value
Control	169.00 ± 3.35	176.17 ± 5.64	7.17 ± 2.80	
Low Dose Amatem	186.00 ± 11.01	181.50 ± 15.66	-4.50 ± 6.44	

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High dose Amatem	162.50 ± 6.10	155.00 ± 4.43	-7.50 ± 5.30
Normal saline	188.00 ± 5.97	183.20 ± 5.39	-4.80 ± 1.85

p>0.05, SEM = standard error of mean, n = 2 There were no statistical significance differences (*P*>0.05) in weights when compared with the control. Values are expressed as mean ± Standard Error of Mean (n=2).

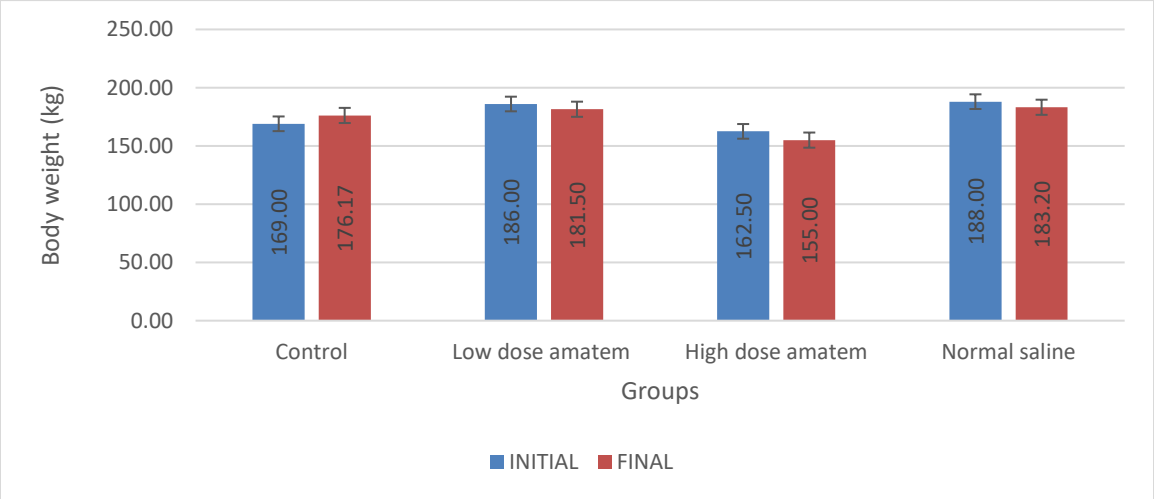

Fig. 1: The body weight of the animals in the experimental groups during pre- and post-administration of drug (*P*>0.05)

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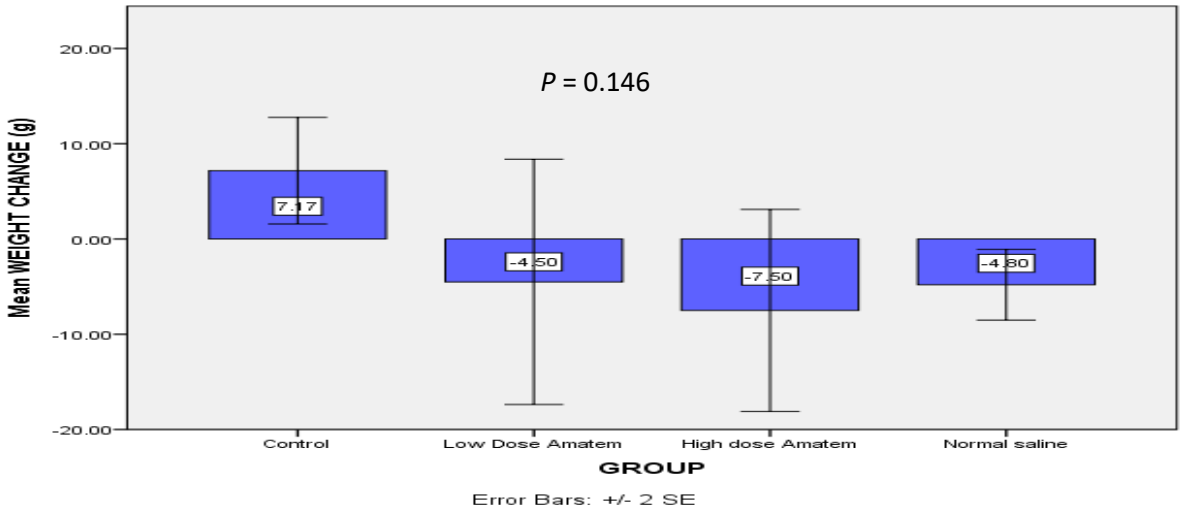

Fig. 2: Graph showing the mean weight change across all groups. There was no significant difference between the groups and control (P≥0.05)

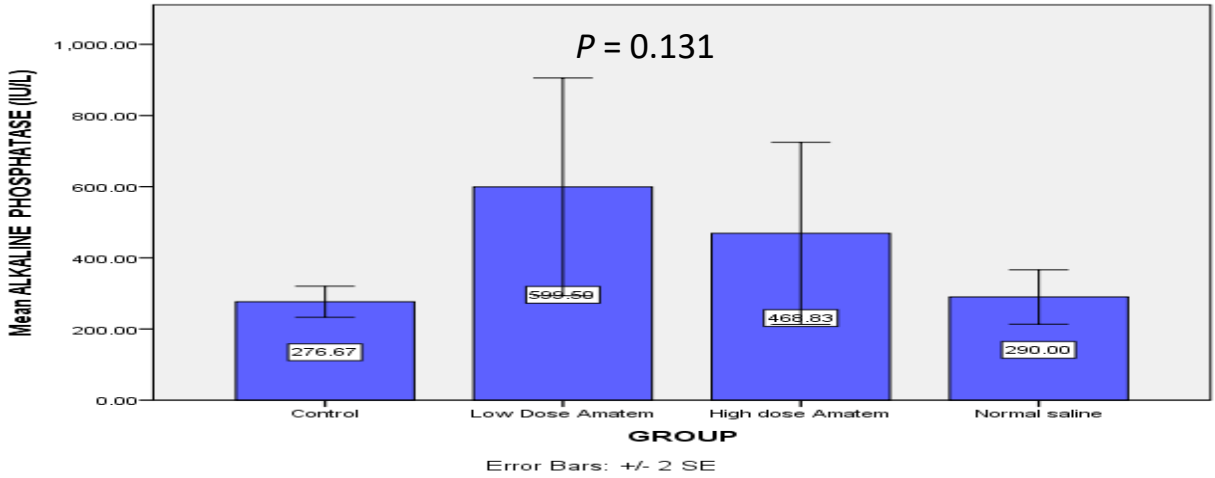

Fig 3: Graph showing the total Alkaline phosphatase level across all groups. There was no significant difference in the Alkaline phosphatase level in the experimental groups when compared to the control group (P≥0.05)

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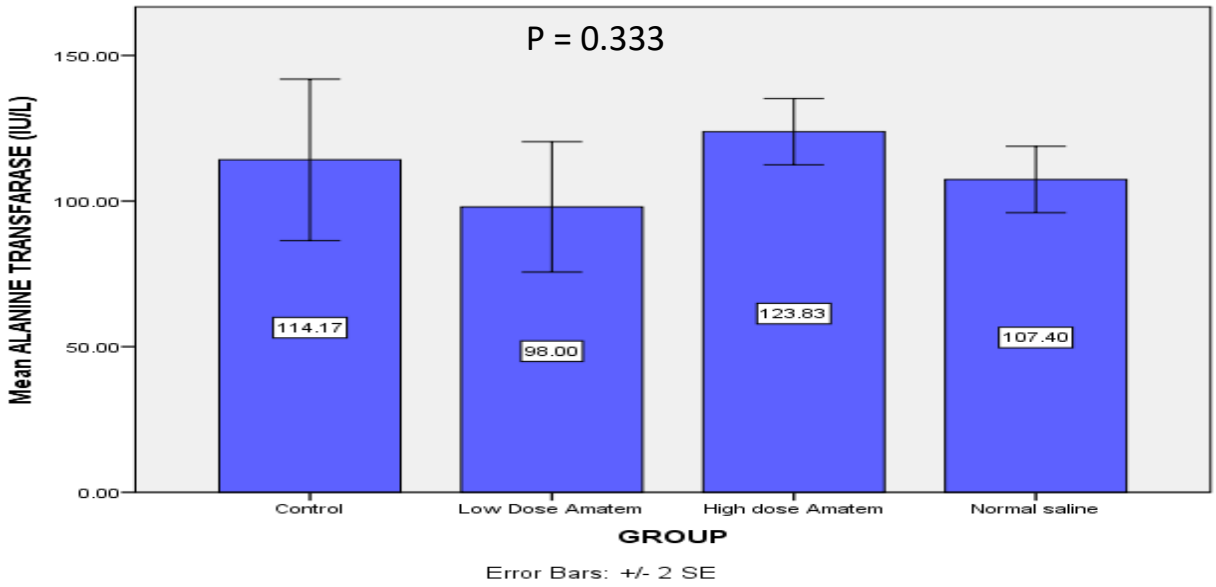

Fig 4: Graph showing the total Alanine transferase level across all groups. There was no significant change in the Alanine transferase level in any of the experimental groups when compared to the control group (P≥0.05)

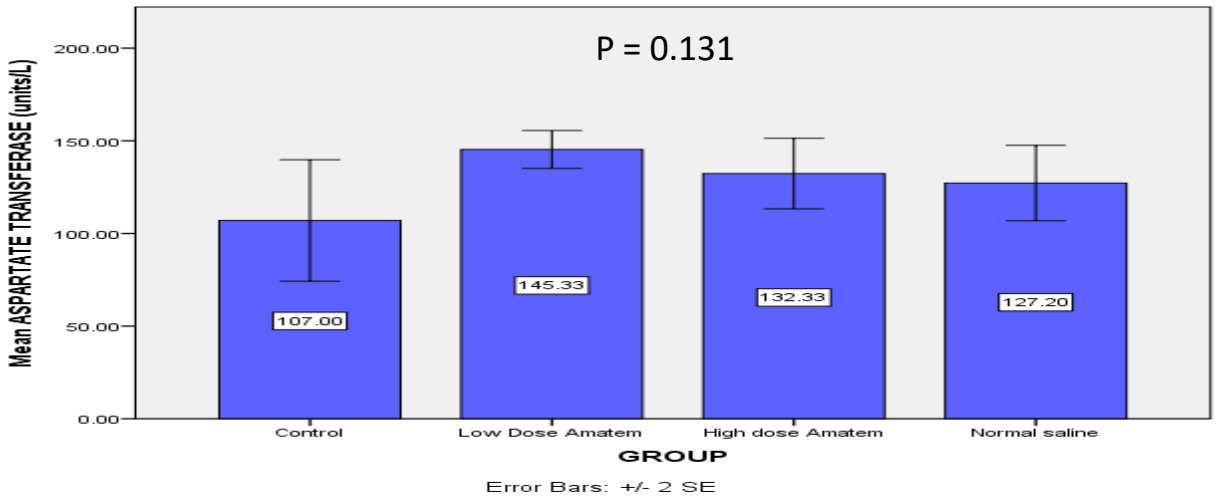

Fig 5: Graph showing the mean Aspartate Transferase level across all groups. There was no significant difference in the Aspartate Transferase level in any of the experimental groups when compared to the control group (P≥0.05)

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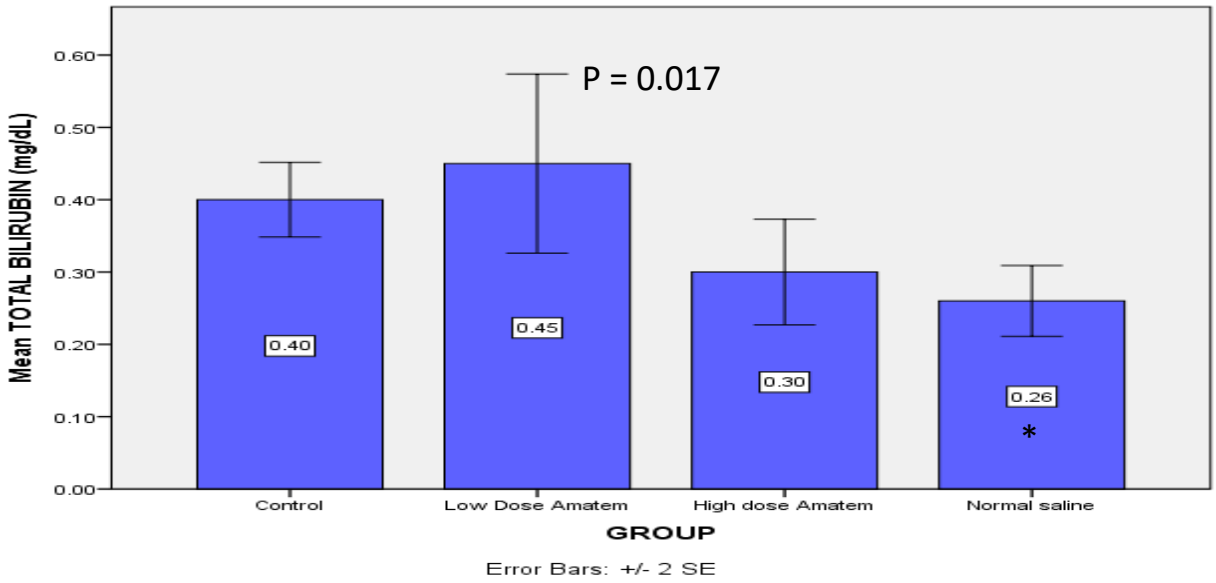

Fig 6: Graph showing the total Bilirubin level across all groups. (*) indicates significant difference. There was significant decrease in the total bilirubin level in the groups given normal saline when compared to the control group (P≤0.05) but insignificant between other groups and the control (P≥0.05)

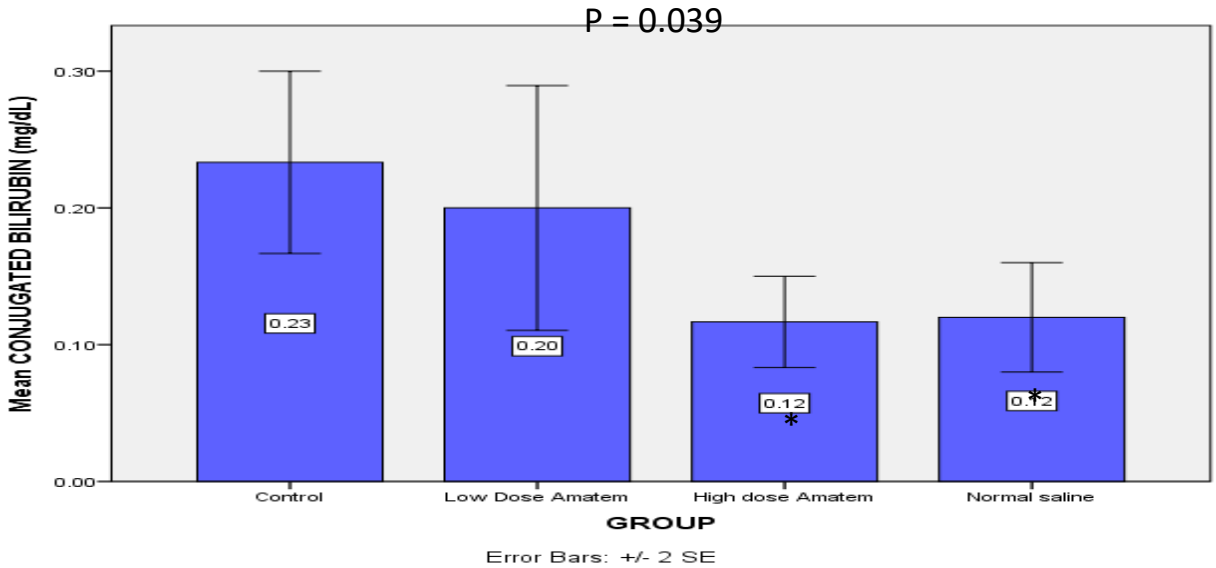

Fig 7: Graph showing the Conjugated Bilirubin level across all groups. (*) indicates significant difference. There was significant decrease in the conjugated bilirubin level in the

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High dose Amatem group and in the Normal saline group when compared to the control group (P≤0.05), but insignificant between the other groups and the control (P≥0.05)

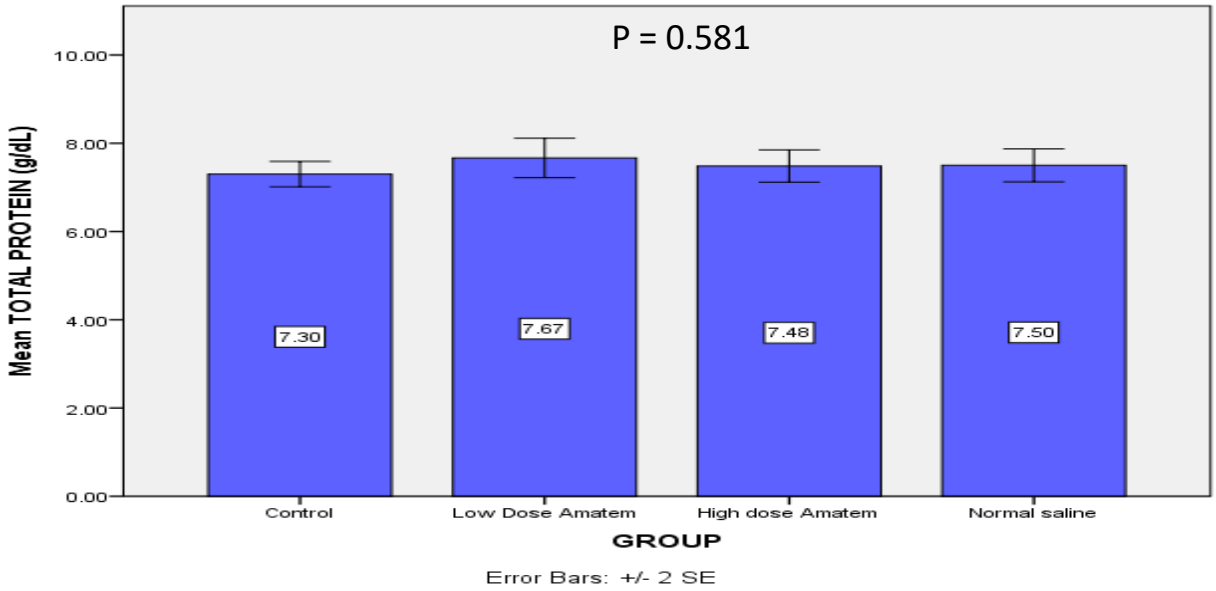

Fig 8: Graph showing the Total Protein level across all groups. There was no significant difference in the Total protein levels in the experimental groups when compared to the control group (P≥0.05)

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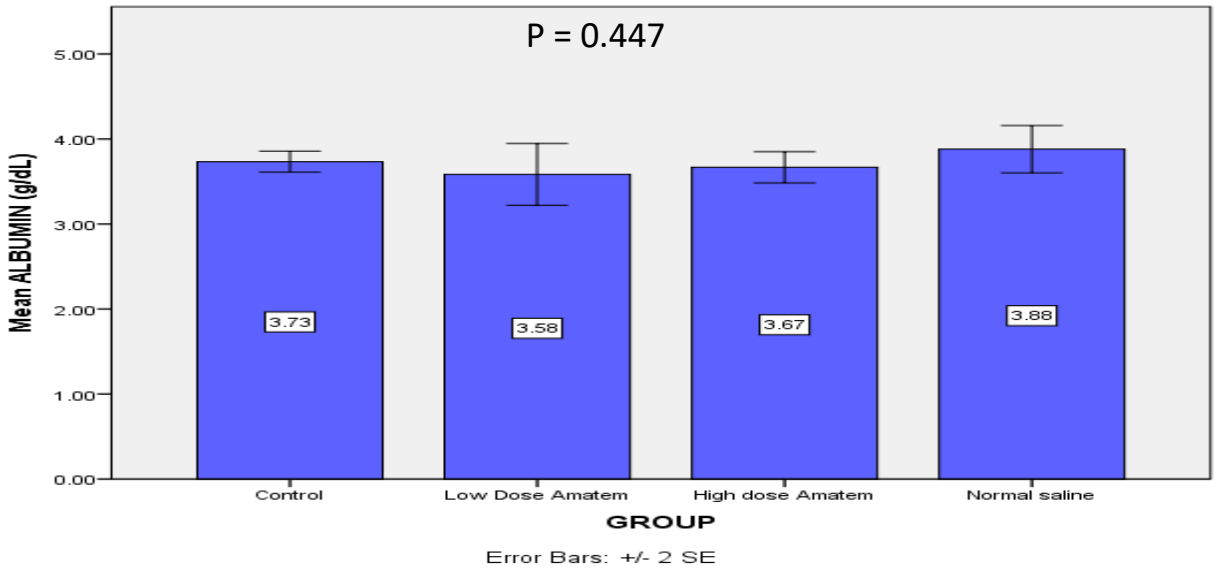

Fig 9: Graph showing the Mean Albumin level across all groups. There was no significant difference in the Albumin level in the experimental groups when compared to the control group (P≥0.05)

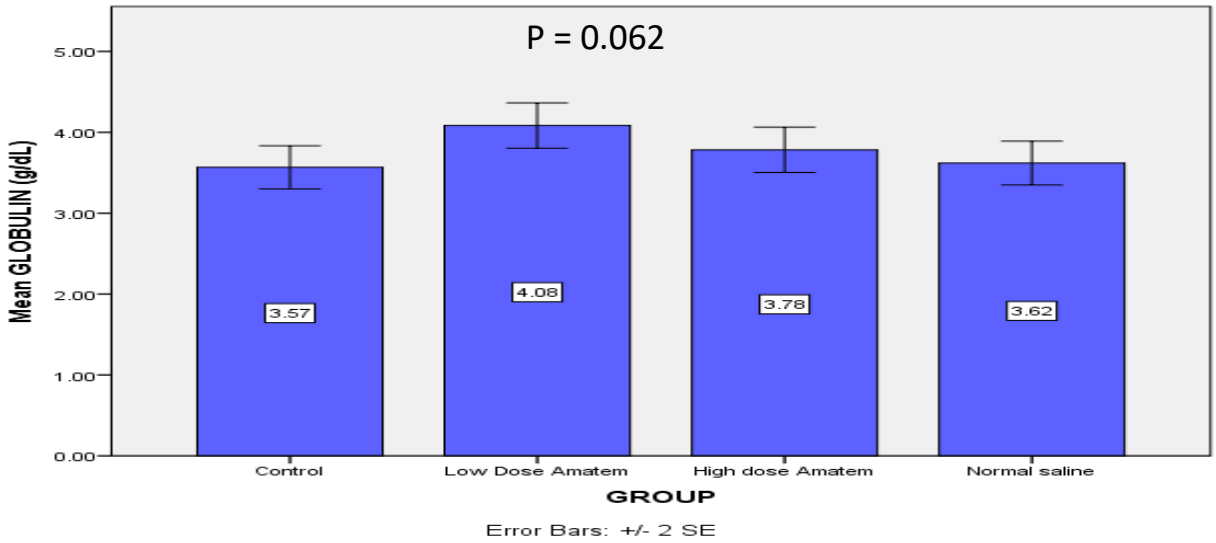

Fig 10: Graph showing the Mean Globulin level across all groups. There was no significant difference in the mean globulin level in the experimental group when compared to the control group (P≥0.05).

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Histological Analysis

Histological analysis done on control group (plate 1 - plate 2) showed liver tissue characterized by normal hepatocytes, sinusoids, central vein and portal triad. Group given Low Dose of Amatem (plate 3 - plate 5) showed liver tissue characterized by marked dilatation of the portal vein, thinness of the wall of the vessel. Group given High Dose of Amatem (plate 6 - plate 7) showed liver tissue characterized by rupture of the blood vessel, congestion of the sinusoids. Group given Normal Saline (plate 8 - plate 9) showed compact hepatocytes, normal portal triad architecture.

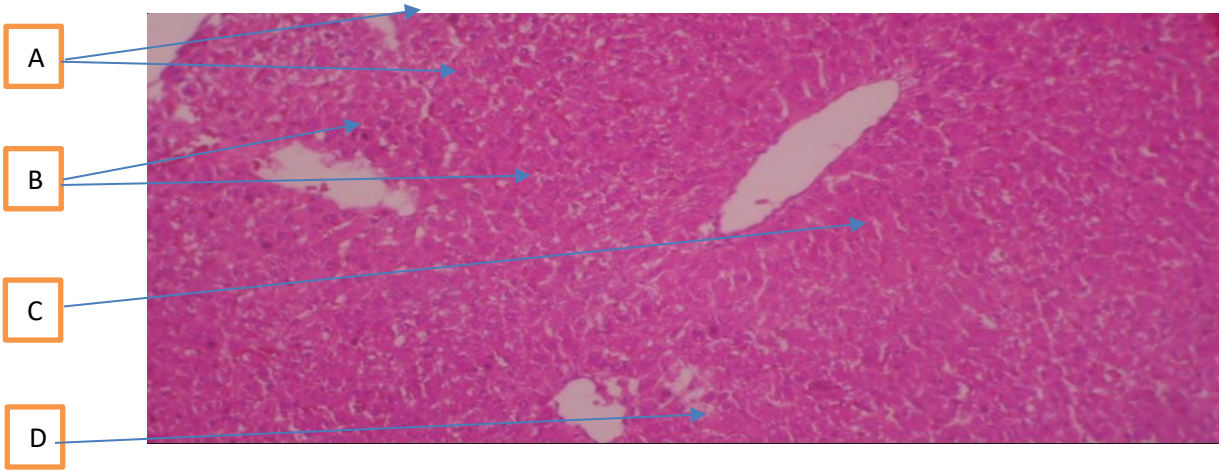

Plate 1. Liver. Control: Composed of A, hepatocytes, B, sinusoids, C, central vein and D, portal vein (H&E x 100).

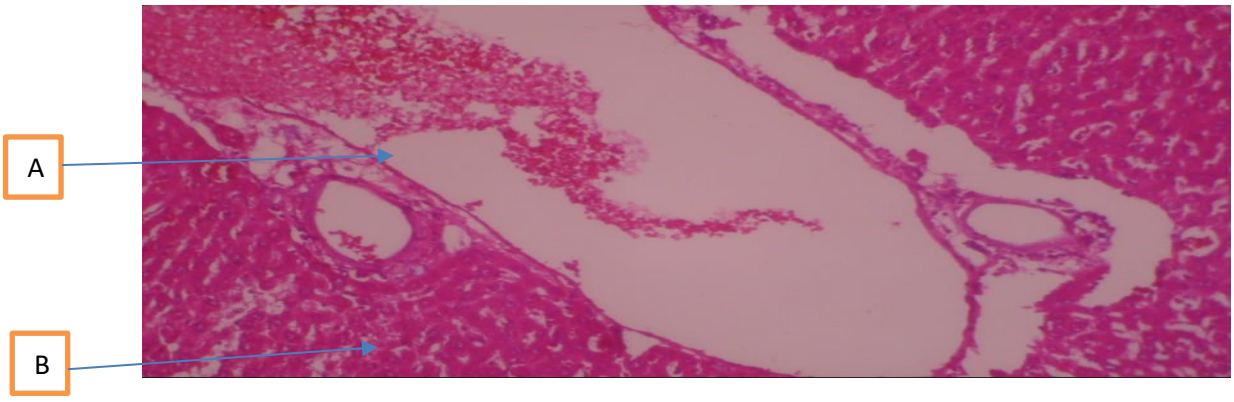

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Plate 2. Rat given low dose Amartem: A, A, marked portal vasodilatation of the central vein and B, kupffer cell activation (H&E x100)

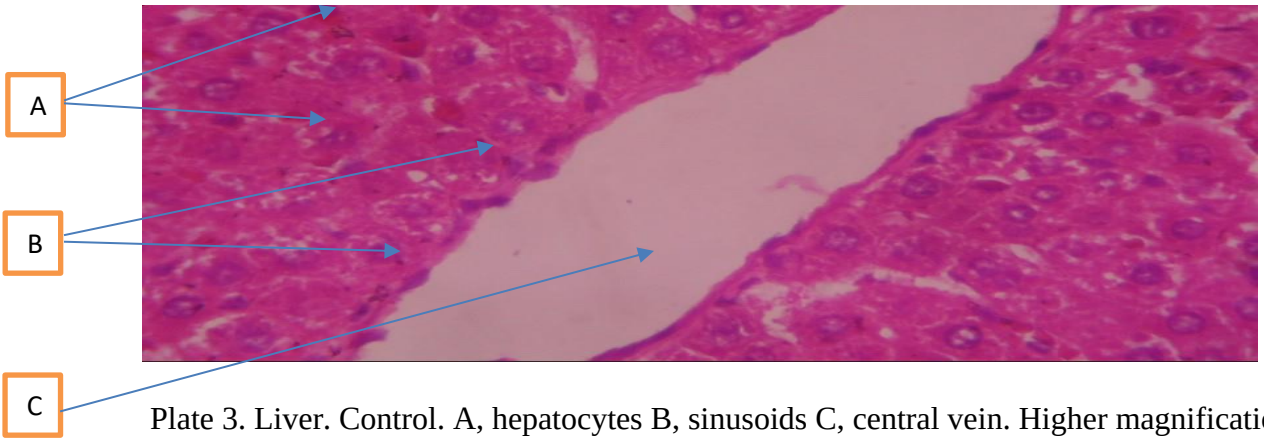

Plate 3. Liver. Control. A, hepatocytes B, sinusoids C, central vein. Higher magnification (H&E x 400)

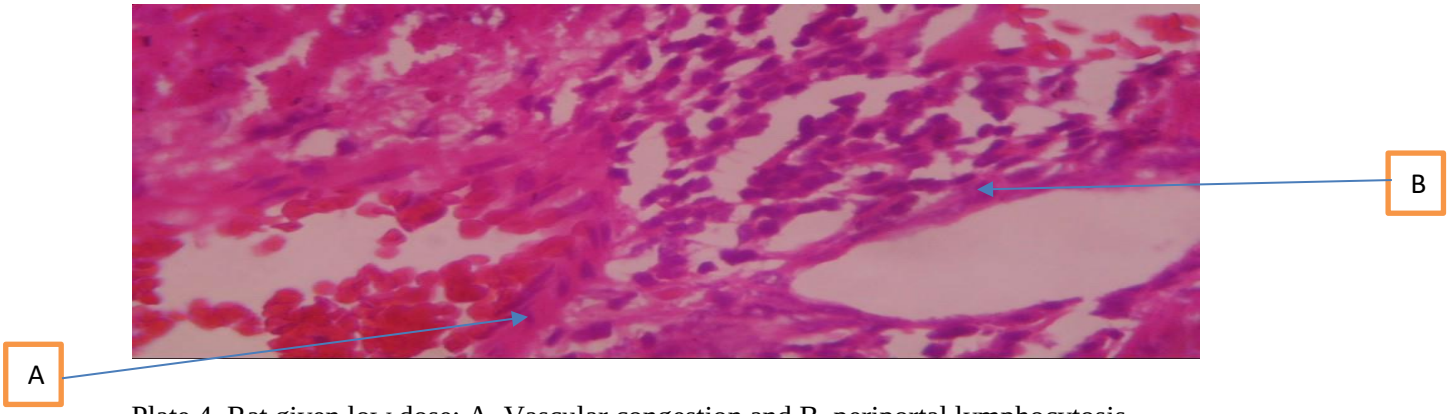

Plate 4. Rat given low dose: A, Vascular congestion and B, periportal lymphocytosis

(H&E x 400)

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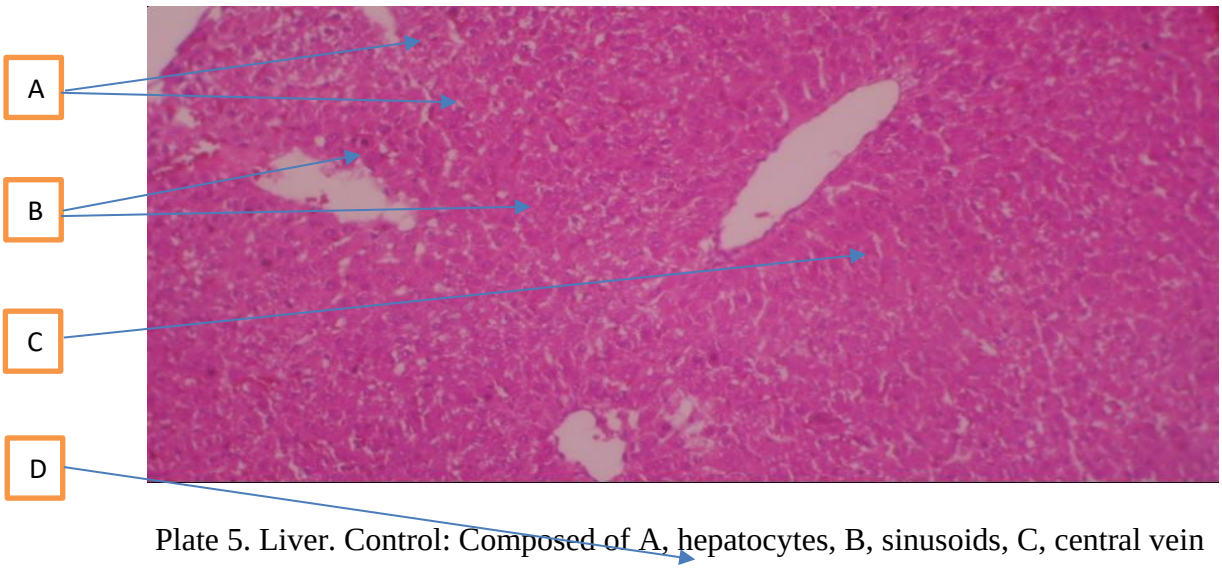

Plate 5. Liver. Control: Composed of A, hepatocytes, B, sinusoids, C, central vein and D, portal vein (H&E x 100)

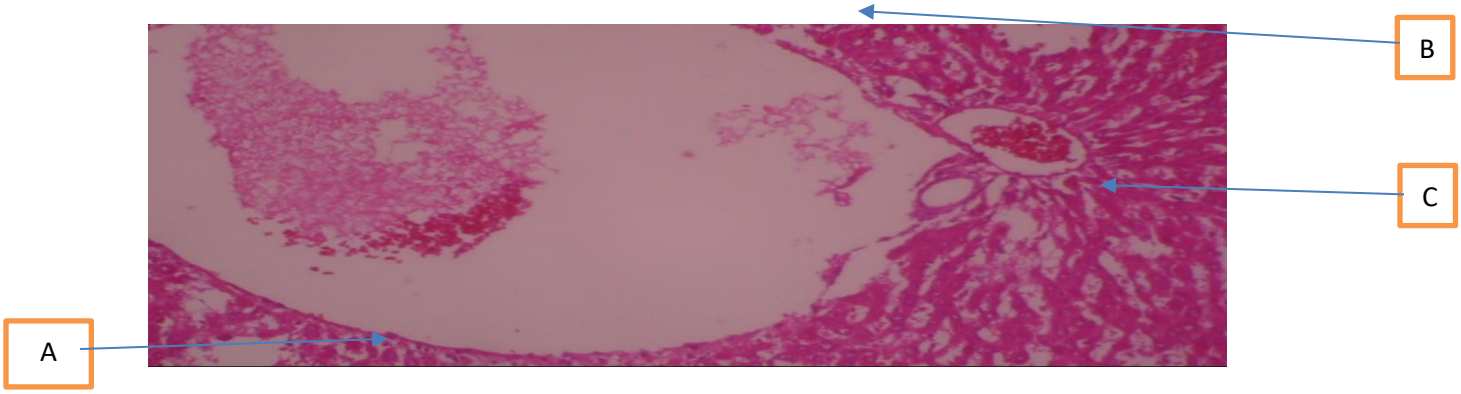

Plate 6. Rat given high dose Amartem: A, marked portal vascular dilatation,

B, Vascular ulceration of the wall of the portal vessl and C, vascular congestion. Thinness ulceration of the portal vessels most notably in the hepatic vein is seen. (H&E x 100)

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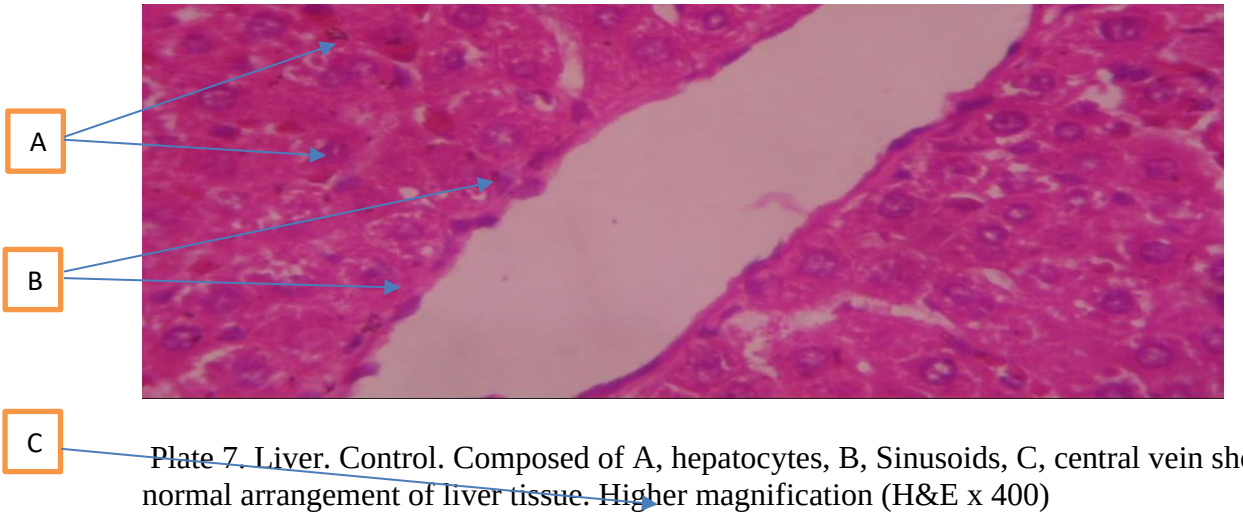

Plate 7. Liver. Control. Composed of A, hepatocytes, B, Sinusoids, C, central vein shows normal arrangement of liver tissue. Higher magnification (H&E x 400)

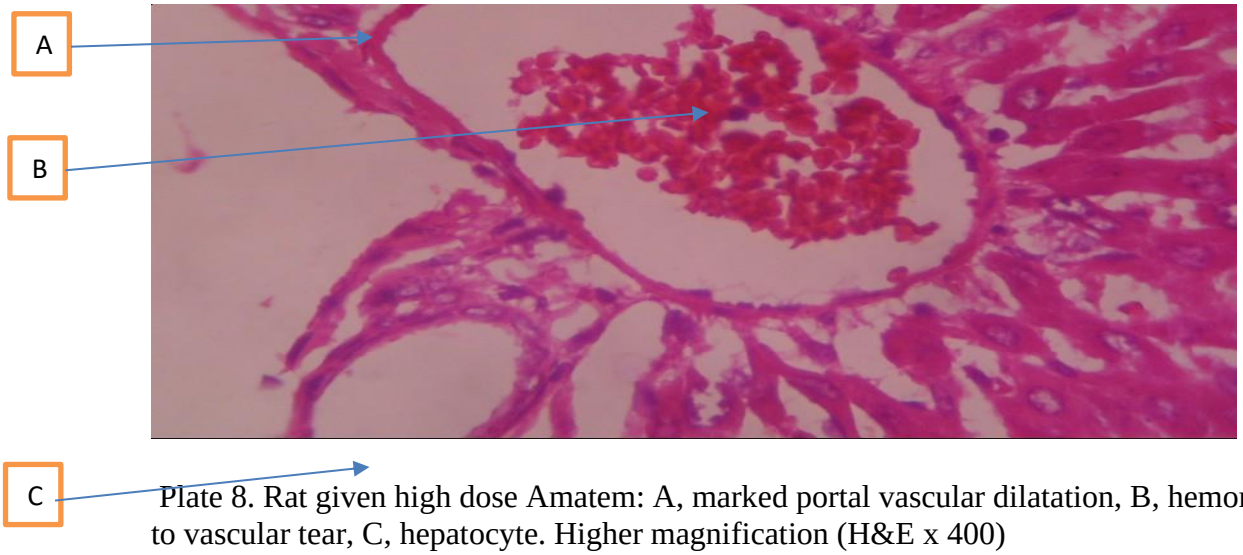

Plate 8. Rat given high dose Amatem: A, marked portal vascular dilatation, B, hemorrhage due to vascular tear, C, hepatocyte. Higher magnification (H&E x 400)

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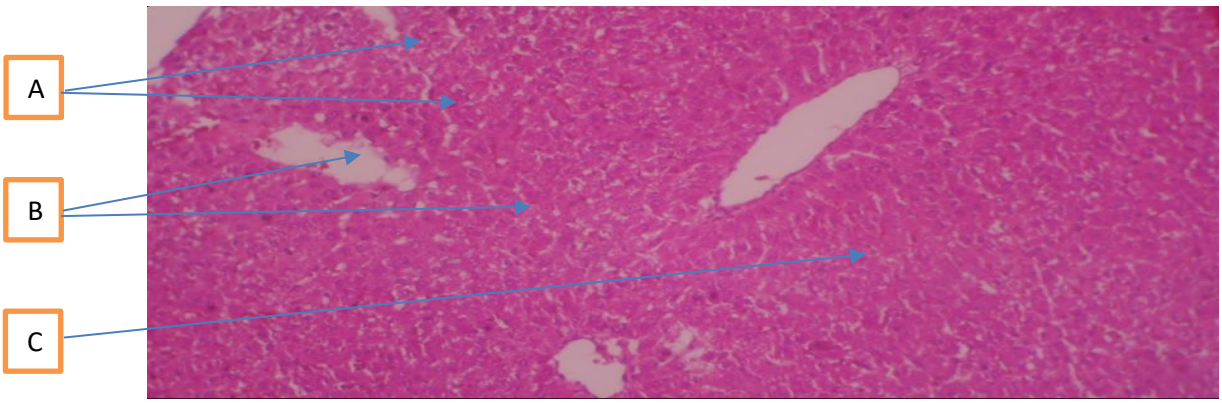

Plate 9. Liver. Control: Composed of A, hepatocytes, B, sinusoids, C, central vein and D, portal vein (H&E x 100)

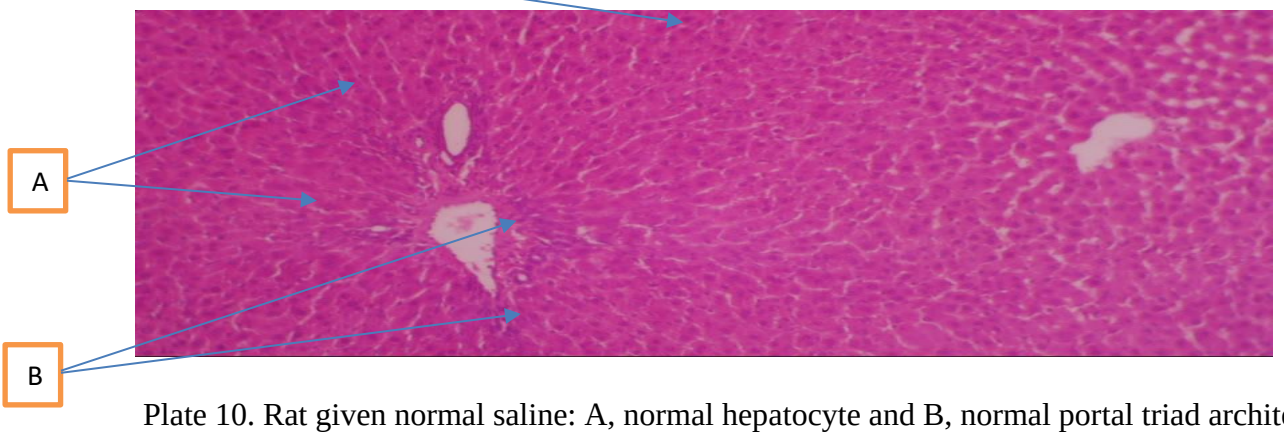

Plate 10. Rat given normal saline: A, normal hepatocyte and B, normal portal triad architecture (H&E x 100)

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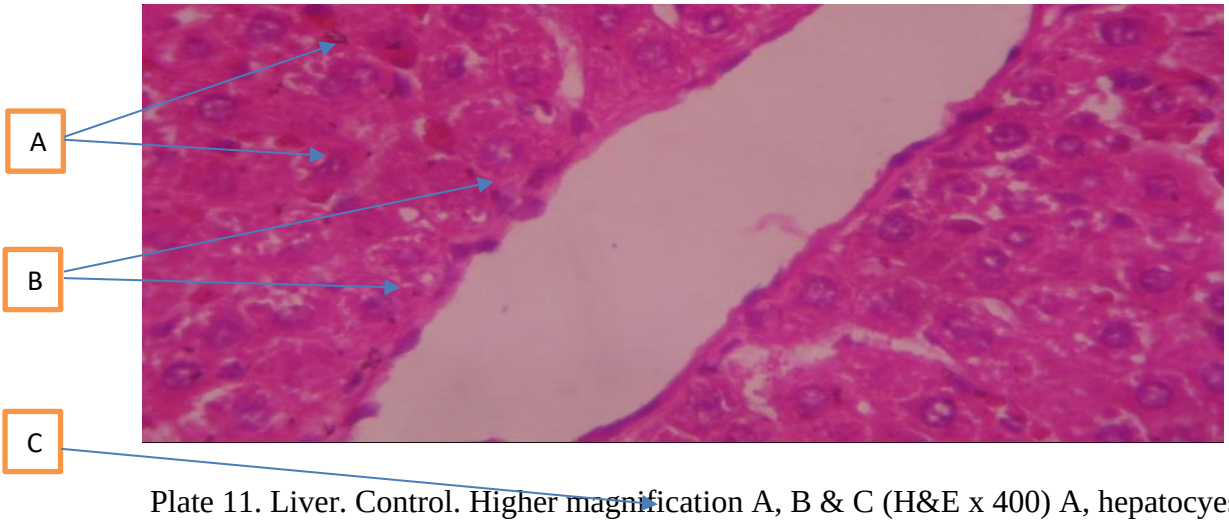

Plate 11. Liver. Control. Higher magnification A, B & C (H&E x 400) A, hepatocyes, B, sinusoids, C, central vein.

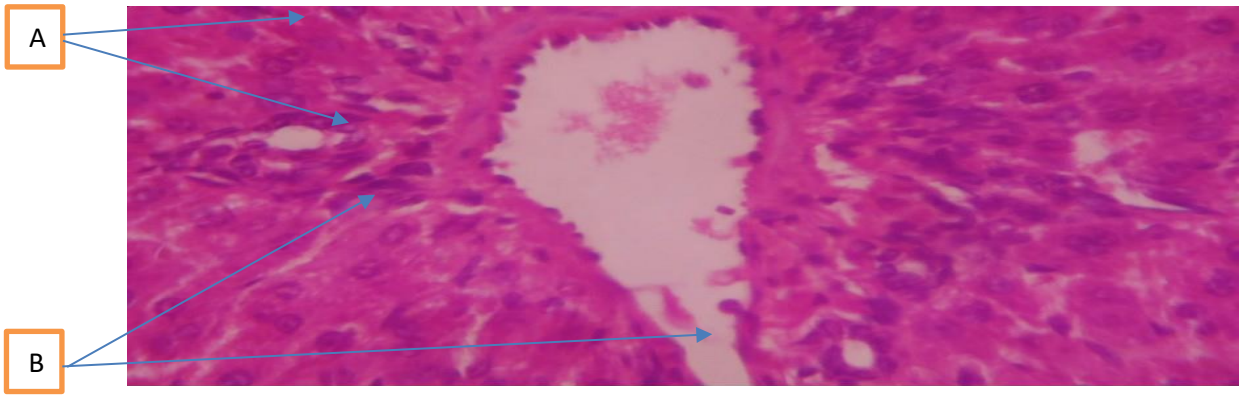

Plate 12. Rat given normal saline: A, normal hepatocytes, B, normal portal triad architecture Higher magnification (H&E x 400).

DISCUSSION

Artemisinin based combination therapy (ACT) is the current standard treatment for uncomplicated malaria caused by Plasmodium falciparum 9. This study reports the histological and biochemical effect of Amatem Forte tablet (an ACT) on the liver. Liver enzymes are well known biomarkers for the prediction of liver toxicity 13. When the liver is injured or inflamed due to exposure to various toxic substances, the level of ALT and AST in the blood are usually elevated. The level of these enzymes in the blood is directly related to the liver damage 14. In the present study, there was no significant difference in AST and ALT

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activities. Elevated ALP activity was observed in both groups that were administered with Amatem but none showed significant increase in ALP activities. Majority of sustained elevated ALP levels are associated with disorders of the liver or bone, or both 15. The present study showed that with increase dosage of Amatem tablets, conjugated bilirubin levels reduce significantly with the high dose compared to control while low dose Amatem resulted in significant increase in serum bilirubin level compared to control. In healthy people, conjugated bilirubin is virtually absent from serum mainly because of the rapid process of bile secretion 16.

Histological analysis done on control group showed liver tissue characterized by normal hepatocytes, sinusoids, central vein and portal triad. Group given low dose of Amatem showed liver tissue characterized by mark dilatation of the portal vein, thinness of the wall of the vessel in which with time it will lead to tearing or rupturing which can then cause hemorrhage and anemia, mobilization and activation of kupffer cells, congestion of Red Blood Cells, lymphocytes were also mobilized in which if they are not physiologically regulated will start attacking the liver cells 17. Group given high dose of Amatem showed liver tissue characterized by rupture of the blood vessel, congestion of the sinusoids. Group given Normal Saline showed compact hepatocytes, normal portal triad architecture.

Limitations of the Study

The imitation of this study is chiefly inadequate research funding and insufficient research team or collaborators. The affect of prolonged use of ACT drugs such as Amatem forte has been discovered to be dangerous and unpalatable with human health in the quest of combating malaria, hence more future research should be done with collaborations of different experts in this field.

CONCLUSION

The study showed that, Amatem Forte Tablets, though an effective drug in combating malaria has tendency to cause damage on the liver. As such, usage of the drug should be based strictly on doctor's prescription so as to minimize this risk.

RECOMMENDATION

The potentiality of the Liver being one of such casualties as revealed from this study worth considering and avoiding as much as possible. Dosage appropriation and proper monitoring may be a key to this. However, like most diseases of the underdeveloped world, post-marketing surveillance is scarce, especially for non-fatal complications. More considerations should be given to post marketing surveillance and observations.

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