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Hepatotoxic effect of *Xylopia aethiopica* Fruit in Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author EOO conceptualized the study, Author PCU designed the study. Author INN managed the literature searches and managed the analyses of the study. Author UO wrote the protocol while author AIA performed the statistical analysis and wrote the manuscript. All authors read and approved the final manuscript

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ABSTRACT

Background: *Xylopia aethiopica* fruit has been reported to possess high medicinal value. Thus, people use it without any regard for its toxicity.
Aim: This study is therefore aimed at investigating its toxicity on the liver of Wistar rats.
Methodology: The fruits of *Xylopia aethiopica* were obtained from new market in Aba, Abia State, Nigeria and were authenticated. They were air-dried and extracted using Soxhlet apparatus and ethanol as solvent. The median lethal dose (LD50) of the extract was determined using standard method. Thirty Wistar rats were divided into five groups of six rats each. Animals in groups A, B, C, and D were administered 129.62, 259.23, 388.85 and 518.46 mg/kg body weight of *X. aethiopica* fruit extract respectively, while those in group E received normal feeds and water only. The administration was done once daily for 28 days via oral route. Hepatic indices were determined using standard methods.
Results: No significant difference was observed when the activities of ALT and AST in animals treated with lower doses of the extract were compared with those in the control group. A significant

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increase was however observed in the activities of ALT and AST in animals treated with higher doses of the extract when compared with those in the control group. ALP activity was observed to increase in experimental animals when compared with those of the control animals. This elevation was however not significant when animals treated with 129.62 mg/kg body weight of extract were compared with the control group. No significant difference was observed in the concentrations of total protein and albumin in animals treated with lower doses of the extract when compared with that of the control group at $P<0.05$. A significant increase was however observed in the concentrations of total protein and albumin in animals treated with higher doses of the extract when compared with those in the control group. The concentration of globulin was only significant when animals treated with259.23 and 518.46 mg/kg body weight of extract were compared with those of the control animals. The extract was observed to inhibit the activities of amylase and lipase respectively in a dose-dependent manner.

Conclusion: This present study showed that extract of *Xylopia aethiopica* fruit is hepatotoxic especially at high dosage. Therefore, its use in folklore medicine should be discouraged.

Keywords: Hepatotoxic; high dosage; liver enzymes; Xylopia aethiopica fruit.

1. INTRODUCTION

Liver is the major organ which plays key roles in processing critical biochemical and physiological phenomena including metabolism and detoxification of endogenous and exogenous compounds, such as drugs and xenobiotics, homeostasis, growth, energy and nutrient supply [1]. Hepatic injury could occur by hepatotoxic agents such as drugs, alcohol, hydrocarbon and viral infections [2]. Liver diseases like jaundice, cirrhosis and fatty liver have been public health concern across the world [3]. Prevalence of chronic liver disease worldwide is 18.5% and cirrhosis is 4.5 to 9.5% while 2 million people die each year. In terms of medication, conventional or synthetic drugs are limited. Moreover they can have serious side effects [4,5]. Due to this fact, a huge number of medicinal plants have been used to figure outhepato-protective activities [6]. Approximately 160 phytochemical constituents originated from 101 plants have been reported to be potentially hepato-protective [7]. At present, medicinal plants have been a vital source of treatment of liver and renal diseases [8].

Xylopia aethiopica Dunal (Annonaceae) is an aromatic plant commonly known as “African pepper”, “Ethiopia or Negro pepper”. It has been used in Europe, Asia and Africa as pepper substitute and spice in local cooking. In Nigeria, the common local names used in different languages to refer to this plant are: “Kimba” in Hausa, “Eeru” in Yoruba and “Uda” in Igbo [8]. Various parts of the plant have been traditionally employed in different therapeutic preparations. The mature fruits of green colour take a brown-black colouration after drying and are used as spices [9].

Chemical components of *Xylopia aethiopica* have been helpful in the prevention and treatment of cancerous tumors. *Xylopia aethiopica* fruits contain alkaloids, flavonoids, terpenoids, fixed oil and volatile aromatic oil [10]. Key constituents are diterpenic and xylopic acids. *Xylopia aethiopica* oil contains carbohydrates and glycosides.

Xylopia aethiopica is known to have myriad chemical constituents with diverse therapeutic and pharmacological properties. These compounds, most of which have been isolated and characterized, include saponins, sterols, carbohydrates, glycosides, mucilage, acidic compounds, tannins, balsams, cardiac glycosides, volatile aromatic oils, phenols [11], alkaloids, rutin and fixed oils. The plant also contains vitamins A, B, C, D, and E, and proteins together with high amounts of minerals like copper, manganese and zinc [11]. *X. aethiopica* fruit has been reported to contain hypoglycemic agents [12]. Furthermore, Ogbuagu et al. [13] reported that the fruit can be used to manage obesity and cardiovascular diseases due to its hypolipidemic potential.Therefore, this study is aimed at investigating its effect on hepatic indices of Wistar rats.

2. MATERIALS AND METHODS

2.1 Collection and Authentication of Plant Materials

The fruits of *Xylopia aethiopica* were obtained from new market in Aba, Abia State and were identified and authenticated by Prof. (Mrs) Margaret Bassey of the Department of Botany and Ecological Studies, University of Uyo with

the voucher number UU/PH/4e. The plant was deposited in the Herbarium of the Department of Pharmacognosy and Natural Medicine, University of Uyo, Akwa-Ibom State, Nigeria.

2.2 Extraction of Plant Materials

The extraction was carried out in the Post-graduate Laboratory of Department of Pharmacognosy and Natural Medicine, Faculty of Pharmacy, University of Uyo, Akwa-Ibom State. It was carried out according to the method described by Ogbuagu et al. [10]. The fruits were washed under running tap water to remove contaminant and air-dried. This plant material was then pulverized using laboratory blender to provide a greater surface area. The pulverized plant material was macerated in 250 mL of 99.8% ethanol (Sigma Aldrich) contained in round bottom flask, which was then attached to a Soxhlet extractor coupled with condenser and heating mantle (Isomantle). It was then loaded into the thimble, which is placed inside the Soxhlet extractor. The side arm is lagged with glass wool. The mixture was heated using the heating mantle (Isomantle) at 60 °C and as the temperature increases it begins to evaporate, moving through the apparatus to the condenser. The condensate then drips into the reservoir containing the thimble. Once the level of solvent reaches the siphon it pours back into the flask and the cycle begins again. This continues until it is exhaustively extracted. The process runs for a total of 13 hours. Once it was set up, it was left to run without interruption as long as water and power supply were not interrupted. The equipment was turned on and off and overnight running was not permitted, and the time split over a number of days. The extract was poured into 1000 mL beaker and concentrated to dryness in water bath (A3672- Graffin Student Water Bath) at 35 °C. The total weight of the marc (residue) and the concentrated extract were recorded, these processes took several days. The dried extract was preserved in the refrigerator at 4°C for further analysis.

2.3 Determination of Median Lethal Dose (LD_{50})

The median lethal dose (LD_{50}) of the extract was estimated using albino mice according to the method described by Airaodion et al. [14]. This method involves two phases:

In Phase one, five groups containing five mice each weighing between 20 g and 27g were fasted for 18 hours. They were respectively administered 1000 mg/kg, 2000 mg/kg, 3000 mg/kg, 4000 mg/kg and 5000 mg/kg body weight intraperitoneally (i.p) and were observed for physical signs of toxicity and mortality for 24 hours. 1000 mg/kg recorded 0% mortality while 2000 mg/kg, 3000 mg/kg 4000 mg/kg and 5000 mg/kg recorded 100% mortality within 24 hours. Based on the value of phase one, phase two was conducted.

In Phase two, twenty albino mice weighing between 20 - 27g were grouped into four of five mice per group and were fasted for 18 hours. Each group was administered 1200 mg/kg, 1400 mg/kg 1600 mg/kg and 1800 mg/kg body weight intraperitoneally (i.p) and was observed for physical signs of toxicity and mortality within 24 hours. 1200 mg/kg recorded 0% mortality while 1400 mg/kg, 1600 mg/kg and 1800 mg/kg recorded 100% mortality within 24 hours. The LD_{50} was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b).

$$LD_{50} = \sqrt{ab}$$

2.4 Experimental Design

Thirty Wistar rats obtained from the University of Uyo, Nigeria were used for this study. They were acclimatized for seven days before the commencement of the experiment. They were weighed and divided into five groups of six rats each. Groups A, B, C, D served as the experimental groups, while group E served as the control. Animals in group A were administered 129.62 mg/kg body weight (10% of LD_{50}) of *X. aethiopica* fruit extract, those in group B were administered 259.23 mg/kg body weight (20% of LD_{50}) of *X. aethiopica* fruit extract, those in group C were administered 388.85 mg/kg body weight (30% of LD_{50}) of *X. aethiopica* fruit extract, those in group D were administered 518.46 mg/kg body weight (40% of LD_{50}) of *X. aethiopica* fruit extract, while those in group E (control) received normal feeds and water only. The administration was done once daily for 28 days via oral route. At the end of 28 days treatment, animals were weighed and recorded, and were sacrificed under ether anaesthesia in a desiccator after an overnight fast. Blood samples were collected via cardiac puncture.

2.5 Determination of Hepatic Indices

Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) activities were

determined usingRandox commercial Enzyme kits according to the method of Reitman and Frankel [15]. Alkaline Phosphatase (ALP) activity was determined by Phenolphthalein Monophosphate method described by Babson et al. [16]. Amylase inhibition assay was determined by the method of Bernfield [17]. Lipase activity was determined using Biorex diagnostic kit according to the methods of Lorentz [18].

2.6 Histopathological Analysis of the Organs

The organs were cut into sizes of about 0.5 cm thick on a slab and fixed in Bouin's fluid for about 24 hours and transferred to ascending alcohol concentration for dehydration. Each piece was directly put into 70% alcohol for six hours and then to 90% alcohol overnight. It was then transferred to 3 changes of absolute alcohol for one hour each, and later put into chloroform for 10 hours and fresh chloroform for about 30 minutes. The tissues were placed vertically in molten paraffin wax inside a metal mould and left overnight to cool and solidify. They were later trimmed and mounted on wooden blocks. Serial sections of 6 microns thick were obtained using a rotatory microtome. The deparaffinize sections were stained routinely with haematoxylin and eosin. Photomicrographs of desired sections were made for further observations.

2.7 Statistical Analysis

Results are expressed as mean ± standard deviation. The levels of homogeneity among the groups were assessed using One-way Analysis of Variance (ANOVA) followed by Tukey's test. All analyses were done using Graph Pad Prism Software Version 5.00 and P values < 0.05 were considered statistically significant.

3. RESULTS

3.1 Median Lethal Dose (LD_{50}) Result

The physical signs of toxicity observed in the animals included excitation, paw licking, increased respiratory rate, decreased motor activity, gasping and coma which was followed by death. In the first phase of the median lethal dose determination, no mortality was recorded in the group treated with 1000 mg/kg body weight of *X. aethiopica* fruit extract. However, 100% mortality was recorded in the groups treated with 2000, 3000, 4000, and 5000 mg/kg body weight of *X. aethiopica* fruit extract respectively. Similarly, in the second phase of medial lethal dose determination, no mortality was recorded in the group treated with 1200 mg/kg body weight of *X. aethiopica* fruit extract while 100% mortality was recorded in the groups treated with 1400, 1600, and 1800 mg/kg body weight of *X. aethiopica* fruit extract respectively as presented in Table 1.

The median lethal dose (LD_{50}) was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b).

$LD_{50} = \sqrt{ab}$
Where a = 1200 mg/kg
b = 1400 mg/kg
LD_{50}= 1296.15 mg/kg

3.2 The Effect of *Xylopia aethiopica* Fruit on Hepatic Indices

The effect of ethanolic extract of *Xylopia aethiopica* fruit on hepatic indices is presented in Figs. 2-9. No significant difference was observed when the activities of ALT and AST in animals treated with lower doses (129.62 and 259.23 mg/kg) of the extract were compared with those in the control group at $P<0.05$. A significant increase was however observed in the activities of ALT and AST in animals treated with higher doses (388.85 and 518.46 mg/kg) of the extract when compared with those in the control group. ALP activity was observed to increase in experimental animals when compared with those of the control animals. This elevation was however not significant when animals treated with 129.62 mg/kg body weight of extract were compared with the control group at $P<0.05$. No significant difference was observed in the concentrations of total protein and albumin in animals treated with lower doses (129.62 and 259.23 mg/kg) of the extract when compared with that of the control group at $P<0.05$. A significant increase was however observed in the concentrations of total protein and albumin in animals treated with higher doses (388.85 and 518.46 mg/kg) of the extract when compared with those in the control group. The concentration of globulin was only significant when animals treated with 259.23 and 518.46 mg/kg body weight of extract were compared with those of the control animals. The extract of *Xylopia aethiopica* fruit was observed to inhibit the activities of amylase and lipase respectively in a dose-dependent manner.

Fig. 1. *Xylopia aethiopica* Fruit

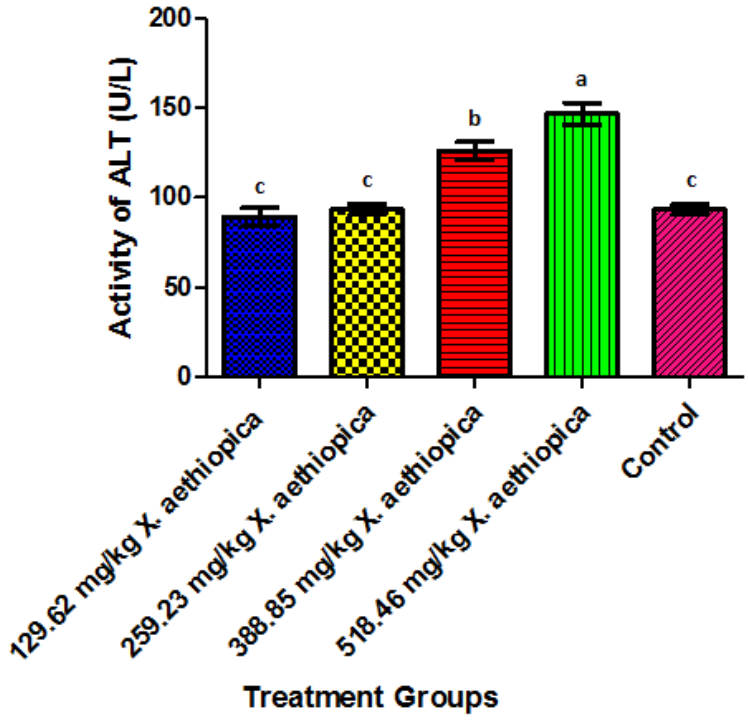

Fig. 2. Effect of *X. aethiopica* fruit extract on the activity of Alanine Amino Transferase (ALT) of animals after 28 days of treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

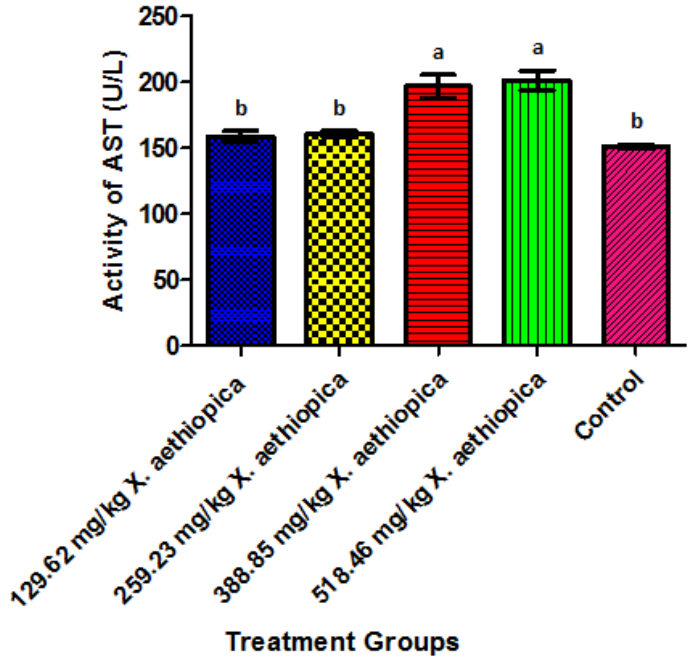

Fig. 3. Effect of *X. aethiopica* fruit extract on the activity of Aspartate Amino Transferase (AST) of animals after 28 days of treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

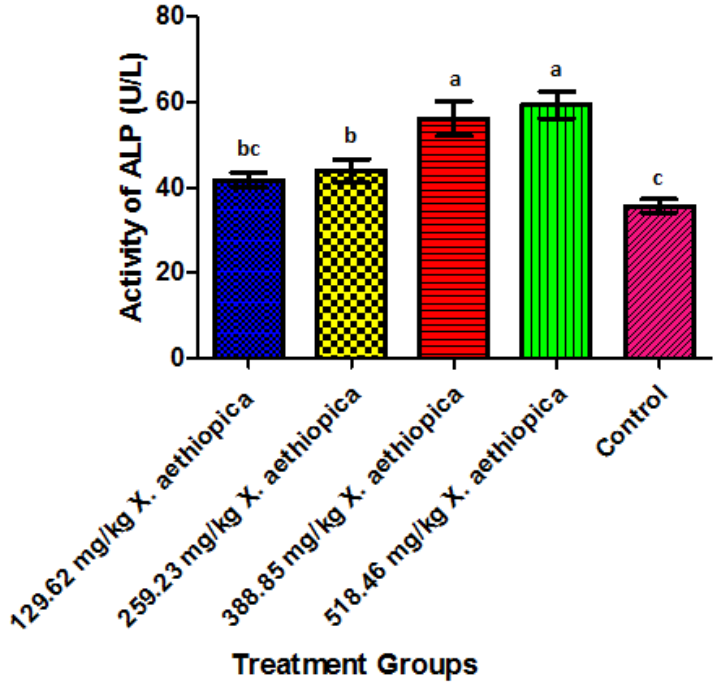

Fig. 4. Effect of *X. aethiopica* fruit extract on the Activity of Alkaline Phosphatase (ALP) of animals after 28 days of treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

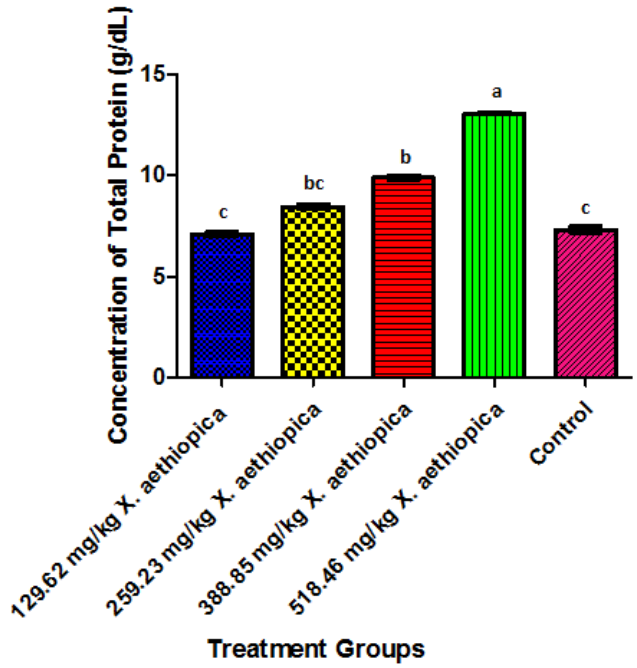

Fig. 5. Effect of *X. aethiopica* fruit extract on the Concentration of Total Protein of Animals after 28 days of Treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

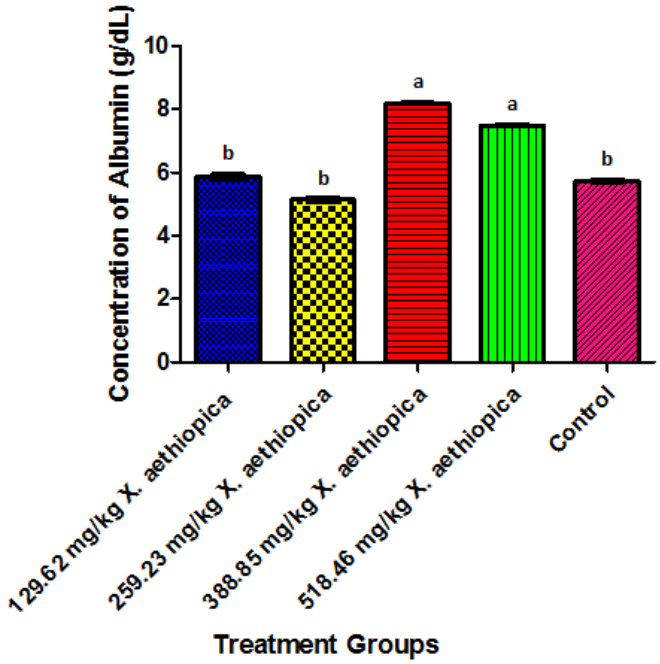

Fig. 6. Effect of *X. aethiopica* fruit extract on the concentration of Albumin of animals after 28 days of treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

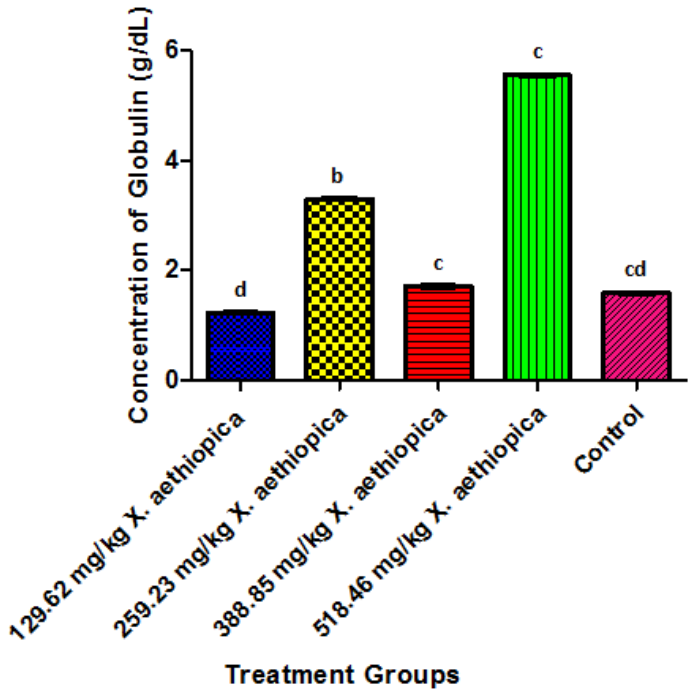

Fig. 7. Effect of *X. aethiopica* fruit extract on the concentration of Globulin of animals after 28 days of treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

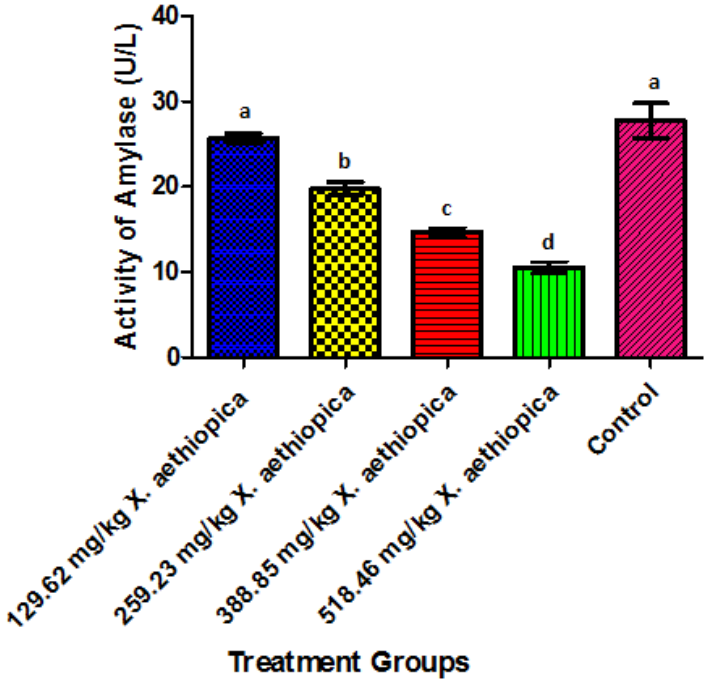

Fig. 8. Effect of *X. aethiopica* fruit extract on the activity of Amylase of animals after 28 days of treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

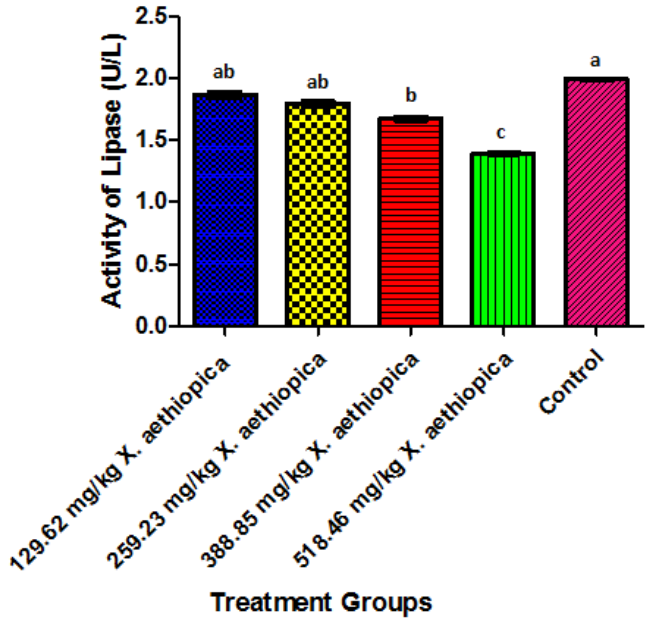

Fig. 9. Effect of *X. aethiopica* fruit extract on the activity of Lipase of animals after 28 days of treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

Table 1. The median Lethal Dose (LD_{50}) of *Xylopia aethiopica* fruit extract

Study Phase/ (Animal)	Dosage of Extract (mg/kg) b.w	No of Mice per Group	No. of Death Recorded	% Mortality
Phase one				
I	1000	5	0	0
II	2000	5	5	100
III	3000	5	5	100
IV	4000	5	5	100
V	5000	5	5	100
Phase two				
I	1200	5	0	0
II	1400	5	5	100
III	1600	5	5	100
IV	1800	5	5	100

LD_{50}= 1296.15 mg/kg

4. DISCUSSION

Evaluation of hepatic biochemical parameters including enzymes (aspartate transaminase, alanine transaminase, and alkaline phosphatase) and metabolites (total proteins and albumin) are very useful in assessing the functional integrity of liver during subacute exposure of chemical substances or natural products/plant extracts [19]. The transaminase (ALT and AST) are enzymes of carbohydrate and amino acid metabolism while alkaline phosphatase is involved in hydrolysis of phosphate bonds. They are often used in assessing the functional integrity of liver, plasma membrane and endoplasmic reticulum [20].

In this study, a significant increase was observed in the activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in animals treated with 388.85 and 518.46 mg/kg body weight of fruit extracts of *X. aethiopica* when compared with those of control animals at P<0.05. At lower doses (129.62 and 259.23 mg/kg) the extract had no significant effect on the activities of ALT and AST. A dose-dependent

increase was also observed in the activities of ALP when experimental animals were compared with control animals. This increase was however insignificant at a low dose of 129.62 mg/kg body weight. It has been reported that an increase in the enzymatic activity of ALT, AST and ALP in the serum directly reflects hepatocellular damage [21]. Results of this study therefore suggest that extract of *X. aethiopica* may be hepatotoxic at high doses. This result is similar to the finding of Oso et al. [22] who reported a significant increase in the activities of AST, ALT and ALP when they investigated the influence of ethanolic extracts of dried fruit of *Xylopia aethiopica* (Dunal) on haematological and biochemical parameters in healthy Wistar rats. This could be that treatment of animals with fruit extracts of *X. aethiopica* stimulated the transcription of the genes involved in glucose uptake, glycolysis and lipogenesis [23]. Glucose represses the induction of inducible operons by inhibiting the synthesis of cyclic Adenosine monophosphate (cAMP) a nucleotide that is required for the initiation of transcription of a large number of inducible enzyme systems including the Lac operon. Cyclic AMP (cAMP) is required to activate an allosteric protein called catabolite activator protein (CAP) which binds to the promoter CAP site and stimulates the binding of ribonucleic acid (RNA) polymerase to the promoter for the initiation of transcription, but cAMP must be available to bind to CAP which binds to deoxyribonucleic acid (DNA) to facilitate transcription. In the presence of glucose, adenylasecyclase (AC) activity is blocked. AC is required to synthesize cAMP from Adenosine Triphosphate (ATP) [24]. Therefore, if cAMP levels are low, CAP is inactive and transcription does not occur. Thus, the effect of glucose in suppressing these inducible enzymes is by lowering cyclic AMP level. The fruit extracts of *X. aethiopica* at high doses elevated cAMP in treated rats, thus the significant increase in these inducible enzymes. ALT is considered most reliable marker of hepatocellular injury because it is solely confined to the liver, unlike AST which is also abundantly present in other body organs such as the kidneys, brain, and heart [25,26]. The significant increase observed in the activities of ALT, AST and ALP in animals treated with high doses of fruit extracts of *X. aethiopica* when compared to the control groups showed that *X. aethiopica* is hepatotoxic. This is in conflict with the findings of Abaidoo et al. [27] who reported a nonsignificant difference when they evaluated the effect of ethanolic fruit extracts of *Xylopia aethiopica* on haematological and biochemical parameters in male rats.

In this study, concentrations of total protein and albumin were observed to have significantly increased in animals treated with 388.85 mg/kg and 518.46 mg/kg body weight of extract when compared with those of control animals at $P<0.05$ respectively. This elevation might suggest a compromise of the synthetic ability of the liver arising from the administration of the extract at higher doses. At high dosage, the extract might have increased the functional activity of the liver by interfering with the equilibrium in the rate of synthesis and destruction, removal or clearance of total protein and albumin from the system of the animals [28]. Such increase in total protein could, however, lead to dehydration which is detrimental to cellular homeostasis [29]. This will negatively affect the metabolic activities of the liver and consequently the health of the animals. Albumin binds and transports metal ions, bilirubin, and drugs. Its level is used to assess the synthetic function of the liver. Significant increase in the level of these parameters is an indication that the extract had stimulated its synthesis in the liver at dosage of388.85 mg/kg and 518.46 mg/kg body weight. Serum protein levels are regulated via synthesis in the liver and its levels thus reflect the synthetic ability of the liver. This result agrees with the findings of Oso et al. [22] who reported a significant increase in total protein and albumin concentrations when they investigated the influence of ethanolic extracts of dried fruit of *X. aethiopica* (Dunal) on haematological and biochemical parameters in healthy Wistar rats.

Fruit extract of *X. aethiopica* used in this study inhibited the activity of amylase in a dose-dependent manner. Amylase is a key enzyme involved in starch breakdown. In humans, the diabetogenic process may be caused by immune destruction of the β-cells in the Islets of Langerhans in the pancreas and this is apparently mediated by white blood cell production of Reactive Oxygen Specie (ROS) [30]. It is believed that inhibition of the enzymes involved in the digestion and uptake of carbohydrates can significantly decrease the postprandial increase of blood glucose level after a mixed carbohydrate diet and therefore can be an important strategy in the management of hyperglycemia linked to type 2 diabetes [31,32]. The result of this present study corresponds with the findings of Adefegha and Oboh [33] who studied the inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside-induced lipid peroxidation in rat pancreas by water extractable phytochemicals from some

tropical spices. The inhibition of amylase by extract of *X. aethiopica* fruit collaborate the significant reduction in blood glucose level observed by Ogbuagu et al. [12]. This effect could be attributed to the presence of biologically active phytochemicals such as phenolic and some non-phenolic constituents of the extract [10].

In consonance to the inhibition of amylase, lipase activity was also observed to be significantly inhibited by the extract of *X. aethiopica* fruit in a dose-dependent manner. Lipase is the enzyme responsible for digestion and absorption of triglycerides. Its inhibition is one of the widest studied methods used to determine the potential activity of natural products to inhibit dietary fat absorption. Decrease in energy intake from dietary fat through inhibition of this enzyme may be an excellent strategy to prevent and treat obesity [34]. The inhibition of lipase by extract of *X. aethiopica* fruit collaborate the significant reduction in triglyceride level observed by Ogbuagu et al. [13].

The results of the histopathological investigation of the liver of animals treated with *X. aethiopica* fruit extracts are presented in plates 1–5. Normal histoarchitecture with numerous hepatocytes, well oriented arrays of sinusoids, and a central vein with organized vascular epithelial layer were observed in the liver of the control group (plate 1). The central vein with mild vascular epithelial distortion, degenerating hepatocytes, and irregular orientation of the arrays of sinusoids were observed in the liver tissue of animals treated with 129.62 mg/kg (10% of LD_{50}) of *X. aethiopica* fruit, while the liver tissue of those treated with 259.23 mg/kg (20% of LD_{50}) of *X. aethiopica* fruit revealed a central vein with altered vascular epithelium, degenerated hepatocytes, wide area of vacuolated hepatocytes and abnormal orientation of arrays of sinusoids. Further investigation revealed that the liver tissue of animals treated with 388.85 mg/kg (30% of LD_{50}) of *X. aethiopica* fruit showed the central vein with vacoulated hepatocytes, wide distribution of microvessi cularsteatosis, and degenerations of the hepatic cells, while those treated with 518.46 mg/kg (40% of LD_{50}) of *X. aethiopica* fruit showed the central vein area with infiltrating inflammatory cells, vacuolated hepatocytes, wide area of degenerating hepatic cells widely spread macrovessi cularsteatosis and irregular orientation in the sinusoidal arrays of the liver tissue. The degeneration of the hepatic tissue by *X. aethiopica* administration correlates with the elevation of hepatic biomarkers observed in this study. This showed that the integrity of the liver has been compromised sequel to *X. aethiopica* fruit administration [35]. Thus, *X. aethiopica* fruit is hepatotoxic especially at high doses. The finding is in agreement with the report by *Obodo* et al. [36] that the administration of *X. aethiopica* can induce hepatic cell damage resulting from the elevation of liver enzymes because of the presence of xylopic acid in its constituent.

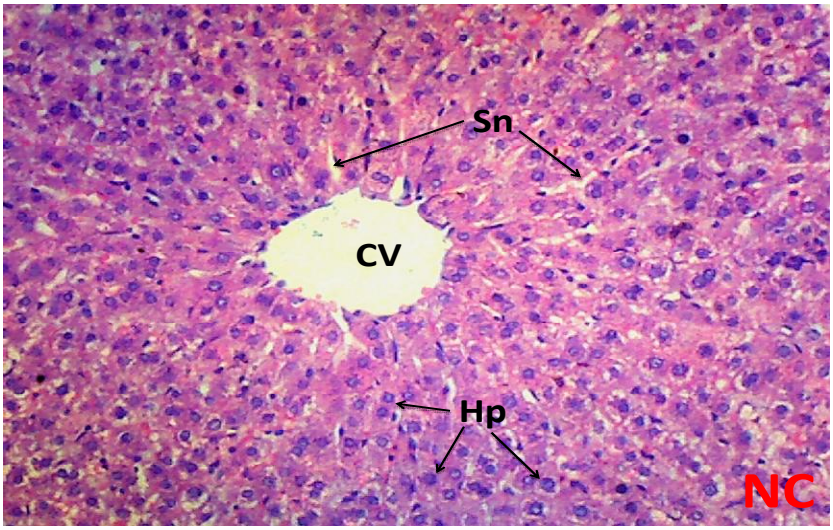

Plate 1. Photomicrograph of the section of the liver tissue of the normal control (NC) group showing normal histoarchitecture of the liver with numerous hepatocytes, well oriented arrays of sinusoids, and a central vein with organized vascular epithelial layer

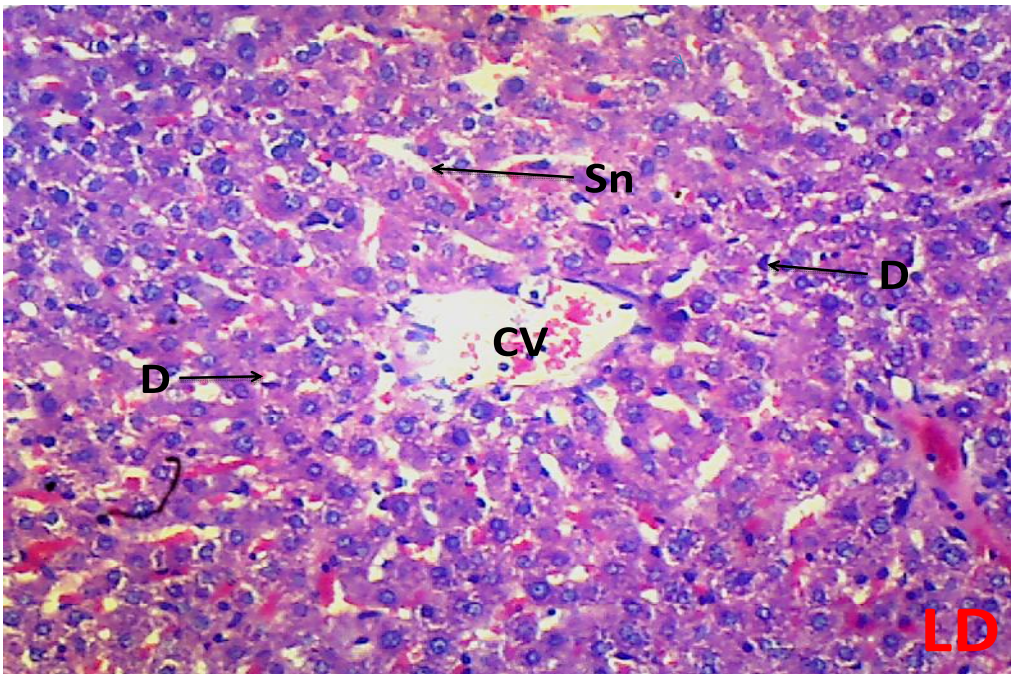

Plate 2. Photomicrograph of the section of the liver tissue of the low dose (LD).The group treated with 129.62 mg/kg of *X. aethiopica* fruit extracts showing the central vein (CV) with mild vascular epithelial distortion, degenerating hepatocytes (D), and irregular orientation of the arrays of sinusoids

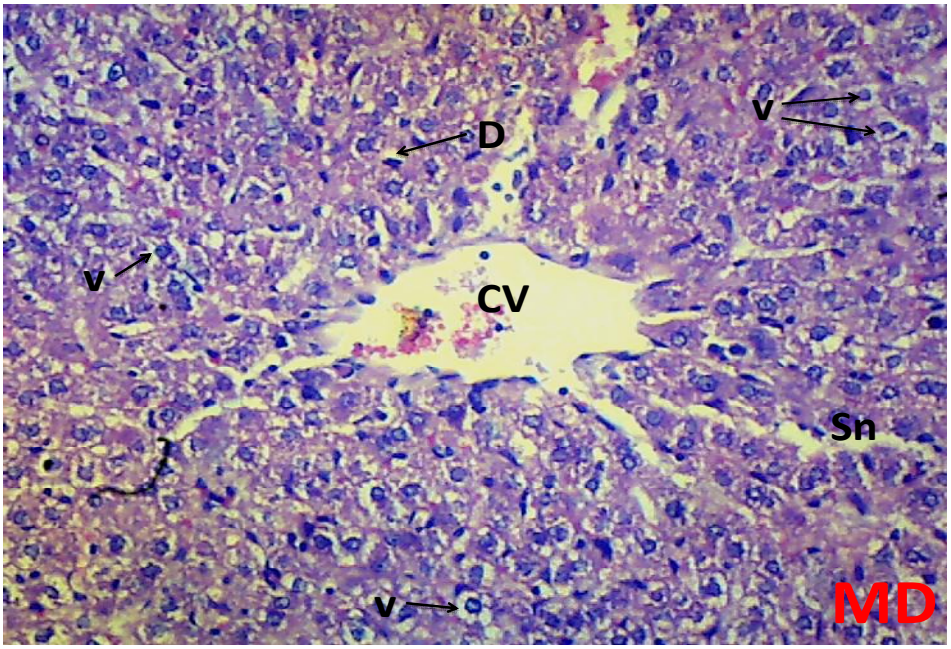

Plate 3. Photomicrograph of the section of the liver tissue of the medium dose (MD).The group treated with 259.23mg/kg of *X. aethiopica* fruit extracts showing the central (CV) area with altered vascular epithelium, degenerated hepatocytes (D), wide area of vacuolated hepatocytes (v) and abnormal orientation of arrays of sinusoids.

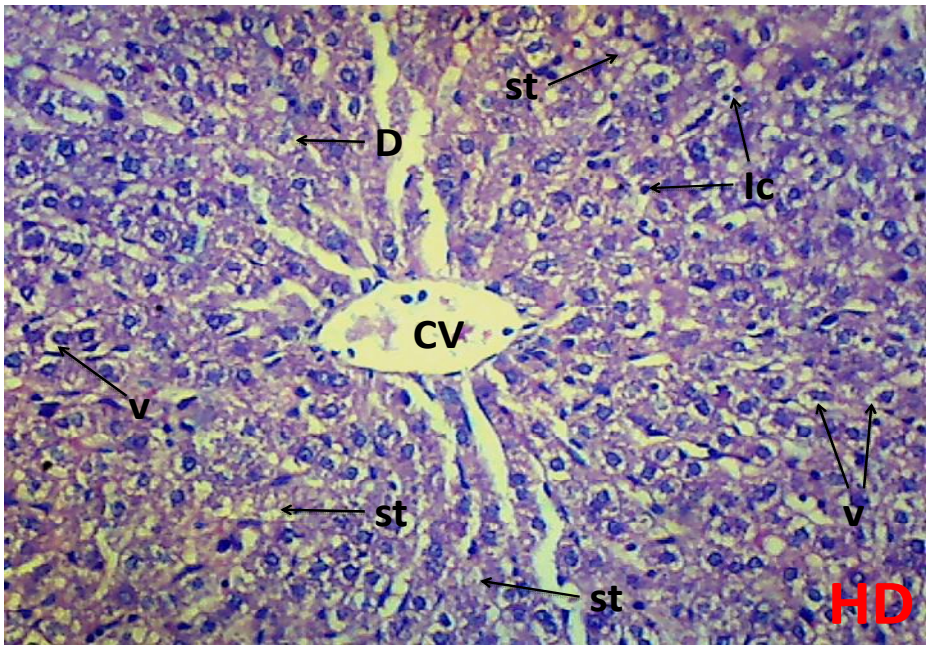

Plate 4. Photomicrograph of the section of the liver tissue of the High dose (HD).The group treated with 388.85mg/kg of *X. aethiopica* fruit extracts showing the central vein with vacoulated hepatocytes (v), wide distribution of microvessicularsteatosis (st), degenerations of the hepatic cells (D)

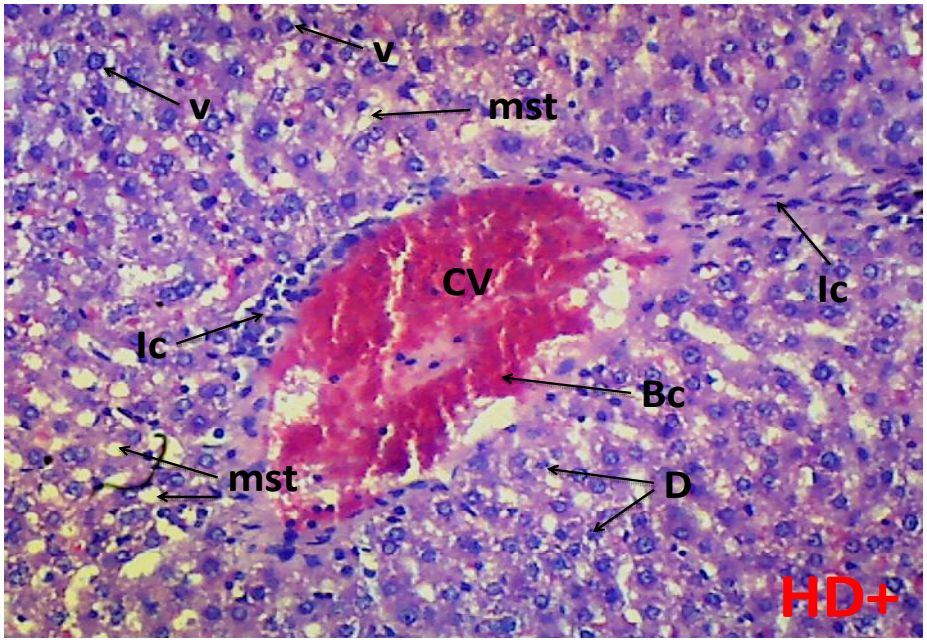

Plate 5. Photomicrograph of the section of the liver tissue of the higher dose (HD The group treated with 518.46mg/kg of *X. aethiopica* fruit extracts showing the central vein area with infiltrating inflammatory cells (IC), vacuolated hepatocytes (v), wide area of degenerating hepatic cells (D) widely spread macrovessi cularsteatosis (mst) and irregular orientation in the sinusoidal arrays.

5. CONCLUSION

This present study showed that extract of *X. aethiopica* fruit is hepatotoxic especially at high dosage. Therefore, its use in folklore medicine should be discouraged.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal ethic Committee approval has been collected and preserved by the author**.**

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mahmood DN, Mamat SS, Kamisan HF, Yahya F, Kamarolzaman FFM, Nasir N et al. Amelioration of paracetamol-induced hepatotoxicity in rat by the administration of methanol extract of *Muntingiacalabura*L. Leaves. Bio Med Research International. 2014;1 -10.
2. Airaodion AI, Ogbuagu U, Ekenjoku JA, Ogbuagu EO, Airaodion EO, Okoroukwu VN. Hepato-protective efficiency of ethanol leaf extract of *Moringa oleifera* against hydrocarbon exposure. International Journal of advances in Herbal and Alternative Medicine. 2019;03(01):32-41.
3. Airaodion AI, Ogbuagu EO. Effect of *Cyperus esculentus* L. (tiger nut) milk on hepatic and renal indices of Wistar rat. *Asian* Journal of Research in Nephrology. 2020;3(2):10-16.
4. Airaodion AI, Megwas AU, Ekenjoku JA, Ngwogu KO, Ngwogu AC. Nephro- and hepato-toxicity of common household insecticides used in Nigeria. International Research Journal of Gastroenterology and Hepatology. 2020;3(2):21-28.
5. Airaodion AI, Alabi OJ, Ogbuagu EO, Atiba FA, Olawoyin DS. Nephro and hepatotoxic effect of air-freshener in Wistar rats. Asian Journal of Research in Nephrology. 2020; 3(2):1-9.
6. Airaodion AI, Ene AC, Ogbuagu EO, Okoroukwu VN, Ekenjoku JA, Ogbuagu U. Biochemical changes associated with consumption (by rats) of “garri” processed by traditional and instant mechanical methods. Asian Journal of Biochemistry, Genetics and Molecular Biology. 2019;2(4): 1-11.
7. Chatterjee TK. Medicinal plants with hepatoprotective properties, in Herbal Opinions, thirded. Books & Allied (P) Ltd., Calcutta. 2000;135.
8. Airaodion AI, Akinmolayan JD, Ogbuagu EO, Esonu CE, Ogbuagu U. Preventive and therapeutic activities of methanolic extract of *Talinum triangulare* leaves against ethanol-induced oxidative stress in Wistar rats. International Journal of Bio-Science and Bio-Technology. 2019; 11(7):85-96.
9. Ogunkunle ATS, Ladejobi TA. Ethnobotanical and phytochemical studies on some species of *Senna*in Nigeria. African Journal Biotechnology, 2006;5(21): 2020-2023.
10. Ogbuagu EO, Ogbuagu U, Unekwe PC, Nweke IN, Airaodion AI. Qualitative determination of the phytochemical composition of ethanolic extract of *Xylopia aethiopica* fruit. Asian Journal of Medical Principles and Clinical Practice. 2020; 3(4):45-52
11. Ezekwesili C, Nwodo O, Eneh F, Ogbunugafor H. Investigation of the chemical composition and biological activity of *Xylopia aethiopica* Dunal (Annonacae). African Journal of Biotechnology. 2010;9(43):7352-7356.
12. Ogbuagu EO, Nweke IN, Unekwe PC, Airaodion AI, Ogbuagu U. Weight gain reduction and hypoglycemic effects of *Xylopia aethiopica* fruit extract on Wistar rats. International Journal of Research and Reports in Hematology. 2020;5(3):1-8.
13. Ogbuagu EO, Unekwe PC, Airaodion AI, Nweke IN, Ogbuagu U**.** Hypolipidemic propensity of ethanolic extract of *Xylopia aethiopica* fruit in Wistar rats. Asian Journal of Research in Cardiovascular Diseases. 2020;2(4):11-22.
14. Airaodion AI, Ekenjoku JA, Ogbuagu EO, Okoroukwu VN, Ogbuagu U. *Carica papaya* leaves might cause miscarriage. Asian Research Journal of Gynaecology and Obstetrics. 2019;2(2): 1-9.
15. Reitman S, Frankel S. A colorimetric method for determination of serum glutamate oxaloacetate and glutamic pyruvate transaminase. American Journal of Clinical Pathology. 1957;28:56-58.

16. Babson AL, Grecley SJ, Coleman CM, Phillips GE. The use of phenolphthalein in monophosphate as a substrate for serum alkaline phosphatase. Clinical Chemistry. 1966;12:482.
17. Bernfield P. Enzymes of starch degradation and synthesis. Adv Enzymol. 1951;2:379–428.
18. Lorentz K. Lipase. In: Thomas L, editor. Clinical laboratory diagnostics. 1st ed. Frankfurt: TH-Books Verlagsge sells chaft. 1998;95-97.
19. Airaodion AI, Ogbuagu EO, Ewa O, Ogbuagu U, Awosanya OO, Adekale OA. Ameliorative efficacy of methanolic extract of *Corchorus olitorius* leaves against acute ethanol-induced oxidative stress in Wistar rats. Asian Journal of Biochemistry, Genetics and Molecular Biology. 2019; 7(6):1-9.
20. Airaodion AI, Ogbuagu EO, Ogbuagu U, Adeniji AR, Agunbiade AP, Airaodion EO. Hepatoprotective effect of *Parkia biglobosa* on acute ethanol-induced oxidative stress in Wistar rats. International Research Journal of Gastroenterology and Hepatology. 2019;2(1):1-11.
21. Ogbuagu EO, Airaodion AI, Ogbuagu U, Airaodion EO. Prophylactic propensity of methanolic extract of *Vernonia amygdalina* leaves against acute ethanol-induced oxidative stress in Wistar rats. International Journal of Bio-Science and Bio-Technology. 2019;11(7):37-46.
22. Oso BJ, Oyewo EB, Oladiji AT. Influence of ethanolic extracts of dried fruit of *Xylopia aethiopica* (Dunal) A. Rich on haemato logical and biochemical parameters in healthy Wistar rats. Clinical Phytoscience. 2019;5(9):1-10.
23. Airaodion AI, Ogbuagu EO, Ekenjoku JA, Ogbuagu U, Airaodion EO. Therapeutic effect of methanolic extract of *Telfairia occidentalis* leaves against acute ethanol-induced oxidative stress in Wistar rats. International Journal of Bio-Science and Bio-Technology. 2019; 11(7):179-189.
24. Airaodion AI, Akinmolayan JD, Ogbuagu EO, Esonu CE, Ogbuagu U. Preventive and therapeutic activities of methanolic extract of *Talinum triangulare* leaves against ethanol-induced oxidative stress in Wistar rats. International Journal of Bio-Science and Bio-Technology. 2019; 11(7):85-96
25. Ogbuagu EO, Airaodion AI, Okoroukwu VN, Ogbuagu U, Ekenjoku JA. Effect of monosodium glutamate on body weight and alanine aminotransferase activity in wistar rats. International Research Journal of Gastroenterology and Hepatology. 2019;2(2):1-8.
26. Airaodion AI, Ngwogu AC, Ekenjoku JA, Ngwogu KO. Hepatoprotective potency of ethanolic extract of *Garcinia kola* (heckel) seed against acute ethanol induced oxidative stress in wistar rats. *International Research Journal of Gastroenterology and Hepatology.* 2020;3(2):1-10
27. Abaidoo CS, Woode E, Alhassan A. An evaluation of the effect of ethanolic fruit extracts of *Xylopia aethiopica* on haematological and biochemical parameters in male rats. *Pelagia Research Library.* 2011;2(2): 39-45.
28. Bashir L, Shittu OK, Busari MB, Sani S, Aisha MI. Safety evaluation of giant African land snails (*Archachatinamaginata*) haemolymph on hematological and biochemical parameters of Albino rats. J Adv Med Pharm Sci. 2015;3(3): 122-130.
29. Shittu OK, Lawal B, Alozieuwa BU, Haruna GM, Abubakar AN, Berinyuy EB. Alteration in biochemical indices following chronic administration of methanolic extract of Nigeria bee *Propolis*in Wistar rats. Asian Pac J Trop Dis. 2015;5(8):654-657.
30. Oberley LW. Free radicals and diabetes. Free Radic Biol Med. 1998;5:113–124.
31. Pinto MS, Ranilla LG, Apostolidis E, Lajolo FM, Genovese MI, Shetty K. Evaluation of antihyperglycemia and antihypertension potential of native Peruvian fruits using *in vitro* models. J Med Food. 2009;12:278–291.
32. Shim YJ, Doo HK, Ahn SY, Kim YS, Seong JK et al. Inhibitory effect of aqueous extract from the gall of *Rhuschinensis* on α-glucosidase activity and postprandial blood glucose. Journal of Ethnopharma cology. 2003;85:283–287.
33. Adefegha SA, Oboh G. Inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside-induced lipid peroxidation in rat pancreas by water extractable phytochemicals from some tropical spices. Pharmaceutical Biology. 2012;50(7):857–865.

34. Sosnowska D, Podsędek A, Redzynia M, Zyzelewicz D. Effects of fruit extracts on pancreatic lipase activity in lipid emulsions. Plant Foods Hum Nutr. 2015;70(3):344-550.
35. Shittu OK, Lawal B, Abubakar NA, Berinyuy BE, Busari MB, Ibrahim AO. Toxicological implications of methanol extract from Nigerian Bee *Propolis* on Some Selected Rat Tissues. J Pharm Biomed Sci. 2015;5(6):499-506.
36. Obodo BN, Iweka FK, Obhakhan JO, Oyadonghan GP, Agbo GE. The effect of *Xylopia aethiopica* leaves on body weight and growth performance. International Journal of Herbs and Pharmacological Research. 2013;2(2):14–19.

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