



Evaluation of the Therapeutic Role of *Citrullus lanatus* and *Annona muricata* Fruit Extracts on Cyhalothrin-induced Toxicity

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Authors' contributions

This work was carried out in collaboration among all authors. Author EEO designed the study, supervised the experiment while authors LKT and AOO carried out the experiment. Author AOO wrote the first draft of the manuscript. Authors EEO and AOO read and jointly approved the final manuscript.

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ABSTRACT

Aim: The aim of this study is to evaluate the therapeutic role of *Citrullus lanatus* and *Annona muricata* fruit Extracts on Cyhalothrin-induced Toxicity.

Experimental Design: The study was a completely randomized design employing relevant statistical tools for analysis and interpretation.

Place and Duration of Study: The study was carried out in the Reproductive Physiology and Genetics Research Laboratory of the Department of Applied and Environmental Biology, Rivers State University, Rivers State. The experiment lasted for 35 days.

Methodology: The body weight of the animals was monitored and recorded twice a week throughout the duration of the experiment. For Biochemical analysis, blood samples were collected by ocular puncture into sterile tubes and serum separated by centrifugation at 2500 g for 10 mins and stored for determination of some liver biomarkers including ALT, ALP, AST, Total Cholesterol and Glucose using their respective kits. For histopathological analysis of Liver and Testis 0.5 g of the each organ was fixed in 10% neutral formalin and sectioned with a digital microtome (AO Spencer, No. 820) at 5 µm thick. Histological sections mounted on slides were stained with

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Hematoxylin and Eosin (H&E). Photomicrographs were generated at X40 magnification and interpreted. Data from biochemical analyses were subjected to one-way ANOVA.

Results: All experimental animals showed a non-significant ($P>0.05$) increase in body weight throughout the experimental period. The range of values for Organ weight observed in the other treatmental groups were closer to that of the control group than the group exposed to Cyhalothrin only. The level of ALP, AST and ALT significantly ($p<0.05$) increased in groups exposed to Cyhalothrin only but reduced with administration of 100% *Citrullus lanatus* and *Annona muricata* extract. Plate 1A shows the normal architecture of seminiferous tubules and spermatogenic elements in the control group, the Seminiferous tubules and epithelium of the group exposed to cyhalothrin only is characterized with large vacuoles devoid of spermatogenic elements. Testicular tissue of animals co-administered *Citrullus lanatus* and *Annona muricata* extracts shows regenerating epithelium filled with maturing spermatozoa.. Photomicrograph of the liver epithelium in the control group shows normal architecture of liver cell filled with normal hepatocytes. Hepatocytes degeneration and lesion in the liver cells of animals exposed to Cyhalothrin only was observed (Plate 2B). Plate 2C and D showed regeneration of hepatocytes with fewer lesion in the liver epithelium while fully regenerated liver epithelium of animals was observed in Plate 2 E.

Conclusion: Cyhalothrin may not have obvious effect on the organ weights, body weight and gonadosomatic indices but silently destroys target cells of the body overtime. Cyhalothrin induced oxidative and reproductive stress in exposed animals while from the groups co-administered *Citrullus lanatus* and *Annona muricata* the therapeutic role of this indigenous fruits on Cyhalothrin-induced toxicity was observed both in the liver and testicular epithelium and therefore can be used as Supplement and a suitable first aid for pesticide related poisoning.

Keywords: Antioxidant; cyhalothrin; hepatotoxicity; reproductive stress; spermatozoa.

1. INTRODUCTION

Man and animals are inadvertently exposed not only to a cocktail of synthetic pyrethroids but also to other forms of Endocrine disrupting chemicals [1]. These chemicals common in cigarette smoke, radiation, pesticides and industrial solvents induce oxidative stress which play a vital role in the pathology of many degenerative diseases and male infertility [2,3]. Majority of this pesticides in use such as Cypermethrin [1,4-6] Deltamethrin [7,8], Permethrin [9], Diclorvos [10] and others caused decrease enzymatic antioxidant levels, increased sex cell abnormalities, birth defects, chromosomal aberrations and reproductive dysfunction [1,6,10].

Cyhalothrin is a pyrethroid, a class of synthetic insecticides that mimics the structure and insecticidal properties of the naturally occurring insecticide pyrethrin which comes from the flower of *Chrysanthemum*. Lambda Cyhalothrin is widely used in Agriculture, homes, industries, schools and hospitals. It is a broad spectrum pyrethroid insecticide that increases physiological, behavioural, reproductive biochemical dysfunctions in laboratory animals [1,10,11]. An antioxidant is a molecule stable enough to donate an electron to a rampaging free radical to neutralize it thus reducing its capacity to cause damage to cells [12]. Some of these antioxidants

are found in fruits and vegetables. *Citrullus lanatus* is a good source of amino acid *citrulline*, vitamin A, C, betacarotene and potassium. The presence of Lycopene helps in the prevention of some chronic diseases. The amount of Lycopene in *Citrullus lanatus* greatly exceeds that of *Solanum lycopersicum*. Lycopene has been studied for its antioxidant properties using animal models such as Sprague-Dawley rats [1,6,10], in human and found to be protective against all forms of cancer [13], neutralizes free radicals and hence prevent disease associated with oxidative stress in humans [14].

Annona muricata belongs to the family Annonaceae. The fruit is rich in vitamin B, C, potassium and fructose among its antioxidant properties [15].

Lambda Cyhalothrin, when given to rats at 150 mg/kg/bw/day daily showed significant decrease in body weight, histopathological analysis of liver showed vacuolar and hydropic degeneration of the hepatocytes and significant decrease in total protein and Albumin, increase in transaminase enzymes [16] while those exposed to 100 mg/kg were found to have an increase in the number of structural chromosomal aberration frequency of micronucleated erythrocytes, no significant difference in total protein and Albumin, significant increase in levels of Urea and Creatinine

between rats in treated and untreated groups. [17]. Extracts of *Annona muricata* was reported to have a mitigating effect on sperm toxicity induced by caffeine, on weight of testes, epididymis, sperm motility, count and sperm head abnormalities in a mammalian model [18]. It has been reported that there was a significant reduction in the levels of luteinizing hormone, testosterone of male rats fed 30 mg/kg/day of Cypermethrin for 70 days while there was an increase in Transaminases and alkaline phosphatase in the same experimental animals [1,11]. Jaiswal, et al. [19] reported the ameliorating effect of *citrus limon* fruit extract on carbofuran induced toxicity. Carbofuran significantly altered the level of activities of ALT, AST and LDH in the liver tissues and serum. The level of SOD, Catalase, GSH also showed significant perturbations in rat liver while administration of *Citrus limon* fruit extract markedly ameliorated the toxicity of Carbofuran by protecting the levels of the aforementioned biomarkers to near the control level. Protective role has been reported [20] of ginger on Lambda-cyhalothrin (LC) insecticide, a decrease in SOD and CAT but an increase in the levels of MDA in lambda-cyhalothrin induced toxicity while LC plus ginger increased the antioxidant enzymes and decreased MDA levels.

However, with the increasing exposure to pesticides and other forms of EDCs, there is an urgent need to explore the therapeutic effect of our indigenous fruits on Cyhalothrin- induced toxicity.

2. MATERIALS AND METHODS

2.1 Experimental Location

The study was carried out in the Reproductive Physiology and Genetics Research Laboratory of the Department of Applied and Environmental Biology, Rivers State University, Port Harcourt Nkpolu-Oroworukwo Rivers State (Coordinates 4°47'50"N 6°58'49"E).

2.2 Experimental Animals

Twenty sexually matured male Sprague-Dawley rats (mean weight 190.23±35.6 g) were obtained from the Department of Biochemistry, University of Port Harcourt, Nigeria. The rats were housed individually in plastic cages under standard conditions (12hL: 12hD) and acclimated for two weeks prior to the commencement of the experiment. All animals were fed with standard rodent pellet and cool clean water ad libitum. The

experiment was conducted according to the institutional animal care protocols at the Rivers State University, Nigeria and followed approved guidelines for the ethical treatment of experimental animals.

2.3 Experimental Design and Procedure

Twenty adult male Sprague-Dawley rats were assigned to five groups (A-E) of 4 (four) rats each. Group (A) received no chemical so it was the control, Group B received 30 mg/kg/bw/day of Cyhalothrin only, Group (C) received 30 mg/kg/bw/day of Cyhalothrin and 5000 mg/kg/bw/day of *Citrullus lanatus* and Group (D) received 30 mg/kg/bw/day of Cyhalothrin and 5000 mg/kg/bw/day of *Annona muricata*. Group (E) received 30 mg/kg/bw/day of Cyhalothrin and 5000 mg/kg/bw/day of equal volume of *Citrullus lanatus* and *Annona muricata*. All the groups were exposed to their treatment by oral gavage for 35 days. All animals were observed daily for behavioral changes, mortality as well as food and water intake. Animals were weighed twice a week and the average weight per week recorded to the nearest 0.01 g.

2.3.1 Biochemical analysis

Blood samples were collected by ocular puncture into sterile tubes and serum separated by centrifugation at 2500 g for 10 mins and stored for determination of some liver biomarkers [21,22].

2.3.2 Histopathological analysis of liver and testis

Known weight of the Liver and Testis were fixed in 10% neutral formalin and sectioned with a digital microtome (AO Spencer, No.820) at 5 µm thick. Histological sections mounted on slides were stained with Hematoxylin and Eosin (H&E) according to Orlu [7]. Photomicrographs were generated with a digital microscope Biosphere Miller B [1,11] at X40 magnification.

2.3.3 Statistical analysis

Data from biochemical analyses were subjected to one-way ANOVA; where significant differences were found, pair-wise mean comparisons were conducted with Tukey test using SPSS 20 software. Significant differences was set at P<0.05.

3. RESULTS

3.1 Effect on Body Weight

The effect of administration of *Citrullus lanatus* and *Annona muricata* on the mean body weight of Sprague-Dawley rats exposed to Cyhalothrin for thirty-five (35) days is presented in Fig. 1.

All the experimental animals showed a non-significant ($P>0.05$) increase in body weight throughout the experimental period. A close look at the Fig. 1 revealed an almost linear graph indicating a gradual increase in body weight.

3.1.1 Effect on organ weight

Table 1 shows the mean weight of vital organs of SD rats exposed to Cyhalothrin with *Citrullus lanatus* and *Annona muricata*.

There was no significant difference ($P>0.05$) between the weight of liver in the control group and that in the treatment groups. The range of values observed in the other treatment groups were closer to that of the control group than the group exposed to Cyhalothrin only.

3.1.2 Gonadosomatic indices

The effect of *Citrullus lanatus* and *Annona muricata* on Gonadosomatic indices of Sprague-Dawley rats exposed to Cyhalothrin is shown in Table 2. Statistical analysis showed no significant difference ($P>0.05$) between the control and treatment groups.

3.2 Potential Hepatotoxicity by Analyzing the Liver Biomarkers

The effect of *Citrullus lanatus* and *Annona muricata* on the Liver biomarkers of Sprague-Dawley rats exposed to Cyhalothrin for thirty-five days is shown in Fig. 1. The level of ALP, AST, and ALT significantly ($p<0.05$) increased in

groups exposed to Cyhalothrin only but reduced with administration of *Citrullus lanatus* and *Annona muricata*. While the level of Total cholesterol increased in group B administered Cyhalothrin only, Glucose level significantly ($P<0.05$) decreased.

3.3 Potential Reproductive Toxicity by Histopathological Analysis of the Testes

Plate 1A shows the normal architecture of seminiferous tubules and spermatogenic elements at x40 magnification. Plate 1B represents animals in the group administered only Cyhalothrin. The gross architecture viewed at magnification X40 shows seminiferous tubules and the seminiferous epithelium with large vacuoles devoid of spermatogenic elements. Both mitotic and meiotic elements have degenerated leaving large spaces without cells. Sections of group 1C and 1D testicular tissue represent animals exposed to Cyhalothrin at 30 mg/kg/bw/day and co-administered *Citrullus lanatus* and *Annona muricata* at 5,000 mg/kg/bw/day respectively for the duration of the experiment. Regeneration of the interstitial cells of Leydig accompanied by spermatogenic elements are visible. The Seminiferous epithelium shows increase in both mitotic and meiotic spermatogenic elements. The lumen is filled with maturing spermatozoa. Some vacuolated sections are still visible.

Plate 1E shows sections of animals exposed to Cyhalothrin and co-administered a combination of *Citrullus lanatus* and *Annona muricata* in ratio 2500 mg/kg/bw/day each to make up 5000 mg/kg/bw/day. The seminiferous epithelium shows normal complement of spermatogenic elements. The lumen is filled with maturing spermatozoa and the interstitial space is repopulated with interstitial cells of Leydig.

Table 1. Mean weight of vital organs of SD rats exposed to cyhalothrin with *Citrullus lanatus* and *Annona muricata*

GRPS	Bodyweight	Liver	Heart	Kidney	Spleen	Sem. Ves
A	193.29±16.88	6.69±0.94	0.61±0.04	1.51±0.22	0.86±0.20	0.47±0.06
B	194.48±17.01	5.55±0.64	0.54±0.05	1.14±0.69	0.66±0.03	0.62±0.15
C	191.44±16.15	6.16±1.25	0.59±0.13	1.27±0.20	0.81±0.19	0.45±0.28
D	194.99±17.78	6.36±1.08	0.62±0.07	1.46±0.21	0.88±0.35	0.74±0.41
E	190.61±16.06	6.51±0.68	0.69±0.08	1.32±0.14	0.75±0.05	0.72±0.09
P>0.05	0.07	0.41	0.11	0.39	0.49	0.26

*Values are Mean±SD. Values are not significantly different ($P>0.05$)

Table 2. Gonadosomatic indices of Sprague-Dawley rats exposed to Cyhalothrin with *Citrullus lanatus* and *Annona muricata*

GRPS	BW	RTW	LTW	PTW	REW	LEW	PEW	PROST	SEM.VES
A	193.29±16.88	0.66±0.10	0.65±0.11	1.31±0.21	0.26±0.06	0.25±0.66	0.51±0.12	0.05±0.01	0.24±0.05
B	194.48±17.01	0.66±0.17	0.65±0.16	1.31±0.34	0.21±0.05	0.21±0.07	0.43±0.13	0.06±0.02	0.38±0.21
C	191.44±16.15	0.61±0.11	0.62±0.09	1.23±0.19	0.21±0.06	0.22±0.04	0.43±0.11	0.03±0.02	0.23±0.13
D	194.99±17.78	0.83±0.07	0.82±0.07	1.65±0.15	0.33±0.04	0.34±0.05	0.67±0.09	0.06±0.03	0.39±0.14
E	190.61±16.06	0.74±0.09	0.77±0.14	1.50±0.23	0.32±0.08	0.34±0.06	0.66±0.14	0.08±0.04	0.40±0.06
P>0.05	0.07	0.08	0.10	0.08	0.07	0.06	0.07	0.36	0.19

*All values are Means ±SD. Values are not significantly different (P>0.05). BW (bodyweight), RTW (Right testicular weight), LTW (left testicular weight), PTW (paired testicular weight), REW (right epididymal weight), LEW (left epididymal weight), PEW (paired epididymal weight), PROST(prostate gland), SEM.VES (seminal vesicle)

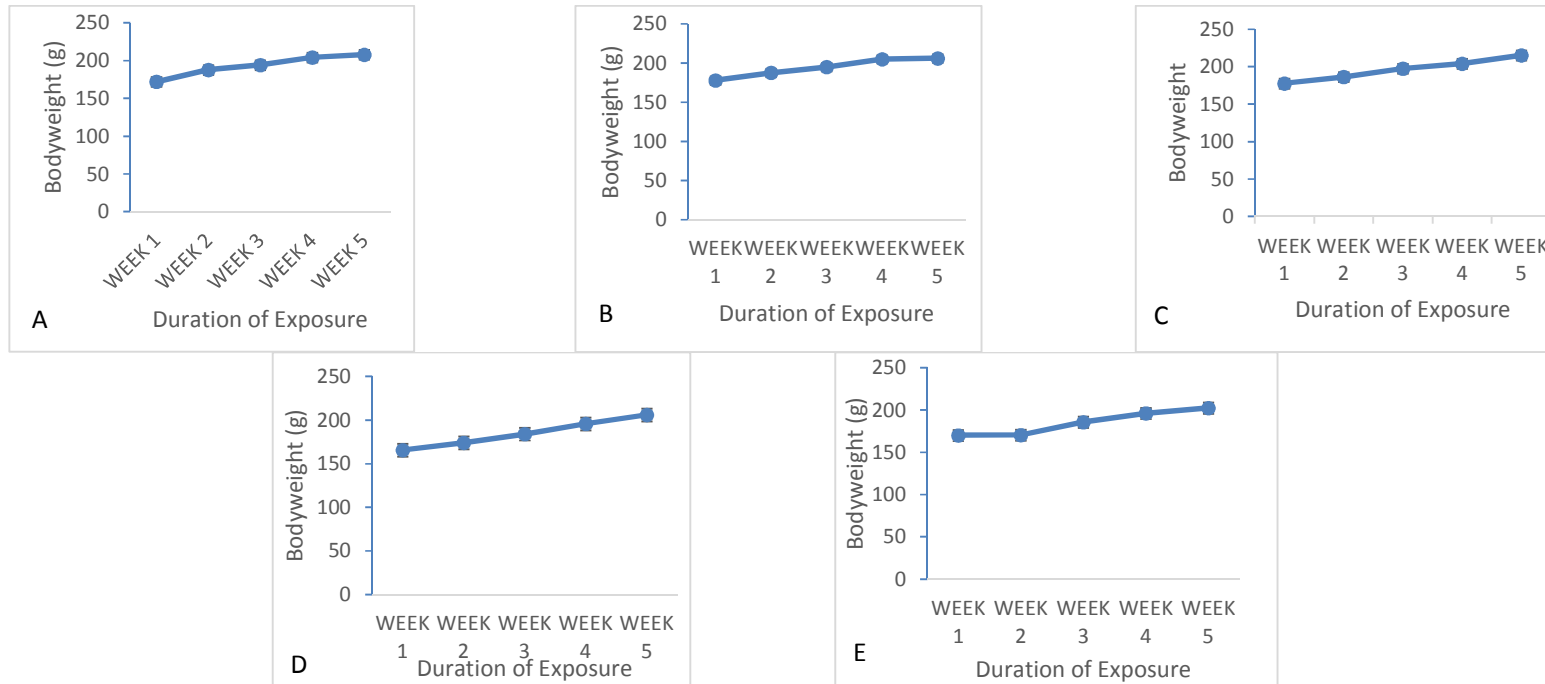


Fig. 1. Body weight of male Sprague-Dawley rats in groups A-E exposed to the treatment for 35 days

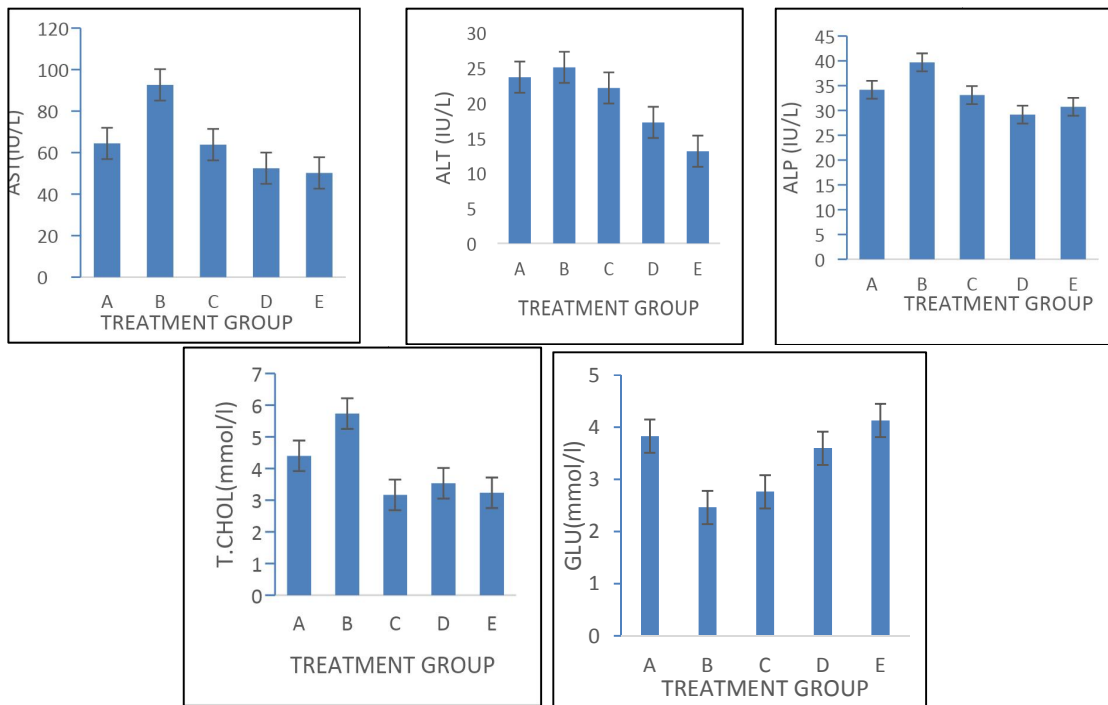


Fig. 2. Different level of ALP, AST, ALT, T. CHOL and GLU with different treatment group

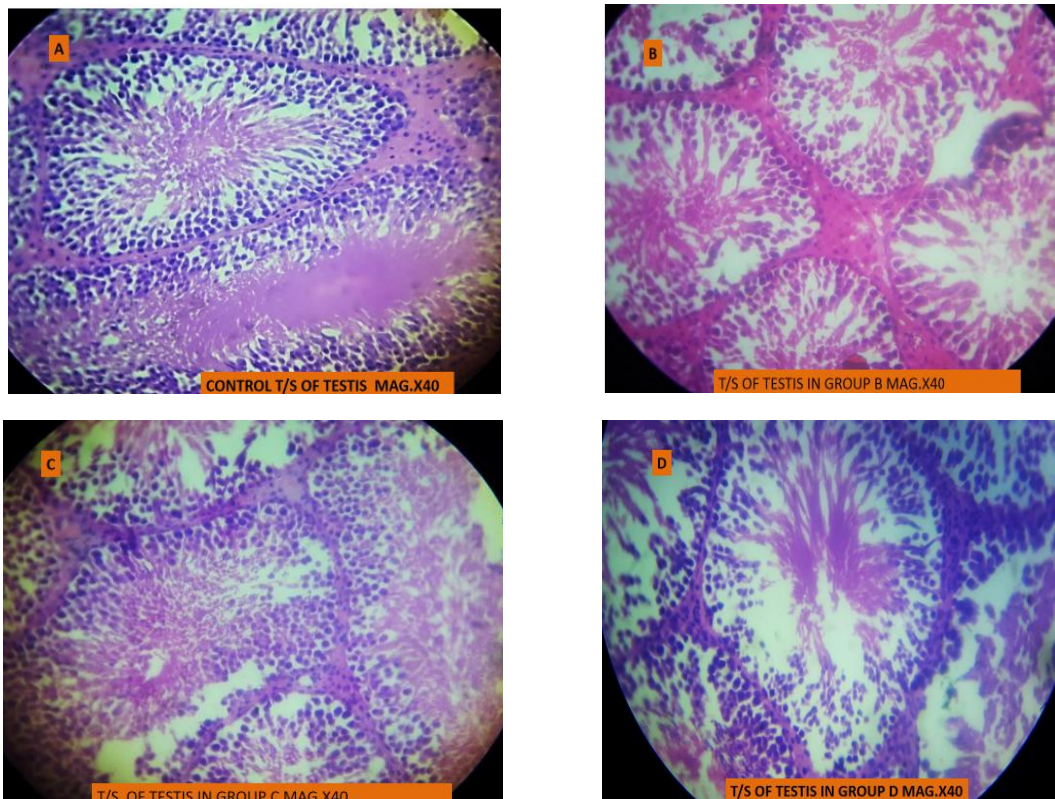
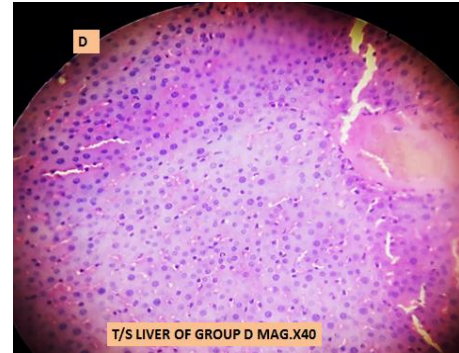
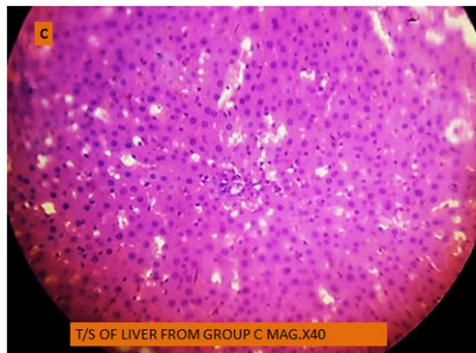
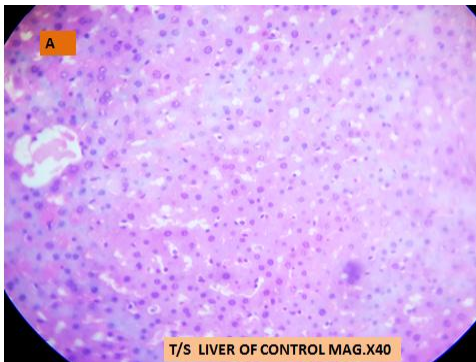




Plate 1 A-E. Transverse section of testes exposed to cyhalothrin co-administered *Citrullus lanatus* and *Annona muricata*

Potential Hepatotoxicity by Histopathological analysis of the liver: Histopathological examination of the transverse section of the liver of the experimental animals is displayed in Plates 2. Plate 2A is the entire epithelium of animals in group A having the normal architecture of liver cell being filled with normal hepatocytes. Hepatocytes degeneration and lesion in the liver cells of animals exposed to 30 mg/kg/bw/day Cyhalothrin for 35 days was observed in plate 2B. Also observed was the infiltration of the central portal vein by the lymphocytes. Plate 2C

and D showed regeneration of hepatocytes with fewer lesion in the liver epithelium of animals exposed to Cyhalothrin at 30 mg/kg/bw/day and co-administered *Citrullus lanatus* and *Annona muricata* at 5,000 mg/kg/bw/day respectively for 35days. Plate 2E revealed fully regenerated liver epithelium of animals exposed to a combination of *Citrullus lanatus* and *Annona muricata* in ratio 2500 mg/kg/bw/day each to make up 5000 mg/kg/bw/day. The hepatocytes have regenerated with various mitotic divisions also being captured.



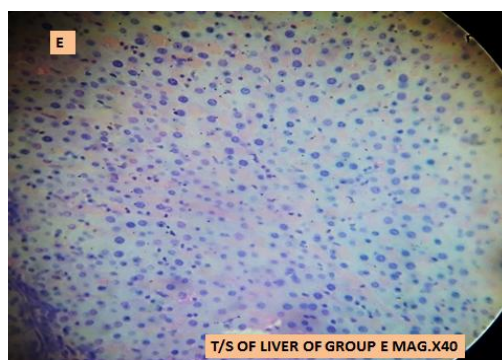


Plate 2. Transverse section of liver of Spague-Dawley rats exposed to cyhalothrin co-administered *Citrullus lanatus* and *Annona muricata*

4. DISCUSSION

Analysis of body weight, organ weight and gonadosomatic indices are criteria for the weight and somatic indices are criteria for the evaluation of systemic toxicity providing an endpoint for the identification of potentially harmful effects of chemicals. In this study there was no significant changes in the body weight, organ weight and gonadosomatic indices of all experimental animals in the groups compared with the control ($p > 0.05$).

Histopathological analysis of the testes shows epithelium devoid of spermatogenic element, an indication that Cyhalothrin induced reproductive toxicity. In Plate 2C, D and E show seminiferous epithelium that is similar to that in plate 2A (the control group) revealing the therapeutic effect of *Citrullus lanatus* and *Annona muricata* against reproductive dysfunction in males.

The liver is the first point of contact for all metabolites. It has a remarkable capacity to regenerate following injuries by undergoing rapid mitotic division as observed in the epithelium of experimental animals in groups C, D and E in this study. This injury to the liver by the pesticides was also indicated by the statistically significant ($p < 0.05$) elevation of all liver biomarkers. The concentrations of the liver biomarkers; Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), decreased significantly ($P > 0.05$) in groups C to E co administered 5,000 mg/kg/bw/day of *Citrullus lanatus* and *Annona muricata* but significantly increased in group B exposed to Cyhalothrin only; an indication that Cyhalothrin induced oxidative stress in exposed rats. The central portal vein was infiltrated with lymphocytes; epithelium became vacuolated due

to hepatocytes degeneration in the group exposed to Cyhalothrin only.

Mitotic division and an increase in the number of hepatocytes in (Plates 2C, D & E) is indicative that most of the metabolic activities are carried out by the hepatocytes necessitating rapid regeneration by mitotic division. The liver micrograph shows an epithelium that has undergone regeneration and the normal architecture restored indicating the therapeutic role of *Citrullus lanatus* and *Annona muricata* on Cyhalothrin-induced toxicity.

Reports by other researchers reported the ameliorating effect of *citrus limon* fruit extract on carbofuran induced toxicity. Carbonfuran significantly altered the level of activities of ALT, AST and LDH in the liver tissues and serum. The level of SOD, Catalase, GSH also showed significant perturbations in rat liver while administration of Citrus limon fruit extract markedly ameliorated the toxicity of Carbofuran by protecting the levels of the aforementioned biomarkers to near the control level [19]. Al-Amoudi [20] reported the protective role of ginger on Lambda cyhalothrin (LC) insecticide, a decrease in SOD and CAT but an increase in the levels of MDA in lambda-cyhalothrin induced toxicity while LC plus ginger increased the antioxidant enzymes and decreased MDA levels.

5. CONCLUSION

Cyhalothrin may not have obvious effect on the organ weights, body weight and gonadosomatic indices but silently destroy target cells of the body overtime. A comparison of the trend in liver biomarkers, histopathological analysis of the liver and testis revealed Cyhalothrin induce oxidative

and reproductive stress in exposed animals while results from groups co-administered *Citrullus lanatus* and *Annona muricata* revealed the therapeutic role this indigenous fruit on Cyhalothin-induced toxicity and therefore should be used as Supplement and a suitable first aid for pesticide related poisoning.

ETHICAL APPROVAL

The experiment was conducted according to the institutional animal care protocols at the Rivers State University, Nigeria and followed approved guidelines for the ethical treatment of experimental animals.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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