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EFFECT OF METHANOL ROOT EXTRACT OF *NAUCLEA LATIFOLIA* SMITH (RUBIACEAE) ON PARACETAMOL-INDUCED TOXICITY IN RATS

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ABSTRACT

Objective: The effect of methanol root extract of *Nauclea latifolia* was investigated in paracetamol-induced toxicity in rats. The investigation was done due to numerous claims of this plant parts in management of poisoning, malaria and gastrointestinal disorders among others. The aim of this investigation is to ascertain whether it can ameliorate paracetamol – induced toxicity in rats, and through what mechanism does it mediate its effects. **Methods:** The root was harvested from the wild, identified and authenticated by a Taxonomist in the Department of Botany and Ecological Studies of this University. It was macerated in methanol for 72 h, filtered and dried to constant weigh. The rats were divided into seven groups of 6 rats per cage. Groups 1 and 2 were administered with normal saline (0.5ml p.o). Groups 3-5 were given extract (40, 80 and 120 mg/kg b.w. of animal, respectively) while group 6 was given silymarin (100 mg/kg; i.p. b.w.). Group 7 received extract (80 mg/kg. p.o.b.w.), 10 min later silymarin (100 mg/kg b.w.) was administered. The above doses of drugs and extract were given for 7 days. On the same day (7^{th} day), groups 2-7 received paracetamol (2000 mg/kg p.o.). All animals were weighed before and after experimentation and were observed for physical signs of toxicity for 24 h and were sacrificed following ether anaesthesia. **Result:** The extract dose - dependently increased the alanine aminotransferase (ALT) and alkaline phosphatase (ALP) concentrations while the increase in aspartate aminotransferase (AST) was not dose - dependent. These effects were statistically significant ($p < 0.001$). There were significant ($p < 0.001$) increases in creatinine and urea plasma concentrations. Total plasma protein decreased in a dose - dependent fashion while the concentration of plasma albumin and total bilirubin remained insignificantly equivocal. However, in the presence of the extract, silymarin decreased the plasma concentrations of creatinine and total protein while urea, albumin and total bilirubin remained elevated. On the electrolyte ions, the extract decreased serum sodium and phosphate concentrations. Potassium and chloride ions were insignificantly changed. The extract lowered concentrations/percentages of haemoglobin, packed cell volume and platelets induced by paracetamol. Other parameters elevated were neutrophils, lymphocytes and monocytes. The effects of extract on the wet weight of testis, epididymis, kidney and spleen were insignificant. There were however increases in the wet weight of liver and total animal weight. **Conclusion:** Mild to moderate increases and decreases of the parameters observed indicated that the extract was moderately toxic. The use of the plant parts in the communities and the effects observed were in part due to the secondary metabolites of the extract.

KEYWORDS: *Nauclea latifolia*, paracetamol, rats, methanol, toxicity.

INTRODUCTION

The use of plants in the treatment of human ailments dates back to the origin of man in the planet Earth. Many plants have been used folklorically for the treatment of different diseases; some have proved to be efficacious while others are continually being investigated. Some of the plants that their active ingredients have been authenticated, elucidated and employed in treatment of diseases are *Digitalis purpurea* and *lanata* respectively. *Pausinystalia yohimbe*, *Atropa belladonna* and *Lepidium imfenii*, among others (Nwafor *et al*., 2007; Gonzales, 2012).

Nauclea latifolia Smith (Rubiaceae), an evergreen multi-stemmed shrub or tree, grows in humid tropical rainforest zone or in savannah woodlands in West and Central Africa and have been employed extensively in ethnomedicine for the treatment of stomach pains, fever and diarrhoea. Others include treatment of nematodes, malaria and tuberculosis (Taiwe *et al*., 2010). In Itak Village in Ikono Local Government Area of Akwa Ibom

State, Nigeria, the decoction of the root is employed as a sexual enhancer in men (Etefia, 2012, Personal com.). Udenwoke (2016) documented the effect of the extract and its fractions on sexual indices, however, cognisance of the fact that the body is a dynamic system and the toxicological effect of the extract has not been investigated, hence the need for this investigation became imperative.

MATERIALS AND METHOD

The root of *Nauclea latifolia* Smith was collected from Itak Village in Ikono Local Government Area of Akwa Ibom State, Nigeria in February, 2016. The plant material was identified and authenticated by a plant Taxonomist, Professor Margaret Bassey of the Department of Botany and Ecological Studies, University of Uyo. The voucher specimen (UHH3550) was prepared and deposited at the Departmental Herbarium. The root was air-dried at room temperature for six days and pulverized using pestle and mortar to coarse powder. About 70 g of the ground root were macerated in 300 ml of methanol for 72 h at 26 ± 2^{o}C and filtered using Whatman paper No.4. The filtrate was evaporated to constant weight in water bath at 40^{o}C and stored in a desiccator until when required.

Animals

Wistar Albino rats of both sexes (weighing 220 – 280 g, respectively) were obtained from the College of Health Sciences Animal House, University of Uyo for the study. They were quarantined in Department of Pharmacology and Toxicology Animal House, for two weeks, and maintained under standard environmental conditions (26 ± 2 ^{o}C, relative humidity 80-85%, 12 h light/12 h dark cycle) and fed with standard rodent diet (Bendel Feeds Ltd, Benin City, Edo State, Nigeria) and water *ad libitum*. The care and handling of the animals were in accordance with the internationally accepted standard Guide for the Care and Use of Laboratory Animals (1966). As adopted and promulgated by the National Institute of Health (NIH publication No. 85 (23), revised 1996) and the related Ethics Regulation of the Faculty of Pharmacy, University of Uyo, Nigeria. All animals were handled with human care.

Phytochemical Screening

As reported by Udenwoke (2016).

Determination of Median Lethal Dose (LD_{50})

As reported by Udenwoke (2016).

Biochemical, haematological and electrolyte analyses

The above analyses were carried out in adult albino rats according to the method of Nwafor and Okanny (2015). The rats were divided into seven groups of 6 rats per cage. Groups 1 and 2 were administered with normal saline (0.5 ml, p.o). Groups 3 - 5 were given extract (40, 80 and 120 mg/kg b.w. of animal, respectively) while group 6 was given silymarin (100 mg/kg; i.p. b.w.). Group 7 received extract (80 mg/kg. p.o.b.w.), 10min later silymarin (100 mg/kg b.w.) was administered. The above doses of drugs and extract were given for 7 days. On the same day (7th day), groups 2-7 received paracetamol (2000 mg/kg p.o.). All animals were observed for physical signs of toxicity for 24 h and were sacrificed the next day following ether anaesthesia. The blood samples were collected and centrifuged at 5000 rpm for 15 min and clear serum was separated, collected and submitted to Diagnostic Laboratory, Department of Chemical Pathology, University of Uyo Teaching Hospital, Uyo, Nigeria for the following investigations: Serum transaminases (alanine aminotransferase, ALT; and aspartate aminotransferase, AST), alkaline phosphatase (ALT), creatinine, urea, total protein and albumin. Others were total bilirubin, sodium, potassium, chloride and phosphate while the whole blood was submitted to Department of Haematology in the same Teaching Hospital. The parameters investigated were haemoglobin, packed cell volume, platelets, white blood corpuscles and differentials. Changes in weight of animals, liver and kidneys were noted. Others were testes, epididymis and spleen.

Statistical Analysis

Multiple comparisons of Mean ± SEM were carried out by one way analysis of variance (ANOVA), followed by Tukey-Krammar multiple comparisons tests. A probability level of less than 5% was considered significant.

RESULTS

Effect of extract on biochemical parameters

The extract showed dose-dependent increase in ALT and ALP concentrations while that of AST was non dose-dependent. These increases were statistically significant ($p < 0.001$). In the presence of extract (80 mg/kg, b.w.), silymarin, an antitoxicant, did not revert the increases in concentrations observed with ALT, ALP and AST respectively (Table 1).

Effect of extract on kidney functions

The effects of extract on creatinine, urea, total protein, albumin and total bilirubin are as shown in Table 2. There were increased creatinine and urea plasma concentrations. These increases were statistically significant ($p < 001$) relative to control. The amount of total plasma protein decreased in a dose-dependent manner while the concentration of plasma albumin and total bilirubin remained insignificantly equivocal. However, in the presence of extract, silymarin decreased the plasma concentrations of creatinine and total protein while urea, albumin and total bilirubin remained elevated.

Effect of extract on electrolyte balance

The effects of the extract on electrolyte ions are as shown on Table 3. The extract decreased the serum sodium concentration in non-dose-dependent manner. In the presence of the extract, silymarin further lowered the serum concentration of the sodium. Similar effect was

observed with the phosphate. The serum concentartions of potassium and chloride were however insignificantly changed.

Effect of extract on haematological indices

The extract lowered the concentrations and percentages of haemoglobin, packed cell volume and platelets induced by paracetamol. Others were the neutrophils, lymphocytes and monocytes. The concentrations of white blood cells were high relative to control. The effects on neutrophils and basophils were however insignificant (Table 4).

Effect of extract on the organs

There was no significant difference between the right and left testes, epididymis and kidney. The mean weight of spleen was also insignificantly affected. The extract (80mg/kg b. w.) showed significant ($p < 0.001$) increase in weight of liver (Tables 5 to 9).

Effect of extract on body weight

The effect of extract on body weight is as shown on Table 10. There was a general increase in the body weight except the group administered with paracetamol in the presence of silymarin which was low.

Table 1: Effect of extract on PCM-induced toxicity in liver function tests in rats

Groups (Doses)	AST (u/L)	ALT (u/L)	ALP (u/L)
Control (NS,10 ml/kg)	125.17 ± 0.12	33.50 ± 0.10	260.01 ± 0.20
PCM (2000 mg/kg)	194.00 ± 0.30[a]	59.67 ± 0.24[a]	284.83 ± 0.14[a]
Extract (40 mg/kg) + PCM	178.50 ± 0.15[a]	52.00 ± 0.11[a]	239.50 ± 0.13[a]
Extract (80 mg/kg) + PCM	244.33 ± 1.05[a]	79.00 ± 0.30[a]	247.17 ± 0.31[a]
Extract (120 mg/kg) + PCM	214.00 ± 1.03[a]	88.33 ± 0.50[a]	262.00 ± 0.11[a]
Silymarin (100 mg/kg) + PCM	180.50 ± 1.10[a]	82.67 ± 0.12[a]	225.50 ± 0.31[a]
Extract (80 mg/kg) +Silymarin + PCM	335.67 ± 0.04[a]	111.17 ± 0.50[a]	237.33 ± 0.22[a]

Values represent Mean ± SEM

Significance relative to control: [a]$p < 0.001$; (n = 6).

NS = Normal saline; PCM = Paracetamol

Table 2: Effect of extract on PCM-induced toxicity in kidney functions in rats

Groups (Doses)	Creatinine (µmol/L)	Urea (mmol/L)	Total Protein (g/L)	Albumin (g/L)	Total Bilirubin (µmol/L)
Control (NS,10 ml/kg)	103.50 ± 0.15	4.65 ± 0.35	66.67 ± 0.04	35.50 ± 0.50	3.48 ± 0.10
PCM (2000 mg/kg)	109.83 ± 0.11[a]	7.39 ± 0.39[c]	71.17 ± 0.11[a]	37.50 ± 0.73	4.52 ± 0.14
Extract (40 mg/kg) + PCM	104.50 ± 0.20[a]	5.77 ± 0.45[a]	65.17 ± 0.05[a]	35.04 ± 1.71	3.20 ± 0.12[c]
Extract (80 mg/kg) + PCM	101.00 ± 0.01[a]	6.30 ± 0.55[a]	64.00 ± 0.13[a]	35.33 ± 0.99	3.62 ± 0.17
Extract(120 mg/kg) + PCM	105.67 ± 0.11[a]	6.17 ± 0.49[a]	63.67 ± 0.06[a]	37.83 ± 0.95[d]	3.58 ± 0.07
Silymarin (100 mg/kg) + PCM	102.50 ± 0.21[a]	4.85 ± 0.43[a]	62.67 ± 0.12[a]	34.60 ± 1.68	3.08 ± 0.18
Extract(80mg/kg) + Silymarin + PCM	93.67 ± 0.13[a]	7.75 ± 0.46[a]	62.00 ± 0.01[a]	36.83 ± 1.11	3.72 ± 0.05[d]

Values represent Mean ± SEM

Significance relative to control: [a]$p < 0.001$; [c]$p < 0.01$; [d]$p < 0.05$; (n = 6).

NS = Normal saline; PCM= Paracetamol

Table 3: Effect of extract on PCM-induced toxicity in electrolyte balance in rats

Groups (Doses)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Phosphate (mmol/L)
Control (NS,10 ml/kg)	151.00 ± 0.73	7.37 ± 0.18	102.33 ± 0.49	4.61 ± 0.16
PCM (2000 mg/kg)	159.17 ± 0.79[a]	7.40 ± 0.33	106.83 ± 0.48[a]	5.18 ± 0.36
Extract (40 mg/kg) + PCM	149.33 ± 0.71[c]	6.80 ± 0.48	104.33 ± 1.02[a]	2.82 ± 0.22[a]
Extract (80 mg/kg) + PCM	148.00 ± 0.37[a]	6.60 ± 0.44[d]	102.17 ± 0.40	2.47 ± 0.31[a]
Extract(120 mg/kg) + PCM	148.33 ± 0.42[a]	8.47 ± 0.50[a]	102.67 ± 0.42	3.47 ± 0.27[a]
Silymarin (100 mg/kg) + PCM	147.83 ± 0.60[a]	6.77 ± 0.31	100.00 ± 0.45	2.59 ± 0.12[a]
Extract(80mg/kg)+Silymarin+PCM	144.83 ± 1.01[a]	7.07 ± 0.31	104.83 ± 0.65[a]	3.16 ± 0.13[a]

Values represent Mean ± SEM

Significance relative to control: [a]$p < 0.001$; [c]$p < 0.01$; [d]$p < 0.05$; (n = 6).

NS = Normal saline; PCM = Paracetamol

Table 4: Effect of extract on PCM- induced toxicity in haematological indices in rats

Group	Hb (g/dL)	PCV (%)	Platelets ($x10^9$/L)	WBC ($x10^9$/L)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)
Control (NS,10 ml/kg)	13.98 ± 0.36	45.95 ± 0.85	593.67 ± 19.92	10.94 ± 0.11	34.03 ± 1.97	62.77 ± 0.00	10.08 ± 0.10	1.00 ± 0.39	0.18 ± 0.07
PCM (2000 mg/kg)	16.53 ± 0.26	49.80 ± 0.93 [a]	645.83 ± 83.07	9.59 ± 0.05 [a]	45.60 ± 3.00 [a]	53.30 ± 0.05 [a]	4.23 ± 0.01 [a]	0.28 ± 0.11 [d]	0.12 ± 0.04
Extract (40 mg/kg) + PCM	14.45 ± 0.52	48.93 ± 1.63 [c]	587.17 ± 93.81	11.92 ± 0.02 [a]	44.73 ± 1.90 [a]	51.08 ± 0.11 [a]	3.40 ± 0.13 [a]	0.47 ± 0.16	0.15 ± 0.02
Extract (80 mg/kg) + PCM	14.35 ± 0.36	47.47 ± 0.83	579.33 ± 39.34	12.13 ± 0.11 [a]	42.48 ± 1.15 [a]	53.67 ± 0.13 [a]	6.67 ± 0.14 [a]	1.58 ± 0.45	0.17 ± 0.02
Extract(120 mg/kg) + PCM	14.48 ± 0.44	48.42 ± 1.29 [d]	542.83 ± 72.18	17.68 ± 0.03 [a]	45.37 ± 2.35 [a]	49.80 ± 0.11 [a]	3.63 ± 0.20 [a]	1.03 ± 0.21	0.17 ± 0.04
Silymarin (100 mg/kg) + PCM	13.90 ± 0.36 [c]	46.52 ± 1.15 [a]	565.17 ± 68.52	11.75 ± 0.04 [a]	46.46 ± 1.34 [a]	49.13 ± 0.12 [a]	9.92 ± 0.40	0.57 ± 0.31	0.25 ± 0.10
Extract (80mg/kg) + Silymarin + PCM	14.80 ± 0.24 [c]	48.07 ± 1.33	536.17 ± 76.93	11.10 ± 0.14 [d]	34.82 ± 3.50	53.85± 0.10 [a]	9.82 ± 0.22	1.42 ± 0.74	0.17 ± 0.08

Values represent Mean ± SEM
Significance relative to control: [a] $p < 0.001$; [c] $p < 0.01$; [d] $p < 0.05$; (n = 6).
NS = Normal saline; PCM = Paracetamol

Table 5: Effect of extract on PCM- induced toxicity in the wet weight of testis in rats

Groups (Doses)	Right Testis (g)	Left Testis (g)
Control (NS,10 ml/kg)	1.04 ± 0.06	1.01± 0.06
PCM (2000 mg/kg)	1.00 ± 0.02	0.99 ± 0.03
Extract (40 mg/kg) + PCM	0.90 ± 0.13 [d]	0.90 ± 0.12
Extract (80 mg/kg) + PCM	1.04 ± 0.07	1.03 ± 0.07
Extract(120 mg/kg) + PCM	1.12 ± 0.02	1.04 ± 0.03
Silymarin (100 mg/kg) + PCM	1.06 ± 0.08	1.16 ± 0.09 [d]
Extract(80mg/kg)+Silymarin+PCM	0.93 ± 0.03	0.99 ± 0.03

Values represent Mean ± SEM
Significance relative to control; [d] $p < 0.05$; (n = 6).

Table 6: Effect of extract on PCM- induced toxicity in the wet weight (grams) of rat epididymis

Groups (Doses)	Right Epididymis	Left Epididymis
Control (NS,10 ml/kg)	0.56 ± 0.06	0.52± 0.06
PCM (2000 mg/kg)	0.42 ± 0.02 [a]	0.43 ± 0.02 [d]
Extract (40 mg/kg) + PCM	0.47 ± 0.07 [d]	0.50 ± 0.05
Extract (80 mg/kg) + PCM	0.50 ± 0.05	0.46 ± 0.04
Extract(120 mg/kg) + PCM	0.50 ± 0.03	0.45 ± 0.03
Silymarin (100 mg/kg) + PCM	0.47 ± 0.05 [d]	0.50 ± 0.05
Extract(80mg/kg)+Silymarin+PCM	0.43 ± 0.03 [d]	0.40 ± 0.07 [c]

Values represent Mean ± SEM
Significance relative to control: [a] $p < 0.001$; [c] $p < 0.01$; [d] $p < 0.05$; (n = 6).

Table 7: Effect of extract on PCM- induced toxicity in the wet weight of rat kidneys

Groups (Doses)	Right Kidney	Left Kidney
Control (NS,10 ml/kg)	0.50 ± 0.03	0.53 ± 0.02
PCM (2000 mg/kg)	0.52 ± 0.01	0.54 ± 0.03
Extract (40 mg/kg) + PCM	0.59 ± 0.07 [d]	0.56 ± 0.05
Extract (80 mg/kg) + PCM	0.61 ± 0.03 [c]	0.53± 0.03
Extract(120 mg/kg) + PCM	0.57 ± 0.04	0.53 ± 0.03
Silymarin (100 mg/kg) + PCM	0.72 ± 0.06 [a]	0.64± 0.04 [a]
Extract(80mg/kg) + Silymarin + PCM	0.50 ± 0.01	0.52± 0.01

Values represent Mean ± SEM
Significance relative to control: [a] $p < 0.001$; [c] $p < 0.01$; [d] $p < 0.05$; (n = 6).

Table 8: Effect of extract on PCM- induced toxicity in the wet weight of rat spleen

Groups (Doses)	Weight (g)
Control (NS,10 ml/kg)	0.60 ± 0.03
PCM (2000 mg/kg)	0.54 ± 0.03
Extract (40 mg/kg) + PCM	0.57 ± 0.03
Extract (80 mg/kg) + PCM	0.57 ± 0.04
Extract(120 mg/kg) + PCM	0.55 ± 0.03
Silymarin (100 mg/kg) + PCM	0.64 ± 0.04
Extract(80mg/kg)+Silymarin+PCM	0.52 ± 0.05

Values represent Mean ± SEM
No significance shown
(n = 6)

Table 9: Effect of extract on PCM- induced toxicity in the wet weight of rat liver

Groups (Doses)	Mean Weight (g)
Control (NS,10 ml/kg)	6.51 ± 0.23
PCM (2000 mg/kg)	6.34 ± 0.23
Extract (40 mg/kg) + PCM	6.51 ± 0.38
Extract (80 mg/kg) + PCM	7.15 ± 0.42[b]
Extract (120 mg/kg) + PCM	7.48 ± 0.34[a]
Silymarin (100 mg/kg) + PCM	7.63 ± 0.34[a]
Extract (80mg/kg) + Silymarin +PCM	6.38 ± 0.24

Values represent Mean ± SEM
Significance relative to control [a]$p < 0.001$; [b]$p < 0.05$ (n = 6)

Table 10. Effect of extract on PCM- induced toxicity in rat weight (grams)

Groups (Doses)	Initial Weight	End Weight	Difference in Weight
Control (NS,10 ml/kg)	154.83 ± 7.93	168.17 ± 8.15	13.34
PCM (2000 mg/kg)	143.83 ± 6.14	154.33 ± 9.48	10.50[a]
Extract (40 mg/kg) + PCM	151.17 ± 7.24	173.33 ± 9.54	12.16[a]
Extract (80 mg/kg) + PCM	157.83 ± 9.39	169.67 ± 11.13	11.84
Extract(120 mg/kg) + PCM	163.33 ± 2.35	167.83 ± 7.90 [a]	4.50
Silymarin (100 mg/kg) + PCM	198.00 ± 8.29	182.33 ± 20.26	-15.67
Extract(80mg/kg) + Silymarin + PCM	141.50 ± 3.15	159.33 ± 2.26	17.83

Values represent Mean ± SEM
Significance relative to control: [a]$p < 0.001$ (n = 6)
NS = Normal saline; PCM = Paracetamol

DISCUSSION

Paracetamol which is widely used as analgesic and antipyretic drug is a typical hepatotoxin. Paracetamol produces acute hepatic damage. This is due to a fraction of paracetamol that is converted via the cytochrome P_{450} pathway to a highly toxic metabolite, N-acetyl-p-benzoquinamine (NAPQI) (Dahlin *et al.*, 1984; Rajkapoor *et al.*, 2008). This compound is normally conjugated with glutathione and excreted in urine. The overdose of paracetamol depletes glutathione stores, leading to accumulation of NAPQI, causing mitochondrial dysfunction (Parmer and Kandakar, 1995) and the development of acute hepatic necrosis in the centrolobular portion of the liver (Rang and Dale, 1987). Several P_{450} enzymes are known to play an important role in paracetamol bioactivation to NAPQI (Reasor and Davis, 1994; Jacks *et al.*, 2004; Baravalia and Chanda, 2011). Alanine aminotransferase (ALT) is a hepatospecific enzyme that is principally found in the cytoplasm of rat liver cells (Benjamin, 1978; Ringler and Dahich, 1979). Aspartate aminotransferase (AST) is an enzyme that is present in high quantities in the cytoplasm and mitochondria of liver cells, the heart, skeletal muscle, kidney and brain (Jacks *et al.*, 2004). That the extract caused increase in serum AST and ALT is an indication of cellular leakage and loss of functional integrity of cell membrane in the liver (Dratman and Lawhorn, 1978).

ALT is more specific to the liver and is thus a better parameter for detecting liver injury. In human, alkaline phosphatase is present in all tissues throughout the entire body, but is particularly concentrated in the liver, bile duct, kidney, bone, intestinal mucosa and placenta. An increase in ALP is an indication of hepatocellular injury which manifests mostly in the hepatobiliary obstruction (Plaa and Hewit, 1989; Muriel and Garcipiana, 1992). That ALP serum concentration in relation to both control and toxicant is lower, suggests less biliary obstruction.

There was observed increase in serum concentrations of creatinine and urea relative to control. These are non-

protein nitrogens which are functions of kidney integrity and do not affect the physiological functions as much as hydrogen (H^+) and potassium (K^+) ions (Guyton, 1981). The decrease in serum total protein concentration reflected decrease in protein catabolism. This was corroborated by non-significant changes in plasma albumin (Nwafor *et al*., 2004). Bilirubin which is a catabolic product of haem showed no significant change relative to control. This result corroborated the little or no effect of ALT on bile duct as haem is excreted in the bile and urine (Okokon *et al*., 2013).

On the ionic analysis, the concentration of intracellular potassium ion (K^+) did not indicate a rise in serum concentration. This effect was also observed in extracellular sodium (Na^+), Cl^- and Po_4^- ions. These effects were not deleterious to the system (Okanny and Nwafor, 2015).

The slight increase in Hb and PCV concentrations could be seen as the ability of the extract to stimulate mild erythropoiesis, while the increase in the WBC could be considered as a compensatory effect following the antigenic property of the toxicant (PCM). This antigenic effect which manifested in lethargy of cells was observed in platelet count. The differentials results were in agreement with WBC, as observed increase and decrease in neutrophils, lymphocytes and monocytes respectively. The inflammatory mediators (Basophils and eosinophils) were not significantly affected (Nwafor *et al*., 2001).

The increase in wet weight of the liver could only be explained as fat infiltration or depositions in the liver as its effect on total protein was negatively significant. The fat deposition may have in part led to increase in body weight (Noorami *et al*; 2010). Changes in wet weight of the testis, epididymis, spleen and kidney could neither be accounted for anabolism nor negative net nitrogenous compound waste.

As reported by Udenwoke (2016), the extract contained alkaloids, tannins, saponins and flavonoid. Others were anthraquinones and cardiac glycosides. It is likely that the increase in transaminases might in part be due to its (extract) estrogenic (steroid) properties since steroid is known to interfere with the integrity of the liver and kidney (Nwafor *et al*., 2004).

The antigenicity of the extract may in part be due to the presence of tannins (Trease and Evans, 1989; Nwafor *et al*., 2001). Drugs that have anti-inflammatory effects for example, acetyl salicylic acid and other non-steroidal anti-inflammatory drugs reduced platelet count (Mackie and Ludlam, 1995; Nwafor *et al*., 2001).

In conclusion therefore, the effect of the extract in paracetamol-induced toxicity in rat may in part be due to its secondary metabolites. However, further work is advocated in the erea of elucidation of the structure of the active ingredients of the extract

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Conflict of Interest

The authors therefore declare that there is no conflict of interest.

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