Journal of Forensic Science and Toxicology

Research Article
Published: 13 Jun, 2019

Multi-Organ Protective Effect of Aqueous Leaf Extracts of *Euphorbia heterophylla* and *Jatropha curcas* against Paracetamol-Induced Toxicity in Albino Rats

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Abstract

The protective effect of aqueous leaf extracts of *Euphorbia heterophylla* and *Jatropha curcas* against paracetamol-induced acute changes in kidney, heart and liver organ function parameters of albino rats were studied. Twenty-five adult male albino rats (180 - 200g) were randomly distributed into 5 groups (I to V) of five animals each. Groups I and II were administered 10 ml of distilled water and 1000 mg of paracetamol per kg body weight respectively. Groups III to V were pretreated with vitamin C (500 mg/kg body weight), *E. heterophylla* (200 mg/kg body weight) and *J. curcas* (1000 mg/kg body weight) respectively 1 h before administration of 1000 mg of paracetamol/kg body weight. Single doses of the drugs/extracts were orally administered daily for 14 days. Administration of paracetamol significantly ($p<0.05$) increased the serum activities of LDH, AST, ALT and ALP as well as the concentrations of bilirubin, urea, creatinine and electrolytes but reduced serum total protein and albumin concentrations of the intoxicated animals in comparison with the control. Treatment of the paracetamol-intoxicated animals with vitamin C and plant extracts significantly ($p<0.05$) countered the observed alterations, with vitamin C and *J. curcas* having more protective effects than *E. heterophylla*. However, treatment with vitamin C and the plant extracts did not significantly ($p>0.05$) protect the animals from overall loss in body weight elicited by acute paracetamol overdose. The results indicate that aqueous leaf extracts of *E. heterophylla* and *J. curcas* have significant protective effect against paracetamol-induced alterations to renal, cardiac and hepatic organ functions.

Keywords: Acetaminophen; Drug overdose; Organ function; Medicinal plants; Vitamin C

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Received Date: *17 May 2019*

Accepted Date: *06 Jun 2019*

Published Date: *13 Jun 2019*

Citation:

Igwe CU, Nwaogu LA, Olunkwa EU, Otaba MA, Nwachukwu N. Multi-Organ Protective Effect of Aqueous Leaf Extracts of Euphorbia heterophylla and Jatropha curcas against Paracetamol-Induced Toxicity in Albino Rats. J Forensic Sci Toxicol. 2019; 2(1): 1007.

Introduction

Paracetamol is a commonly used Over-the-Counter (OTC) analgesic and antipyretic drug. It is available as a component of a surfeit of combination OTC and prescription medications and or as a single-component medication. It is safe at therapeutic doses but causes fatal hepatic necrosis and failure in overdose [1]. It is one of the best known experimental models of hepatotoxicity [2]. Paracetamol is reported to induce a wide spectrum of toxicities especially when taken in large single dose either alone or in combination with an equally large amount of alcohol [3,4]. These toxicities are often pansystemic, involving virtually all organs/systems in the body. In the liver and kidneys, paracetamol overdose causes potentially fatal hepatotoxicity and nephrotoxicity, respectively [4]. Paracetamol toxicity remains a major intolerable side-effect of the clinical use of paracetamol in all age-groups, with limited available conventional therapeutic and chemoprophylactic options. Thus, the present study was aimed at investigating the protective effect of the aqueous leaf extracts of *Euphorbia heterophylla* and *Jatropha curcas* against paracetamol-induced toxicity in albino rats.

E. heterophylla, also known as *E. geniculate*, *E. pronifolia*, *Poinsettia geniculata* and *P. heterophylla,* is a tropical annual weed with characteristic milky latex. It is commonly called *nono-kunchiya* in Hausa, *egele* or *aka-ito* in Igbo and *adimeru* in Yoruba, Nigeria [5]. *E. heterophylla* leaf is used in traditional medical practices as laxative, and therapeutic agent against gonorrhea, migraine and heart aches, and have potential to eliminate wart [6,7]. It has been used for the treatment of constipation, bronchitis and asthma, as well as to accelerate wound healing, and as a purgative [8]. The leaves of *E. heterophylla* are commonly used as a lactogenic agent by taking a decoction of it or by massaging the breast with the poultice to induce milk flow. The latex of the plant is used as insecticide and poisons [7,9]. Previous biological studies have reported antibacterial and anti-inflammatory activities as well as the wound healing potentials of the leaf of *E. heterophylla* [9].

The skin irritant, anti-tumour/cancer and recently anti-HIV activities of Euphorbia species have also been reported in *E. heterophylla* leaf [7,10].

J. curcas L. is commonly known as physic nut, purging nut, pig nut or jablota. It is a multipurpose shrub or small tree belonging to the family of Euphorbiaceae. *Jatropha curcas* L originated in Central America, but now thrives in many parts of the tropics and sub-tropics of Africa and Asia [11]. Preparations of all parts of the plant, including seeds, leaves and stem-bark, fresh or as a decoction, are used in traditional medicine and for veterinary purpose [12]. It is used in different parts of the world as antiseptic, cicatrizant, depurative, haemostatic, and as a rubefacient. It is also a folk remedy for eczema, dermatitis, carbuncles, and burns [13]. The leaf, seed extract and seed oil of Jatropha gives sensitive microbicidal activity. *J. curcas* contains higher steroids, terpenoids (mainly, phorbol ester), flavonoids and alkaloids (mainly, jatrophine) compounds in the leaf and seed in comparison to other species of Jatropha. Previous studies revealed the presence of antibacterial agents in different parts of *Jatropha curcas* [11]. It is speculated that high antibacterial and antifungal activities of different extracts of Jatropha may be due to the presence of phenolic compounds [14]. Extracts of *J. curcas* act as a strong painkiller and may have a mode of action different from conventional analgesics, such as morphine and other pharmaceuticals [15]. The extract is comparable to paracetamol but reportedly anagonistic in activity at similar or higher doses. This analgesic effect of *J. curcas* was attributed to its anti-inflammatory effect [16]. Phytochemical analysis of the methanol extract used in formulating herbal ointment showed the presence of glycosides, alkaloids, saponins, tannins, flavonoids, resins, sterols, terpenoids, and carbohydrates [13]. Traditionally, it is used to cure diseases like cancer, piles, snake bites, paralysis and dropsy [16]. Extracts from the leaves and stem of *J. curcas* plant popularly called *Anyaso-obara* or *Ogwo-nma* by the local people of Igboland in Nigeria are used to treat wounds and sores [12]. The roots are used for treating chest disease or may be cooked with gruel and given to patients suffering from kidney diseases. The leaves have been used as haemostatic agent and for the treatment of fever and jaundice [16]. Its use in the treatment of various organ-related diseases indicates potential protective effect against drug-induced damage to organs and tissues.

Materials and Methods

Plants collection and extract preparation

The leaves of *Jatropha curcas* and *Euphorbia hetrophylla* were collected from bushes around Eziobodo in Owerri West L.G.A of Imo State. They were authenticated at the Department of Forestry and Wildlife, Federal University of Technology, Owerri (FUTO). The leaves were air-dried for two weeks and then oven-dried at a temperature of 50°C for 4 h. The dried leaves were ground using pestle and mortar to powder form and stored separately in labeled air tight containers. Five hundred grams (500 g) of each leaf powder was soaked in 1000 ml of distilled water for 48 h and filtered with what man filter paper No. 1. The filtrates were evaporated to dryness and then made into a suspension in 100 ml of 0.5% Tween 80 solvent using a 500 ml beaker and filtered again. The filtrates were evaporated in an electric oven at 50°C to obtain the stock concentrates which were refrigerated at 4°C. Working extract doses of 200 mg/kg and 1000 mg/kg for *E. heterophylla* and *J. curcas* respectively were prepared from the stocks with distilled water as diluent.

Paracetamol and Vitamin C preparation

Paracetamol and vitamin C (Emzor Pharmaceuticals Ltd., Nigeria) were obtained at Orchad Pharmacy, Owerri. Each tablet contains 500 mg of paracetamol was dissolved in 10 ml of distilled water while each tablet of vitamin C containing 100 mg of ascorbic acid was dissolved in 1 ml of distilled water. These were reconstituted and administered at doses of 1000 mg/kg and 500 mg/kg body weight to the animals respectively.

Laboratory animals

Laboratory animals used were made up of 25 adult male albino rats weighing between 180 g and 200 g, obtained from the Veterinary Department, University of Nigeria, Nsukka. The animals were housed in cages under standard environmental conditions of temperature (30 ± 1°C), humidity (60 ± 0.2%) and a 12 h light/dark cycle in the Animal House of Department of Biochemistry, Federal University of Technology, Owerri for 14 days to acclimatize. The animals were fed with standard rodent diet (Vital Feeds Ltd., Nigeria) and water *ad libitum*.

Grouping of the animals

The animals were randomly divided into 5 groups (I to V) of 5 rats each such that the weight differences within and between groups did not exceed ± 20% of the average weight of all the animals. Group I served as the untreated control and were orally administered single daily dose of 10 ml/kg of distilled water only. Group II served as the model control and were orally administered single daily dose of 1000 mg/kg of paracetamol. Group III animals were pretreated with single oral dose of 500 mg/kg of vitamin C solution 1 h before the oral administration of 1000 mg/kg of paracetamol. Group IV animals were pretreated with single oral dose of 200 mg/kg of *E. heterophylla* leaf extract 1 hour before the oral administration of 1000 mg/kg of paracetamol. Group V animals were pretreated with single oral dose of 1000 mg/kg of *J. curcas* leaf extract 1 h before the oral administration of 1000 mg/kg of paracetamol. The chosen dose ranges for paracetamol and the plant extracts used was based on reports of earlier studies conducted on their median lethal dose (LD_{50}). The LD_{50} of the extracts is 2600 g for *J. curcas* [17] and 208 g for *E. heterophylla* [7,18]. The administration of the paracetamol and plant extracts was done once every twenty-four (24) hours for total period of fourteen days.

Sample collection

The animals were all weighed on the first and last days of treatment. At the end of the treatment period, they were fasted overnight and then sequentially anaesthetized with diethyl ether for about 20 to 30 seconds. About 4 to 5 mL of whole blood was collected by cardiac puncture from each animal with a 21 gauge needle mounted on 5 mL syringe. Each blood sample was gently dispensed into a well labeled 10 ml capacity plain sample bottle, allowed to clot and centrifuged at 2000 rpm for 15 min to separate the serum from the clot. The sera obtained were stored frozen until required for biochemical analysis.

Biochemical Analyses of Sera Samples

Liver and cardiac function profile

The activities of serum aminotransferases were assayed with the aid of AST and ALT kits (Randox Laboratories Ltd, U.K) as described by Reitman and Frankel [19]. Alkaline phosphatase (ALP) activity was assayed by colometric method [20] with the aid of Teco Alkaline Phosphatase Reagent kit (Teco Diagnostics, Ca, USA). Total protein

Table 1: Liver and cardiac function parameters of paracetamol intoxicated albino rats treated with aqueous leaf extracts of *E. heterophylla* and *J. curcas*.

Parameters	GROUPS				
	Control	Paracetamol	Vitamin C	*E. heterophylla*	*J. curcas*
LDH (IU/L)	328.62 ± 9.26^{a}	448.84 ± 10.00^{b}	332.62 ± 8.02^{a}	352.66±13.09^{c}	336.63 ± 7.27^{ac}
AST (U/l)	21.90 ± 0.78^{a}	50.63 ± 1.72^{b}	25.64 ± 0.99^{c}	42.06 ± 2.88^{d}	37.32 ± 0.42^{e}
ALT (U/l)	18.06 ± 0.09^{a}	27.28 ± 0.26^{b}	18.74 ± 0.16^{a}	24.91 ± 0.16^{c}	20.99 ± 0.73^{d}
ALP (IU/L)	60.16 ± 0.13^{a}	75.00 ± 0.63^{b}	63.11 ± 1.68^{c}	72.42 ± 0.09^{d}	68.15 ± 1.16^{e}
Total protein (g/dl)	6.06 ± 0.05^{a}	5.07 ± 0.07^{b}	5.54 ± 0.01^{c}	5.46 ± 0.04^{c}	5.69 ± 0.02^{c}
Albumin (g/dl)	4.11 ± 0.08^{a}	3.51 ± 0.03^{b}	3.79 ± 0.06^{c}	3.76 ± 0.04^{c}	3.89 ± 0.05^{c}
Total bilirubin (mg/dl)	0.48 ± 0.01^{a}	0.67 ± 0.01^{b}	0.54 ± 0.02^{c}	0.60 ± 0.02^{d}	0.58 ± 0.02^{d}

Values are mean ± standard deviation. Values with different alphabet letters per row are statistically significant ($p \leq 0.05$)

Table 2: Kidney function and electrolyte parameters of paracetamol intoxicated albino rats treated with aqueous leaf extracts of *E. heterophylla* and *J. curcas*.

Parameters	GROUPS				
	Control	Paracetamol	Vitamin C	*E. heterophylla*	*J. curcas*
Urea (mg/dl)	29.92 ± 0.30^{a}	35.36 ± 0.37^{b}	31.98 ± 0.12^{c}	32.64 ± 0.12^{c}	31.83 ± 0.31^{c}
Creatnine (mg/dl)	0.52 ± 0.01^{a}	0.83 ± 0.04^{b}	0.62 ± 0.02^{c}	0.72 ± 0.04^{d}	0.72 ± 0.03^{d}
Na^{+} (mEq/L)	150.00 ± 2.50^{a}	170.08 ± 3.04^{b}	155.17 ± 2.48^{ac}	164.91 ± 3.83^{c}	160.04 ± 3.04^{c}
K^{+} (mEq/L)	5.49 ± 0.06^{a}	5.81 ± 0.09^{b}	5.61 ± 0.06^{ac}	5.74 ± 0.07^{bc}	5.73 ± 0.08^{bc}
CL^{-} (mEq/L)	105.00 ± 2.20^{a}	120.000 ± 2.63^{b}	107.83 ± 1.32^{ac}	115.00 ± 2.20^{d}	111.84 ± 2.63^{cd}
HCO_3^{-} (mmol/L)	28.96 ± 1.00^{a}	21.01 ± 1.30^{b}	26.98 ± 0.80^{ad}	24.00 ± 1.40^{c}	25.00 ± 2.40^{cd}

Values are mean ± standard deviation. Values with different alphabet letters per row are statistically significant ($p \leq 0.05$)

and albumin were determined by the biuret and bromocresol green methods [20] with the aid of Randox total protein and albumin reagent kits. Serum total bilirubin was determined by colometric method [21] with the aid of Randox bilirubin reagent kit, while Lactate Dehydrogenase (LDH) activity was assayed by optimized kinetic assay method [22] using LDH test kit (Span Diagnostics Ltd, India).

Kidney function and electrolyte profile

Serum urea nitrogen and creatinine concentrations were determined using colorimetric methods based on Berthelot urease and Jaffe reactions [20] with the aid of Randox urea and creatinine reagent kits (Randox Laboratories Ltd, U.K). Serum sodium, potassium, chloride and bicarbonate concentrations were determined using colometric methods [20] with the aid of commercially available reagent kits (Teco Diagnostics Ca, USA).

Organ weight measurement

The heart, liver and kidney of the anesthetized animals were excised and gently rinsed off of blood in normal saline, blotted dry and weighed on a filter paper placed on a mettler weighing balance.

Statistical analysis

Data obtained from experimental groups were expressed as mean ± standard deviation. The data were analyzed using one-way analysis of variance (ANOVA) and Turkey Post HOC test with the aid of GraphPad Prism Version 5.3 (GraphPad, USA). Values for $p \leq 0.05$ were considered statistically significant.

Results

The effect of treatment with vitamin C and aqueous leaf extracts of *E. heterophylla* and *J. curcas* on the liver and cardiac function indices of paracetamol intoxicated animals are shown in Table 1. Treatment with paracetamol increased significantly ($p<0.05$) the serum AST, ALT, ALP, and LDH activities as well as the total bilirubin concentration of the animals in comparism with the control. Administration of vitamin C and the plant extracts significantly ($p<0.05$) reduced the observed effects of paracetamol intoxication on serum enzyme activities and bilirubin concentrations of the treated animal groups. Paracetamol administration significantly ($p<0.05$) reduced the serum total protein and albumin concentrations of the animals in comparism to the control. However, there was a significant ($p<0.05$) increase in the protein and albumin levels following treatment of the paracetamol intoxicated animals with vitamin C and the plant leaf extracts.

Table 2 shows the kidney function and electrolyte profile of the paracetamol intoxicated animals treated with vitamin C and aqueous leaf extracts of *E. heterophylla* and *J. curcas*. Paracetamol intoxication increased significantly ($p<0.05$) the serum urea, creatinine, sodium, potassium and chloride ion concentrations but reduced the bicarbonate ion concentration of the animals in comparism with the control. Treatment of the animals with the plant extracts significantly ($p<0.05$) attenuated the observed effects of paracetamol intoxication as serum concentrations of the kidney function and electrolyte parameters were lowered in the animal groups treated with vitamin C and aqueous leaf extracts of *E. heterophylla* and *J. curcas*.

Changes in body and organ weights (g) of the paracetamol intoxicated animals treated with vitamin C and aqueous leaf extracts of *E. heterophylla* and *J. curcas* are shown in Table 3. Paracetamol intoxication significantly ($p<0.05$) elicited an overall reduction in the body weights of all the animals administered paracetamol, whether treated or not, but more significant effect on the untreated group. On the other hand, paracetamol intoxication did not change significantly ($p>0.05$) the kidney organ weight of the animals but reduced their heart organ weight in comparism with the control and Vitamin C groups. Treatment of the paracetamol intoxicated animals with aqueous leaf extracts of *E. heterophylla* and *J. curcas* significantly ($p<0.05$) reduced the kidney and heart organ weights of the animals.

Table 3: Body and some organ weights of paracetamol intoxicated albino rats treated with aqueous leaf extracts of *E. heterophylla* and *J. curcas*.

Parameters	GROUPS				
	Control	Paracetamol	Vitamin C	*E. heterophylla*	*J. curcas*
Initial Body weight (g)	139.25 ± 1.55	159.58 ± 13.01	189.00 ± 3.70	143.50 ± 8.23	149.43 ± 10.07
Final Body weight (g)	160.90 ± 4.19	140.75 ± 9.64	163.03 ± 2.30	128.00 ± 5.83	133.75 ± 7.18
% Change in body Wt (g)	15.55 ± 0.56^{a}	-13.36 ± 0.19^{b}	-13.76 ± 0.36^{b}	-10.80 ± 0.27^{c}	-10.49 ± 0.34^{c}
Kidney (g)	1.14 ± 0.08^{a}	1.16 ± 0.07^{a}	1.15 ± 0.07^{a}	0.90 ± 0.03^{b}	0.89 ± 0.01^{b}
Heart (g)	0.56 ± 0.07^{a}	0.45 ± 0.08^{b}	0.50 ± 0.08^{ab}	0.38 ± 0.05^{bc}	0.43 ± 0.05^{bc}
Liver (g)	5.63 ± 0.58^{a}	5.21 ± 0.70^{ab}	6.01 ± 0.85^{a}	4.23 ± 0.33 ^{b}	5.06 ± 0.22^{ab}

Values are mean ± standard deviation. Values with different alphabet letters per row are statistically significant ($p \leq 0.05$)

Acute paracetamol intoxication as well as treatment with the plant extracts did not significantly ($p<0.05$) affect the treated animals' liver organ weights.

Discussion

Paracetamol elicits tissue cellular toxicity via lipid peroxidation mediated principally by the highly reactive intermediate, N-Acetyl-ParabenzoQuinonimine (NAPQI) [23]. NAPQI acts by covalently binding to intracellular and membrane localized macromolecules of liver cells leading to release of intracellular contents including the cytosolic liver enzymes into the extracellular environment [4]. Thus, paracetamol toxicity is often associated with significant elevation in the activity of circulating liver enzymes particularly the aminotransferases (ALT and AST). These enzyme markers are known indicators of hepatocellular injury [4,24].

Results of the present study showed a marked elevation in the activities of serum liver enzymes of the animals administered paracetamol overdose. This is indicative of cellular leakage and loss of functional integrity of hepatocellular cell membranes. Hepatocellular necrosis leads to increased activity of liver function markers in the blood. Among these, AST and ALT represent 90% of increased total enzyme activity in liver injury [25]. In terms of cellular localization, AST is similar to ALT in that both enzymes are associated with liver parenchyma cells. The only difference is that ALT is found predominantly in the liver with clinically negligible quantities found in the cardiac muscles, skeletal muscles, kidneys, brains, and red blood cells, while AST is found to be clinically important in both liver and heart related conditions [4,7].

Paracetamol intoxication also resulted in elevation in the activity of serum Lactate Dehydrogenase (LDH), an enzyme normally localized in the cytoplasm of cells and thus extruded into the serum when cells are damaged or necrotic. Measurement of total LDH and AST activities are useful when the heart is suspected to be diseased [26]. LDH-1 is the most abundant isoenzyme from cardiac muscle, and is utilized in the diagnosis of acute myocardial infarction. When the serum activity of LDH-1 exceeds that of LDH-2 (since the opposite is generally true in serum from healthy individuals), a phenomenon which has been referred to as the LDH1-2 flip, it is strongly indicative of damage to cardiac tissue and possibly due to acute myocardial infarction [27].

Alkaline Phosphatase (ALP) activity was also elevated following paracetamol intoxication in the animals. ALP is reported to be present in a large number of cells but only in a few cells is the activity sufficient to be of clinical significance [28]. It is found localized in the hepatobiliary regions of liver tissue, but is also associated with osteoblastic activity in the bone [7,29]. Thus high activity of ALP in the blood serum is commonly related to its increased synthesis by cells lining bile canaliculi usually in response to cholestasis and increased biliary pressure [25].

Treatment of the paracetamol intoxicated animals with vitamin C and extracts of *E. heterophylla* and *J. curcas* significantly ($p<0.05$) reduced the elevated activities of LDH, AST, ALT and ALP towards their respective normal values as observed in the control animals. This is an indication of stabilization of plasma membrane as well as repair of cardiac and hepatic tissue damages elicited by the acute paracetamol toxicity. The observed changes can be considered as expression of the functional improvement of hepatocytes, which may be caused by an accelerated regeneration of parenchymal cells. Effective control of ALP activities probably points towards an early improvement in the secretory mechanism of the hepatic cells.

Protein metabolism is a major role of the liver. A healthy functional liver is required for the synthesis of the serum proteins except for the γ globulins. Hypoproteinaemia is a feature of liver damage due to significant fall in protein synthesis. Albumin, the major serum protein, is decreased in chronic liver disease and is generally accompanied by an increase in the β and γ globulins as a result of production of IgG and IgM [25,30]. Hypoproteinaemia and hypoalbuminaemia were observed after acute paracetamol intoxication but was significantly ($p<0.05$) countered by treatment with vitamin C, *E. heterophylla* and *J. curcas* extracts.

Measurement of serum bilirubin is one of the most sensitive tests employed in the diagnosis of hepatic diseases. Bilirubin in the blood is solely conjugated for excretion by the hepatocytes. Results of the present study showed that acute paracetamol intoxication elicited elevated serum bilirubin in the rats. Hyperbilirubinaemia is normally observed due to excessive heme destruction and blockage of the biliary tract. As a result of blockage of the biliary tract, there is a mass inhibition of the conjugation reaction and release of unconjugated bilirubin from damaged and dead hepatocytes [25]. Results of our study, showed that administration of vitamin C, *E. heterophylla* and *J. curcas* significantly ($p<0.05$) decreased the serum bilirubin concentration of the treated animals which suggests that they offered hepato-protection against paracetamol-induced organ damage to the animals.

Changes in blood creatinine and urea nitrogen concentrations are indicative of renal function alterations [31]. In the present study, increased creatinine and urea concentrations were observed among the paracetamol intoxicated animals. However, treatment of the paracetamol toxicity with vitamin C and extracts of *E. heterophylla* and *J. curcas* reduced significantly ($p<0.05$) the elevated creatinine and urea concentrations. Creatinine is removed from the plasma by glomerular filtration and is then excreted in the urine without being

reabsorbed by the tubules to any significant extent. In addition, when plasma concentration of creatinine increases above normal, the kidney can also excrete it through the tubules. Consequently, blood creatinine levels in renal disease generally do not increase until renal function is substantially impaired [32]. Normal renal function depends on a normal filtration rate. A high glomerular filtration rate leads to increased excretion of creatinine. In addition, plasma creatinine concentration may not exceed the upper limit of the reference range until the glomerular filtration rate, and therefore the creatinine clearance has been significantly hampered [33]. Changes in blood creatinine are normally paralleled by changes in blood urea [33]. This observation is supported by the finding of significant attenuation of both the increased blood creatinine and urea concentrations by treatment with vitamin C, *E. heterophylla* and *J. curcas*. This indicates that treatments with the leaf extracts have ameliorative effects to the apparent renal injury caused by the paracetamol intoxication.

Elevated sodium concentration was observed after administration of paracetamol. However, the hypernatraemia observed was significantly ($p<0.05$) reduced by treatment with vitamin C, and extracts of *E. heterophylla* and *J. curcas.* Sodium is the major cation of extracellular fluid. It plays a central role in the maintenance of the normal distribution of water and the osmotic pressure in the various fluid compartments with most of it contained in the extracellular body fluids [20]. Administration of high doses of paracetamol also resulted in increased serum potassium concentration. Elevated potassium concentration (hyperkalaemia) is often associated with renal failure, dehydration, shock or adrenal insufficiency. Interestingly, the observed elevation in serum potassium concentration was significantly ($p<0.05$) attenuated after treatment with vitamin C, *E. heterophylla* and *J. curcas.* Potassium is the principal cation of intracellular fluid. It is also an important constituent of the extracellular fluid due to its influence on muscle activity. Its intracellular function parallels its extracellular function of influencing acid-base balance and osmotic pressure, including water retention [20]. Similarly, there was an elevated serum chloride ion concentration following paracetamol intoxication, which was significantly ($p<0.05$) reduced after treatment with vitamin C and aqueous extracts of *E. heterophylla* and *J. curcas.* Chloride, a major blood anion, is important in the maintenance of the cation/anion balance between intra- and extra-cellular fluids. This electrolyte is therefore essential to the control of proper hydration, osmotic pressure, and acid/base equilibrium. Elevated serum chloride concentration is usually associated with dehydration, hyperventilation, congestive heart valve, and prostatic or renal obstructions [20]. Serum bicarbonate concentration was significantly ($p<0.05$) lowered in the paracetamol intoxicated rats, while administration of vitamin C, *E. heterophylla* and *J. curcas* led to normalization of the bicarbonate concentration of the treated animals. Carbon dioxide (CO_2) in serum or plasma exists primarily as dissolved CO_2 or bicarbonate (HCO_3^-) [30]. The decrease in plasma bicarbonate content observed may likely be as a result of metabolic acidosis induced by administration of paracetamol. In pathologic conditions such as in glomerulonephritis, pyloric obstruction, diarrhea, diabetes mellitus, etc., acidosis or alkalosis could be anticipated. Blood bicarbonate alterations are used in the diagnosis and treatment of numerous potentially serious disorders associated with changes in body acid-base balance and hydration [20].

Acute paracetamol intoxication, as well as treatment with vitamin C and aqueous extracts of *E. heterophylla* and *J. curcas* reduced significantly ($p<0.05$) the body weights of the treated animals in comparism with the control. A study of the relative percentage changes in body weights of the animals shows that all the animals exposed to paracetamol intoxication, whether treated or not, had a drop in weight. This indicates a negative influence of paracetamol toxicity on body weight. The results indicate that paracetamol intoxication may have induced physiological distress in the animals preventing them from feeding normally or digesting, absorbing and utilizing effectively the nutrients present in their feed, which may have elicited the observed reduction in weight. Similarly, it was also observed that paracetamol toxicity reduced the liver and heart organ weights but not the kidney organ weights of the animals. This could also be a resultant effect of reduced feed intake, overall growth and gain in body weight. Treatment of the intoxicated animals with the extracts of *E. hetrophylla* and *J. curcas*, unlike vitamin C, significantly ($p<0.05$) reduced further the organ weights of the treated animals in comparism with the control. These observations may be attributed to a synergistic effect of the paracetamol and extracts, acting as xenobiotics, on the organs. However, this effect of the extracts on the organ weights may not be detrimental since the functional parameters of the organs as earlier discussed were not hampered by the administration of the extracts.

Conclusion

In the light of the results obtained in this study, it is clear that aqueous leaf extracts of *J. curcas* and *E. heterophylla* have protective effects against acute paracetamol-induced hepato-, cardio- and nephro-toxicity but did not protect against paracetamol-induced relative loss in body and organ weights. Thus aqueous leaf extracts of *J. curcas* and *E. heterophylla* could serve as promising source of drugs for the treatment of liver and kidney related ailments. However, caution should be taken in their use for medicinal and food purposes for humans and grazing animals, because of the observed negative effect on body and organ weights.

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