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Safety Evaluation of Aqueous Extract of *Crateva adansonii* Leaves on Selected Tissues of Rats

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Abstract
The phytochemical constituents and safety of aqueous extract of *Crateva adansonii* leaves on rats were investigated. Forty rats were grouped into 4 (A-D) of 10 animals each. Group A rats received 1 mL of distilled water, while groups B, C and D received equal volume corresponding to 325, 650 and 1300 mg/kg body weight of the extract, respectively, for seven days. Five rats were sacrificed from each group 24 h after 7 doses, while the remaining five were sacrificed 24 h after discontinuing the administration for another 7 days (recovery period, day 14). Phytochemical screening revealed the presence of saponins (2.36%), alkaloids (1.34%), tannins (0.94%), phenolics (1.06%), flavonoids (0.09%), phlobatannins (0.54%) and anthraquinones (0.47%). The extract significantly increased ($P<0.05$) the kidney, small intestine and serum activities of alkaline phosphatase (ALP), liver and serum γ-glutamyl transferase (Υ-GT), levels of serum globulin, white blood cells and lymphocytes, whereas the liver aspartate aminotransferase (AST) activity decreased. By the end of the recovery period, the levels of these biomolecules compared well ($P>0.05$) with their respective controls. In contrast, the increases in the serum total protein, ALP and AST as well as decreases in liver alanine aminotransferase (ALT), serum chloride and sodium ions were sustained during the recovery period. Furthermore, the levels of serum albumin, total and conjugated bilirubin, urea, creatinine, potassium, bicarbonate, haematological parameters and computed organ-body weight ratios were not significantly ($p>0.05$) altered. The histology of the kidney and small intestine were preserved whereas there was mild degeneration and congestion of the hepatocytes surrounding the central veins in the liver. Overall, the extract caused mild, selective and reversible changes in the haematological profile and biochemical parameters of organ function. Therefore, because the rats recovered from the assault of the extract, the plant may still be explored as oral remedy.

Keywords: *Crateva adansonii;* Organ dysfunction; Selective toxicity; recovery; transient effect, histoarchitecture

Introduction

Herbal medicine is gaining popularity in developing countries as has been estimated that 80% of the world population depend mainly on traditional medicine involving the use of plant extract (WHO, 1977). Various plants have been reported to be used in the treatment of several ailments. These include *Pterocarpus osun* used in the treatment of eczema, acnes, asthma and candidiasis (Gill, 1992), as well as *Annona senegalensis* in the treatment of diarrhoea, disease of the joints, respiratory diseases, conjunctivitis, wounds, snakebites, trypanosomiasis, jaundice, haemorrhoids, feminine

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barrenness, convulsions, ovarian cancer, fever, and asthenia (Neuwinger, 1996). One other plant claimed to be used in folklore medicine without recourse to its safety is *Crateva adansonii*.

Crateva adansonii DC (family: Capparidaceae) is known as sacred garlic pea or temple plant (English), *eegun orun* or a*janaka* (Yoruba-western Nigeria), *ungududu* (Hausa-northern Nigeria) and *amakarode* (Igbo-eastern Nigeria). It is native to Japan, Australia, Southeast Asia and several south Pacific Islands (Jacobs, 1964; Sharma, 1993; Ndanikou *et al.*, 2009). It is a small tree that grows up to 3 - 10 m tall with 3-foliated leaves. The flowers are white and appear when the tree is completely without leaves, while the edible fruit which is 3.5 - 5 mm large is spherical in shape. The plant has been claimed to be used as an antipyretic, a rubefacient and to counter irritation as well as to manage conditions such as bladder and kidney diseases, skin diseases, urinary diseases, rheumatoid arthritis, snake and insect bites (Quisumbing, 1951; Irvine, 1961; Nadkarni, 1976; Gill, 1992; Ashton *et al.*, 1997; Gupta *et al.*, 2006; Maruthupandian and Mohan, 2010; Ogbole *et al.,* 2010).

There are several scientific reports on the constituents and pharmacological activities of the plant. For instance, the stem bark has been reported to contain phenols, saponins, flavonoids, tannins, terpenoids, alkaloids and cardiac glycosides (Patil and Gaikwad, 2011) while saponins, terpenoids, cardiac glycosides and steroids are contained in the leaves (Chichioco-Hernandez and Paguinan, 2009). Furthermore, the inhibition of the growth of some pathogenic fungi and bacterial species, antimutagenic activity of the leaves and immune suppressing activity of the terpenoid (lupeol) isolated from the plant have been scientifically validated (Bani *et al.*, 2006; Sahoo *et al.*, 2008; Chichioco-Hernandez and Paguinan; 2009; Patil and Gaikwad, 2011).

Despite these pharmacological reports and wide spread use of the plant, information on the safety or toxicity appears scanty. Therefore, this study was set out to assess the safety of the aqueous extract of *C. adansonii* leaves on the haematological and biochemical parameters of organ damage. The organs (liver, kidney and small intestine) have been carefully selected because of their role in the detoxification, excretion and absorption of the plant extract. The histological examination was also carried out to corroborate it with alterations in the biochemical parameters. The dose of 650 mg/kg body weight was arrived at from ethnobotanical survey, while the 325 and 1300 mg/kg body weight represent half and two-fold of the 650 mg/kg body weight, respectively.

Materials and methods

Plant material and authentication

Fresh leaves of *Crateva adansonii* collected from a farmstead in Gbole village, Oyun Local Government Area of Kwara State, Nigeria, in December, 2006, were identified at the Herbarium Unit of the Department of Plant Biology, University of Ilorin, Ilorin, Nigeria.

Experimental animals

Forty albino rats (*Rattus norvegicus*) weighing between 190 and 210 g were obtained from the Small Animal Holding Unit of the Department of Biochemistry, University of Ilorin, Ilorin. The animals were kept in clean plastic cages placed in a well-ventilated house with optimum condition (temperature: 22±3 °C; photoperiod: 12 h natural light and 12 h dark; humidity: 40-45%). They were allowed unrestricted access to commercial pelleted rat chow (Bendel Feeds and Flour Mills, Ewu, Edo State, Nigeria) and water. The cages were cleaned daily. The study was carried out according to the Guide for the Care and the Use of Laboratory Animals of the Institute of Laboratory Animal Resources, Commission of Life Sciences, National Research Council, USA (ILAS, 1997).

Assay kits

The assay kits for GGT, AST, ALT, ALP and albumin were products of Randox Laboratories Ltd, United Kingdom. All other reagents used were of analytical grade and were prepared in distilled water.

Preparation of extract

The procedure described by Yakubu *et al.* (2005) was adopted for the preparation of aqueous extract of *C. adansonii* leaves. Briefly,

the fresh leaves were oven dried at 40 ^{0}C to a constant weight, ground into powder and stored in a plastic container. A known weight (500 g) of the powder was extracted in 7 L of distilled water and then left undisturbed for 48 h after an initial vigorous stirring. This was later filtered with Whatman No.1 filter paper and the filtrate concentrated using the steam from water bath set at 100 °C to give a greenish brown slurry of 101.12 g (percentage yield of 20.22%). This was then reconstituted in distilled water to give the required doses of 325, 650 and 1300 mg/kg body weight of the extract used in the present study.

Phytochemical screening

The aqueous extract of *C. adansonii* leaves was screened for its phytochemical constituents according to the procedures described by Odebiyi and Sofowora (1978). The detected phytochemicals were quantified as described for alkaloids (Henry, 1973), saponins (Brunner, 1984), flavonoids, phlobatannins and anthraquinones (El-Olemy *et al.,* 1994), phenolics (Edeoga *et al.*, 2005) and tannins (Van-Burden and Robinson, 1981).

Animal grouping and extract administration

Forty albino rats of Wistar strain were randomly assigned into four groups (A-D) of ten animals each. Animals in group A (control) received 1 mL of distilled water once daily for seven days while those in groups B, C and D were treated like those in group A except 1 mL of the extract corresponding to 325, 650 and 1300 mg/kg body weight respectively was administered. Five animals from each group were sacrificed 24 h after their last doses (treatment period) while administration was discontinued to the remaining five animals in various groups for another seven days before their sacrifice 24 h later (recovery period).

Preparation of tissue homogenates and serum

The procedure described by Yakubu and Akanji (2011) was adopted for the preparation of serum and tissue homogenates. Briefly, the animals were sacrificed under ether anaesthesia and an aliquot of the blood was collected into sample bottles containing EDTA for haematological analyses. Another 5 mL of the blood was allowed to clot at room temperature for forty-five minutes and then centrifuged at 503 x g for 10 min. The serum was then kept frozen for 12 h before being used for the biochemical analyses. The animals were thereafter quickly dissected and the liver, kidneys (decapsulated), and small intestines (emptied of waste) removed, cleaned, weighed and stored in ice-cold 0.25 M sucrose solution. The organs were then homogenized separately in ice-cold 0.25 M sucrose solution (1:4w/v). The homogenates were centrifuged at 1398 x g for 15 min and the resulting supernatant stored frozen for 24 h.

Haematological studies

Automated Haematologic Analyzer (Sysmex Haematology Systems, Sysmex Ameria Inc., model no. KX-21N, Kobe, Japan) was used to determine the levels of haemoglobin (Hb), packed cell volume (PCV), red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cells (WBC), neutrophils, lymphocytes and platelets.

Determination of biochemical parameters

The biochemical analytes were determined for protein (Gornall *et al.*, 1949), AST and ALT (Reitman and Frankel, 1957), ALP (GSCC, 1970), GGT (Rosalki and Tarlow, 1974), albumin (Doumas *et al.*, 1971), bilirubin (Evelyn and Malloy, 1938), urea (Veniamin and Vakirtzi, 1970), creatinine (Blass *et al.*, 1974), globulin, Na^+, K^+, bicarbonate and chloride ions (Tietz, 1995).

Computation of organ-body weight ratios and histopathological examination

The organ-body weight ratios were computed by expressing the absolute weight of the organs to the body weight of the animals, while the procedure described by Krause (2001) was used for histopathological examination.

Statistical analysis

Data were expressed as the means of five determinations +/- SEM. Statistical analysis was

done using Analysis of Variance (ANOVA) and Duncan's Multiple Range Test (DMRT) at 95% confidence level.

Results

Phytochemical screening revealed that the aqueous extract of *C. adansonii* leaves contained alkaloids, tannins, phenolics, saponins, flavonoids, phlobatannins and anthraquinones (Table 1). The extract was very rich in saponins followed by alkaloids and phenolics, while others were less than 1% of their starting materials (Table 1).

The extract significantly increased (P<0.05) the activities of ALP in the kidney, small intestine and serum of the animals (Table 2). By the end of the 7 days recovery period, the activity of the enzyme in the kidney and small intestine had compared well (P>0.05) with their controls at all the doses investigated. In contrast, the increase in the activity of ALP in the serum of the animals during the treatment period was not significantly (P>0.05) different in the recovery period (Table 2).

The extract also significantly increased (P<0.05) the activity of GGT in both the liver and serum of the animals. During the recovery period, the enzyme activity compared favourably with their respective controls in both the liver and serum of the animals treated with 325 and 650 mg/kg body weight, whereas at 1300 mg/kg body weight, the enzyme activity was not significantly (P>0.05) different from the increase obtained during the treatment period (Table 3). Although, the activity of ALT decreased in the liver during both the treatment and recovery periods, the serum ALT activity was not significantly (P>0.05) altered at all the experimental doses during these periods (Table 3). Furthermore, liver AST activity decreased during the treatment period whereas the enzyme activity compared favourably with the control during the recovery period. In contrast, the serum AST activity increased during both the treatment and recovery periods (Table 3).

The total protein increased during both the treatment and recovery periods whereas the albumin and conjugated bilirubin content in the serum of the animals were not significantly (P>0.05) altered (Table 4). The extract increased the globulin content in the serum of the animals during the treatment period whereas the serum globulin content compared favourably (P>0.05) with their control values during both the treatment and recovery periods in all the extract treated groups except those administered 1300 mg/kg body weight where the total bilirubin reduced significantly (P<0.05) during the periods (Table 4).

All the doses of the extract did not significantly (P>0.05) affect the levels of urea, creatinine, potassium and bicarbonate ions in the serum of the animals in both the treatment and recovery periods (Table 5). In contrast, the levels of sodium ions in the serum of the animals decreased significantly (P<0.05) during the periods under investigation. However, the extract at 650 and 1300 mg/kg body weight significantly reduced (P<0.05) the chloride ions during the treatment and recovery periods (Table 5).

The extract did not significantly (P>0.05) alter the levels of Hb, PCV, MCH, MCHC, MCV, RBC, platelets and neutrophils of the animals throughout the experimental periods (Tables 6). In contrast, the levels of WBC and lymphocytes increased significantly (P<0.05) only during the treatment period. The values of these haematological parameters compared favourably with those of the controls during the recovery period (Table 6).

The computed liver-, kidney-, and small intestine body weight ratios of the rats were not significantly (P>0.05) different from those of their respective controls during both the treatment and recovery periods (Table 7).

The extract at the highest dose of 1300 mg/kg body weight disrupted the histoarchitecture of some of the organs of the animals (Figures 1a, b, c, 2a, b, c and 3a, b, c). For instance, while the histoarchitecture of the small intestine and kidney were preserved (Figures 1a, b, c and 3a, b, c), there were mild degeneration and congestion of the hepatocytes surrounding the central veins as evidenced by the dilated sinusoids (Figure 2b). These changes were, however, not restored during the recovery period (Figure 2c).

Discussion

The presence of various organic compounds would confer different chemical properties on any

Table 1: Some phytochemical constituents of aqueous extract of *Crateva adansonii* leaves

Phytochemicals	Concentration (%)
Alkaloids	1.34 ± 0.01
Tannins	0.94 ± 0.02
Phenolics	1.06 ± 0.02
Saponins	2.36 ± 0.02
Flavonoids	0.09 ± 0.00
Phlobatannins	0.54 ± 0.02
Anthraquinones	0.47 ± 0.02

Each value represents mean of 3 determinations ± S D.

Table 2: Alkaline phosphatase activities of selected tissues of rats administered aqueous extract of *Crateva adansonii* leaves (U/mg protein)

	Kidney		Small intestine		Serum	
Doses (mg/kg body weight)	7	14	7	14	7	14
Control	358.63 ± 54.20^{a}	354.67 ± 74.70^{a}	10.57 ± 2.18^{a}	12.36 ± 1.56^{a}	1.83 ± 0.08^{a}	1.96 ± 0.13^{a}
325	377.24 ± 54.40^{b}	355.15 ± 42.30^{a}	21.47 ± 4.02^{b}	12.98 ± 1.71^{a}	3.28 ± 0.55^{b}	2.99 ± 0.30^{b}
650	379.38 ± 42.70^{b}	352.29 ± 32.70^{a}	19.40 ± 6.09^{b}	13.55 ± 0.79^{a}	3.16 ± 0.41^{b}	2.89 ± 0.17^{b}
1300	379.19 ± 65.20^{b}	357.21 ± 56.20^{a}	21.83 ± 4.57^{b}	13.03 ± 0.35^{a}	3.28 ± 0.32^{b}	2.99 ± 0.15^{b}

Values are means ± SEM of 5 determinations. Values carrying different superscripts down the column for each organ are significantly different (P<0.05). Values on day 7 represent the treatment period while those on day 14 indicates the recovery period

Table 3: Selected enzyme activities (U/mg protein) of liver and serum of rats administered aqueous extract of *Crateva adansonii* leaves

		Control		325 mg/kg bodyweight		625 mg/kg bodyweight		1300 mg/kg bodyweight	
		Liver	Serum	Liver	Serum	Liver	Serum	Liver	Serum
GGT	7	4.09 ± 0.17^{a}	1.15 ± 0.06^{a}	4.68 ± 1.13^{b}	1.86 ± 0.13^{b}	4.47 ± 0.08^{b}	1.81 ± 0.06^{b}	5.56 ± 0.73^{b}	1.94 ± 0.04^{b}
	14	4.05 ± 0.27^{a}	0.96 ± 0.04^{a}	4.06 ± 0.17^{a}	0.93 ± 0.08^{a}	4.04 ± 0.17^{a}	0.63 ± 0.05^{a}	5.69 ± 0.11^{b}	1.66 ± 0.05^{b}
ALT	7	12.37 ± 0.40^{a}	2.27 ± 0.67^{a}	10.27 ± 1.97^{b}	2.03 ± 0.23^{a}	7.09 ± 1.13^{c}	2.18 ± 0.25^{a}	6.58 ± 0.93^{d}	2.10 ± 0.38^{a}
	14	17.85 ± 0.40^{a}	2.71 ± 0.32^{a}	15.92 ± 0.45^{b}	2.52 ± 0.12^{a}	15.89 ± 0.69^{b}	2.45 ± 0.19^{a}	13.93 ± 1.15^{c}	2.45 ± 0.45^{a}
AST	7	208.89 ± 3.70^{a}	1.65 ± 0.73^{a}	180.44 ± 4.90^{b}	3.89 ± 0.14^{b}	133.03 ± 9.40^{c}	3.75 ± 0.21^{b}	124.48 ± 15.20^{d}	4.92 ± 0.40^{c}
	14	209.57 ± 8.70^{a}	1.36 ± 0.94^{a}	205.63 ± 15.70^{a}	3.53 ± 0.47^{b}	207.76 ± 8.86^{a}	3.60 ± 0.65^{b}	209.57 ± 6.70^{a}	3.60 ± 0.47^{b}

Values are means ± SEM of 5 determinations. Values carrying different superscripts down the column for each organ and enzyme are significantly different (P<0.05). Values on day 7 represent the treatment period while those on day 14 indicates the recovery period. GGT = gamma-glutamyl transferase, ALT = alanine transaminase, AST = aspartate transaminase

Table 4: Liver function indices of rats administered aqueous extract of *Crateva adansonii* leaves

Doses (mg/kg body weight)	Total protein (g/L)		Albumin (g/L)		Globulin (g/L)		Total Bilirubin (μmol/L)		Conj. Bilirubin (μmol/L)	
	7	14	7	14	7	14	7	14	7	14
Control	49.50 ± 5.54^{a}	52.17±6.08^{a}	32.33 ± 0.72^{a}	32.67 ± 1.09^{a}	17.17 ± 4.97^{b}	19.50 ± 5.27^{a}	1.87 ± 0.21^{a}	1.93 ± 0.07^{a}	0.27 ± 0.05^{a}	0.27 ± 0.07^{a}
325	65.17 ± 1.83^{b}	65.67±1.67^{b}	33.67 ± 1.44^{a}	34.67 ± 2.84^{a}	35.50 ± 1.03^{b}	19.00 ± 3.89^{a}	1.97 ± 0.12^{a}	2.03 ± 0.07^{a}	0.27 ± 0.07^{a}	0.27 ± 0.08^{a}
650	70.83 ± 2.65^{c}	64.83±3.14^{b}	33.67 ± 1.44^{a}	34.33 ± 1.09^{a}	35.17 ± 4.02^{b}	20.50 ± 3.09^{a}	1.83 ± 0.15^{a}	1.94 ± 0.06^{a}	0.26 ± 0.03^{a}	0.25 ± 0.03^{a}
1300	69.83 ± 2.61^{c}	66.33±4.49^{b}	32.67 ± 0.27^{a}	34.00 ± 1.86^{a}	37.33 ± 2.76^{b}	20.33 ± 2.73^{a}	0.90 ± 0.06^{b}	1.23 ± 0.07^{b}	0.27 ± 0.05^{a}	0.27 ± 0.07^{a}

Values are means ± SEM of 5 determinations. Values carrying different superscripts down the column for each parameter are significantly different (P<0.05). Values on day 7 represent the treatment period while those on day 14 indicates the recovery period

Table 5: Kidney function indices of rats administered aqueous extract of *Crateva adansonii* leaves

Parameter	Control		325 mg/kg bodyweight		650 mg/kg bodyweight		1300 mg/kg bodyweight	
	7	14	7	14	7	14	7	14
Urea (mmol/L)	5.03 ± 0.20^{a}	5.07 ± 0.50^{a}	4.13 ± 1.00^{a}	5.30 ± 0.41^{a}	5.03 ± 0.05^{a}	5.70 ± 0.06^{a}	5.13 ± 0.32^{a}	5.37 ± 0.38^{a}
Creatinine (μmol/L)	35.33 ± 2.10^{a}	35.67 ± 2.40^{a}	33.00 ± 2.20^{a}	34.33 ± 1.20^{a}	33.67 ± 2.70^{a}	35.00 ± 1.70^{a}	33.33 ± 2.00^{a}	35.67 ± 1.00^{a}
Na^{+} (mmol/L)	140.67 ± 0.70^{a}	140.67 ± 0.70^{a}	136.00 ± 0.50^{b}	137.33 ± 1.40^{b}	134.33 ± 1.20^{b}	133.00 ± 2.05^{b}	131.00 ± 1.20^{c}	135.67 ± 1.09^{b}
K^{+} (mmol/L)	6.80 ± 0.50^{a}	7.00 ± 1.00^{a}	6.80 ± 0.30^{a}	6.37 ± 0.30^{a}	6.60 ± 0.60^{a}	6.83 ± 0.30^{a}	6.53 ± 0.20^{a}	6.20 ± 0.20^{a}
Cl^{-} (mmol/L)	119.33 ± 1.20^{a}	121.00 ± 1.10^{a}	117.67 ± 1.80^{a}	116.67 ± 1.20^{a}	116.00 ± 1.20^{a}	112.67 ± 2.20^{b}	97.67 ± 3.50^{c}	112.67 ± 2.30^{b}
HCO_3^{-} (mmol/L)	21.33 ± 0.50^{a}	21.00 ± 0.50^{a}	22.00 ± 0.00^{a}	20.67± 1.10^{a}	21.33 ± 0.50^{a}	20.67 ± 0.50^{a}	20.67 ± 1.10^{a}	19.33 ± 0.50^{a}

Values are means ± SEM of 5 determinations. Values carrying different superscripts down the column for each parameter are significantly different (P<0.05). Values on day 7 represent the treatment period while those on day 14 indicates the recovery period

Table 6: Haematological parameters of rats administered aqueous extract of *Crateva adansonii* leaves

Parameter	Control		325 mg/kg bodyweight		650 mg/kg bodyweight		1300 mg/kg bodyweight	
	7	14	7	14	7	14	7	14
Hb (g/L)	11.57 ± 1.00^{a}	11.97 ± 1.30^{a}	10.53 ±0.80^{a}	12.77 ± 0.60^{a}	11.30 ± 0.80^{a}	11.30 ± 0.60^{a}	11.63 ±0.80^{a}	10.73 ± 0.60^{a}
PCV (%)	34.00 ± 3.10^{a}	34.33 ± 3.90^{a}	32.00 ± 2.50^{a}	34.67 ± 1.80^{a}	33.33 ± 2.40^{a}	33.33 ± 1.80^{a}	34.33 ± 2.40^{a}	32.67 ± 2.00^{a}
MCHC (g/dL)	33.33 ± 0.50^{a}	33.67 ± 0.30^{a}	33.67 ± 0.30^{a}	33.67 ± 0.30^{a}	33.67 ± 0.30^{a}	34.00 ± 0.00^{a}	33.33 ± 0.30^{a}	33.67 ± 0.30^{a}
RBC (x 10^{12}/L)	5.18 ± 0.30^{a}	4.92 ± 0.50^{a}	5.10 ± 0.40^{a}	4.64 ± 0.20^{a}	5.19 ± 0.30^{a}	4.78 ± 0.30^{a}	5.07 ± 0.45^{a}	4.72 ± 0.30^{a}
MCH (pg)	22.33 ± 2.70^{a}	22.00 ± 1.20^{a}	21.00 ± 3.40^{a}	22.67 ± 1.30^{a}	22.67 ± 2.60^{a}	21.00 ± 2.80^{a}	22.33 ± 2.80^{a}	22.67 ± 1.7^{a}
MCV (fL)	66.00 ± 7.60^{a}	65.67 ± 1.20^{a}	66.00 ± 9.60^{a}	66.00 ± 0.50^{a}	66.33 ± 7.30^{a}	66.33 ± 0.28^{a}	65.67 ± 8.60^{a}	66.00 ± 0.50^{a}
WBC (x10^{9}/L)	9.80 ± 0.20^{a}	10.10 ± 1.00^{a}	11.93 ± 1.60^{b}	10.23 ± 1.40^{a}	12.57 ± 1.60^{b}	9.90 ± 1.30^{a}	11.37 ± 0.70^{b}	9.90 ± 2.60^{a}
Platelets (x10^{9}/L)	99.00 ± 6.00^{a}	100.67 ± 4.50^{a}	102.00 ±4.50^{a}	101.33 ± 2.00^{a}	99.33 ± 5.70^{a}	95.33 ± 2.90^{a}	98.00 ± 7.30^{a}	97.67 ± 5.20^{a}
Neutrophils (%)	29.33 ± 0.10^{a}	29.33 ± 1.40^{a}	28.67 ± 0.50^{a}	29.33 ± 1.10^{a}	28.33 ± 1.07^{a}	28.67 ± 2.80^{a}	27.67 ± 3.3^{a}	27.33 ± 3.90^{a}
Lymphocytes (%)	68.67 ± 6.00^{a}	69.33 ± 0.50^{a}	73.33 ± 0.50^{b}	68.00 ± 1.90^{a}	76.00 ± 1.90^{c}	69.00 ± 0.20^{a}	79.33 ± 2.90^{d}	70.67 ± 0.09^{a}

Each value is a mean of 5 determinations ± SEM. Values along the same column with different superscripts are significantly different (p < 0.05).
Values on day 7 represent the treatment period while those on day 14 indicates the recovery period. Hb=Haemoglobin; PCV=Packed Cell Volume; MCHC=Mean Corpuscular Haemoglobin Concentration MCV=Mean Corpuscular Volume; RBC=Red Blood Cells; WBC=White Blood Cells

Table 7: Organ/body weight ratios of rats administered aqueous extract of *Crateva adansonii* leaves

Dose (mg body Weight)	Liver		Kidney		Small intestine	
	7	14	7	14	7	14
Control	0.0324±0.003^{a}	0.0341±0.001^{a}	0.0056±0.001^{a}	0.0051±0.000^{a}	0.0286±0.002^{a}	0.0380±0.002^{a}
325	0.0332±0.001^{a}	0.0322±0.001^{a}	0.0055±0.000^{a}	0.0055±0.000^{a}	0.0295±0.008^{a}	0.0330±0.002^{a}
650	0.0313±0.001^{a}	0.0372±0.001^{a}	0.0051±0.000^{a}	0.0056±0.000^{a}	0.0349±0.001^{a}	0.0370±0.003^{a}
1300	0.0325±0.002^{a}	0.0331±0.000^{a}	0.0054±0.001^{a}	0.0059±0.000^{a}	0.0336±0.002^{a}	0.0352±0.002^{a}

Values are means ± SEM of 5 determinations. Values carrying different superscripts down the column are significantly different (P<0.05). Values on day 7 represent the treatment period while those on day 14 indicates the recovery period

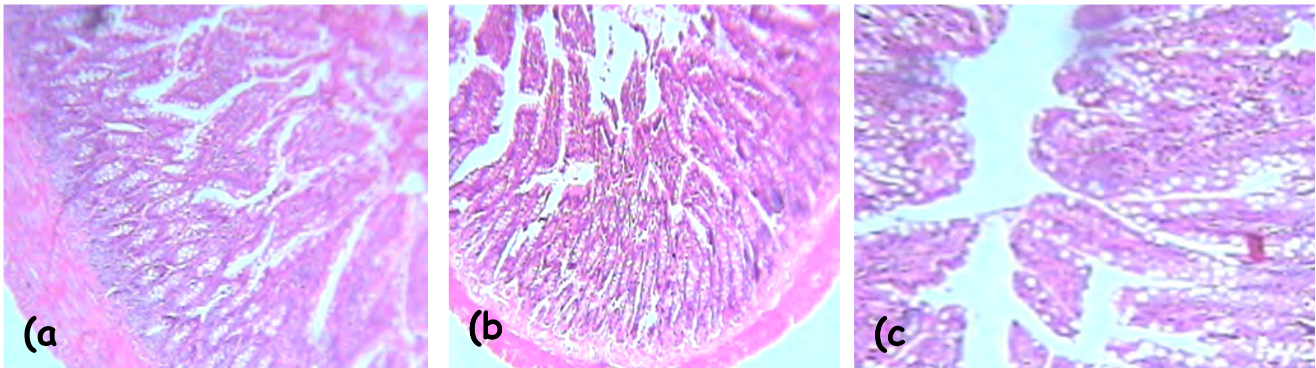

Figure 1: (a). Photomicrograph of the small intestine of rats administered distilled water (mg x 100; H & E). (b) Photomicrograph of small intestine of rat treated with the 1300 mg/kg body weight of the extract for 7 days (treatment period) (mg x 100; H & E). (c) Photomicrograph of small intestine of rat treated with the 1300 mg/kg body weight of the extract for 7 days (treatment period) and left untreated for another 7 days (recovery period) (mg x 100; H & E)

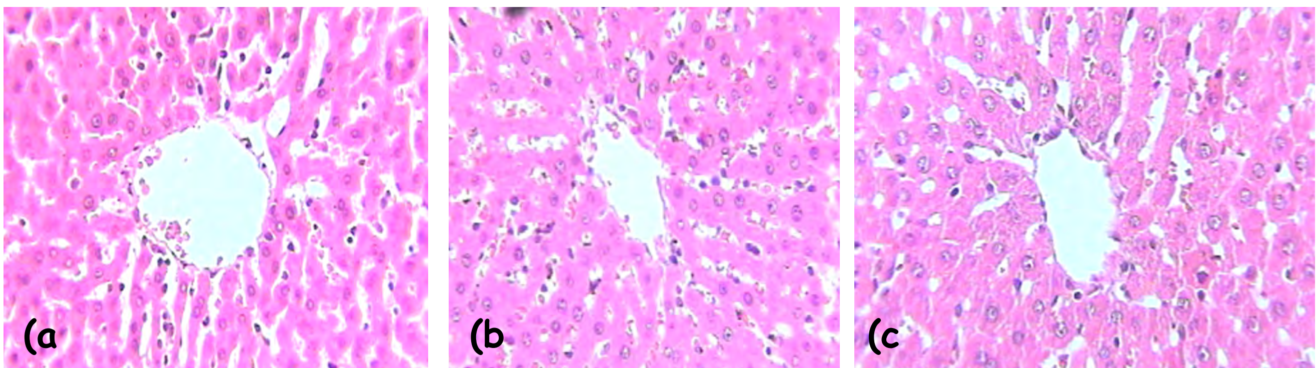

Figure 2: (a). Photomicrograph of the liver of rats administered distilled water (mg x 400; H & E). Photomicrograph of liver of rats treated with the 1300 mg/kg body weight of the extract for 7 d (treatment period) (mg x 400; H & E). (c) Photomicrograph of liver of rat treated with the 1300 mg/ body weight of the extract for 7 days (treatment period) and left untreated for another 7 days (recov period) (mg x 400; H & E).

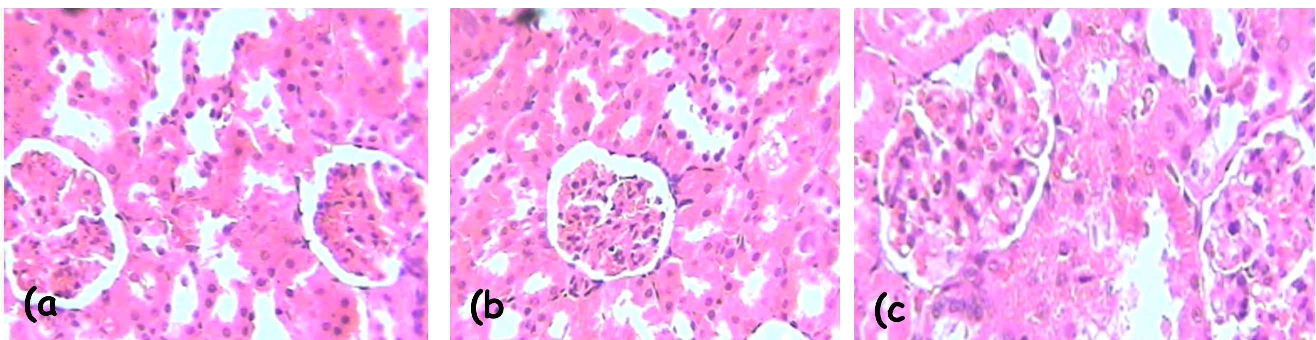

Figure 3: (a) Photomicrograph of the kidney of rats administered distilled water (mg x 400; H & E). Photomicrograph of the kidney of rats treated with the 1300 mg/kg body weight of the extract for 7 days (treatment period) (mg x 400; H & E). Photomicrograph of the kidney of rat treated with the 1300 mg/kg body weight of the extract for 7 days (treatment period) and left untreated for another 7 days (recovery period) (mg x 400; H & E)

influence their biological and toxicological effects. For example, tannins, which have been reported along with flavonoids and phenolics to have antioxidant activity, may also have negative effects by chelating iron and thus impairing its bioavailability. This may lead to anaemia if consumption is prolonged. Saponins have been reported to prevent colon cancer and possess anti-hyperglycaemic potential (Malinow *et al.*, 1977; Rao and Sung, 1995; Olaleye, 2007). On the other hand, they have also been reported to have a wide range of effects such as life-threatening toxicities for certain animal species (Shidelar, 1980), disruption of biological membranes resulting in escape of large quantities of metabolites and generation of free radicals (Francis *et al.*, 2002; Nandi *et al.,* 2004; Sparge *et al.*, 2004). Therefore, the documented pharmacological activities and the toxicity profile of the aqueous extract *C. adansonii* leaves reported in the present study may be attributed to any or combination of the phytochemical constituents in the botanical.

ALP is a 'marker' enzyme for the plasma membrane and endoplasmic reticulum (Wright and Plummer, 1974) and is often used to assess the integrity of the plasma membrane and endoplasmic reticulum (Akanji *et al.,* 1993). The enzyme transfers ions and metabolites across the cell membrane. The increase in the activity of ALP in the small intestine and kidney could be a consequence of activation of the enzyme or an increase in the rate of the synthesis of the enzyme induced by the components of the extract. The attenuation of the pattern of enzyme activity to their control values in the kidney and small intestine during the period when the administration was discontinued suggests recovery by the animals. This is an indication that the toxicity of the extract was mild and transient. Furthermore, the increase in the ALP activity in the serum during both the treatment and recovery periods could be a consequence of leakage of the enzyme from other tissues apart from small intestine and kidney or a reduced rate of clearance of the enzyme from the serum (Mayne, 2005). This increase could indicate an enhanced functional activity of the organs (kidney and small intestine) (Brain and Kay, 1927), since there will be an increase in the rate of ion transport across the cell membranes in these tissues.

GGT is a membrane-bound enzyme and the most sensitive enzymatic indicator of hepatobiliary disease (Mayne, 2005). The increase in GGT in the liver of the animals could be due to *de novo* synthesis since there was also similar pattern of increase in the serum. The increase in GGT activity in the liver will lead to an increased rate of amino acid transfer and glutathione metabolism in the liver. The increase in the serum enzyme, on the other hand, could be a consequence of leakage by other tissues not investigated in the present study into the serum. It is worthy of note that the liver of the animals recovered with respect to this enzyme following the administration of 325 and 650 mg/kg body weight. The animals did not, however, recover from the effect of the highest dose used in the present study.

The aminotransferases (ALT and AST) are 'markers' of liver damage and can thus be used to assess liver cytolysis with ALT being a more sensitive biomarker of hepatotoxicity than AST (Pramyothin *et al.*, 2006). The reduction in the activity of the aminotransferases from the liver without the corresponding increase in the serum enzyme could be due to inhibition of the enzyme activity by components of the extract (Akanji *et al.,* 1993), inactivation of the enzyme molecule *in situ* (Umezawa and Hooper, 1982), or depletion of important molecules required by the enzyme for maximum activity (Yakubu *et al.,* 2003). The loss in the activity of these enzymes in the liver will adversely affect carbohydrate and amino acid metabolism, thereby affecting energy production. It appears that the extract might have selectively affected the aminotransferases since there was reversal only for AST in the liver of the animals.

The concentrations of total protein, albumin, bilirubin (total and conjugated), globulin, urea, creatinine and electrolytes are useful 'markers' of secretory, synthetic and excretory functioning of the liver and kidney (Yakubu and Musa, 2012). The increase in the total protein content suggests a

compromise of the synthetic ability of the liver. This was further supported by a similar increase in the globulin content of the animals. Although, albumin, total and conjugated bilirubin were not significantly altered in the present study, it is still possible that the extract exhibited selective functional toxicity on the liver. The extract might have increased the functional activity of the liver by interfering with the metabolism (anabolism) of total protein and globulin while it might not have interfered with the equilibrium in the rate of synthesis and destruction, removal or clearance of albumin, total and conjugated bilirubin from the system of the animals. However, the animals did not recover fully from the assault of the extract since the levels of the total protein were not restored back to the control value. Increase in total protein could, however, lead to dehydration which is detrimental to cellular homeostasis. This will negatively affect the metabolic activities of the liver and consequently the health of the animals.

The kidneys regulate the excretion of urea and reabsorption of electrolytes into the blood. Filtration occurs at the glomeruli while reabsorption takes place in the renal tubules (Mayne, 2005). When there is compromise of normal glomerular function, substances normally cleared by the kidneys such as urea and creatinine accumulate in the biological fluid. The absence of an effect on the levels of serum urea, creatinine, potassium and bicarbonate suggests that the normal excretion of these biomolecules and elctrolytes by the kidney was not been adversely affected by the extract. Furthermore, the decreases in the levels of sodium and chloride ions suggest that some aspects of tubular functioning as it relates to these electrolytes have been compromised. This will adversely affect electrolyte balance and homeostasis. It is not immediately clear why the extract altered the levels of only some electrolytes amongst the indices of kidney function investigated in the present study, but it may not be unconnected with the property of selective toxicity earlier suggested in this study (Yakubu and Musa, 2012).

Haematological analysis provides a valuable tool that can be used to clinically investigate presence assess the health status of an animal as it plays an important role in the physiological, nutritional and pathological status of an animal (Kakade *et al.*, 1972; Babatunde *et al.*, 1992). Haematological assessment can be used to determine the deleterious effects of foreign components on the blood and also explain blood-related functions of chemical compounds including those of plant origin (Yakubu *et al.*, 2007). The lack of an effect on RBC and factors relating to it (RBC, Hb, PCV, MCH, MCHC, MCV) as well as some relating to WBC such as platelets and neutrophils suggest that the rate of synthesis or destruction of these blood cells was not adversely affected and further emphasizes the selective toxicity of the extract. White blood cells defend the body against infections or any foreign body. Elevated values may indicate a boost in immunological activity, a pathological condition, infection, severe physical stress, or tumour (leukaemia) (Qiao *et al.,* 1991; Dean, 2005; Singh *et al.*, 2008). Therefore, the increased levels of WBC and lymphocytes might be an indication that the extract was able to enhance the rate of synthesis of these blood indices over the rate of destruction or clearance from the biological fluid (Yakubu and Musa, 2012). This reason could also be responsible for the elevated levels of serum globulin in the present study.

Organ-body weight ratio is a useful marker of cellular swelling, atrophy or hypertrophy (Amresh *et al.*, 2008). Therefore, the absence of an effect on the computed organ-body weight ratios suggest that the extract did not cause any form of swelling, atrophy and hypertrophy on the organs. This was further supported by the histological findings in the present study to some extent, anyway. Although, there was mild degeneration of the hepatocytes, it is possible that the degenerative changes was not sufficient enough to produce atrophy or organ constriction. In addition, changes in the levels of biochemical indices following the administration of chemical compounds, including plant extracts, could be an earlier event preceding gross morphological changes in the organ(s), it is not always in all cases that the alterations in biochemical indices following the administration of chemical

compounds including plant extracts could be an earlier event preceding gross morphological changes in the organ(s). In addition, it is not in all cases that the alterations in biochemical parameters of an organ is supported by histoarchitectural alterations (Aboyade *et al.*, 2009). Therefore, the mild degeneration of the hepatocytes surrounding the central vein of the liver, amongst other organs investigated in this study, may be due to the proximity and the involvement of the organ in detoxifying foreign compounds, including plant extracts. The inability of the liver to recover from the assault of the extract suggests that structural toxicity was chronic. The absence of histoarchitectural changes in the kidney and small intestine is a further indication of the organ-specific structural toxicity of the extract.

In conclusion, the results of this study indicate that administration of aqueous extract of *Crateva adansonii* leaves at the doses of 325, 650 and 1300 mg/kg body weight caused mild, selective and reversible changes in the haematological profile and biochemical parameters of dysfunction in the small intestine, liver and kidney of the animals. The functional toxicity on the organs was, in most cases, transient since the animals recovered from the assault of the extract. The extract exhibited structural but selective toxicity on the histoarchitecture of only the liver of the animals. In view of the recoveries made by the rats from the assault of the botanical, even at the highest dose of 1300 mg/kg body weight in the present study, the use of the plant for therapeutic purposes should not be discouraged.

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