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Research Article
Subacute Toxicity Profile of the Leaves of *Colocasia esculenta* [L. Schott] in Albino Rats

[1]N.C. Azubike, [1]P.U. Achukwu, [1]C.N. Okwuosa, [2]D.C. Nwachukwu, [1]O.S. Onwukwe and [1]A.O. Onyemelukwe

[1]Department of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, College of Medicine, Enugu Campus, University of Nigeria, Nigeria
[2]Department of Physiology, Faculty of Medical Sciences, College of Medicine, Enugu Campus, University of Nigeria, Nigeria

Abstract

Background: Colocasia esculenta leaves are employed traditionally in the treatment of hepatic ailments, constipation, stomatitis, among others. **Objective:** This study reports the sub-acute toxicity effects of *C. esculenta* (CE) crude aqueous leaves extracts in albino rats. **Methodology:** Daily doses of 400 and 800 mg kg^{-1} b.wt. of crude aqueous extracts of the fresh and dried leaves of CE were administered orally to different sets of rats for 28 days. Body weights, Relative Organ Weights (ROW), haematological analysis, serum biochemical assay and histopathological changes of vital organs were used to evaluate the toxic effects of the extracts after treatments. **Results:** Results revealed that treatment with CE causes adverse effects on body weight. The tested doses did not provoke significant changes in haematological and biochemical parameters of rats except an increase in alkaline phosphatase of treated rats ($p<0.05$). The ROW were normal except those of the kidneys and testes. Mild histopathological changes were observed in kidney, lungs and intestines. **Conclusion:** Results provided evidence that sub-acute oral administration of crude aqueous extracts of CE leaves at doses lower than 1000 mg kg^{-1} may not exert toxic effects on haematological and some biochemical parameters but may exert selective toxicity in few visceral organs.

Key words: *Colocasia esculenta*, aqueous extracts, sub-acute toxicity, histopathology, haematological, biochemical parameters

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Corresponding Author: N.C. Azubike, Department of Medical Laboratory Sciences, Enugu Campus, University of Nigeria, Nigeria Tel: +2348036711136

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Colocasia esculenta L., Schott is an herbaceous perennial plant belonging to the family of Araceae. It is commonly known as Cocoyam and is believed to be one of the earliest cultivated plants. The crop is grown throughout the humid tropics and the corms/tubers serve as staple food throughout sub-tropical and tropical regions of the world. However, the fresh or sun-dried leaves are used as leafy vegetables which hold an important place in the diet of some parts of Sub-Saharan Africa. *Colocasia esculenta* leaves have been shown to contain nutrients which include iron, calcium, phosphorus, vitamin C, thiamine, niacin and riboflavin[1,2]. Previous phytochemical screening revealed the presence of alkaloids, saponins, flavonoids and terpenoids[3].

The edible tuber and leaves of *C. esculenta* edible are used traditionally for the treatment of hepatic ailments[4]. The leaf juice pacifies stomatitis, alopecia, general weakness, constipation and hemorrhoids[5,6]. *Colocasia esculenta* has been reported to possess antihyperglycaemic[7], hypoglycemic[8], hypolipidemic[9], antioxidant[10], anti-inflammatory[11], antihypertensive[12], antifungal[13] and antibacterial[14] activities.

Previous data on acute toxicity studies according to OECD guidelines showed that the tolerated dose was beyond 5 g kg^{-1} b.wt.,[3,7] however, scientific information on the sub-acute toxicity studies have not yet been reported. Therefore, the present research deals with the sub-acute toxicological testing of fresh and sun-dried *C. esculenta* leaves in rodents.

MATERIALS AND METHODS

Plant material: The leaves of the *C. esculenta* plant were collected from a farm in Enugu metropolis, Enugu State, Nigeria during the month of May, 2011. A sample of the plant material was authenticated by comparison with a standard voucher sample (UNH No. 379[a]) preserved in the herbarium section of the Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Nigeria, Nsukka.

Preparation of crude extracts: About 500 g each of fresh and sun-dried *C. esculenta* leaves were grinded separately using a gasoline grinding machine. The fresh leaves were grinded into fine-textured paste in a grinding machine while th e sun-dried leaves were crushed into fine powder. Crude aqueous extracts of the fresh and sun-dried leaves [FLE and DLE, respectively] were prepared by maceration in 700 mL each for 4 h in distilled water. Each of the extract was filtered through clean muslin cloth and the resultant filtrates were concentrated in an evaporator so as to achieve a desired concentration. The extracts were stored at 4±2°C in a refrigerator until needed.

Experimental animals and housing: Twenty-five apparently healthy male albino Wistar rats weighing 160-185 g were obtained from the Animal House Unit of the Department of Physiology, Faculty of Basic Medical Sciences and housed at the Animal House of the College of Medicine, Enugu Campus, University of Nigeria, in clean wire-mesh cages which had openings beneath for exit of rats' faeces to prevent coprophagy. They were weighed and grouped into five (A-E) according to their weights. Two weeks of acclimatization was allowed before the commencement of the study. Animal housing was maintained under controlled environmental conditions of light (12 h light/dark cycle) and temperature (25±2°C). They were fed *ad libitum* with commercial rat feed (Top Feeds® limited, Ibadan, Nigeria) and clean water. All the animal experiments were performed in in conformity with institutional protocols and the guidelines for care and use of animals for scientific research[15].

Experimental design and conduct: The animals in each group were treated orally, once daily, for 28 days. Group A (control) received 10 mL kg^{-1} of distilled water. Groups B and C were treated with doses of 400 and 800 mg kg^{-1} b.wt., of FLE, respectively, while groups D and E received 400 and 800 mg kg^{-1} of DLE, respectively. The animals were monitored daily for signs of toxicity. Blood samples were obtained on days 0, 14 and 28 via retrorbital puncture into EDTA-K_3 bottles for the estimation of some haematological parameters. Blood samples were also obtained after the last day of the experiment, into plain tubes for the estimation of some biochemical parameters. The rats were anaesthetized using mild chloroform, some visceral organs [liver, kidneys, lungs, heart, spleen, stomach, intestines, testis and epididymis] were excised and necropsy was performed by gross examination of the organs for any changes.

Haematological assay: Packed Cell Volume (PCV), haemoglobin concentration (Hb), total leucocytic, red blood cell and platelet counts were determined according to the methods described by Lewis *et al.*[16].

Biochemical parameters: Serum alkaline phosphatase (ALP) was estimated using the method of Roy[17] provided by Teco Diagnostics, USA. Alanine transaminase (ALT) and aspartate

transaminase (AST)] were assayed using the end technique of Reitman and Frankel[18] provided by Randox Laboratories Ltd., UK. Serum urea levels were estimated using Urease/Berthelot's reaction and creatinine levels were assayed using Jaffe's method as described by Sood[19] (Randox Laboratories Ltd., UK).

Body and organ weight measurement: At the end of the treatments, the body weight of each rat from the control and treated groups were measured and recorded. Selected organs including the liver, kidney, spleen, lungs, testes, heart, epididymis and stomach which were excised immediately after the sacrifice, trimmed of fat and connective tissue, blotted with filter paper and weighed on a balance. The relative organ weights [ratio of organ weight and the animal's body weight (at the end of experiment)×100] were calculated.

Histopathological analysis: The excised tissues were fixed in 10% formal saline for 24 h and further processed using the conventional paraffin wax embedding technique for light microscopical examination. The paraffin-embedded tissues were sectioned at 5 microns and stained using the Haematoxylin and Eosin [H and E] staining procedure[20]. The histological sections were examined using an Olympus™ light microscope.

Statistical analysis: Data obtained were expressed as the mean Value±Standard Error of Mean [SEM] and statistically assessed using statistical computer software program, SPSS version 20. One way analysis of variance [ANOVA] was used to determine main effects on treatment groups while Tukey's post-hoc test was used for multiple comparisons. Statistical significance between the control and treated groups was considered at probability levels $p<0.05$, <0.01 and <0.001.

RESULTS

Signs of toxicity: All the rats survived the treatment period of 28 days and showed no obvious sign of toxicity. However, rats treated with the dose of 800 mg kg^{-1} DLE slightly displayed signs of weakness towards the last 7 days of treatment.

Effect of extracts on body weights in rats: Only rats in FLE 400 mg kg^{-1} b.wt., treated group gained weight over the course of this study in a manner similar to the control group (Fig. 1a). However, statistically significant differences in percentage (%) change in body weights ($p<0.05$ and $p<0.001$) were greater for DLE-treated groups [400 and 800 mg kg^{-1} b.wt., respectively] when compared to controls (Fig. 1b).

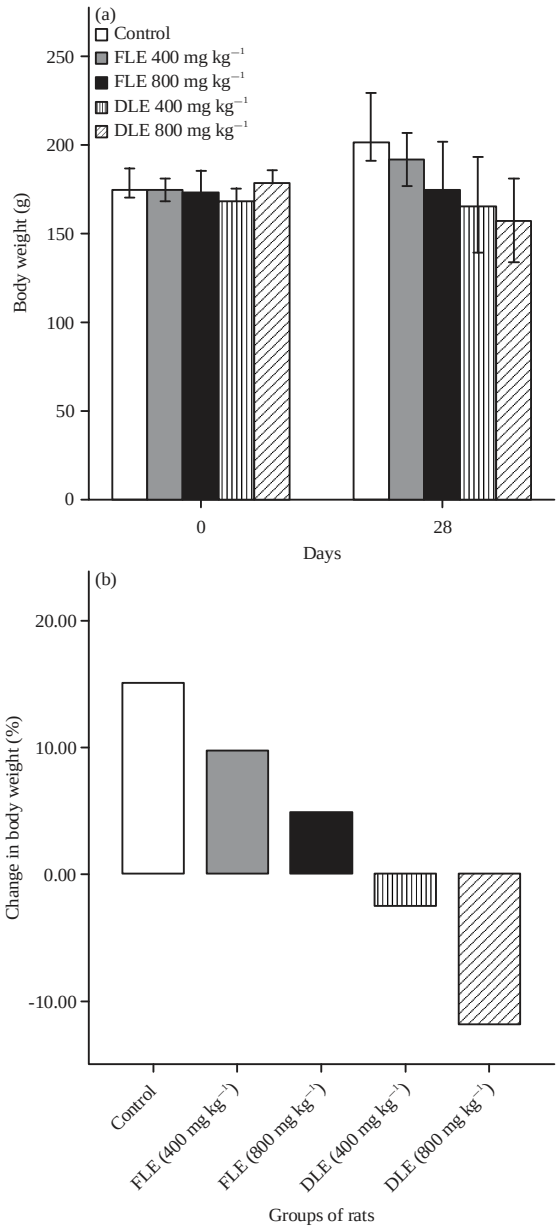

Fig. 1(a-b): Bar charts showing the effects of treatment with *C. esculenta* leaves crude aqueous extracts of fresh (FLE) and sun-dried (DLE) on (a) Body weight and (b) Percentage change in body weight

Effect of extracts on haematological parameters: The results of haematological parameters of control and daily treated rats with the crude aqueous extracts of the fresh, boiled and sun-dried leaves of *C. esculenta* on days 0, 14 and 28 are shown in Table 1. These results show that there were no significant changes observed in all parameters of the treated animals when compared with control values obtained same day.

Table 1: Haematological parameters of rats treated with crude aqueous extracts of fresh (FLE) and sun-dried (DLE) leaves of *Colocasia esculenta*

		Groups				
Parameters	Days	A (Control)	B (FLE 400 mg kg^{-1})	C (FLE 800 mg kg^{-1})	D (DLE 400 mg kg^{-1})	E (DLE 800 mg kg^{-1})
Haematocrit (%)	0	42.80±1.59	44.00±1.41	41.00±1.00	41.00±0.95	44.40±1.83
	14	40.20±1.93	45.20±1.74	39.00±2.59	37.40±1.47	41.20±1.36
	28	40.00±1.52	39.00±0.71	41.20±1.11	40.60±1.29	40.40±1.69
Haemoglobin	0	10.72±0.39	10.32±0.39	10.84±0.16	10.68±0.45	10.90±0.53
(g dL^{-1})	14	11.92±0.67	10.85±0.86	11.80±0.58	11.36±0.43	10.96±0.54
	28	10.24±0.25	10.00±0.59	9.52±0.83	8.88±0.27	10.12±0.63
Platelet (10^{9} L^{-1})	0	428.00±13.33	444.00±24.72	480.00±27.22	484.00±29.07	463.00±40.93
	14	659.40±37.14	466.80±53..47	601.20±57.85	521.40±36.59	519.00±49.93
	28	421.20±32.31	452.20±41.41	346.20±43.76	582.60±51.36	490.60±79.96
RBC (10^{12} L^{-1})	0	7.51±0.33	7.38±0.48	8.10±0.49	7.85±0.45	7.64±0.44
	14	7.64±0.62	7.94±0.74	8.42±0.25	8.25±0.37	7.96±0.39
	28	7.73±0.50	8.26±0.25	8.52±0.46	8.40±0.73	7.95±0.76
WBC (10^{9} L^{-1})	0	12.24±1.70	10.59±0.39	13.92±0.69	11.10±0.96	10.93±0.98
	14	16.12±1.73	12.70±1.36	15.84±1.09	16.65±2.39	14.74±2.41
	28	10.94±1.32	12.13±1.42	12.72±0.85	11.54±1.83	10.86±1.29

Values are expressed as Mean±SEM, Significance when compared with control *(p<0.05), RBC: Red blood cell, WBC: White blood cell

Table 2: Biochemical parameters of experimental rats after treatment with oral doses of crude aqueous extracts of fresh (FLE) and sun-dried (DLE) leaves of *Colocasia esculenta* for 28 days

	Groups				
Parameters	A (Control)	B (FLE 400 mg kg^{-1})	C (FLE 800 mg kg^{-1})	D (DLE 400 mg kg^{-1})	E (DLE 800 mg kg^{-1})
ALT (IU L^{-1})	42.40±5.88	24.80±3.26	24.20±8.08	27.60±4.53	16.80±1.43
AST (IU L^{-1})	89.40±8.00	71.20±8.30	53.80±3.65*	82.00±6.78	67.80±4.57
ALP (IU L^{-1})	103.00±5.37	142.75±3.86*	136.08±3.06*	134.75±4.53*	121.00±7.11
Urea (mg dL^{-1})	6.42±0.69	7.61±1.05	7.19±0.58	7.78±0.24	9.10±0.78
Creatinine (mg dL^{-1})	2.08±0.10	1.80±0.09	2.40±0.69	1.68±0.05	1.12±0.05

Values are expressed as Mean±SE, Significance when compared with control *(p<0.05)

Table 3: Effect of oral doses of crude aqueous extracts of fresh (FLE) and sun-dried (DLE) leaves of *Colocasia esculenta* on relative organ weights of rats treated for 28 days

	Groups				
Organ index	A (Control)	B (FLE 400 mg kg^{-1})	C (FLE 800 mg kg^{-1})	D (DLE 400 mg kg^{-1})	E (DLE 800 mg kg^{-1})
Liver	4.28±0.33	5.28±0.91	4.06±0.09	4.75±0.23	3.76±0.14
Kidney	0.63±0.04	0.80±0.07	0.73±0.04	0.78±0.03	0.90±0.09*
Testis	0.61±0.08	0.72±0.12	0.86±0.14	0.76±0.07	1.41±0.10*
Epididymis	0.37±0.04	0.66±0.09	0.57±0.09	0.51±0.09	0.48±0.04
Heart	0.37±0.04	0.37±0.05	0.43±0.05	0.43±0.02	0.52±0.02
Lungs	0.68±0.09	0.75±0.10	0.55±0.03	0.78±0.12	0.77±0.14
Spleen	0.38±0.08	0.64±0.12	0.59±0.05	0.45±0.07	0.65±0.16
Stomach	0.86±0.04	0.84±0.13	0.80±0.03	0.87±0.03	0.84±0.05

Values are expressed as Mean±SE, Significance when compared with control *(p<0.05)

Effect of extracts on serum biochemical parameters: The results of blood clinical chemistry parameters are shown in Table 2. A decrease in ALT and AST values in all treatment groups was observed although not statistically significant (p>0.05). However, a significant decrease (p<0.05) in AST was observed in group of rats treated with 800 mg kg^{-1} FLE when compared to the control. The ALP values were significantly raised (p<0.05) in all treatment groups except in group E when compared to control. No significant differences were observed in urea and creatinine values when compared to control.

Gross examination of internal organs and relative organ weight of rats: Upon gross examination of the excised internal organs of the rats, no detectable abnormality was revealed. All the organs were apparently normal when examined. The relative organ weights of all treated rats and control are shown in Table 3. Treatment with the aqueous extracts of CE leaves at any dose did not illustrate any significant change in the relative organ weights of the liver, heart, spleen, epididymis, lungs and stomach when compared to control. However, few alterations were observed in the

relative weights of kidneys and testes of rats treated with 800 mg kg^{-1} b.wt., DLE which showed a statistically significant decrease ($p<0.05$) when compared with the control.

Histological findings: Microscopical examination of the organs isolated from the rats at sacrifice revealed no histopathological alteration in the control rats. Presence of tubular casts (arrows indicated) was observed in the kidney of rats treated with high dose groups of FLE and DLE (Fig. 2b and f, respectively) while some glomeruli of rats treated with DLE were mildly constricted (Fig. 2f). The lungs of FLE-treated rats showed alveolar septal thickening (Fig. 2h). The intestines of all treated rats showed mild thickening of walls by cellular infiltrates (Fig. 3 and 4). All other organs (liv er, heart, spleen, stomach and testis and epididymis) of treated rats showed apparently normal histological features when compared with the control.

DISCUSSION

Colocasia esculenta is a plant widely grown for its edible tubers but the consumption of the leaves is uncommon. Several studies on the tubers have been conducted[21-23]. However, there is paucity of information on the toxicological profile of the leaves. In the present study, the potential toxicity of *Colocasia esculenta* leaves administered over a 28-day period using rodent models was assessed.

The results from the present study showed no mortality of the experimental animals after treatments with the extracts. This finding correlates with a previous report which revealed no mortality of treated rats for up to a dose of 5 g kg^{-1} b.wt., administered once in an oral acute toxicity study[3]. However, upon daily treatment for 28 days with lower doses in this work, markedly decreased body weights of rats especially with the higher doses of CE extracts was observed. The possible mechanisms for the weight gain retardation may be via manipulation of thermogenesis, appetite suppression or by blocking of fat and glucose absorption[24]. The observed effect on body weight may be attributed to the abundant amounts of saponins and alkaloids which have been found to be present in the extracts[3]. These phytochemicals have been shown previously to possess anti-obesity effects[25,26]. Thus, it may be inferred that extract of CE may be harnessed for the management of obesity.

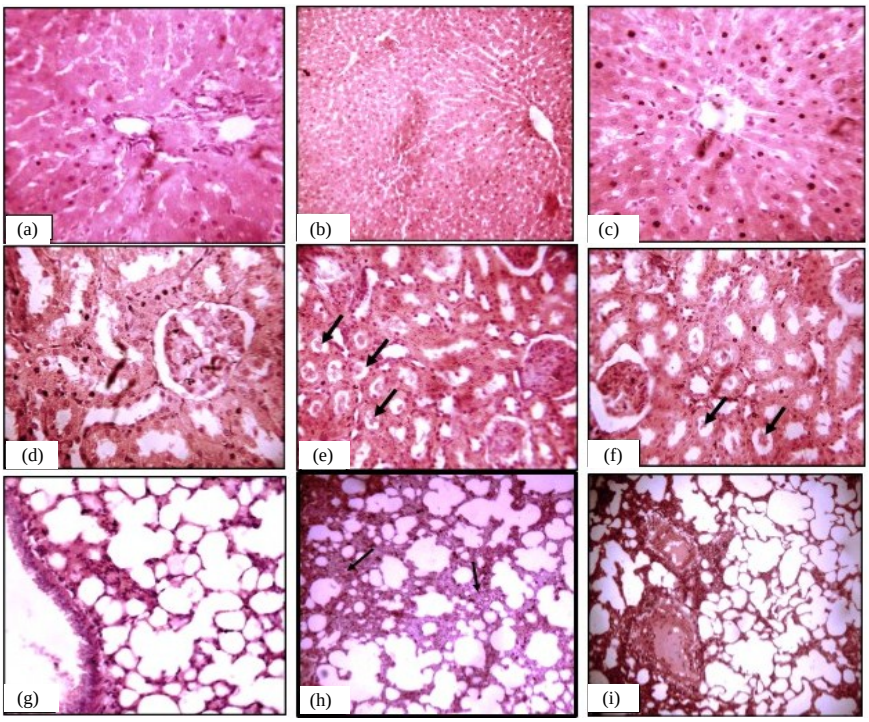

Fig. 2(a-i): Photomicro graphs of (a) Liver, (d) Kidney, (g) Lungs sections from control, (b, e and h) FLE-treated and (c, f and I) DLE-treated rats [Stain: H and E]

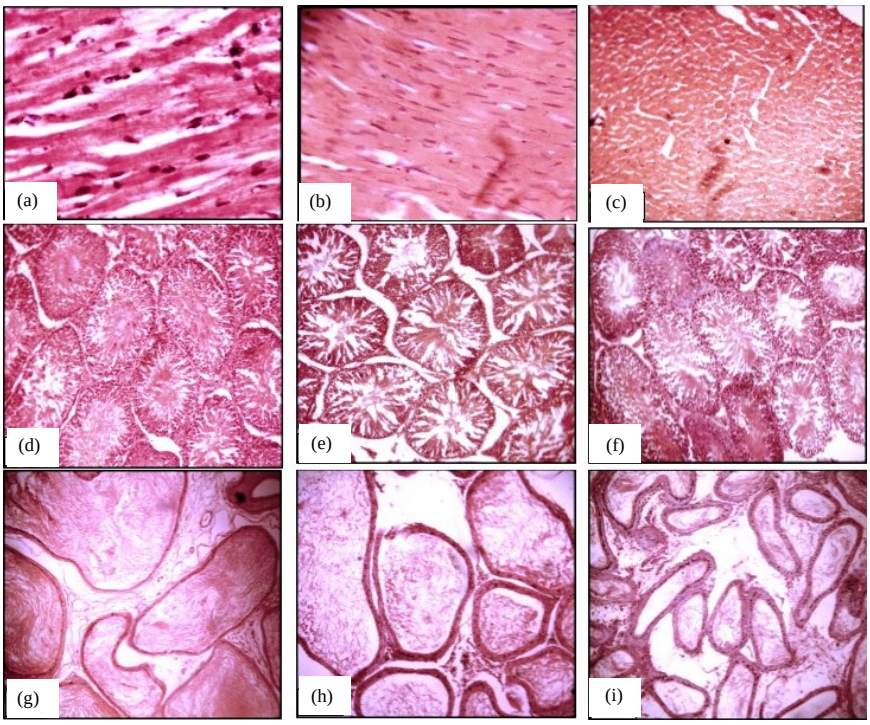

Fig. 3(a-i): Photomicrographs of (a) Heart, (b) Testis, (g) Epididymis sections from control, (b, e and h) FLE-treated and (c, f and i) DLE-treated rats [Stain: H and E]

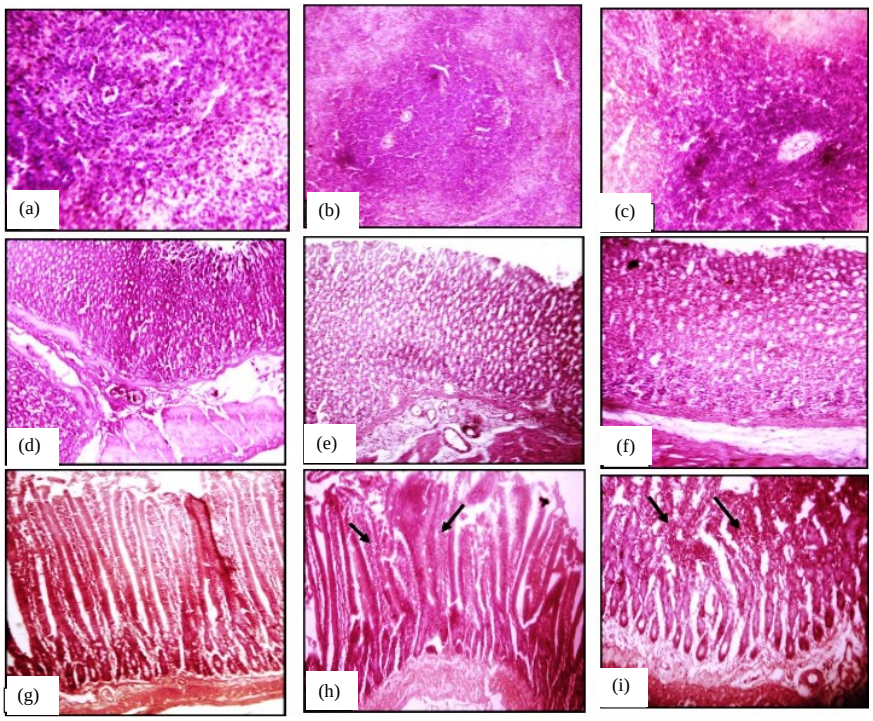

Fig. 4(a-i): Photomicrographs of (a) Spleen, (d) Stomach, (g) Intestine sections from control, (b, e and h) FLE-treated and (c, f and i) DLE-treated rats [Stain: H and E]

Organ weight changes have long served as a sensitive indicator for changes to organs chemically induced by toxic agents and have conventionally been used to predict the toxicity of a test article[27,28]. The estimated relative weights of some target organs; liver, heart, spleen, stomach, lungs and epididymis, were not affected in the sub-acute study. The absence of significant changes in these organs connotes that ingestion of the aqueous leaf extract of *C. esculenta* did not induce any inflammation or anomalous growth of these organs which would otherwise have resulted in altered Relative Organ Weights (ROW) in treated rats. However, significantly increased weights of the kidneys and testes of rats treated with 800 mg kg^{-1} of the sundried leaves were observed. This finding may be attributed to the small size of the organs and the significant weight loss of rats in that group, and thus cannot be considered as a manifestation of toxicity. Since, ROW is an index used for the estimation of the weight of an organ in relation to the body weight of the animal[29]. It can thus be deduced that the markedly decreased body weight of the rats caused an increase in the organ indices of the kidneys and testes. Peters and Boyd[30] emphasized that if administration of a drug or substance produces loss of body weight, the organ changes should be related to the weight loss and not necessarily to direct effects of the drug. It has also been previously documented that precaution be taken in interpretation of ROW data and rather suggested the use of absolute weights as ROW can lead to erroneous conclusions and misinterpretation of drug effects[31].

The blood system is one of the most sensitive targets for toxic compounds, since the blood is the main medium for transport for many drugs and xenobiotics[32]. The evaluation of blood parameters in this study was therefore considered relevant. The results obtained from the blood picture suggest CE did not have any significant effect on the parameters measured. Therefore, it is plausible to assume that the extract is non-haematotoxic.

Hepatotoxic and renotoxic effects related to the use of plant-based products have been reviewed[33,34], hence the need of serobiochemical analysis in toxicity studies. In the liver, the serum aminotransferases [alanine transaminase (ALT) and aspartate transaminase (AST)] are known to increase markedly in response to damage or disruption of the target organ[35,36]. Both AST and ALT are found in the cytoplasm of hepatocytes but ALT is the most specific marker enzyme for the liver and thus a better parameter for detecting liver injury. In the present study, serum levels of ALT and AST were found to be lower in CE-treated groups after 28 days. This finding is clinically insignificant and less well understood than is that of increased activity[37]. The histopathological examination of the liver correlates well with this finding indicating no significant CE-induced cellular lesions. The observed decreased levels of ALT and AST seems to suggest some hepatoprotective potential of the plant extract. Nevertheless, this speculated hepatoprotective effect need to be scientifically established in further studies.

Conversely, significantly increased levels of alkaline phosphatase (ALP) were observed in almost all the treatment groups. The ALP which are mostly found around the lining of the bile canaliculi and sinusoidal surface of hepatocytes, are excreted normally through bile by the liver. They are a group of enzymes found primarily in bones and liver while small amounts are produced by cells lining the intestines, kidney and placenta[38]. Since, the histological architecture of the livers from rats in all treatment groups in this study showed no sign of toxicity within and around the centrilobular regions and most especially, the portal regions, it therefore contradicts the suggestion of cholestasis as being the cause of the increased serum ALP levels. Perhaps, the histomorphological alteration which presented as marked inflammatory cellular infiltration in the intestinal tissues of CE-treated rats may have resulted to the increased serum ALP levels. It has been previously documented that higher ALP activity occurs in the rat intestinal mucosa than in the liver[39]. However, this draws attention for further studies to determine which isoenzyme of ALP is increased with CE administration.

Furthermore, serum urea and creatinine levels which are good indicators of kidney function[35,40], appeared unchanged after CE treatments when compared with the control. It is well established that the kidneys are the target organs involved in drug elimination and therefore are exposed to the toxic effects of exogenous compounds[41]. Upon microscopical examination, the mild changes such as presence of tubular casts and constriction of the glomeruli which were observed in the kidneys of some treatment groups may be due to direct or indirect action of the test substance on the renal tissues. However, these changes appear not to have affected the integrity of the organ due to the unchanged biochemical parameters.

CONCLUSION

Toxicity of the crude aqueous extract of *Colocasia esculenta* leaves in rats via oral route is low. However, caution should be exercised in its use especially at high doses. Further studies are required for understanding the mechanism of action for the observed effects.

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