International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG(USA) Volume 5, Issue 9 - 2018

Research Article

DOI: http://dx.doi.org/10.22192/ijarbs.2018.05.09.017

Acute and Sub-chronic Toxicity Study of *Euphorbia serrata* Ethanol Extracts in Adult Male Albino Rats

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Abstract

Despite ethno-medicinal benefits of *Euphorbia serrata*, very few studies have described the potential toxicity. This study evaluates the *in vivo*toxicity effect of ethanolic leaf extracts of *E.serrata* in adult male albino rats. Acute toxicity test was carried out with modified Lorke′s method. Fifteen male rats weighing 130-160 g were used for the sub-chronic study. The rats were divided into three groups 1-3 (n=5), Group 3 served as control, Groups 1 and 2 received 200 mg/kg and 400 mg/kg body weight doses of the extract. Treatment lasted for twenty- eight days. Acute toxicity test carried out showed that the leaf extracts of *E. serrata* at a single dose of 5000 mg/kg produced treatment related signs of toxicity and mortality in the tested animals. The LD_{50} of this plant was 3808 kg/mg which is less than 5000 kg/kg. In the repeated dose 28- days oral toxicity study,the administration of 200 mg/kg and 400 mg/kg of *E. serrata* extracts per body weight revealed no significant change ($p > 0.05$) in relative organ weight, oxidative stress and cardiac function, and heamatological parameters. Significant difference ($p<0.05$) was recorded in the liver and renal functionand body weight change of the rats for 28 days compared control group. The use of *E.serrata* extracts is relatively safe, but the results suggest that hepatic and renal toxicity may occur with prolonged high doses.

Keywords: *Euphorbia serrata*, Usage, Complication, Mortality, Toxicity, Adverse effects.

1. Introduction

Euphorbia serrata is a species of spurge known by the common names serrated spurge and saw tooth spurge. It belongs to the family Euphorbiaceae, the genus *Euphorbia* is the largest in the plant family, containing about 2000 known species and ranging from annuals to trees. It is an annual plant and has small size (Soforowa, 1982). It is native to Europe and North Africa but is present elsewhere as a weedy introduced species. It is a monoecious herb, shrub or tree and often succulent, especially those originating in Africa and Madagascar (Zargari, 1993). All contain latex and have unique flower structure and grow from 20 centimetres to about half a metre in height. The leaves are of three types, lower median and upper or ray leaves whorled or opposite free or connate. All or most leaves are usually sessile rarely shortly petiolate,

stipulate, not simple, toothed penni or palm nerved (Ali and Nasir, 1986). The fruit is a spherical capsule about half a centimeter wide containing tiny gray seeds. *Euphorbia* plants have played an important role in the life of human beings especially as source of medicinal products (Leland *et al.*, 2006). It is an annual plant and has small size (Soforowa, 1982).
Euphorbiaceae is the largest family of angiosperm having 300 genera and 5000 species. In Nigeria, these species arefound – *E. hirta, E. heterophylla, E. splendes, E. milli, E. prostata, E. thymifolia, E. tirucalli* and *E. desmondi* (Ekeke and Ndukwu, 2014), *E. serrata* and other species. The natural products of *Euphorbia* plants have played an important role in the life of human beings throughout history as regards individual use (Leland *et al*., 2006). Different species of *Euphorbia* are used in folk medicine for the treatment of various ailments such as skin diseases, intestinal parasites and warts. The extracts of *Euphorbia* species have been found to have significant anti-inflammatory, analgesic, haemostatic and wound healing properties (Singla and Pathak, 1989). It has been reported that *Euphorbia* possesses anti-arthritic, anti-convulsant, anti-eczema, anticancer, antidiabetic, antimicrobial, anti-inflammatory, antispasmodic, antitumor, antitussive properties, hormonal and myelopoiesis properties (Eberle*et al*., 1999; Valente *et al*., 2003; Ferreira *et al*., 2006; Luo and Wang, 2006). Various species of the genus *Euphorbia* are used for the treatment of cancer, diarrhea and bronchial asthma (Glavez*et al*., 1993).

Euphorbia serrata is used in Nigeria for the treatment of ailments such as skin diseases, gonorrhea, migraines, intestinal parasites and warts. The plant lattices have been used in fish poisons, and insecticides (Uzair*et al.,* 2009). The stem is used for the treatment of asthma, bronchitis and various lung complaints. The whole plant is used in the treatment of athlete's foot, dysentery, enteritis and skin conditions. Loh*et al*. (2009) reported analgesic, anti-inflammatory and anti- mutagenicity activities of the plant. Antioxidant properties of *E. serrata* have also been claimed (Basma*et al*.,2011).The present study was undertaken toevaluate the acute and sub- chronic toxicity using animal model

2. Materials and Methods

2.1 preparation of leaf extracts of *Euphorbia serrata*

Fresh sample of *Euphorbia serrata*were collected from Imo state. The identification and verification of the plants species was conducted at Green fingers Garden Okigwe Road, Imo State by a Taxonomist, Mr. Moore. The powdered *Euphorbia serrrata*leaves were extracted by ethanol as solvents for a period of 72 hours. The extracts were concentrated *in-vacuo* at 40^{o} C, evaporated to dryness and the residues obtained were stored in a freezer at -80^{o} C until needed for further study. The given quantities were diluted in 1 % DMSO and distilled water and administered by oral gavage.

2.2 Acute toxicity testing

The acute toxicity profile was carried out and median lethal dose (LD_{50}) was calculated using method of Lorke (1983). Eighteen male rats aged 5- 9 weeks old (130 - 160 g) were used in this study. Nine rats (9) were divided into 3 groups of 3 rats each. *E.serrata* ethanol extracts were dissolved in 1% DMSO and administered orally (only once) in the first phase at a single dose of 10 mg/kg, 100 mg/kg and 500 mg/kg body weight of *E. serrata*, the rats were observed forbehavioural changes and mortality. In the second phase, nine rats were divided into 3 groups of 3 rats each and administered orally at a single dose of 1000 mg/kg, 2900 mg/kg and 5000 mg/kg body weight of *E. serrata* and observed for behavioural changes and mortality.

2.3 Sub-chronic Oral toxicity testing

Fifteen male rats weighing 130 -160 g were used in this study. The albino rats were divided into seven groups labelled 1, 2 and 3 with each group consisting of five rats.Groups 1 and 2 were experimental groups while Group 3 was the control.Groups 1 & 2 were orally administered 200 mg /kg and 400 mg/kg body weight dose of ethanol leaf extracts of *E. serrata* dissolved in 1% DMSO daily for 28 dayswith the aid of an orogastrictube.The extracts were administered daily for twenty-eight days during which food and water were also given daily. Body weight of all the rats in the groups was recorded weekly.

2.4 Termination of the experiment

On the 29th day, the rats were sacrificed by cervical decapitation and blood was collected by ocular puncture (media cantus) using ordinary capillary tube and cardiac puncture using syringe and needle. Blood samples were collected into non- heparinized and EDTA- containing tubes for measurements biochemical parameters and for haematological analyses, respectively. Each animal was laid on a dissecting board and a pair of scissors used to open the animal by cutting through vertical mid-line from neck to peritoneum (Osaro *et al*., 2016).

2.5 Organ weight and histopathology

The kidney, the liver and the heart were excised and weighed. Relative Organ Weight (ROW) was calculated by expressing absolute organ weight as percentage of the total body weight. The kidney, liver and heart were collected for histological studies. The tissues were washed in normal saline and fixed immediately in medium of 10 % solution of buffered formalin for 48 hours, dehydrated with alcohol, embedded inparaffin, cut into 4-5 µm thick sections, and stained with haematoxylin –eosin dye for photomicroscopic observation.

2.6 Statistical Analysis

All values are expressed as mean ± SEM. Comparison between groups were performed using one way analysis of variance (ANOVA) and differences between treated groups and control accepted at $p<0.05$.

3. Results

3.1 The acute oral toxicity

The acute oral toxicity test showed that the ethanolic leaf extract of *E. serrata,* at a dose of 5000 mg/kg body weight had adverse effect on the albino rats. The LD_{50} of the plant was therefore estimated to be less than 5000 mg/kg**.** From the acute oral toxicity study the ethanol extracts of *E. serrata,* demonstrated mortality when the animals received up to 5000 mg/kg body weight of the extract orally (Table 1).

Table 1: Acute oral toxicity of ethanol extracts *E.serrata.*

	E.serrata dosage (mg/kg) body weight	Mortality		*E.serrata* dosage (mg/kg) body weight	Mortality
Phase I			Phase II		
Group1	10	0/3	Group 4	1000	0/3
Group2	100	0/3	Group 5	2900	0/3
Group3	500	0/3	Group6	5000	2/3

3.2 Sub-chronic oral toxicity

The sub-chronic oral toxicity result showed that the daily oral administration of *E. serrata* extracts for 28 days did not induce any obvious symptom of toxicity in rats, including the highest dose tested, 400 mg/kg body weight. No deaths or obvious clinical signs were found in any groups throughout the experimental period. Physical observation of the treated rats throughout the study indicated that none of them showed signs of toxicity in their skin, fur, eyes, mucous membrane, or behavioural changes, diarrhoea, tremors, salivation, sleep or coma. Weekly weight gains were observed during the study period compared to the control group

3.3 The effect of ethanol leaf extracts of *E.serrata on* body weights of albino rats

In the evaluation of the sub-chronic toxicity effect of the ethanol extracts of *E. serrata*on the body weights of the albino rats, the result showed that there was significant difference in mean body weight of the rats administered with 200 mg/kg and 400 mg/kg for 28 days when compared to control group .

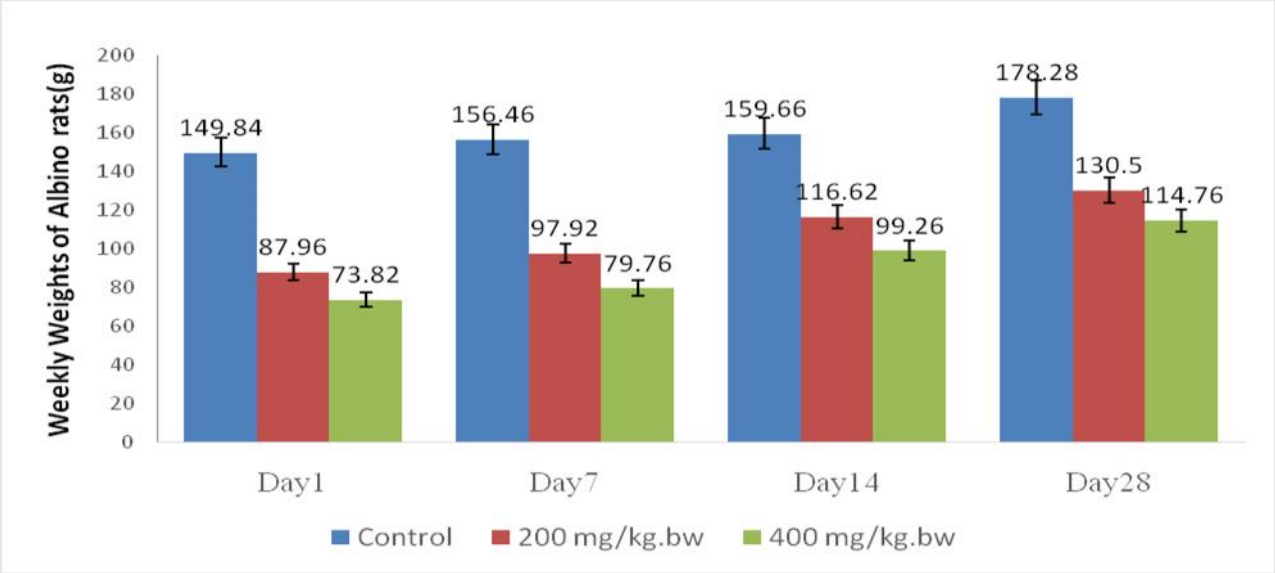

Figure 1: The effect of ethanol extracts of *E.serrata on* body weights of albino rats.

The administration of the ethanol extracts of *E. serrata* at various doses (200 mg/kg and 400 mg/kg) for 28 days showed that there was increase ($P<0.05$) in weekly body weights of Albino rats. However, there was decrease in weekly weights of treated groups of Albino rats when compared to control groups (Fig 1).

3.3 The effects of ethanol leaf extracts of *E. serrata* on liver and renal parameters in Albino rats.

The result of the ethanol extracts of *E. serrata* on liver and renal parameters of albino rats showed that there were significant differences in the liver and renal function of treated groups compared to the control group. The total protein (TP), Albumin (ALB), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), urea and creatinine activities significantly increased ($P<0.05$) in a dose-dependent fashion when the rats received doses (200 mg/kg and 400 mg/kg) of the ethanol extracts.

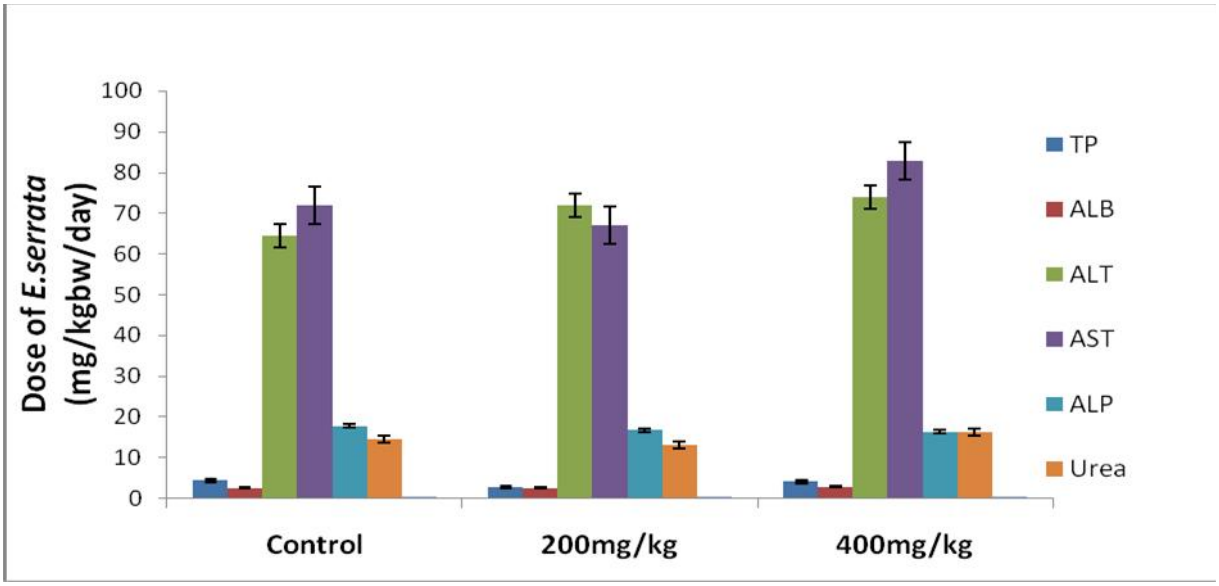

Figure 2: The effects of ethanol leaf extracts of *E. serrata* on liver and renal parameter in Albino rats.

Alkaline phosphatase (ALP), activity was highest in control group when compared to treated groups. The activities of Alanine aminotransferase (ALT), and Aspartate aminotransferase (AST) were high in both control and treated groups compared to other parameters (Fig 2).

3.4 The effects of ethanol leaf extract of *E.serrata* on oxidative stress and cardiac parameters in albino rats.

The effect of ethanol extracts of *E. serrata* on oxidative stress and cardiac parameters in albino rats when compared to the control group showed that there was no significant difference in the oxidative stress and cardiac function of the rats. The catalase (CAT), glutathione peroxidase (GPX), reduced glutathonine (GSH), melondialdehyde (MDA), Lactate dehydrogenase (LDH) and C-Reactive protein (CRP) activities significantly increased($p<0.05$) in a dose–dependent fashion compared to the control group. Albino rats that received 200 mg/kg of ethanolic *E.serrata* extracts had higher superoxide dismutase (SOD) activity than those that received 400mg/kg dose. We observed that there were higher activities of Lactate dehydrogenase (LDH) and Glutathione peroxidase (GPx) in both the control and the treated groups (Fig 3).

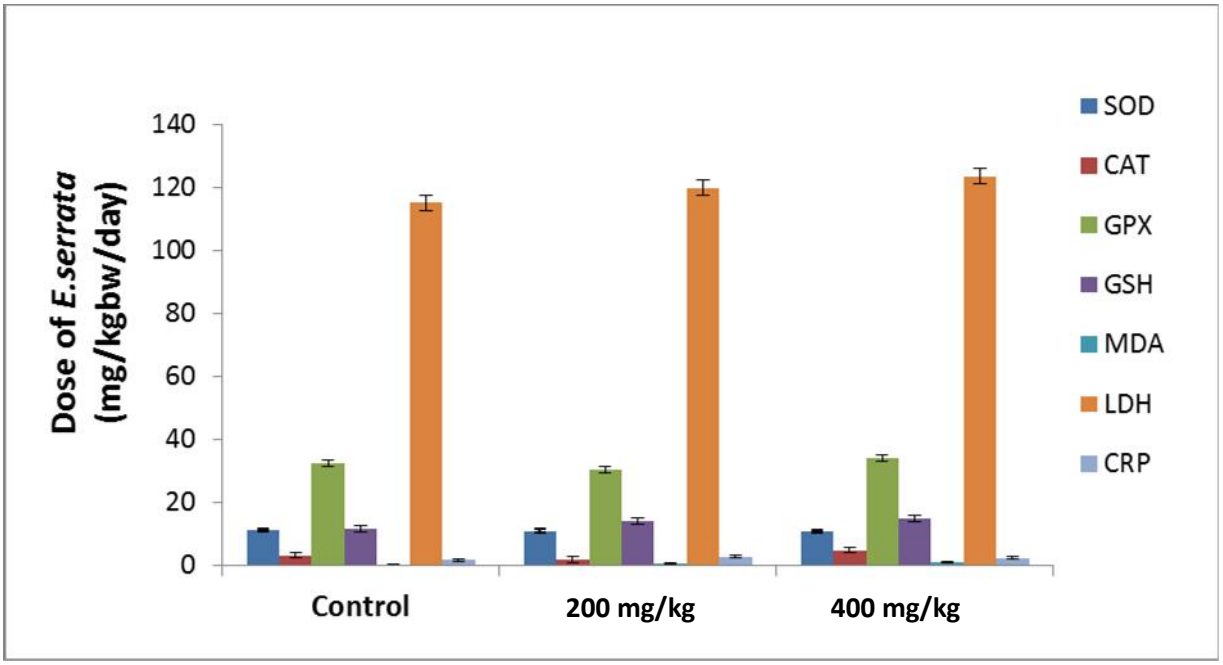

Figure 3: The effects of ethanol leaf extract of *E. serrata* on oxidative stress and cardiac parameters in albino rats

3.5 The effect of ethanol extracts of *E.serrata* on haematological profiles in Albino rats.

The of ethanol extracts of *E. serrata* on albino rats, showed that there was no significant difference in the hematological profile of the albino rats. The concentration of the hematological profile: Hemoglobin (HB), white blood cell (WBC), Red blood cell (RBC), packed cell volume (PCV) and platelets, was higher in the control group compared to treated groups

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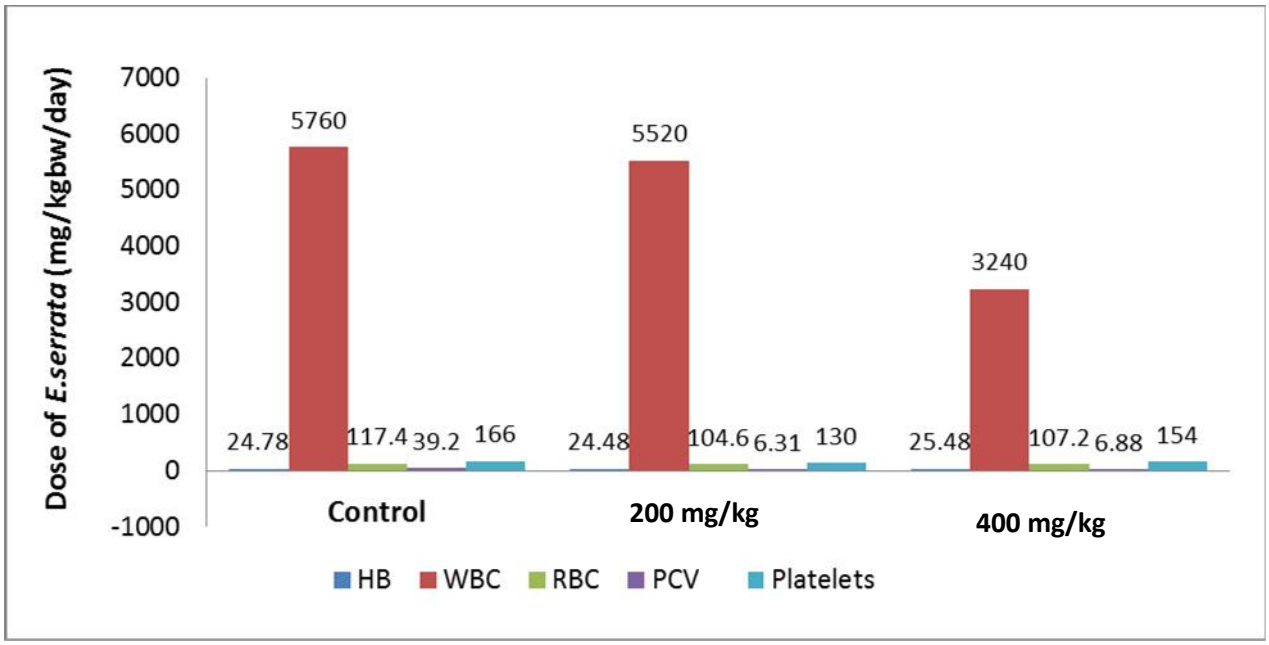

Figure 4: The effect of ethanol extracts of *E. serrata* on haematological profiles in Albino rats

The white blood cell concentration was higher in 200 mg/kg dose than in 400 mg/kg dose in treated group with *E. serrata* but highest in control group compared to the other parameters (Fig 4)

3.6 Relative organ weights of rats treated with ethanol extracts in sub-chronic toxicity study.

The analysis showed that there was no significant difference ($p>0.05$) in the relative organ weights of each organ recorded in the treatment group compared to the control. The relative organ weights of the rats that received various doses of the ethanol extract of *E. serrata*, was not significantly different ($p>0.05$) from those of the control group. The groups treated with 200 mg/kg and 400 mg/kg body weight of extracts showed no significant gain in weight of liver, kidney and heart (Table 2).

Table 2: Relative organ weights of rats treated with ethanol extracts in sub-chronic toxicity study.

Organ	Control	200 mg/kg	400 mg/kg	P-Value
Heart	0.44±0.005	1.57±1.61	1.46±1.49	0.519
Liver	2.965±0.005	11.21±11.53	11.14±11.45	
Kidney	0.73±0.01	2.72±11.53	2.65±2.73	

Data are shown as Mean ± SEM (n=5 for each group)

3.7 The effect of *E. serrata* extracts (200 and 400 mg/kg) on liver histomorphology of albino rats in sub-chronic oral toxicity study.

Fig 5 (a &b) sections of the liver showed hepatic lobules consisting of normal hepatocytes arranged in radiating interconnecting cords around the central veins. The hepatic cords radiate towards the periphery of the lobules where it meets with the components of the portal triad (hepatic artery, hepatic vein and bile duct.

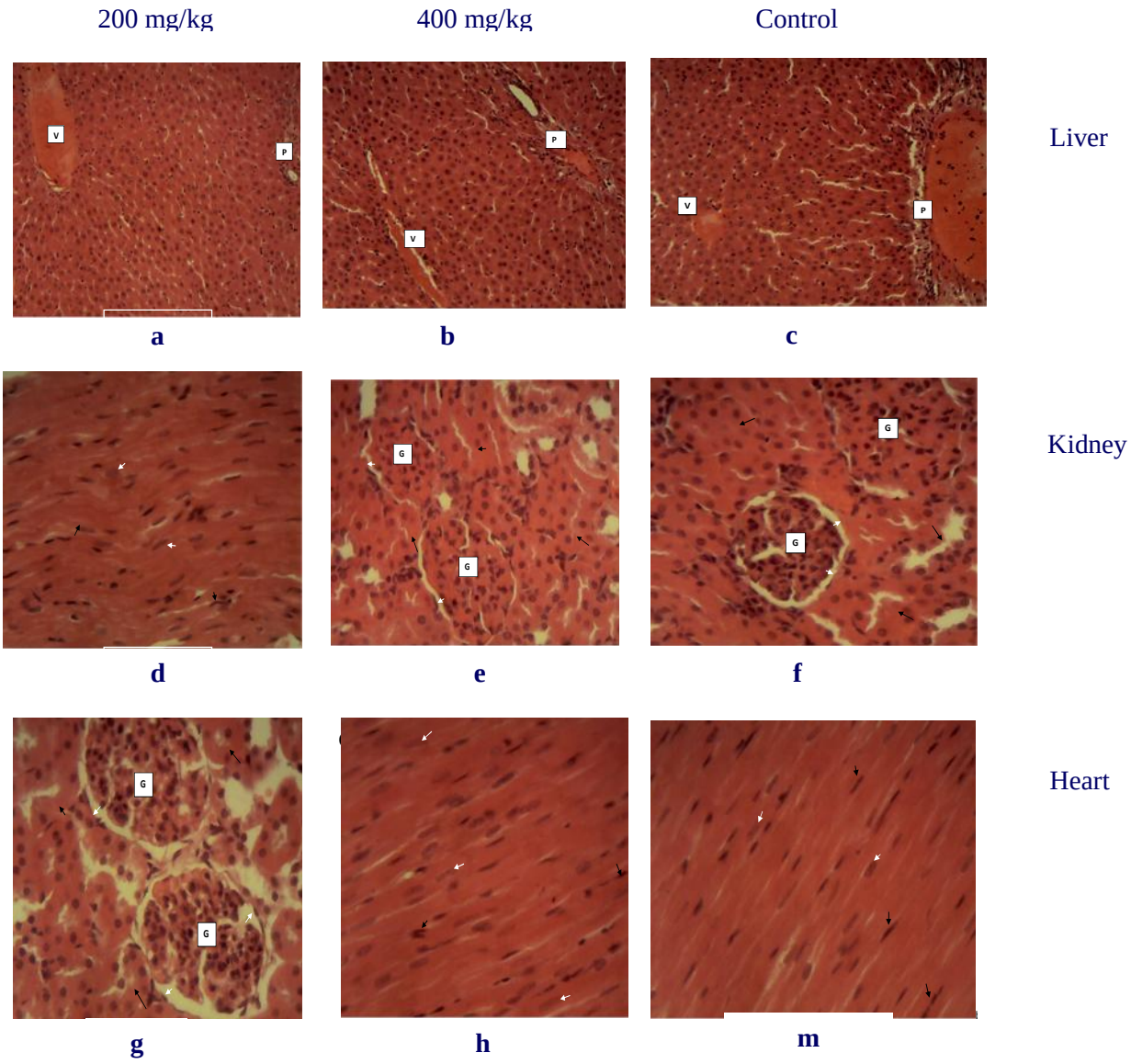

Fig 5: The effects of 200 mg/kg and 400 mg/kg of ethanolic leaf extracts of *E. serrata on* various rat organ histomorphologies in sub chronic oral toxicity study: *(*a), (b),and (c): Liver ; (d) , (e) and (f): Kidney; (g),(h) and (m): Heart

Legend: Central vein (V); portal area (P).Nucleus of cardiomyocyte, (white arrow); Pericyte (black arrow).Glomerulus (G); Bowman's capsule (white arrow); Renal tubules (black arrow).Glomerulus (G); Bowman's capsule (white arrow); Renal tubules (black arrow).

3.8 The effect of *E. serrata* extracts (200 and 400 mg/kg) on kidney histomorphologies of albino rats in sub-chronic oral toxicity study.

The sections of the kidney showed the normal renal histo-architectures. Normal Glomeruli in their Bowman's capsules surrounded by normal renal tubules (proximal convoluted tubules, pars recta, distal convoluted tubules and collecting duct) suspended in a highly vascularised connective tissue matrix (renal interstitium) were also observed. Sections of the kidney collected showed the renal histo-architectures.

3.9 The effect of *E. serrata* extracts (200 and 400 mg/kg) on heart histomorphology of albino rats in sub-chronic oral toxicity study.

Fig.5 (g & h)sections of the heart showed that the normal myocardial histo-architectures and showed normal epicardial, myocardial and endocardial layers. The myocardium showed normal myocytes arranged in overlapping bundles, surrounded by a rich network of blood vessels and capillaries embedded in a connective tissue matrix. The myocytes contain single centrally located oval to elongated hypochromatic nuclei. Fibroblasts of the connective tissue matrix appear as spindle shaped cells with spindle shaped hyperchromatic nuclei.

4. Discussion

The LD_{50} of the extracts was found to be 3808 mg/kg.bw. *E. serrata* belongs to a family Euphorbiaceae that is known to be toxic. This is in consonance with the study carried out by Rant *et al*., (2013) where they investigated cytotoxic effect of the aerial part of the plants *E. milli* and *E. pulcherima*. Their result revealed that the crude alcoholic and ethyl acetate extracts showed excellent cytotoxic activity. Moreover, if a high dose (e.g 5000 mg/kg) is found to be survivable, there is no need for conducting further acute testing (NRC, 2006). In this study *E serrata*, ethanolic extracts at a dose of 5000mg/kg had adverse effect on the tested rats.

The effect of the ethanol extracts of *E. serrata*, on the body weight serves as a sensitive indication of the general health status of animals. However, weight gains were observed in all animals administered with 200 mg/kg and with 400 mg/kg of *E. serrata*, in weekly weights of albino rats during 28 days. However there was decrease in weekly weights of treated groups of albino rats when compared to the control group. It can be stated that *E. serrata*, extract did interfere to some extent with the normal metabolism of the animals as corroborated by the significant difference from animals in the control group. The treated group did not show any significant alteration in water or food consumption (data not shown). The weekly gain in body weight in treated groups could be as a result of increment in food and water intake. Loss of appetite is often synonymous with weight loss due to disturbance in the metabolism of protein, fat or carbohydrate (Ezeonwumelu*et al.*, 2011). This result is in consonance with earlier findings of Kwan *et al*., (2013), who carried out an investigation on the acute and sub chronic toxicity study of *Euphorbia hirta* L. methanol extracts in rats. They observed that increment in food and water intake is responsible for the increment in body weight gain. Also the observed increase in weekly body weight of the treated groups could be attributed to the nutritional value of *E. serrata*, extracts (Kwan *et al*., 2013; Ezeonwumelu *et al.*, 2011; Duke, 1997).

The result of the effect of ethanol extract of *E. serrata* on liver and renal function in albino rats showed that there were significant differences in the liver and renal function of the rats compare to control group. Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), urea and creatinine activities significantly increase ($P<0.05$) dose-dependent fashion when compared to control group. Total protein (TP) activity was higher in control group than in treated groups. The rats that received 200 mg/kg and 400 mg/kg doses had a higher albumin (ALB) and Aspartate aminotransferase activities compare to control group. In evaluating the toxicity of drugs and plant extracts the assessment of the liver and kidney is a very important index, as both are necessary for the survival of the organism (Olurunisola *et al.*, 2012).

The significant changes in the liver and renal function of treated groups with *E. serrata*, this result agrees with findings of Tarkang *et al.*, (2012), who carried out an investigation on the acute and chronic toxicity of the aqueous and ethanol leaf extracts of *Carica papaya* Linn in Wister rats. They also observed a dose-dependent increase in AST and suggested that sub-acute administration of *Carica papaya* extracts caused hepatocellular damage. The significant increase in AST with *E. serrata*, suggests that administration of higher doses of this extract may induce the destruction of the liver cells. Also the kidney function indices evaluation for *E. serrata*, correlates with the findings of Muhammad *et al.*, (2011), who carried out an investigation on the acute and sub-chronic toxicity of kernel extract of *Sclerocanya birrea* in rats. They reported that a significant increase in urea and creatinine was observed when the experimental rats received higher doses of the kernel extract of *Sclerocanya birrea* ranging from 3000 to 4000 mg/kg body weight.

The effect of ethanol extracts of *E. serrata* on hematological profile in albino rats, the result of the analysis showed that there was no significant difference on hematological profile in Albino rats. The concentration of the hematological profile:

Hemoglobin (HB), white blood cell (WBC), Red blood cell (RBC), packed cell volume (PCV) and platelets, their concentration was higher in the control group compare to treated groups. We also observed that white blood cell concentration was higher in 200 mg/kg dose than in 400 mg/kg dose in treated group with *E.serrata* but highest in control group. We also observed that white blood cells concentration was high when compared to other parameters. Sub-chronic administration of the ethanol extract of *E.serrata*, on treated and control groups, the results show no significant effect (P>0.05) in the hematological profile of rats suggesting that *E. serrata*, may not be toxic to the blood system. But significant decrease (P>0.05) in hematological profile as dose of extracts increased from 200mg/kg to 400mg/kg may be toxic to the blood system compared to control.

The liver, kidney and heart did not show any significant difference in weight. These insignificant increase and decrease in body weight could have been as a result of variation in size of internal organs (Chunlarattharaphorn *et al*., 2007), it may also be as a result of toxicity induced by leaf extracts.

The microscopic examination of the liver, kidney and heart of rats treated with various doses of *E. serrata*, extract did not show any changes in colour compared with the control group. The first hand indication of toxicity of chemical or biological substances is the hypertrophy of the organs. However, no hypertrophy was observed in organs of rats treated with *E. serrata.* There were no pathologies recorded in the histological sections of the vital organs (liver, Kidney and heart) of experimental rats administered with 200 mg/kg and 400 mg/kg body weight of *E. serrata* extracts.

5. Conclusion

These findings conclude that the ethanolic leaf extracts of *E. serrata* exhibited low chronic toxicity to the experimental animals, implying minimal deleterious effect following use.

Conflict of Interests

The authors of this paper have no conflict of interests.

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Quick Response Code

DOI:10.22192/ijarbs.2018.05.09.017

How to cite this article:

Ugenyi Assumpta U., Ozoh Patrick O., Ukwandu N. C., Mgbemena Ifeyinwa C., Okorie Chioma C., Onyeocha Ignatius O., Okereke Josephat N ., Ogbulie Toochukwu E., Adjero Lawrencia A. (2018). Acute and Sub-chronic Toxicity Study of *Euphorbia serrata* Ethanol Extracts in Adult Male Albino Rats. Int. J. Adv. Res. Biol. Sci. 5(9): 164-173.

DOI: http://dx.doi.org/10.22192/ijarbs.2018.05.09.017