European Journal of Medicinal Plants

29(1): 1-10, 2019; Article no.EJMP.47285
ISSN: 2231-0894, NLM ID: 101583475

Acute and Sub-acute Toxicity Assessment of *Euphorbia lateriflora* (Schum and Thonn) in Wistar Albino Rats

Olubukola Sinbad Olorunnisola[1*], Adewale Adetutu[1], Abiodun Olusoji Owoade[1], Folorunsho Ayodeji Ajayi[2], Adedoyin Adetutu Ajibade[1] and Peter Adegbola[1]

[1]Department of Biochemistry, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Nigeria.
[2]Department of Physiology, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All the authors participated in designing the study and the interpretation of results. Authors AAA and PA participated in the laboratory work and performed the statistical analysis. Authors OSO, AA, AOO and FAA wrote the first draft of the manuscript. Authors AAA and PA managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/EJMP/2019/v29i130147
Editor(s):
(1) Dr. Roberta Cristiane Ribeiro, Universidade Federal Rural do Rio de Janeiro, UFRRJ, Seropedica, Brazil.
(2) Prof. Marcello Iriti, Professor of Plant Biology and Pathology, Department of Agricultural and Environmental Sciences, Milan State University, Italy.
Reviewers:
(1) Wilson Obidah, Modibbo Adama University of Technology, Nigeria.
(2) Joshua Raji, Florida International University, USA.
(3) Senthilkumar Rajagopal, Rayalaseema University, India.
Complete Peer review History: https://sdiarticle4.com/review-history/47285

Original Research Article

Received 26 November 2018
Accepted 12 February 2019
Published 19 September 2019

ABSTRACT

Aims: The toxicity of ethanol whole plant extract of *Euphorbia lateriflora* was assessed in Albino Wistar rats.
Methodology: The LD_{50} was at single dose of 5000 mg/kg body weight, the sub-acute dosage of the extract was administered orally at 250 and 500 mg/kg b.w.t twice daily for 7 days and the effect of the extract on liver, kidney, and haematological parameters was assessed and recorded during these periods.

**Corresponding author: E-mail: osolorunnisola@lautech.edu.ng;*

Results: The result of the oral acute toxicity study at single high dose of 5000 mg/kg/bwt shows that the LD_{50} of the extract is greater than 5000 mg/kg/bwt. After 7 days of oral administration, 500 mg/kg/bwt of the extract caused a significant ($p<0.05$) decrease in the packed cell volume. At 500 mg/kg/bwt, the extract caused a significant ($p<0.05$) increase in ALP, total protein and albumin and decrease in serum electrolytes (N_a^+, k^+ and Cl^-). Histopathological analysis revealed the expansion of fibrous spaces in the liver and thickening of the glomerular basement of the kidney in the group fed with 500 mg/kg/b.w.t of extracts.

Conclusion: In conclusion, the dose and time-dependent selective organ toxicity effect of this extract suggested that the extract might be relatively unsafe for consumption at especially high concentrations.

Keywords: Toxicity; kidney; liver; haematology; LD_{50}.

1. INTRODUCTION

Medicinal plants had a long dated history in the management of several human diseases. They play important role in the development of potent therapeutic agents and have contributed significantly toward the development of modern medicine [1]. The therapeutic properties attributed to medicinal plants are linked to phytochemicals such as terpenoids, saponins, phenolic compounds and alkaloids [2,3]. Several studies have shown that the bioactivities of medicinal plants include anti-malaria, anti-microbial, anti-inflammatory, antioxidant, and anti-diabetic properties [3,4,5].

The major advantages of medicinal plants over the conventional drugs seems to be their perceived efficacy, low cost and the low incidence of serious adverse effects [6,7]. This claim has however, been challenged as some medicinal plants have demonstrated some toxicological effects in both human and animals [8]. Therefore, it should be stressed that before the use of traditional medicinal plants, the safety should be ascertained [9]. Furthermore, it is necessary for medicinal plants to be evaluated for safety or toxicity and necessary recommendations be made regarding their use [10].

Euphorbia lateriflora (Schum and Thonn) also known in Yoruba as “Enu opiri” and “Fidda sartse” in Hausa, is a shrub with smooth-gracious and erect branches [11]. The latex of the plant is used for the treatment of ringworm, and in a dilute aqueous solution as purgative [11,12]. The leaves are also useful in the treatment of dermatoses [11,12]. Several studies have revealed the pharmacological potential of this plant. According to Obi et al. [13], *E. Lateriflora* extract exhibited antiviral activity in human carcinoma cell line. However, for proper recommendation, and public awareness on the safety of the plant extracts, the acute and sub-acute toxicity effects of the ethanol whole plant extracts was investigated on Albino rats.

2. MATERIALS AND METHODS

2.1 Plants Collection

Whole plant of *E. lateriflora* was obtained within Ogbomosho North LGA, Oyo State Nigeria through the help of a traditional healer. Ogbomoso North lies between latitude 8.156697 and longitude 4.264409. The plant was identified and authenticated by Prof. A.T.J Ogunkunle of the Department of Pure and Applied Biology, Ladoke Akintola University of Technology, Oyo State Nigeria. The plant sample was deposited in the University Herbarium.

2.2 Preparation of Plant Extract

The ethanol extraction of the plant sample was carried out by using modified method of Mbaka et al. [14]. Brifely, 400 g of the pulverized plant sample was loaded in a soxhlet extractor in batches for 5 h each and subjected to extraction with ethanol. After extraction, mixtures were concentrated at 48°C using rotary evaporator and the concentrate was kept in a refrigerator (4°C) until use.

2.3 Experimental Animals

Thirty male albino rats (Wistar stock) weighing between 150-200 g were obtained from the Department of Anatomy Animal House, Ladoke Akintola University of Technology Ogbomosho Oyo State, Nigeria. They were acclimatized for a period of one week and kept under the normal 12 h light/dark cycle. The animals were allowed

access to food and water *ad libitum* throughout the study period. The animal feed was specially prepared from chick Grower's mash (Feed Mill Company Ogbomosho Oyo State, Nigeria). Animals were handled following the standard protocol on animal care and use.

2.4 Experimental Design

2.4.1 Determination of LD_{50}

Ten (10) rats were used for this study. After 7 days acclimatization, the rats were fasted over night but allowed access to water prior to dosing. The up and down method by Dixon, [15] was used. The method involves testing the rats, one at a time in a staircase method i.e. limit test which involves either starting with the lowest dose (2000 mg/kg/bwt) and increasing the dosage if no death or toxic effect is noticed or starting with the highest dose (5000 mg/kg/bwt) and reducing the dosage if death occurs at the highest dose. The animals were weighed and dosed with a limit dose of 5000 mg/kg body weight of the freshly prepared ethanol whole plant extract of *Euphorbia lateriflora.* The rats were monitored for 72 hours for any change in behaviour.

2.4.2 Sub-acute toxicity test

The sub-acute toxicity study was performed for the ethanol whole plant extracts of *Euphorbia lateri*flora. Rats were randomly separated into 3 groups (5 rats per group) and were orally administered with 1/10 and 1/20 LD_{50} respectively for *Euphorbia lateriflora*. At the end of 7 days of twice administration daily, all surviving rats were sacrificed by decapitation and the internal organs examined.

- Group A= control rats given 1ml distilled water (no ethanolic plant extract)
- Group B= rats given 1/10 of the LD_{50} of ethanolic plant extract. (500 mg/kg)
- Group C= rats given 1/20 of the LD_{50} of ethanol whole plant extract (250 mg/kg).

2.5 Collection of Blood Samples

Animals were anaesthetized with chloroform and decapitated. Blood samples were then collected into heparinized and non heparinized tubes. Those in heparinized tubes was used for haematological evaluation while the non heparinized were centrifuged and serum was analysed for biochemical parameters.

2.6 Haematological and Serum Biochemical Parameters

Haematological parameters assayed included red blood cell (RBC) and white blood cell (WBC) counts platelets, haematocrit, and haemoglobin (Hb) estimation. Erythrocyte indices (mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), and mean corpuscular haemoglobin (MCH)) was determined from values obtained from red blood cell (RBC) count, Hb concentration, and packed cell volume (PCV) values. All haematological parameters were analysed using the automated method with automatic analyser "Haematology Auto-analyser sysmex KX-21N". The biochemical analysis evaluated includes the serum activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase, creatinine, urea, and total protein level. Electrolytes such as sodium, chloride and Potassium were also assayed.

2.7 Histopathology

The histological procedures were done according to the method of Avwioro, [16]. The kidney and liver were removed and fixed into 10% buffered formalin in labelled bottles. Dewax in Xylene for 15 mins, Taken through Absolute Alcohol, 95% and 70% Alcohol. Rinsed the section in water, Stain in Harris haematoxylin for 5 mins, Rinse in water, Differentiate in 1% acid alcohol briefly, Rinse in water, Blue under running tap water for 10 mins, Counterstain with 1% aqueous Eosin for 2 min, Rinse in water, Dehydrate in ascending grades of alcohol and Clear in xylene and Mount in DPX.

2.8 Statistical Analysis

All data were calculated and expressed as mean ± SEM using Graph Pad Prism Software and were considered significant at ($p<0.05$).

3. RESULTS

3.1 LD_{50} Determination

Animals treated with 5000 mg/kg/bwt of the ethanolic extract of *E. lateriflora* showed no changes in behaviour and no apparent toxicity symptoms after 72 hrs post treatment. The rats survived the highest dose, hence, it was concluded that the LD_{50} of the plants extracts is greater than 5000 mg/kg/bwt.

3.2 Sub-Acute Toxicity Tests

3.2.1 Effect of whole plant extract of *E. lateriflora* on haematological parameters of rats

Table 1 showed the effects of the administration of *Euphorbia lateriflora* on the haematological parameters of rats. Administration of *Euphorbia lateriflora* whole plant extract at 250 mg/kg/b.w.t showed no significant ($p<0.05$) effect on the WBC, RBC, HGB, Platelet, Neutrophil and Lymphocyte but significantly ($p<0.05$) reduced the packed cell volume (HCT) when 500 mg/kg/b.w.t of the extract was administered in rat.

3.3 Effect of *E. lateriflora* on Biochemical Parameters of Rats

The results presented in Table 2 showed the effects of *Euphorbia lateriflora* administration at 250 mg/kg/bwt and 500 mg/kg/bwt on serum liver markers (ALT, AST, ALP and GGT). The administration of *Euphorbia lateriflora* had no significant ($p<0.05$) effects on the serum activity of ALT, AST and GGT at both doses but a significant ($p<0.05$) increase was observed in serum ALP activity when the extracts treated groups were compared with the control.

3.4 Effect of *Euphorbia lateriflora* on Electrolyte Concentration

In Table 3, treatment of rats with 250 mg/kg/bwt of *Euphorbia lateriflora* had no significant ($p<0.05$) effects on the serum sodium, potassium and calcium concentration when compared with the control, but treatment with 500 mg/kg/bwt significantly ($p<0.05$) decreased the serum sodium and chloride concentration. No significant ($p<0.05$) difference was observed between the serum potassium concentration of the control rats and rats treated with 250 mg/kg/bwt of *Euphorbia lateriflora* while a significant ($p<0.05$) decrease was observed in the serum pottasium concentration of rats treated with 500 mg/kg/bwt of *Euphorbia lateriflora* when compared with the control group In addition, *Euphorbia lateriflora* at 250 mg/kg/bwt and 500 mg/kg/bwt showed no significant effects on the serum urea and creatinine concentration.

Table 1. Toxic effects of *Euphorbia lateriflora* administration on haematological indices

Haematological parameters	Control	*Euphorbia lateriflora* (mg/kg)	
		250	500
WBC $10^{3/NL}$	10.2±0.45	10.5±0.90	11.3±1.56
NEUTROPHILS %	25±4.38	27.4±8.10	35.8±6.28
LYMPHOCYTE %	74±6.62	70.5±8.84	64.0±9.37
RBC $\times 10^{6/N\ L}$	0.09±0.01	0.09±0.05	0.12±0.10
HGB g/dl	13.0±0.37	13.1±0.51	13.8±0.78
PCV %	39.4±1.15	38.3±0.95	35.4±0.54**
MCV	95.0±0.48	94.2±0.74	90.0±0.57
MCHC g/dl	450.7±87.62	445.1±69.30	440.0±57.16
PLATELET $\times 10^{3/NL}$	783±51.71	574±76.39	680 ±120.83
PCT L/L	0.60±0.19	0.57±0.14	0.59±0.30

*Values were expressed as mean ± SEM and considered significant at p-value <0.05. *significant difference when compared with the Control group. #significant difference when the 250 mg group is compared with 500 mg dosage group*

Table 2. Serum liver markers in *Euphorbia lateriflora* and *Terminalia Ivorensis* toxicity

Parameters	Control	*Euphorbia lateriflora* (mg/kg)	
		250	500
ALT(U/L)	7.74±0.22	6.9±0.27	7.16±0.15
AST(U/L)	6.86±0.23	7.2±0.2	6.2±0.52
ALP(U/L)	36.28±0.29	42.6±0.29***	51.48±0.27***#
GGT(U/L)	40.57±0.25	39.1±0.12	39±0.13

*Values were expressed as mean ± SEM and considered significant at P value <0.05. *significant difference when compared with the Control group. #significant difference when the 250 mg group is compared with 500 mg dosage group. n=5*

The effects of *Euphorbia lateriflora* on the serum total protein, bilirubin and albumin level are showed in Table 4. Significant ($p<0.05$) increase was observed in the serum total protein and albumin level of rats treated with 500 mg/kg/bwt of *Euphorbia lateriflora* when compared with the group treated with 250 mg/kg/bwt and the control group. No significant ($p<0.05$) difference was observed in the total protein level of the control rats and the rats treated with 250 mg/kg/bwt of *Euphorbia lateriflora*, while a significant ($p<0.05$) increase was observed in the serum albumin level of rats treated with 250 mg of *Euphorbia lateriflora* when compared with rats in the control group. No significant ($p<0.05$) difference was observed in the serum bilirubin level of rats treated with *Euphorbia lateriflora* when compared with the control rats.

Table 3. Electrolytes concentration in *Euphorbia lateriflora* and *Terminalia Ivorensis* toxicity

Parameters	Control	*Euphorbia lateriflora* (mg/kg)	
		250	500
Sodium(N_a^+)	166.95±0.03	166.08±0.21	160.82±3.67**#
Potassium(k^+)	4.61±0.05	3.33±0.18	2.08±0.12*
Chloride(Cl^-)	51.44±0.19	48.8±0.36	45.34±0.14*
Urea (mg/dl)	56.3±0.19	56.18±0.21	57.86±0.11
Creatinine (mg/dl)	4.9±0.13	4.1±0.15	3.22±0.12

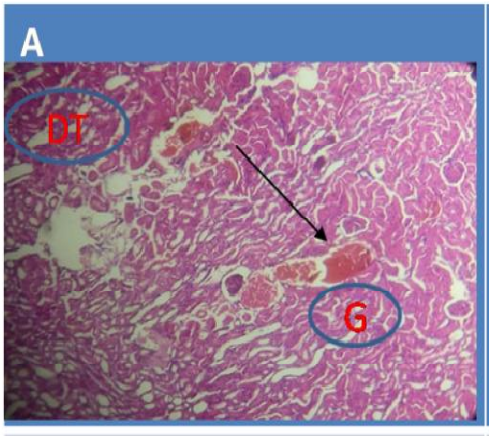
*Values were expressed as mean ± SEM and considered significant at P value <0.05. *significant difference when compared with the Control group. #significant difference when the 250 mg group is compared with 500 mg dosage group. n=5*

Table 4. Effect of *Euphorbia lateriflora* on protein concentration

Parameters	Control	*Euphorbia lateriflora* (mg/kg)	
		250	500
Total protein (g/dl)	68.68±0.32	69.88±1.08	77.56±1.29***#
Total bilirubin (mg/dl)	2.86±0.10	3.16±0.09	3.84±0.13
Albumin (g/dl)	39.86±0.10	46.70±0.27***	50.32±0.22***#

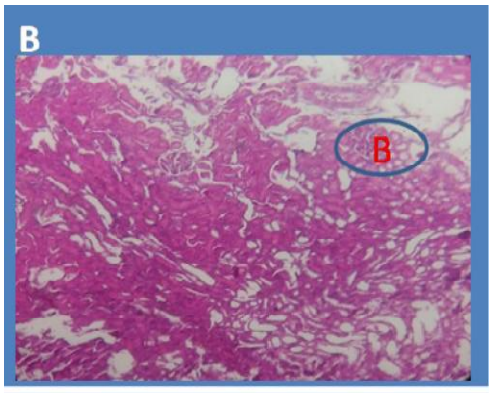
*Values were expressed as mean ± SEM and considered significant at P value <0.05. *significant difference when compared with the Control group. # significant difference when the 250 mg group is compared with 500 mg dosage group. n=5*

3.5 Histopathological Studies



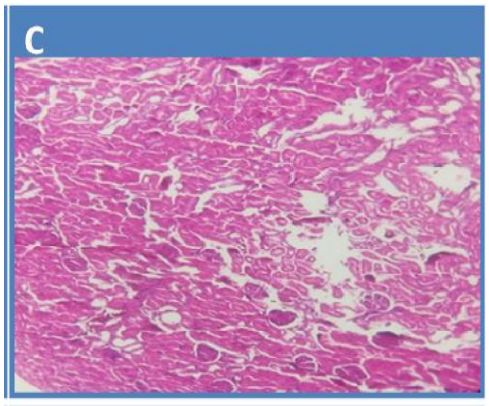
Showed renal tissue with preserved architecture, No abnormality seen, the glomeruli and tubules appear normal, No inflammatory cells and no cellular atypia seen.

Fig. 1. Photomicrograph of kidney Section of normal rat. MG X100, H&E stain



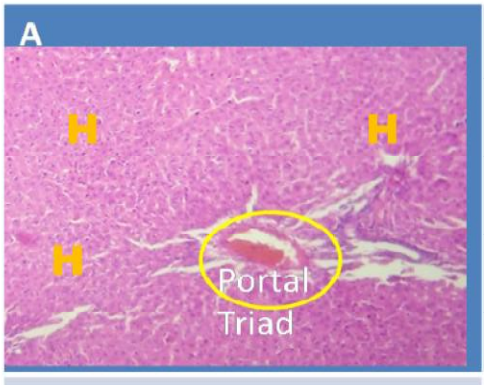
Showed renal parenchyma with preserved architecture, No cellular atypia, both glomeruli and tubules appear normal

Fig. 2. Photomicrograph of kidney section of rat treated with 250 mg/kg of *E. lateriflora*. MG X100, H&E stain



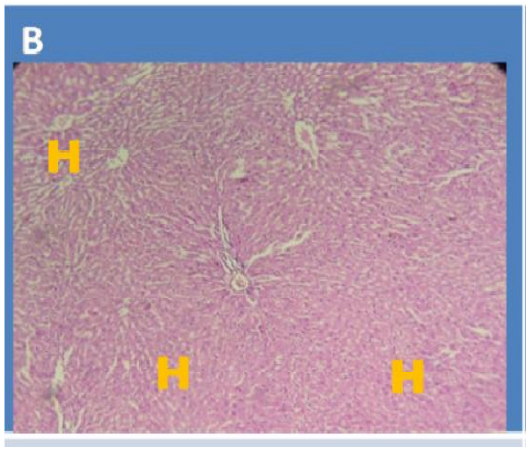
Glomerular basement thickening. No cellular atypia, dense eosinophillic substances distort through renal parenchyma

Fig. 3. Photomicrograph of kidney section of rat treated with 500 mg/kg of *E. lateriflora*. MG X100, H&E stain



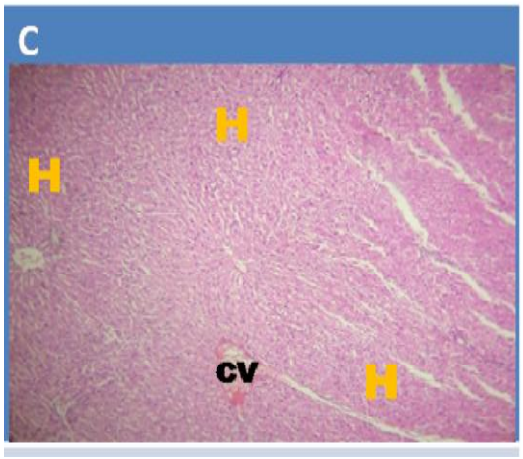
Showed liver parenchyma with preserved architecture

Fig. 4. Photomicrograph of liver section of normal rat. MG X100, H&E stain



Showed liver with parenchyma, central veins (CV) and partial vasculature appears normal

Fig. 5. Photomicrograph of liver section of rat treated with 250 mg/kg of *E. lateriflora*. MG X100, H&E stain



Showed liver with parenchyma, there is expansion of partial spaces by fibrous spaces. Central veins and partial vasculature appears normal. No cellular atypia

Fig. 6. Photomicrograph of liver section of rat treated with 500 mg/kg of *E. lateriflora*. MG X100, H&E stain

4. DISCUSSION

Determination of LD_{50} is usually the initial step in the evaluation of the toxicity of a substance [10]. The LD_{50} provides information on the dose of the test substance that is lethal to the test subject. In this study, 5000 mg/kg/bwt of *E. lateriflora* had no lethal effect on the rats. Furthermore, data from acute toxicity study may provide initial information on the likely toxic effect of a substance and help to arrive at a dose of a new compound (s) [9].

Liver, being the organ responsible for the metabolism of most xenobiotics is particularly susceptible to chemical injury [17] while the kidney functions in getting rid of the body waste materials that are either ingested or produced by the detoxification process of the liver. Hence, they are predisposed to damages upon accumulation of these toxic metabolites or chemicals [18]. In this study, we investigated the toxic effects of *E. lateriflora* on the liver and kidney of rat.

Biochemical indices monitored in the serum included electrolytes and other secretory substances of the liver and kidney that can be used as markers for assessing the functional capacities of the organs [10]. Alteration in these

parameters indicates impairment in the normal functions of the organs. The various biochemical parameters assessed in this study are useful indices for evaluating toxicity of plant extracts in animals [19-21].

The result of this study showed that the ethanol extracts of *E. lateriflora* have no hepatotoxic effects in rats. Increase in serum activity of AST, ALT, ALP and GGT is usually an indication of damage to the liver cells. These enzymes are mainly localized in the liver and are released into circulation upon damage to the hepatic cells. Thus, the changes in the activity and concentration of these enzymes could reflect the extent of hepatotoxicity. Ethanolic whole plant extracts of *E. lateriflora* caused no alteration in some of these serum biomarkers, thus might not be toxic at the tested dose.

The liver synthesizes most serum protein [22]. The parenchymal cells are responsible for the synthesis of albumin, fibrinogen and other coagulation factors and most of globulin b and a [23]. The quantitative changes in some of these serum protein could have negative effects on the normal functioning of a cell and may also reflects impairment in the secretary functions of the liver [9].

The result of this study further affirmed the non-hepatotoxic nature of *E. lateriflora* as it produced no changes in the serum total protein and bilirubin level at 250 mg/kg/bwt but increased total protein and albumin when administered at 500 mg/kg/bwt. Nutritional status and disease state are known to affect the serum albumin level thereby affecting the blood osmotic pressure [10]. In this study, the increased observed in albumin level might be a reflection of increased appetite in the rats.

Bilirubin is derived from haemoglobin upon degradation of RBC. It is a metabolic breakdown product of heme and it is one of the most commonly used liver function test [24]. Abnormal increase in serum bilirubin is indicative of liver impairment. The observation in this study suggested that *E. lateriflora* had no toxicological effects at 250 mg/kg/bwt but might be slightly toxic at 500 mg/kg/bwt.

Evaluation of haematological parameters can be used to determine the extent of deleterious effects of *E. lateriflora* extracts on the blood, it can also be used to explain blood related functions of a plant extract or its product [20]. Changes in red blood cell, mean corpuscular volume, mean corpuscular Hb and platelets could be used to assess erythropoiesis, morphology and osmotic fragility of the RBC [25]. The extracts of *E. lateriflora* caused no significant changes in the haematological parameters thus might be non-toxic at the tested dose.

Furthermore, renal function indices are usually needed to assess the normal functioning of the different parts of the nephron [26]. In addition, serum electrolyte, uric acid, urea and creatinine concentration could give an insight into the effects of plant extract on the tubular and glomerular functions of the kidney [10]. The result in Table 3 showed that the administration of *E. laterifolia* is non-toxic to the kidney. Glomerular filtration process removes creatinine from plasma and then excretes it in the urine without reabsorption by the tubules to any significant extent. In addition, when the plasma level increases above normal, creatinine could also be excreted through the tubules. The implication is that the serum creatinine level in renal disease generally does not increase until the renal function is substantially impaired [27]. However, high serum urea and creatinine level may be an indication of renal failure [17]. Normal renal function depends on a normal filtration rate. In this study, *E. laterifolia* had no toxic effect on the renal function at both doses. This observation is consistent with earlier findings of Usman et al. [12] on *E. laterifolia.*

The microscopic examination of the kidney and liver of rats treated with 250 mg/kg/bwt and 500 mg/kg/bwt of *E. lateriflora* supported the results of the biochemical analysis. In the liver, the architecture of the parenchyma was preserved; the central veins and Partial vasculature appear normal, no cellular atypia, no inflammatory exudates. The entire tissue appears normal and no cellular atypia. Generally, any damage to the parenchyma liver cells result in the elevation of both transaminases in the blood [28]. Hence, the insignificant changes in serum ALT and AST activity observed in *E. lateriflora* treated group.

The renal histopathology study also revealed preserved kidney architecture. Both the glomeruli and tubules appear normal, no inflammatory cells and no cellular atypia in the control and *E. lateriflora* treated group. Rise in urea and creatinine level is only observed when a marked damage to functional nephron occur [29]. Therefore, the observation in this study might be

associated with the preservation of the renal and liver integrity.

5. CONCLUSION

This study showed that the extract of *E. lateriflora* is relatively safe for consumption when consumed at very low dose. Therefore, medicinal plant could be maximized for providing relief to various disease; however, the public must be informed on the need to exercise caution while using medicinal plants to meet their health care need.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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