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INVESTIGATION OF ACUTE AND REPEATED DOSING ORGANOTOXICITY POTENTIAL OF ETHANOL ROOT EXTRACT OF *SOLANUM ERIANTHUM* IN WISTAR RATS

ADEYEMI Isaac Oluwole [1*] AKINYELE Adeyemi Patrick[2], OLANIRAN Samuel Folarin[1], OJO Ezekiel Opeyemi[3].

[1]Department of Pharmacology, Obafemi Awolowo University, Ile-Ife, Nigeria.
[2]Department of Pharmacology and Toxicology, Federal University Oye-Ekiti, Ekiti State, Nigeria.
[3]Department of Medicine/Department of Pharmacology and Therapeutics, Ekiti State University, Ado-Ekiti, Ekiti State.

***Corresponding Author's Email:** isaacon@oauife.edu.ng

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Abstract

Background: *Solanum erianthum* root (SER) extract is used in traditional medicine to treat dysentery, fever and for pain management. This study examined the toxicity and safety profile of ethanol extract of SER in rats.
Materials and Method: The median lethal dose (LD_{50}) of SER was determined using Lorke's method. Groups of rats were administered 250, 500 and 750 mg/kg of the ethanol extract of SER daily for 28 days, this was followed by 21 days of recovery study. Various endpoints of toxicity on the kidney, liver including haematological and biochemical parameters as well as histopathological examination were assessed.
Result: The LD_{50} of SER was determined to be greater than 5000 mg/kg. There was no significant difference across the weight and haematological parameters as well as the lipid profile across all the doses investigated when compared to control in the repeated dose toxicity and recovery studies. The results of biochemical evaluations of liver and kidney injury biomarkers in the serum suggest varying degree of effects on the organs marked by significant increases in serum aspartate transaminase (AST), alanine transaminase (ALT), urea and creatinine. Histopathological examination revealed that the extract caused dose dependent inflammation and vascular congestion to the live and kidney in the toxicity study. However, these effects resolved significantly in the recovery study.
Conclusion: The ethanol extract of SER is safe for acute use but has potential to induce largely reversible toxic effects on the liver and kidney following prolonged repeated administration.

Keywords: *Solanum erianthum,* organotoxicity, haematology indices, biochemical indices, histoarchitectures, histopathology, serum and lipid profile.

List of Abbreviations: ALT – Alanine Aminotransferase; **ANOVA** – Analysis of Variance; **AST** –Aspartate Aminotransferase; **BD** – Bile duct; **CVD** – Cardiovascular Disease; **DCT**– Distal Convoluted Tubule; **DM 750** – Digital Microscope 750; **ELISA**– Enzyme-Linked Immunosorbent Assay; **HCT**– Hematocrit; **HDL**– High-Density Lipoprotein
HGB– Hemoglobin ; **HPV**– Hepatic portal vessels; **K_3 EDTA** – Tripotassium Ethylenediaminetetraacetic Acid; **LD_{50}** – Median Lethal Dose (lethal dose for 50% of the test population); **LDL**– Low-Density Lipoprotein; **MCH**– Mean Corpuscular Hemoglobin; **MCHC**– Mean Corpuscular Hemoglobin Concentration; **MCV** – Mean Corpuscular Volume; **OECD TG** – Organisation for Economic Co-operation and Development Test Guideline; **PC-3** – Prostate Cancer Cell Line-3; **PCT** – Proximal Convoluted Tubule; **RBC** – Red Blood Cell; **SER** – *Solanum erianthum* root; **UNESCO** – United Nations Educational, Scientific and Cultural Organization; **VLDL** – Very-Low-Density Lipoprotein; **WBC** – White Blood Cell; **WHO** – World Health Organization

Introduction

Since ancient times, herbs were widely used as the main treatment strategy for treating diseases. Currently, this botanical medicine is increasingly becoming popular throughout the world, especially in developing countries, where medicinal plants are available, accessible, and are at the reach of the poor people. Despite the claims and validated pharmacological activities of many herbal products, there is a dearth of information about the safety of many of the products.

A medicinal plant is any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes or which is a precursor for synthesis of useful drugs. Over 90% of traditional medicine recipes/remedies contain medicinal plants (Sofowora *et al.,* 2013). According to the WHO, more than 80% of the world's population rely more often on traditional drugs, mainly plants, serving as the main source of health care (Jamshidi-Kia, 2018). It is widely believed that herbal remedies are very safe and devoid of adverse effects, this assumption is a fallacy and also very misleading. This misconception is not limited to the developing countries, it also exists in highly developed countries where the populace often resort to natural products without any proper awareness or information on the associated risks, particularly in the event of excessive or chronic use. This usually leads to wrong use and habitual intake of natural products and has also led to severe poisoning and acute health problems (UNESCO, 2013). The genus *Solanum* is considered to be one of the largest and most complex genera among the angiosperms and the most representative and largest genus of the family *Solanaceae.* It is comprised of about 2000 species distributed across subtropical and tropical regions of Asia, tropical Africa, non-arid Africa, Americas, Australia, and India (Kaunda and Zhang, 2019). *Solanum erianthum,* commonly called Potato tree, can be found at elevations from sea level to 1,500 m (4,900 ft) in a variety of habitats, including riparian zones, dry forests (Felger *et al*., 2001). It often grows in disturbed areas such as roadsides, fields, and waste places, and may be considered a weed (Modise and Mogotsi, 2008).

The seeds are burnt to ash and given for 7 days to cure sterility in males (Sachin and Shinde, 2019). The main groups of compounds found in the essential oil from the fruits of *S. erianthum* were sesquiterpenes; sesquiterpenes and its derivatives are used as anti-cancer, immunosuppressive and anti-inflammatory agents and these oils possess strong antimicrobial activity in addition to the potent cytotoxic potential against Hs 578T and PC-3 cells in human breast and prostate tumor cells respectively. *Solanum erianthum* leaf has excellent antioxidant activity and a broad range of medicinal properties, this could justify the use of the plant in the treatment of various diseases by traditional medical practitioners in South-western Nigeria (Alawode *et al.,* 2017). The anti-inflammatory activities of *Solanum erianthum* root was validated by Chen *et al*., (2013) and the anti-inflammatory components were isolated. However, despite the widespread and traditional uses of *S. erianthum*, there are no scientific evidences on the safety and toxicity of the root of this plant. This study, therefore, aimed at investigating the LD_{50} of the ethanol extract of *Solanum erianthum* root in Wistar rats; and the effects of graded doses of the extract on haematologic and biochemical indices, as well as histopathological changes in some organs of the rats following a 28-day repeated dosing and recovery studies with a view to providing scientific information on the toxicity profile of the root of the plant.

It is frequently stated in scientific literatures and reports that 80% of people in Asian and African countries (or sometimes that 80% of the world's population) use traditional medicine practitioners to meet their primary healthcare needs (Adeyemi *et al*, 2010; Oyinlola, 2016; Oyemitan *et al*, 2019). There are documented evidences of incidences of organ toxicity from prolonged ingestion of medicinal herbs. Despite this reported toxicity, the patronage of medicinal plants and related products is on the increase, due to supposed safety, availability and affordability. The increasing patronage also come with increasing tendencies for abuse, arising from indiscriminate uses, thereby necessitating the need to establish the safety of medicinal plants. In addition, the resounding calls for the integration of traditional medicine practice into the conventional modern medicine, make the determination and documentation of the safety/toxic risk potentials of medicinal plants imperative (Oladotun *et al.,* 2020). These toxic effects include gastrointestinal disturbances, allergic reactions, renal injuries, hepatic injuries, complications of the haematological, cardiovascular and neurological systems, carcinogenic effects and death. The severities of these effects depend on duration of consumption as well as the amount of the traditional herbal medicines consumed. Without specific investigations, only acute and severe adverse effects are likely to be identified. It should be emphasised that the absence of evident toxic effects of a medicinal plant does not mean that the plant is totally safe or devoid of adverse effects (Ahmet *et al.,* 2016). The safety of natural products is a priority before they are acceptable for consumption (Ajayi *et al.*, 2020). Ethnomedicinally, the extract of *S. erianthum* root is taken orally to treat rheumatism, dysentery, blood disorders, fever, fracture, bruises, stomach ache, abdominal and body pains (Chang *et al.*, 2003; Sachin and Shinde, 2019) and could therefore be used for a short time or repeatedly for a long period of time.

Acute toxicological studies investigate the toxic effects produced by a single large-dose exposure to a toxicant lasting no longer than 24 hrs. This may result in severe biological effects (morbidity or mortality) to the organism (Merlin *et al.,* 2019). The acute toxicity study may provide initial information on the mode of toxic action of an agent, act as the basis for classification and labelling, and help in deciding the dose of novel compounds in animal studies (National Research Council, 2006). The starting point for toxicological classification of chemicals uses the median lethal dose (LD_{50}) value (Merlin *et al.,* 2019), if a high dose (e.g., 5000 mg/kg) is found to be survivable, no further

acute testing will be conducted (National Research Council, 2006). In this study, the LD_{50} of the ethanol extract of *S. erianthum* root was determined to be greater than 5000 mg/kg. At the highest dose of 5000 mg/kg, there was transient lethargy and hypo-activity which resolved within 12 hrs of administration and there was no mortality within twenty-four hours of observation. The result of the acute toxicity study is in agreement with that of Olusegun *et al.* (2016) on the ethanol extract of the leaves of the same plant. This suggests that the extract at the limit dose is non-toxic and safe in oral formulations (Olusegun *et al.,* 2016). Toxicity study should be carried out with a minimum of three doses (low, medium, and high doses) in experimental animals and the toxic effects compared with data from a control group of animals (Parasuraman, 2011). Based on the result of LD_{50} determination, three working doses of 250, 500 and 750 mg/kg body weight were chosen for repeated dose toxicity study. These doses are in agreement with the doses used in the toxicity study of the ethanol extract of the leave of the same plant as reported by Uzoekwe *et al.* (2021).

Materials and Methods

Collection of Plant Material and Extraction

Solanum erianthum root was collected between July - September 2020, from the wild on the campus of Obafemi Awolowo University (OAU), Ile-Ife, Nigeria. The plant was identified and authenticated by Mr. I. O. Ogunlowo of the Department of Pharmacognosy, Faculty of Pharmacy of the institution. The roots were carefully washed with water, chopped into small sizes, air dried under shade for three weeks, and pulverised to a coarse powder using a Fritsch® laboratory mill. A total of 4 kg of the pulverized root was used for extraction. At each instance, a 250 g part of the 4 kg powdered material was macerated in 500 ml of 70 % ethanol for 72 hours with intermittent shaking carried out manually. The extract was filtered, first, using muslin cloth and then using Whatman filter paper (number 1). It was then concentrated to dryness using rotary evaporator at 40°C. The extraction process yielded 170.2 g of sticky, black extract. The extracted material was stored at −4°C until further use.

Experimental Animals

Healthy, male and nulliparous female wistar rats (120 – 150 g) were obtained from the animal house, Department of Pharmacology, Faculty of Pharmacy, OAU, Ile-Ife. They were kept in well-ventilated cages in the animal house under 12 h light/12 h dark cycle at a temperature of 25 ± 2 °C. They were acclimatised for 7 days before onset of the study. Standard rodent pellet diet and water was provided *ad libitum*. All animal experiments were carried out according to guidelines of Health Research and Ethical Committee, Institute of Public Health, OAU and the HREC No.: IPH/OAU/12/1833 was issued on 25th January, 2022.

Single Dose (Acute) Toxicity Study

Determination of the LD_{50} was conducted in accordance with Lorke's method (Lorke, 1983) as previously reported by Oyemitan *et al.* (2014). This was carried out in two phases. In the first phase of the study, nine animals were randomly divided into three groups of three animals per group; animals in each group were administered 10, 100, 1000 mg/kg body weight of the extract respectively; the animals were observed for signs of toxicity and mortality for 24 hours. The second phase was conducted following the result of the first phase. Animals were divided into three groups of one animal each and they were administered 1600, 2900, and 5000 mg/kg body weight of the extract and they were also observed for signs of toxicity and mortality for 24 hours. The rats were further observed once a day up to 14 days following treatment for behavioural changes and signs of toxicity and/or death and the time of death.

Repeated Dose/ Recovery Studies

The repeated dose toxicity study was conducted in accordance with the 28 days repeated dose OECD TG 407 as previously reported by Daniyan *et al.* (2021). Forty-eight (48) rats were randomly divided into 4 groups of twelve rats (six female and six male) each. Group I served as the control and received 1 ml/100 g body weight distilled water daily while groups II, III and IV were administered 250, 500, and 750 mg/kg body weight of ethanol extract of *S. erianthum* root respectively. All the animals were weighed on days 0, 7, 14, 21 and 28. Detailed physical examinations, including the onset and duration of visible toxicological effects were recorded daily for 28 days. Thereafter, animals in each group were randomly divided into two sub-groups of 3 males and 3 females each (n = 6). The male and female animals were kept in separate cages. Despite the use of both male and female rats, this research did not explore sex differential toxicological activities of the *S. erianthum* root extract because the number of male and female rats used for each group (n=6: 3 male, 3 female). A set of sub-group was regarded as test set, while the other was regarded as the recovery set. Animals in the test set were sacrificed on day 29, while the animals in the recovery set were allowed access to food and water *ad libitum* for additional 21 days of non-dosing period. The weights of animals in the recovery set were taken on days 35, 42 and 49 of the study and were sacrificed on day 50 of the experiment.

Sacrifice of Experimental Animals

At the end of the repeated dose toxicity and recovery studies, the animals were weighed and euthanized by cervical dislocation, blood samples from each animal were collected via cardiac puncture into two types of sample bottles; the K3 EDTA and plain sample bottles. The kidneys, liver and brain of each animal were carefully harvested and weighed. A kidney and 1 g section of the liver of each rat were stored at -4^{o}C while the second kidney, the remaining sections of the liver, and the brain of each animal were fixed in 10% formal saline for histopathological examination.

Weight parameters were calculated using the formula below:

$$\text{Relative organ weight} = \frac{\text{Absolute organ weight (g)} \times 100}{\text{Body weight of animal on the day of sacrifice (g)}}$$

$$\text{Relative body weight} = \frac{\text{Body weight of animal on the day of sacrifice (g)} \times 100}{\text{Body weight of animal on day 0 (g)}}$$

$$\text{Organ:Brain ratio} = \frac{\text{Absolute organ weight (g)}}{\text{Absolute brain weight (g)}}$$

Histopathology Study

The kidney, liver and brain of the animals which were fixed in formal saline were sectioned and stained with haematoxylin and eosin following standard protocols. They were then viewed under the microscope and photomicrographs taken with a Leica DM750 Camera Microscope (400X) for analyzing any change in the cells.

Biochemical Studies

The blood samples collected in plain sample bottles were centrifuged at 3000 rpm for 5 min at room temperature. The separated sera obtained were collected into labelled sterile sample bottles and kept in the freezer at -4 ^{0}C for further analyses. All the biochemical parameters (Serum Aspartate Transaminase, Alanine Transaminase, Creatinine, Urea, Triglycerides, high density lipoproteins, low density lipoproteins) were estimated by using their respective Elabscience® ELISA Kits. The kits were manufactured in the United States of America. The tissue homogenates of these organs were prepared in the phosphate buffer (0.1 M, pH 7.4, 4°C) with a ratio of 1:10. The homogenates were centrifuged at 6,000 rpm and 4°C for 10 min. The supernatant from each sample was collected and used for the estimation of the same parameters as the serum.

Haematological Assays

One mL of blood was collected in the K3 EDTA sample bottles, stirred slightly, and kept at room temperature up to a maximum of 3 to 4 h for haematological analyses. The haematological parameters estimated include Red Blood Cells (RBC), Haematocrit (HCT), Haemoglobin (Hgb), White Blood Cells (WBC), and WBC differentials.

2.10 Statistical Analyses:

The results were analysed using one way analysis of variance (ANOVA) followed by Student's Newman-Keuls post hoc test using Graphpad Prism (7.0). All data were presented as mean ± standard error of mean (SEM) and the level of significance was set at 95% confidence level ($P<0.05$).

Results

Acute Toxicity

The result for LD_{50} study of SER is summarised in Table 1. There was no visible sign of mortality and mortality after acute oral administration in both stages of the study. The LD_{50} for ethanol extract of *S. erianthum* root in rats was therefore determined to be equal or greater than 5000 mg/kg.

Table 1: Result of LD_{50} Determination

Group	Dose (mg/kg)	No. of Death	% Mortality
Stage 1 (n = 3)			
1	10	0/3	0
2	100	0/3	0
3	1000	0/3	0
Stage 2 (n = 1)			
1	1600	0/1	0
2	2900	0/1	0
3	5000	0/1	0

Mortality ratio = x/n = 0. Where x = number of mortality, n = sample size

Repeated Dose and Recovery Studies
Cage Side Observations

Generally, transient lethargy and scratching of the body (especially the mouth region) was observed in each animal immediately after the administration of the extract and this disappeared few minutes after the administration. There was one mortality (female rat) in 750 mg/kg dose group on the night of the day 10 of the study. Lethargy was observed in some animals that received 500 and 750 mg/kg. However, animals that received 250 mg/kg and the vehicle only were normoactive throughout the study. Furthermore, the animals that were hypoactive during the repeated dose study showed marked improvement in the first week (day 1-8) of the recovery study and normoactivity was observed from day 9 till the end of the study.

Effect of Ethanol Extract of *Solanum erianthum* Root on Relative Body Weight

The results of the effect of ethanol extract of *Solanum erianthum* on relative body weight in repeated dose toxicity and recovery studies are summarised in Table 2.

The repeated dose study showed 38.8% increase in relative body weight at 250 mg/kg, followed by control (36.7 %), then 500 mg/kg (28.3%), and lastly, 750 mg/kg (13.7%). The control of the recovery stage showed 62.2 % increase in relative body weight, followed by 500 mg/kg (46.5%), then 250 mg/kg (41.2%) and lastly 750 mg/kg (35.4%). The lowest growth rates in both the repeated and recovery studies were seen at 750 mg/kg. The result following the repeated dose showed no statistically significant difference ($p<0.05$) in the relative body weight for the 250 mg/kg and 500 mg/kg doses. Notably, from Day 14 to Day 28, the 750 mg/kg dose elicited reduction in the relative body weight when compared with the control, though the reductions were not statistically significant. For the recovery groups, reduction in the relative body weight was observed across the three test doses (250, 500 and 750 mg/kg), and this occurred from Day 21 to Day 50. These reductions were not statistically significant.

Table 2: Relative Body Weight Result for Repeated Dose Toxicity and Recovery Studies

RELATIVE BODY WEIGHT (%)							
DOSE	**DAY 1**	**DAY 7**	**DAY 14**	**DAY 21**	**DAY 28**	**DAY 35**	**DAY 42**	**DAY 50**
TEST GROUP								
Control	100.0 ± 0.00	110.8 ± 2.30	118.4 ± 3.00	127.0 ± 3.77	136.7 ± 3.73	-	-	-
250 mg/kg	100.0 ± 0.00	111.1 ± 1.67	123.0 ± 3.38	127.9 ± 6.27	138.8 ± 9.02	-	-	-
500 mg/kg	100.0 ± 0.00	111.2 ± 2.99	112.6 ± 7.41	122.1 ± 8.77	128.3 ± 11.31	±-	-	-
750 mg/kg	100.0 ± 0.00	107.9 ± 2.23	106.9 ± 6.12	107.3 ± 7.33	113.7 ± 8.37	-	-	-
RECOVERY GROUP								

Control	100.0 0.00	±	110.7 2.48	±	123.8 3.00	±	132.5 4.07	±	142.9 5.40	±	148.8 6.911	±	155.7 7.261	±	162.2 7.348	±									
250 mg/kg	100.0 0.00	±	108.9 1.61	±	117.4 3.66	±	123.0 5.14	±	125.7 7.87	±	126.9 0.95	±	133.3 12.91	±	141.2 14.20	±									
500 mg/kg	100.0 0.00	±	111.7 2.36	±	117.4 2.76	±	124.1 3.60	±	130.8 6.20	±	131.1	±	9.23	140.5	±	9.76	146.5 10.06	±							
750 mg/kg	100.0 0.00	±	107.8 2.27	±	112.5 2.57	±	117.5 3.07	±	120.4 1.80	±	125.2	±	2.06	130.7	±	2.92	135.4 3.05	±							

Effect of Ethanol Extract of *Solanum erianthum* Root on Relative Organ Weight

The results of the effect of ethanol extract of *Solanum erianthum* on relative organ weights in repeated dose toxicity and recovery studies are summarised in Figure 2 and Figure 3 respectively.
The results following the repeated dose and recovery studies showed no statistically significant difference ($P > 0.05$) in the relative organ weights for both the assessed organs (liver, kidney and brain) across all doses investigated (250, 500, and 750 mg/kg) when compared to control.

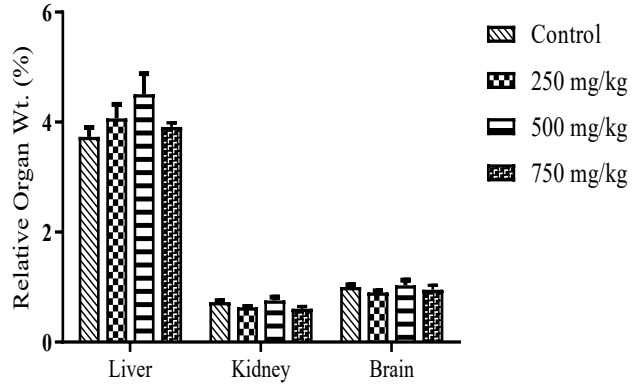


Figure 1: Relative organ (Liver, Kidney and Brain) weights following repeated dose study

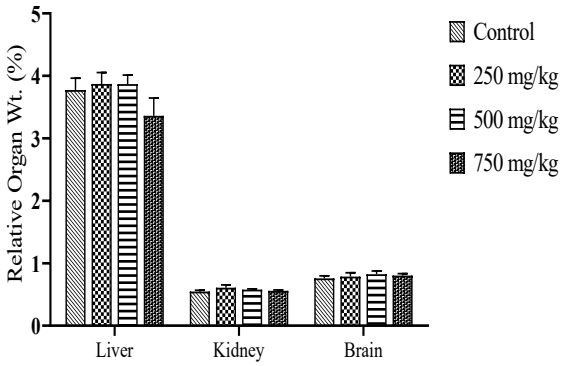


Figure 2: Relative organ (Liver, Kidney and Brain) weights following recovery study

Effect of Ethanol Extract of *Solanum erianthum* Root on Organ-to-Brain Weight

The results of the effect of ethanol extract of *Solanum erianthum* on liver-to-brain and kidney-to-brain weight both repeated dose and recovery studies are summarised in Figures 3 and 4 respectively.
The results following the repeated dose and recovery studies showed no statistically significant difference ($P > 0.05$) in the organ-to-brain weight for both the liver and kidney across all doses investigated (250, 500, and 750 mg/kg) when compared to control.

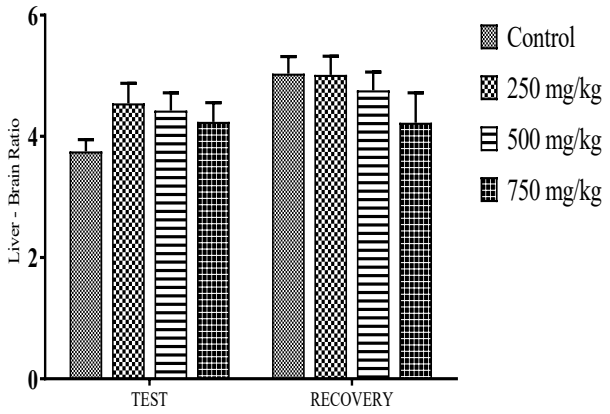


Figure 3: Liver-to-Brain weight following repeated dose toxicity and recovery studies

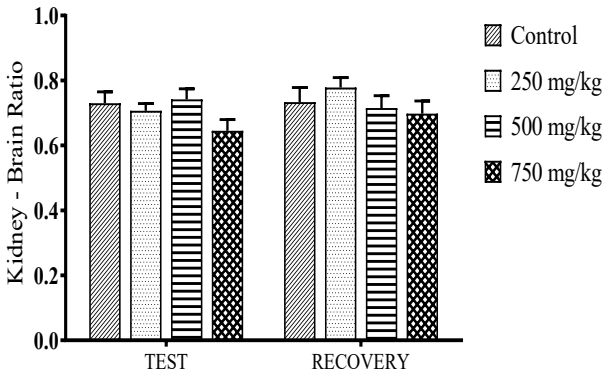


Figure 4: Kidney to Brain weight following repeated dose toxicity and recovery studies

Effect of Ethanol Extract of *Solanum erianthum* Root on Haematology

The results of the effect of ethanol extract of *Solanum erianthum* on haematology in repeated dose and recovery studies are summarised in Tables 3 and 4 respectively.
The results revealed that there was no statistically significant change ($P > 0.05$) in all the investigated haematology parameters including Haematocrit, Haemoglobin, WBC, RBC, Platelets, Neutrophils, Lymphocytes, MCV, MCH, and MCHC across the doses investigated (250, 500, and 750 mg/kg) when compared to control, in both the repeated dose and recovery studies.

Table 3: Haematology Result for Repeated Dose Toxicity Study

PARAMATERS	CONTROL	TREATMENT GROUP		
		250 mg/kg	500 mg/kg	750 mg/kg
Haematocrit (%)	40.00 ± 1.89	38.52 ± 2.18	38.48 ± 3.00	40.73 ± 1.73
Haemoglobin (g/dl)	12.82 ± 0.67	11.75 ± 0.64	11.95 ± 0.83	13.15 ± 0.35
WBC ($\times10^3$/ µl)	6.03 ± 0.36	5.02 ± 0.33	5.53 ± 0.51	6.55 ± 0.42
RBC (millions/ mm^3)	6.75 ± 0.42	6.48 ± 0.46	6.41 ± 0.53	6.76 ± 0.41
Platelets ($\times10^3$/ µl)	759.67 ± 50.83	757.17 ± 49.72	776.17 ± 41.04	765.50 ± 60.46
Neutrophils (%)	37.33 ± 2.09	41.00 ± 2.63	36.33 ± 2.39	41.50 ± 2.09
Lymphocytes (%)	62.67 ± 2.09	59.00 ± 2.63	63.67 ± 2.39	58.50 ±2.09
MCV (fl)	59.55 ± 1.07	59.77 ± 1.05	60.20 ± 1.00	60.70 ± 1.64
MCH (pg)	18.58 ±0.22	18.50 ± 0.64	18.78 ± 0.52	18.52 ± 0.31
MCHC (g/dl)	31.53 ± 0.50	30.35 ± 0.57	31.18 ± 0.56	31.80 ± 0.60

n = 6; results expressed as mean ± SEM.

Table 4: Haematology Result for Recovery Study

PARAMETER	CONTROL	TREATMENT GROUP		
		250 mg/kg	500 mg/kg	750 mg/kg
Haematocrit (%)	40.05 ± 0.90	42.62 ± 1.50	40.90 ± 1.66	44.64 ± 1.84
Haemoglobin (g/dl)	12.67 ± 0.34	12.95 0.40	12.78 ± 0.60	13.80 ± 0.45
WBC ($\times10^3$/ µl)	5.77 ± 0.62	6.00 ± 0.54	5.60 ± 0.50	6.32 ± 0.60
RBC (mil/ mm^3)	7.30 ± 0.25	7.15 ± 0.17	6.73 ± 0.22	8.00 ± 0.57
Platelets ($\times10^3$/ µl)	748.50 ± 36.30	771.17 ± 67.95	754.83 ± 56.14	845.00 ± 58.77
Neutrophils (%)	35.83 ± 3.75	32.17 ± 3.42	42.50 ± 2.32	32.20 ± 2.60
Lymphocytes (%)	64.17 ± 3.75	67.83 ± 3.42	57.50 ± 2.32	67.80 ± 2.60
MCV (fl)	55.02 ± 1.30	59.60 ± 1.27	60.68 ± 0.87	56.62 ± 3.42
MCH (pg)	17.42 ± 0.40	18.15 ± 0.52	18.62 ± 0.48	18.70 ± 0.10
MCHC (g/dl)	31.62 ± 0.29	30.42 ± 0.46	30.75 ± 0.48	30.98 ± 0.42

Effect of Ethanol Extract of *Solanum erianthum* Root on Serum Biochemistry

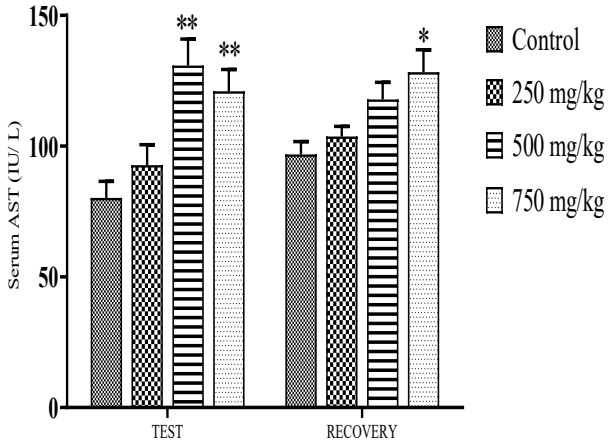
The results of the effect of ethanol extract of *Solanum erianthum* on serum biochemistry for repeated dose toxicity and recovery studies of serum AST, serum ALT, serum urea and serum creatinine are summarised in Figures 5, 6, 7 and 8 respectively while the results of serum lipid profile for repeated dose toxicity and recovery studies are summarised in Table 5.

The results showed no statistically significant difference ($P > 0.05$) in the investigated kidney biomarkers (serum urea and serum creatinine) across all the investigated doses (250, 500, and 750 mg/kg) when compared to control, in both the repeated dose and recovery studies. Similarly, there was no statistically significant difference ($P > 0.05$) in the serum lipid profile including triglyceride, cholesterol, LDL, and HDL across all the investigated doses (250, 500, and 750 mg/kg) when compared to control, in both the repeated dose and recovery studies. However, there were varying levels of statistically significant differences in the investigated liver biomarkers (AST and ALT) when compared to control. Serum AST showed statistically significant increase at 500 and 750 mg/kg while there was no statistically significant difference at 250 mg/kg when compared to control in the repeated dose study. However, the recovery study showed statistically significant increase only at 750 mg/kg while there was no statistically significant difference at 500 and 250 mg/kg when compared to control. Serum ALT showed significant increase across all the investigated doses (250, 500, and 750 mg/kg) when compared to control in both the repeated and recovery studies.

Table 5: Serum Lipid Profile Result for Repeated Dose Toxicity and Recovery Studies

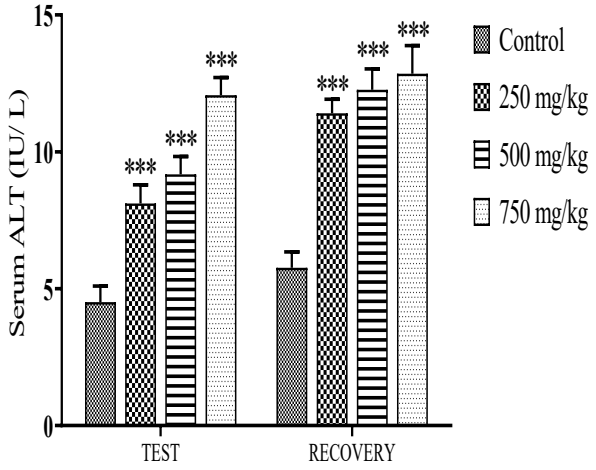
PARAMETER	SUB-GROUP	CONTROL	TEST GROUP		
			250 mg/kg	500 mg/kg	750 mg/kg
Triglyceride (mmol/L)	**Test**	0.98 ± 0.08	1.07 ± 0.03	1.08 ± 0.03	1.02 ± 0.04
	Recovery	1.05 ± 0.03	1.11 ± 0.02	1.11 ± 0.08	1.02 ± 0.04
Cholesterol (mmol/L)	**Test**	2.08 ± 0.06	2.02 ± 0.01	2.02 ± 0.03	1.99 ± 0.01
	Recovery	2.03 ± 0.02	2.07 ± 0.04	2.06 ± 0.01	2.04 ± 0.03
HDL (mmol/L)	**Test**	0.25 ± 0.01	0.26 ± 0.01	0.29 ± 0.02	0.29 ± 0.02
	Recovery	0.22 ± 0.01	0.28 ± 0.03	0.23 ± 0.02	0.24 ± 0.02
LDL (mmol/L)	**Test**	1.27 ± 0.07	1.24 ± 0.03	1.19 ± 0.05	1.23 ± 0.04
	Recovery	1.25 ± 0.04	1.20 ± 0.07	1.26 ± 0.05	1.35 ± 0.08

n = 6; results expressed as mean ± SEM.



values for each analysis are as follows:
Test = 0.001; R = 0.0079.

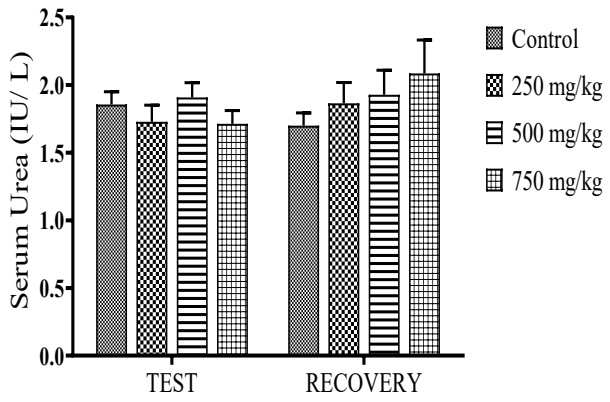
Figure 5: Serum AST result following repeated dose toxicity and recovery studies



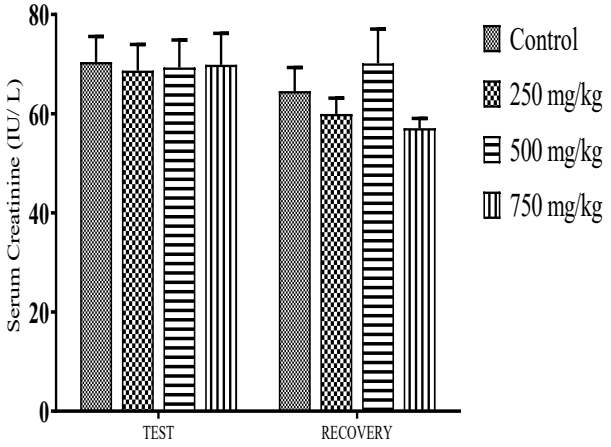
P

The P values for each analysis are as follows:
Test, P < 0.0001; Recovery, P < 0.0001

Figure 6: Serum ALT result following repeated dose toxicity and recovery studies



ure 7: Serum urea result following repeated dose toxicity and recovery studies



Fig

Figure 8: Serum creatinine result following repeated dose toxicity and recovery studies

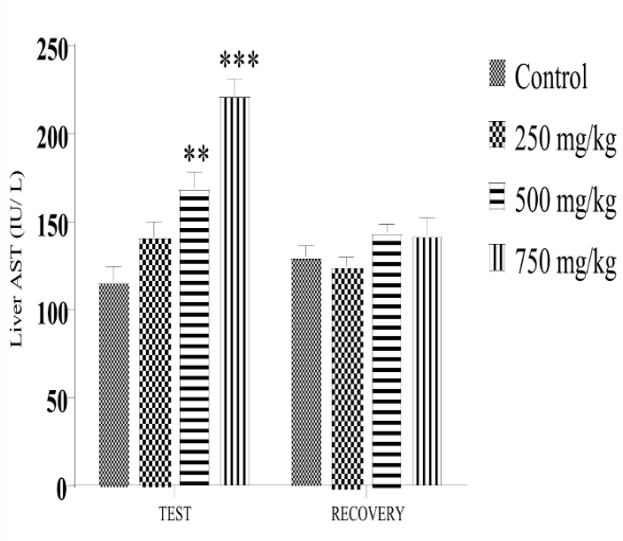
Effect of Ethanol Extract of *Solanum erianthum* Root on Liver Homogenates Biochemistry

The result for AST showed statistically significant increase at 500 and 750 mg/kg while there was no statistically significant difference at 250 mg/kg when compared with the control in repeated dose study. However, the recovery study shows no statistically significant difference across all the investigated doses (250, 500 and 750 mg/kg) when compared with the control. Liver ALT results showed statistically significant decrease and increase at 250 mg/kg and 750 mg/kg respectively while there was no statistically significant difference at 500 mg/kg when compared with the control. However, the recovery study shows no statistically significant decrease across all the investigated doses (250, 500 and 750 mg/kg) when compared with the control. The results of the liver lipid profile analysis in the repeated dose study showed statistically significant decrease in cholesterol, HDL and LDL across all the investigated doses (250, 500 and 750 mg/kg) when compared with the control.

Table 6: Liver Homogenate Lipid Profile for Repeated Dose Toxicity and Recovery Studies

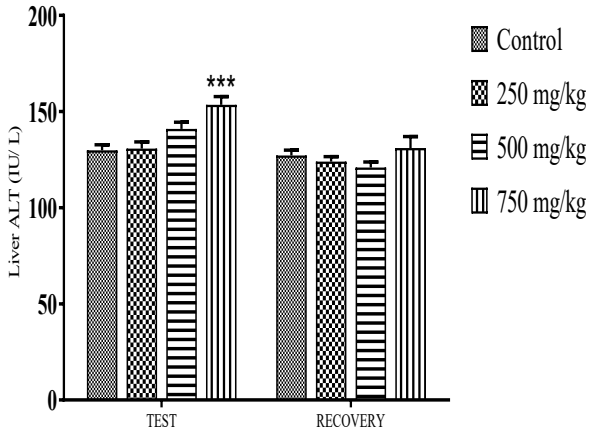
PARAMETER	SUB-GROUP	CONTROL	TEST DOSES		
			250 mg/kg	500 mg/kg	750 mg/kg
Triglyceride	Test	0.93 ± 0.06	***0.40 ± 0.04	***0.49 ± 0.11	**0.60 ± 0.06
	Recovery	1.00 ± 0.06	1.12 ± 0.05	1.09 ± 0.04	1.08 ± 0.17
Cholesterol	Test	5.46 ± 0.01	5.39 ± 0.02	5.42 ± 0.03	5.43 ± 0.03
	Recovery	5.42 ± 0.03	5.38 ± 0.02	5.38 ± 0.02	5.39 ± 0.03
HDL	Test	2.23 ± 0.00	2.21 ± 0.01	2.21 ± 0.01	2.21 ± 0.01
	Recovery	2.23 ± 0.02	2.20 ± 0.02	2.23 ± 0.02	2.25 ± 0.03
LDL	Test	2.83 ± 0.05	2.99 ± 0.04	2.91 ± 0.08	2.92 ± 0.03
	Recovery	1.98 ± 0.15	2.14 ± 0.19	2.17 ± 0.22	2.11 ± 0.24

The P values for each analysis are as follows: Triglyceride (T = 0.0002, R = 0.7849); Cholesterol (T = 0.3653, R= 0.6025); HDL (T = 0.4059, R = 0.4840); LDL (T = 0.2000, R = 0.8908).
n = 6; results expressed as mean ± SEM.



The P values for each analysis are as follows:
Test, < 0.0001; Recovery = 0.1331

Figure 9: Liver AST result following repeated dose toxicity and recovery studies



The P values for each analysis are as follows:
Test, < 0.001; Recovery = 0.2677

Figure 10: Liver ALT result following repeated dose toxicity and recovery studies

Effect of Ethanol Extract of *Solanum erianthum* Root on Kidney Homogenates Biochemistry

The results of repeated dose study showed statistically significant increase in kidney urea across all the investigated doses (259, 500 and 750 mg/kg) when compared with the control. However, the recovery study showed no statistically significant difference in kidney urea across all the investigated doses when compared with the control. For the repeated dose study, the creatinine level of the 750 mg/kg group was significantly higher than that of the control. No significant difference was observed in the kidney creatinine levels between the three test doses of *Solanum erianthum.*

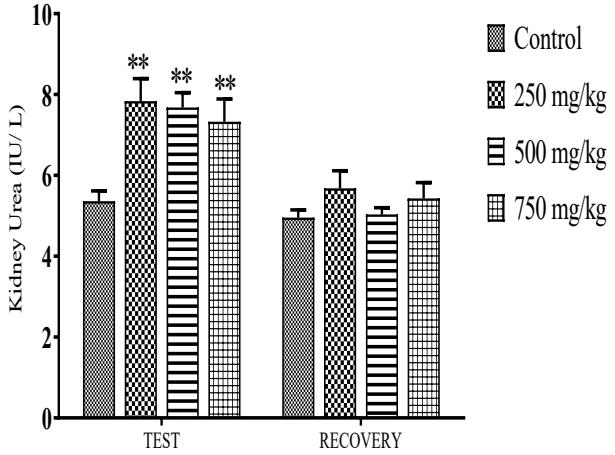


Figure 11: Kidney urea result following recovery studies

The P values for each analysis are as follows:
Test = 0.0033; Recovery = 0.3230

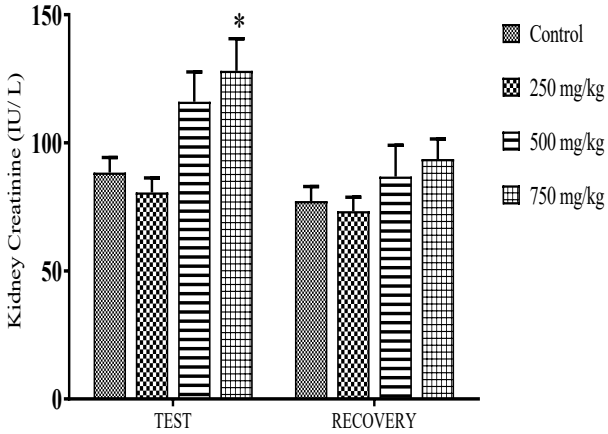


Figure 12: Kidney creatinine result following dose toxicity and repeated dose toxicity and recovery studies

The P values for each analysis are as follows:
Test = 0.0058; Recovery = 0.3405

Liver Histology

Generally, the photomicrographs of the liver histoarchitecture following both the repeated dose administration (Plate 1) and the recovery studies (Plate 2) revealed that the liver tissue composed predominantly of the hepatic parenchyma and portal regions, the hepatocytes appeared polygonal and were disposed in sheet with well outlined nucleus. The hepatocytes were separated by the sinusoids with thin endothelial lining. The portal region composed of branches of the hepatic portal vessels and bile duct. Photomicrographs showed the presence of activated Kupffer cells across the investigated doses (250, 500 and 750 mg/kg). Individually, the liver histology revealed carrying degree of obvious presence of pathological lesions when compared with the control. There were vascular congestions in the portal region at the 250 mg/kg dose, while there were vascular congestion and dose dependent inflammation of hepatocytes in the portal region at 500 and 750 mg/kg when compared with the control. The recovery histology showed normal histoarchitecture of the liver cross section at 250 mg/kg. Activated Kupffer cells and mild inflammation of hepatocytes in the portal region at 500 mg/kg while foci of the congestion and mild inflammation of hepatocytes in the portal region was seen at 750 mg/kg when compared with the control.

Kidney Histology

Photomicrographs of kidney histoarchitecture following both the repeated dose administration (Plate 3) and the recovery studies (Plate 4). Generally, sections showed renal tissues consisting of the renal corpuscles and the renal tubules consisting of several segments. The corpuscles were made up of the glomerulus, surrounded by the podocytes and separated by a defined Bowman's space. The renal tubules (proximal convoluted and distal convoluted) were lined by columnar-cuboidal epithelium with the proximal convoluted tubule (PCT) showing densely packaged microvilli forming a brush border. Individually, the photomicrographs of the investigated doses (250, 500 and 750 mg/kg) following the repeated dose administration showed varying degree of obvious presence of pathological lesions when compared with the control. There were interstitial congestions at 250 mg/kg, interstitial congestion with surveiling white blood cells was seen at 500 mg/kg, while there was marked interstitial congestion and inflammation in 750 mg/kg group when compared with the control. The recovery kidney histology showed normal histoarchitecture cross section at the 250 and 500 mg/kg doses, however, there was no resolution of the inflammation in the 750 mg/kg dose after the 21-day recovery period.

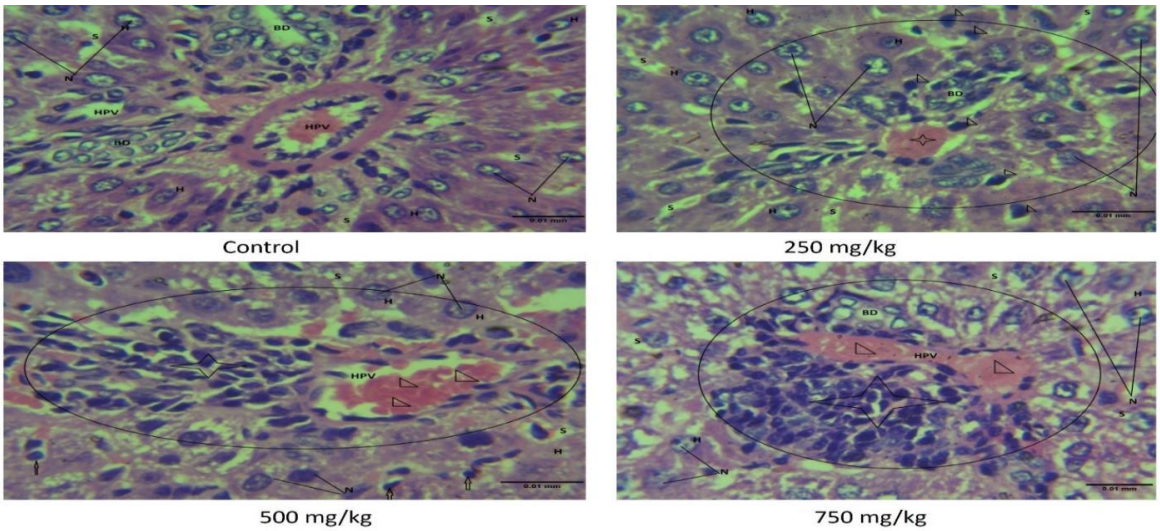


Plate 1: Photomicrographs of the liver following 28 day repeated dosing with the ethanol extract *S. erianthum* root.
H = Hepatocytes; N = Nucleus, S = Sinusoids, Arrow = activated Kupffer cells; Cicle = Portal region; HPV = Hepatic portal vessels; BD = Bile duct; Arrow head = Vascular congestion; Star = periportal inflammation; Stain = H&E; Magnification = ×400. (a) showing normal liver histoarchitecture, (b) - (d) showing dose dependent pathological lesions including vascular congestion and periportal inflammation.

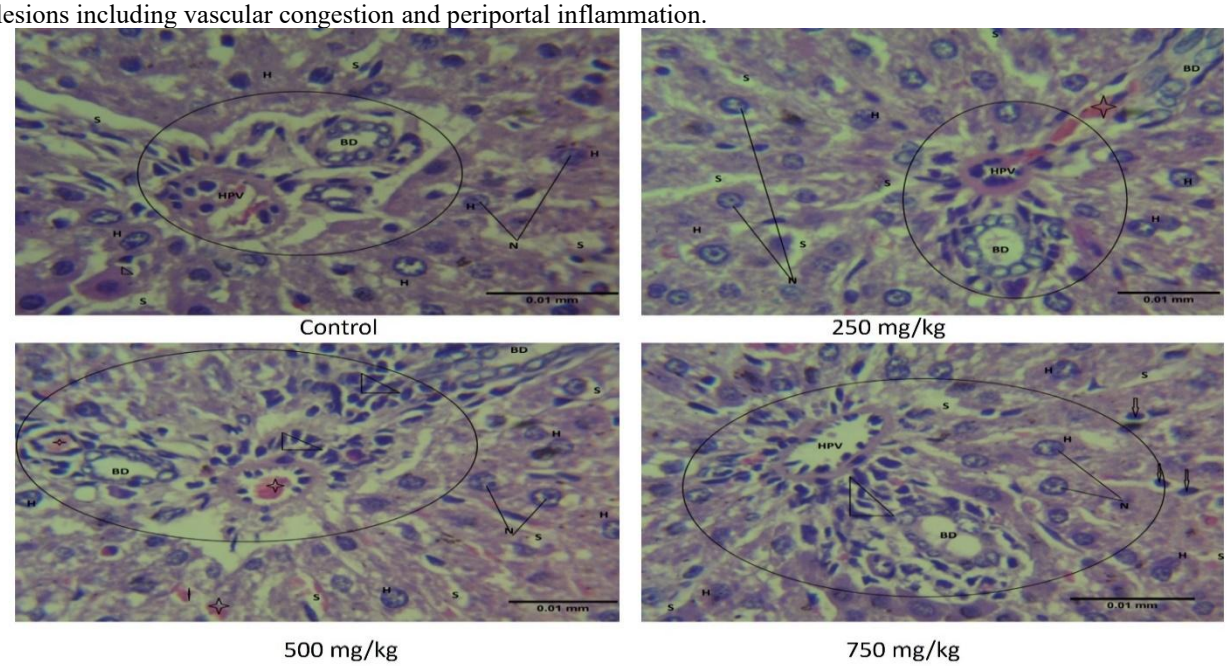


Plate 2: Photomicrographs of the liver following the recovery study
H = Hepatocytes; N = Nucleus, S = Sinusoids, Arrow = activated Kupffer cells; Circle = Portal region; HPV = Hepatic portal vessels; BD = Bile duct; Arrow head = Vascular congestion; Star = periportal inflammation; Stain = H&E; Magnification = ×400. (a) & (b) showing normal liver histoarchitecture, (c) showing mild periportal inflammation and activated kupffer cells & (d) showing foci of vascular congestion and periportal inflammation.

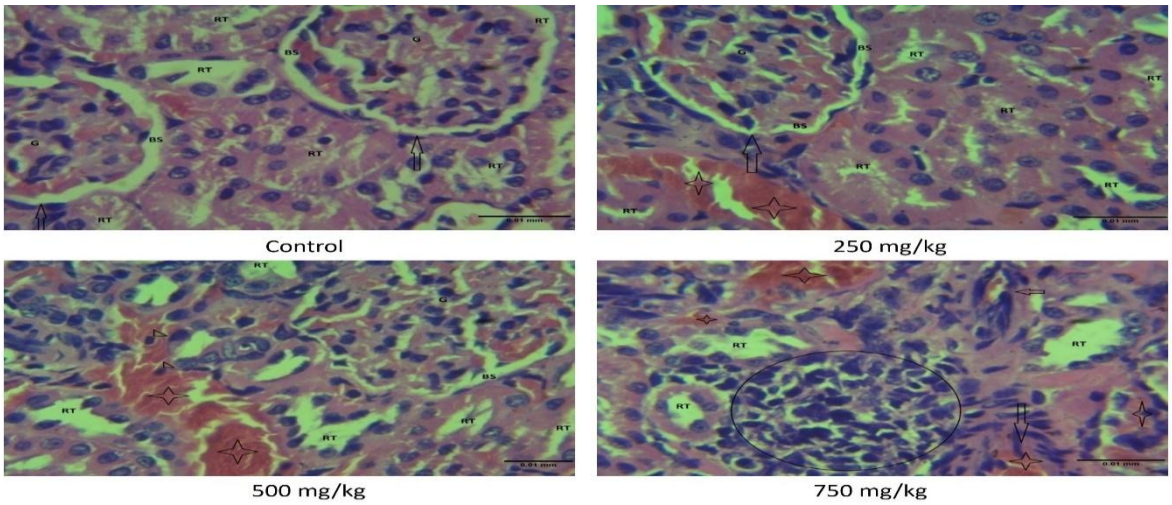


Plate 3: Photomicrographs of the kidney following 28-day repeated dosing with the ethanol extract *S. erianthum* root. Arrow = Renal corpuscle; G = Glomerulus; BS = Bowman's space; Renal tubules (RT) = PCT (Proximal convoluted tubules) & DCT (Distal convoluted tubules); Star = Congestion; Arrow head = Surveilling white blood cells; Circle = Interstitial inflammation; Stain = H&E; Magnification = × 400. (a) showing normal kidney histoarchitecture, (b) showing congested interstitium, (c) showing congested interstitium with surveiling white blood cells and, (d) showing congested interstitium & marked interstitial inflammation.

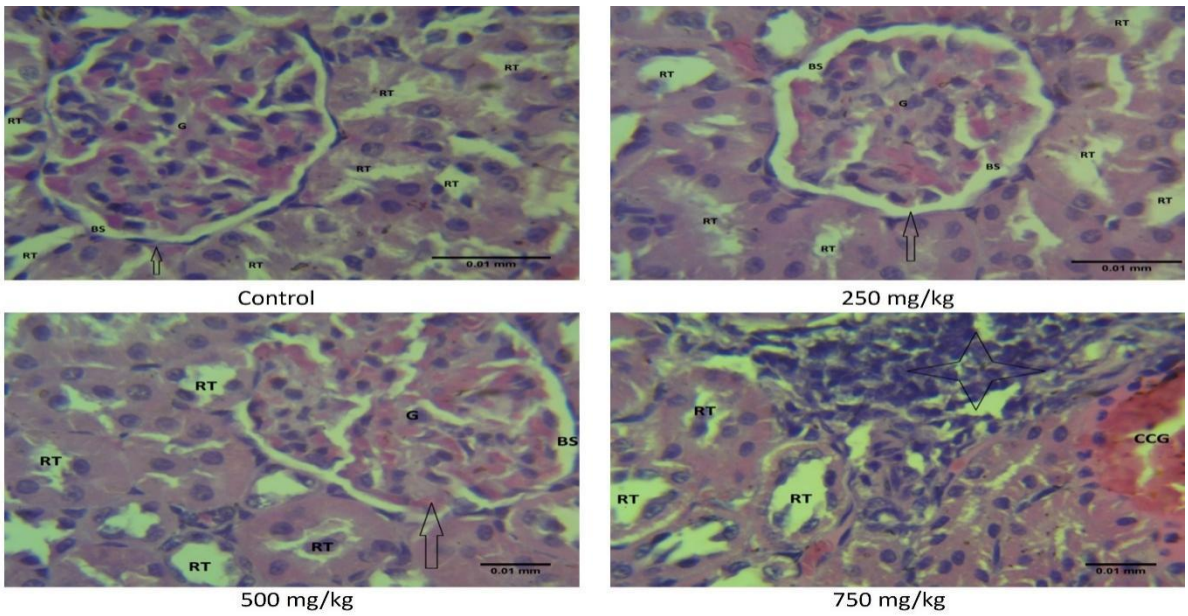


Plate 4: Photomicrographs of the kidney following the recovery study
Arrow = Renal corpuscle; G = Glomerulus; BS = Bowman's space; Renal tubules (RT) = PCT (Proximal convoluted tubules) & DCT (Distal convoluted tubules); CCG = Congestion; Star = Interstitial inflammation; Stain = H&E; Magnification = ×400. (a), (b) & (c) showing normal kidney histoarchitecture, and (d) showing congested interstitium & marked interstitial inflammation.

Discussion

Plants have provided a vast repository of phytochemicals of medicinal value for the treatment and/or management of different health conditions. Plant-based products are generally believed to be safe but the toxicological profiling many of them have revealed high levels of toxicity. *Solanum erianthum* root has been validated for its pharmacological activities in a broad range of disease conditions (Alawode *et al.,* 2017). However, despite the widespread and traditional uses *S. erianthum*, there are no scientific evidences on the safety and toxicity of the root of this plant. This study therefore assessed the safety of the plant through the median lethal dose (LD_{50}) of the ethanol extract of *S. erianthum* root in Wistar rats and its effects on relative organ weights and its effects on haematologic, biochemical and histological parameters.

Available evidence has shown that body weight gain, organ weights and organ - brain weight ratio are important and sensitive indices of toxic effects. Essentially, organ – brain weight ratio is a more relevant index for toxicity in cases where significant variations in body weight is inevitable, as test materials that alter body weight generally do not alter brain weight (Shobo *et al.,* 2019). The findings of this study showed that the relative organ weight and relative organ to brain ratio in all the dose levels in both the toxicity and recovery studies do not differ significantly when compared to control. However, a dose dependent reduction in relative body weight which became statistically significant in the third ($P = 0.02$) and fourth ($P = 0.03$) weeks at 750 mg/kg was noticed across all the tested doses from the second week of the toxicity study to the end of the study. According to Lu (Lu, 1996), remarkable change in relative organ weight between treated and untreated animals is an indicator of toxicity as organ weight is affected by the suppression of body weight. In this study, despite the effect of the extract on the relative body weight, there was no corresponding effect on the relative organ weight, this suggest that either the investigated doses are not high enough or the duration of the study is not long enough for the extract to exert significant effect in the relative organ weight and relative organ to brain ratio of experimental animals.

The haematopoietic system is one of the most sensitive targets of toxic compounds and is an important index of physiological and pathological status in man and animals (Diallo *et al.,* 2010). Previous studies have shown that haematological parameters were very sensitive and could be used as reliable indicators for determining the intrusion of toxic substances (Rahman *et al.,* 2001). In this study, the results of the haematological parameters across the investigated doses did not differ significantly ($P > 0.05$) when compared to control in both the toxicity and the recovery studies. Uzoekwe *et al.* (2021) reported that the leaf extracts of *S. erianthum* caused statistically significant difference in the haematological profile of the tested animals across the tested doses ((250, 500 and 750 mg/kg) when compared to control.

This suggests that the leave and the root of *S. erianthum* have different effects on the blood.

Serum liver function tests provide information about the status of the liver. The liver enzymes (aminotransferases; ALT and AST) describe its cellular integrity, while albumin and total protein levels describe its functionality (Adeoye and Oyedapo, 2004). AST and ALT are principally produced by the liver cells and any assault to the liver may lead to an increase in the serum level of these enzymes (Adedapo *et al.,* 2004). High levels of liver enzymes are signs of hepatocellular toxicity (Brautbar and Williams, 2002), whereas a decrease may indicate enzyme inhibition (Akanji *et al.,* 2013). However, ALT is a more sensitive marker of liver damage or toxicity since AST is also found in abundance in kidneys, testes, cardiac and skeletal muscles (Akanji *et al.,* 2013). In addition, enzyme activities in the tissues are often used as marker to ascertain early toxic effects of administered foreign compounds to experimental animals (Adesokan and Akanji, 2004). The effect of *S. erianthum* root extract on the liver parameters (AST and ALT) in serum and liver homogenates were examined in this study. Serum AST showed dose dependent statistically significant increase across the investigated doses when compared to control in the toxicity study, while statistically significant increase in serum AST was noticed only at 750 mg/kg in the recovery study. Liver AST also showed dose dependent statistically significant increase across the investigated doses when compared to control in the toxicity study, but showed no statistically significant change in the recovery study, this suggests that the extract exerts reversible dose dependent injury to the liver (Adedapo *et al.,* 2004). Serum ALT showed the same level of statistically significant increase ($P < 0.0001$) across the investigated doses when compared to control in both the toxicity and recovery studies. However, Liver ALT showed statistically significant increase, no statistically significant change and statistically significant decrease in 750, 500 and 250 mg/kg doses respectively but no statistically significant change when compared to control in the recovery study. The results of liver ALT suggests that the extract exerts a reversible dose dependent injury on the liver while the serum ALT suggests an irreversible dose independent injury to the liver.

The OECD guideline stipulates that microscopic and gross examination of organ(s) of interest should be included as constituents of pathology data in describing oral toxicity (OECD, 2008). The histology of the liver showed dose dependent injury to the liver evident by the presence of marked vascular congestion and periportal inflammation across the investigated doses when compared to control in the toxicity study. Upon the withdrawal of the extract in the recovery study, there was total recuperation at 250 mg/kg, while the marked evidence of liver injury became mild at 500 and 750 mg/kg. The histology examination suggests that the extract caused reversible dose dependent effect on the liver. The histology report is in agreement with the biochemical results of serum AST, liver AST and liver ALT of this study. It also agrees with the toxicity report of Uzoekwe (2021) on the toxicity profile of ethanol extract of the leaves of the same plant at the same investigated doses.

One of the parameters used for the assessment of the functionality of the liver is serum total protein. A reduction in serum level of total protein depicts reduced synthetic function, which is evident in liver damage or diseases; an increase in this parameter is usually seen in cancerous conditions, or following high protein diet (Daniyan *et al*, 2021). In the toxicity study groups, the 750 mg/kg dose of *S. erianthum* root extract significantly increased the liver total protein, however the other doses did not significantly affect the total protein. The three doses

In the toxicity study groups, the result of liver total protein showed statistically significant increase at dose 750 mg/kg when compared to control but there was no statistically significant change across all the investigated doses in the recovery group when compared to control. This suggests that the extract affects the functionality of the liver at high doses in the toxicity group and the toxic effect is reversed over time after the withdrawal of the *S. erianthum*.

The levels of urea and creatinine in the blood are assessed to check the functionality of the kidneys (Gounden *et al.,* 2021). Serum urea is usually increased in acute and chronic renal diseases; urea clearance falls as the kidney fails

and as a result, urea tends to accumulate with diseased kidneys that are unable to excrete these substances at normal rate; this will raise blood urea level (Vasudevan, 2017). In this study, there was statistically significant increase in kidney urea across all the investigated doses when compared to control in the repeated dose study; however, the recovery study showed no statistically significant change in kidney urea across all the investigated doses when compared to control, thus suggesting a reversible toxic effect of the extract on the kidney at the investigated doses. The serum urea showed no statistically significant across all the investigated doses when compared to control in both repeated dose and recovery studies, thus suggesting that the extract has no toxic effects on the kidney at the investigated doses. Creatinine is the by-product of creatinine phosphate in muscle, and it is produced at a constant rate by the body. For the most part, creatinine is cleared from the blood entirely by the kidney; serum creatinine is a more accurate assessment of renal function than urea; however, urea is increased earlier in renal disease (Gounden *et al.,* 2021). In this study, there was no statistically significant change in serum creatinine across all the investigated doses when compared to control in both repeated dose and recovery studies; however, there was statistically significant increase in kidney creatinine only at 750 mg/kg when compared to control in the toxicity study while there was no statistically significant change in kidney creatinine across all the investigated doses when compared to control in the recovery study. The kidney creatinine results suggest a reversible dose dependent injury to the kidney while the serum creatinine result suggests that the investigated doses of the extract were harmless to the kidney.

The histology examination of the kidney showed dose dependent pathological lesions evident by the marked presence of congested interstitium and inflammation across the investigated doses when compared to control in the toxicity study. Although the pathological lesions seen at 250 and 500 mg/kg in the toxicity study resolved in the recovery study, however, mild lesions were still present at 750 mg/kg when compared to control. The result of the histology examination also suggests that the extract caused a reversible dose dependent effect on the kidney and this is in agreement with the biochemical kidney creatinine results.

Lipid profile is the collective term given to the estimation of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides. An extended lipid profile may include very low-density lipoprotein (VLDL).

This is used to identify hyperlipidemia, many forms of which are recognised risk factors for cardiovascular diseases and sometimes pancreatitis (Abdulmumin *et al.,* 2020). Hyperlipidaemia is defined as the elevation of fasting total cholesterol and/or triglyceride (TG) level, which is recognized as a risk factor of cardiovascular diseases (CVD) (Nelson, 2013). Hypertriglyceridemia is a risk factor of CVD such as myocardial infarction and atherosclerosis (Syed-Badrul *et al.,* 2020). In this study, there was no statistically significant difference ($P > 0.05$) in the serum lipid profile including triglyceride, cholesterol, LDL, and HDL across all the investigated doses when compared to control, in both the repeated dose and recovery studies, thus suggesting that the extract is not likely to cause any cardiovascular disease that may be attributed to lipid concentrations (Akanmu *et al.,* 2013). However, the results of the liver lipid profile analysis showed reversible statistically significant decrease in triglyceride across all the investigated doses when compared to control, this suggests the potential of the extract in treating hypertriglyceridemia and its related cardiovascular diseases (Syed-Badrul *et al.,* 2020).

The results of the selective effects of the extract on male and female rats suggest that the extract has potentials to cause toxic effects on both sexes. The results revealed that the liver of male rats may be more vulnerable to these effects. This is seen in the more prominent increases in the levels of the investigated liver injury biomarkers (ALT and AST) in both the serum and the liver homogenates when compared to female rats. The significant increases in lymphocytes seen across all the investigated doses in male rats, which was absent in females rats also suggest that the male rats are likely to be more susceptible to the effects of the extract than the female rats. The creatinine results of the kidney homogenate however suggest that the kidney of female rats may be more affected by the extract than the kidneys of male rats.

Conclusion

In conclusion, this study established that the median lethal dose (LD_{50}) of ethanol extract of *S. erianthum* root is greater than 5000 mg/kg body weight. The extract did not elicit any significant deleterious effect on the relative body weight, serum lipid profile, serum creatinine, serum urea and the haematological parameters of the animals used for the study. The *S. erianthum* root however elicited varying level of deleterious effects on the serum AST, serum ALT and liver homogenate lipid profile. The deleterious effects were largely dose dependent and were mostly reversed in the recovery groups for the lowest dose (250 mg/kg). The SER impacted toxic effects on the kidney and liver cells which included vascular congestion and inflammation. The toxic effects elicited on the liver and kidney tissues were completely reversed at the 250 and 500 mg/kg doses but partial reversal was observed at the 750 mg/kg dose.

Conflicts of interest

The authors have not declared any conflict of interest.

Acknowledgement

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