Journal of Applied Pharmaceutical Science Vol. 6 (10), pp. 113-123, October, 2016
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2016.601016
ISSN 2231-3354 

Protective Effects of *Solanum erianthum* D. Don Leaf Extract on Lead-Induced Toxicity in Adult Wistar Rats

Olusegun Babalola*, John Agbi, Adeleke Badiora, Oladayo Areola

Department of Biochemistry, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.

ARTICLE INFO

Article history:
Received on: 01/02/2016
Revised on: 05/03/2016
Accepted on: 18/05/2016
Available online: 29/10/2016

Key words:
Lead-induced toxicity, *Solanum erianthum*, ethyl acetate fraction, acute toxicity, sub-chronic toxicity, histology.

ABSTRACT

The possible protective effects of the ethyl acetate fraction of *Solanum erianthum* ethanol leaf extract on lead-induced toxicity in adult Wistar rats were investigated. Phytochemical constituents, antioxidant and membrane stabilizing activities of the ethanol extract and its fractions were determined using standard procedures. Acute and sub-chronic oral toxicity studies were carried out. The rats were treated orally with lead (10 mg/kg b. wt) and extract (100 mg/kg b. wt). The blood samples, liver, and kidney were collected for the estimation of biochemical and organ parameters, and histomorphological studies. The ethyl acetate fraction had the highest antioxidant activities and high membrane stabilizing potentials when compared to the crude extract and other fractions. Significant elevations were observed in plasma albumin, creatinine and urea levels in group treated with lead only. The activities of plasma ALT and AST were significantly increased in group treated with lead alone. Treatment with ethyl acetate fraction significantly decreased ($p < 0.05$) the elevated ALT, AST, urea and creatinine levels. The histology evidence showed progressive degeneration of the liver and kidney tissues in lead treated groups while the administration of *S. erianthum* showed appreciable degrees of protection to both the liver and kidney. The study concluded that ethyl acetate fraction of *S. erianthum* has protective effects against lead-induced toxicity in adult Wistar rats.

INTRODUCTION

Lead (Pb) is a poisoning metal, which is ubiquitous in both organic (tetraethyl lead) and inorganic (lead nitrate, lead acetate, lead chloride) forms in the environment and is one of the major heavy metals used in industrial activities, like in automobile, paint, ceramic, plastic, etc industries because of its unique properties namely softness, high malleability, ductility, low melting point and resistance to corrosion (Shalan *et al*., 2005). This in turn has led to a manifold increase in the occurrence of free lead in biological systems and the inert environment, and hence remains a considerable occupational and public health problem, which is known to cause a number of adverse effects in both men and women (Flora *et al*., 2012). When lead is absorbed, it is conjugated in the liver and passed to the kidney, where a small quantity is excreted in urine and the rest accumulates in various body organs (Sidhu and Nehru, 2004). This affects many biological activities at the molecular, cellular and intercellular levels, which may result in morphological alterations that can remain even after lead level has fallen (Flora *et al*., 2006; Ibrahim *et al*., 2012). This may also result in lowering of seminal plasma protein with concomitant rise of free amino acid in blood in lead exposed workers as evidence of the alteration in protein metabolism, suggesting disturbance in cellular nutritional status, necessary for cell survival, and its proper function (Naha and Chowdhury, 2005). Many heavy metals, including Pb, are known to induce over production of reactive oxygen species (ROS) and consequently enhance lipid peroxidation, decrease the saturated fatty acids and increase the unsaturated fatty acid contents of membranes (Malecka *et al*., 2001). Also, it has been shown that lead enhances the production of ROS in a variety of cells resulting in oxidative stress (Xienia *et al*., 2000) which represents an imbalance between the production of free radicals and the biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage (Flora *et al*., 2011).

* *Corresponding Author*
Email: doctorbablo @ yahoo.com;
Telephone: +2348037143321

ROS are the byproducts of degenerative reactions in many tissues, which affect the regular metabolism by damaging the cellular components (Foyer and Noctor, 2002). In addition, ROS are highly reactive to membrane lipids, protein and DNA. They are believed to be the major contributing factors to stress injuries and to cause rapid cellular damage (Shehab *et al* 2010; Afify and El-Beltagi *et al*., 2011).

Under the influence of lead, onset of oxidative stress occurs on account of two different pathways operating simultaneously; first comes the generation of ROS, like hydroperoxides ($HO^{2\bullet}$), singlet oxygen and hydrogen peroxide (H_2O_2), and second, the antioxidant reserves become depleted (Flora *et al*., 2012).

Solanum erianthum, also known as potato tree, is a significant source of natural antioxidants, which might be helpful in preventing the progress of various oxidative stresses (Mahadev *et al*. (2015). It is a fast growing, evergreen shrub or small tree, reaching a height of 4 – 10 m and stem up to 20 cm in diameter, unarmed, densely woolly hairy with soft stellate hairs (Mild, 2009). 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), and moist forests. It often grows in disturbed areas (Hammer, 2004), such as roadsides, fields, and waste places, and may be considered a weed (Modise and Mogotsi, 2008).

Solanum erianthum possesses steroidal saponins and steroidal alkaloids that are used in the pharmaceutical industry as steroid precursors to produce anti-inflammatory corticosteroids, contraceptive steroids, and anabolic steroids (Modise and Mogotsi, 2008). In West Africa, a decoction of the leaves is used as a diuretic and purgative to cure malaria, leprosy and venereal diseases and to stimulate the liver functions (Modise and Mogotsi, 2008). Essential oils in the fruits and leaves of *S. erianthum* have been studied for their cytotoxicity as well as their traditional uses in medicine, especially for skin diseases and stomach-related ailments (Essien *et al*., 2012).

Lead toxicity has been recognized as a major public health risk, particularly in developing countries, resulting in various deleterious effects on the renal and hepatic systems, mainly through increased oxidative stress. Research has shown that *Solanum erianthum* contains phytochemicals with antioxidant activities that can prevent or subdue the generation of oxidative stress. The study therefore investigated the possibility of utilising the leaf extract of *Solanum erianthum* in the management of lead-induced toxicity.

MATERIALS AND METHODS

Collection and Identification of Plant Material

Fresh leaves of *Solanum erianthum* D. Don were collected from Sekona Village, Osun State, Nigeria. The plant was identified and authenticated at IFE Herbarium, Department of Botany, Obafemi Awolowo University, Ile-Ife, Nigeria. The voucher specimen was deposited in the Herbarium and the specimen identification number is IFE-17429.

Reagents and Chemicals

All the reagents used in the study were of analytical grade and were obtained from reputable sources. 1, 1-diphenyl-2-picrylhydrazyl hydrate (DPPH), Follin-Ciocalteu's phenolic reagent, sodium carbonate, sodium hydroxide, Gallic acid, Ascorbic acid (Vitamin C), ferric chloride, Quercetin and aluminium chloride were obtained from Sigma Fine Chemicals Limited, Upsalla, Sweden and British Drug House (BDH) Chemicals Limited, London.

Alanine aminotransferase, aspartate aminotransferase, total bilirubin, urea, creatinine and albumin diagnostic kits were obtained from Randox Laboratories Ltd, United Kingdom. All solutions, buffers and reagents were prepared with glass distilled water and stored in the refrigerator at 4 ^{O}C.

Experimental Animals

Adult Wistar rats used in this study were obtained from the animal house, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria. The animals were acclimatized for eight weeks, fed with standard commercial pellet diet obtained from Ogooluwa feeds, Ile-Ife and given access to water *ad libitum*. The rats were housed under standard conditions, at natural light and dark cycle.

Preparation of Extract and Fractions of *Solanum erianthum*

The dried leaves of *Solanum erianthum* (2.0 kg) was ground into fine smooth powder using impact mill. The powdered leaves (500 g) was soaked in 70% ethanol (7.5 L) for 72 hours, and filtered afterwards with a double layered cheese cloth. This was then filtered using filter paper (Whatman No. 1) and concentrated to dryness using a rotary evaporator Model ED-100. The ethanol extract (20 g) was taken up in distilled water (200 ml). The filtrate was partitioned sequentially with hexane (100 ml x 4), ethyl acetate (100 ml x 4) and butanol (100 ml x 4) in capped separating funnel. The content was vigorously shaken, allowed to settle and carefully separated.

The same fractions were combined and concentrated in rotary evaporator separately. The fractions and aqueous residue were dried, weighed, labeled and kept in the desiccators until needed for further analyses.

Phytochemical Screening of the Extract and Fractions

The phytochemical screening of the extract and fractions was carried out using standard procedures as described by the earlier reports of Sofowora (2006).

Membrane Stabilization Activity

The red blood cell membrane stabilizing activity assay was carried out using the method of Oyedapo *et al*. (2010).

Preparation of Bovine Red Blood Cell

Fresh bovine blood samples were collected in an anticoagulant (trisodium citrate 3.8%). Blood samples were centrifuged at 3000 rpm on a Bench centrifuge Model 800D for 10 minutes at room temperature. The supernatants (plasma) were carefully removed while the packed red blood cell was washed in fresh normal saline (0.85% w/v NaCl). The process of washing and centrifugation were repeated four times until the supernatants were clear. Then, bovine erythrocytes (2% v/v) were prepared as reported by Oyedapo *et al*. (2010).

Membrane Stabilizing Activity

The membrane stabilizing activity assay was carried out using the method of Oyedapo *et al*. (2010) using 2% (v/v) bovine erythrocyte suspension while diclofenac was used as standard drug. The assay mixtures consisted of 1ml of hyposaline (0.25% w/v) sodium chloride, 0.5 ml of 0.15 M sodium phosphate buffer, pH 7.4, 0.5 ml of 2% (v/v) bovine erythrocytes suspension, 0.0 – 1.4 ml of drug (standard, extract and fractions) and final reaction mixtures were made up to 4.0 ml with normal saline. Drug was omitted in the blood control, while the drug control did not contain the erythrocytes suspension.

The reaction mixtures were incubated at 56^0C for 30 minutes on a water bath, followed by centrifugation at 5000 rpm on Gallenkamp Bench Centrifuge for 10 minutes at room temperature. The absorbance of the released haemoglobin was read at 560 nm. The percentage membrane stability was estimated using the expression:

$$\text{Percentage membrane stability} = \frac{100 - (\text{Abs of test drug} - \text{Abs of drug control})}{\text{Abs of blood control}} x100$$

Where the blood control represents 100% lysis or zero percent stability.

***In vitro* Antioxidant Studies**

Ferric Reducing Antioxidant Power (FRAP) Assay

The FRAP assay used antioxidants as reductants in a redox linked colometric method with absorbance measured with spectrophotometer (Benzie and Strain, 1999).

Determination of Total Phenol Content

The total phenol content of the extract/fractions of *Solanum erianthum* was determined using the Folin – Ciocalteu's method of Singleton and Rossi (1965) as described by Gulcin *et al.* (2003). The total phenol content of the plants was expressed as mg gallic acid equivalent (GAE)/g fresh weight.

Determination of 1, 1-Diphenyl-2-Picrylhydrazyl Hydrate (DPPH) Radical Scavenging Activity

The hydrogen or radical scavenging properties of the extracts was determined using the stable radical 1, 1 –diphenyl-2-picrylhydrazyl hydrate (DPPH) according to the method of Blois (1958) and as described by Brace (2001).

The antioxidant activity (AA) was calculated using the formula:

$$\text{Percentage scavenging activity} = \frac{\text{Absorbance (control)} - \text{Absorbance (sample)} \times 100}{\text{Absorbance (control)}}$$

The 50% inhibitory concentration (IC_{50}) was obtained from a linear regression plot of percentage inhibition against concentration of the extract.

Determination of Total Flavonoid Content

The determination of the total flavonoid content of the plant extract/fractions was based on the aluminium chloride colorimetric method according to the method of Zhilen *et al*. (1999) and as described by Miliauskas *et al*. (2004). The total flavonoid content of the plant extract/fractions was expressed as mg Quercetin equivalents per gram of the plant extract.

Acute Toxicity Study (LD_{50} Determination)

Acute toxicity study was carried out in two phases, according to the procedure of Lorke (1983) with slight modifications. The LD_{50} was estimated from the plot of percentage mortality versus logarithm of concentrations.

Sub-chronic Toxicity Study

The study was carried out as follows; a total of thirty-five adult albino rats [Wistar strain (weight between 140 - 260 g)] were used for the experiment and were randomly grouped into seven groups (five rats in each group) and were subjected to every-other-day oral dose treatments for forty-two days as follows: Rats in group 1 (control) were administered normal saline. Rats in group 2 were administered lead only (10 mg/kg b. wt). Rats in group 3 were administered extract only (100 mg/kg b. wt). Rats in group 4 were co-administered lead (10 mg/kg b. wt) + ethyl acetate fraction (100 mg/kg b. wt). Rats in group 5 were pre-administered lead (10 mg/kg b. wt) + ethyl acetate fraction (100 mg/kg b. wt). Rats in group 6 were post-administered lead (10mg/kg b. wt) + ethyl acetate fraction (100 mg/kg b. wt). Rats in group 7 (positive control) were administered lead (10 mg/kg b. wt) + vitamin E (100 mg/kg b. wt).

The rats were weighed before the commencement of treatments and thereafter weighed weekly throughout the duration (42 days) of the study.

At the end of the 42-day experiment, the rats fasted 24 hours and were sacrificed. The blood samples were collected by cardiac puncture into heparinized bottles for estimation of biochemical parameters and the organs such as the liver and kidney were excised, weighed, rinsed with normal saline and stored for further biochemical and histomorphological studies.

Preparation of Blood Plasma and Tissue Homogenate

The blood collected in heparinized bottle was centrifuged using Bench centrifuge (Model 90-2) at 4000 rpm for 10 min to separate supernatant and residue. The supernatant (plasma) was collected using dry Pasteur pipette, stored in sterile vial and kept in freezer for biochemical analyses. Liver and kidney were surgically removed and a 10% (w/v) tissue homogenates were prepared by homogenizing the liver and kidney separately in phosphate buffer solution, pH 7.4.

The homogenates were centrifuged at 4000 rpm for 15 minutes and the supernatant was collected as a source for the assessment of hepatic marker enzymes, and kidney function parameters.

Estimation of Creatinine Concentration

The creatinine concentration was estimated using Jaffe's-alkaline picrate method as described by Chawla (1999) using Randox kit.

Estimation of Urea Concentration

Plasma urea was estimated as described by Weatherburn (1967) using Randox kits.

Estimation of Protein Concentration

Biuret reaction as described by Gornall *et al.* (1949) using bovine albumin as standard was used for the estimation of the total protein from the extract.

Estimation of Albumin Concentration

The bromocresol purple (BCP albumin) procedure as modified (Pinnell and Northam, 1978) was employed to estimate the concentration of albumin in the plasma using commercially available Randox kit.

Estimation of Total Bilirubin Concentration

Bilirubin concentration in the serum was determined according to the method of Jendrassisk and Grof (1938). Total bilirubin was determined in the presence of caffeine, which releases albumin bound bilirubin, by the reaction with diazotized sulphanilic acid.

Assay for Alanine Aminotransferase (EC 2.6.1.2) Activity

The activity of alanine aminotransferase was assayed based on the colorimetric method of Reitman and Frankel (1957) using a commercially available Randox kit.

Assay of Aspartate Aminotransferase (EC 2.6.1.1) Activity

The activity of aspartate aminotransferase was assayed based on the colorimetric method of Reitman and Frankel (1957) using a commercially available Randox kit.

Histopathological Analysis

Portions of the tissue from liver and kidney were used for histopathological examination. Histopathological analysis was carried out using standard methods.

Statistical Analysis

Data are expressed as mean ± SEM. Comparisons between different groups were done using one way analysis of variance (ANOVA) followed by Tukey – Kramer multiple comparisons test. A probability level of less than 0.05 was accepted as statistically significant.

RESULTS

The phytochemical constituents of the various plant materials are given in the Table 1 below. The results show the presence of various secondary metabolites (phytochemicals) like tannin, saponin, alkaloids, flavonoids, cardiac glycoside etc. the inferences of these phytochemicals were based on the formation of coloured precipitate formed after carrying out the various tests.

Table 1: Phytochemical Constituents of *Solanum erianthum* Ethanol Leaf Extract and its Fractions.

Extract/Fraction	CEE	n-HF	EAF	n-BF	AqF
Phytochemicals					
Alkaloids	++	+	+	+	+
Cardiac Glycosides	++	+	+	++	+
Flavonoids	++	+	++	+	+
Saponins	+++	-	-	+	+++
Tannins	++	-	+	++	++
Triterpenes	++	+	+	+	+
Steroids	+	+	+	-	-

(+) represent positive result and (-) represent negative result, CEE = Crude ethanol fraction, n-HF = n-Hexane fraction, EAF = Ethyl acetate fraction, AqF = Aqueous fraction and n-BF = Butanol fraction.

Table 2 showed the yield of ethanol extract from 500 g of dried powdered leaves of *Solanum erianthum* was 72.8 g representing 14.56% of the starting materials while the yield of the fractions was given as 41.20% (8.24 g) for aqueous residues, 22.04% (4.408 g) for n-butanol, 20.25% (4.05 g) for ethyl acetate fractions and 4.8% (0.96 g) for n-hexane,

Table 2: Percentage Yields and Concentrations of Total Phenol and Total Flavonoid Constituents Contained in *S. erianthum* Leaves.

Extract/ Fraction	Extraction Yields % Yield (w/w)	Total Flavonoid Content QE (mg/g)	Total Phenol Content GAE (mg/g)
Crude ethanol	14.56	11.47 ± 1.80	42.74 ± 2.36
Ethyl acetate	20.25	74.79 ± 2.99	98.38 ± 5.31
n-Butanol	22.04	11.22 ± 4.79	76.70 ± 0.29
n-Hexane	4.8	39.10 ± 0.90	8.78 ± 5.90
Aqueous	41.20	10.78 ± 0.00	18.53 ± 8.55

Data are expressed as Mean ± SEM, (n = 3), QE = Quercetin equivalent, GAE = Gallic acid equivalent.

The results of 1, 1-diphenyl-2-picrylhydrazyl hydrate **(**DPPH) radical scavenging activity of crude ethanol extract and fractions of *Solanum erianthum* is shown in Table 3.

Table 3: 1, 1-Diphenyl-2-Picrylhydrazyl Hydrate (DPPH) Radical Scavenging Activity of *S. erianthum* Ethanol Leaf Extract and its Fractions.

Extract/Fraction Conc. (mg/ml)	C EE	EAF	n-BF	AqF	n-HF	Vit-E
			Percentage Inhibition			
0.5	44.03 ± 0.95	67.15 ± 0.72	49.11 ± 1.62	14.79 ± 0.43	15.07 ± 1.71	89.61 ± 0.23
0.25	28.54 ± 1.63	50.20 ± 1.21	31.93 ± 1.10	8.58 ± 1.47	7.09 ± 0.27	70.92 ± 7.74
0.125	18.21 ± 0.96	28.47 ± 0.40	15.63 ± 0.83	2.37 ± 0.86	-0.36 ± 0.96	22.95 ± 4.23
0.0625	4.52 ± 0.67	17.98 ± 0.66	12.64 ± 0.72	2.48 ± 1.00	2.74 ± 0.32	7.02 ± 3.54
0.03125	3.83 ± 0.78	7.60 ± 1.26	6.37 ± 0.67	-0.06 ± 0.59	-2.56 ± 0.21	3.91 ± 1.69
0.01563	0.93 ± 1.01	2.47 ± 0.70	-1.61 ± 2.36	2.20 ± 2.63	-5.84 ± 1.19	4.06 ± 5.58
0.00781	1.33 ± 0.78	-0.23 ± 0.38	-1.77 ± 2.67	-2.65 ± 0.40	-4.88 ± 0.95	-
			IC_{50} (mg/ml)			
	0.53 ± 0.01	0.33 ± 0.00	0.48 ± 0.01	1.60± 0.05	1.39 ± 0.10	0.02 ± 0.00

Data are expressed as Mean ± SEM, (n = 3). CEE = Crude ethanol extract, EAF = Ethyl acetate fraction, n-BF = Butanol fraction, AqF = Aqueous fraction, n-HF = Hexane fraction, Vit - E = Vitamin E and IC_{50} = Half maximal inhibitory concentration.

Table 4: The Ferric Reducing Antioxidant Power (FRAP) Assay of *S. erianthum* Crude Ethanol Extract and its Fractions.

Extract/Fraction	Ascorbic Acid Equivalent (mg/g)
Crude ethanol extract	76.59 ± 2.88
Ethyl acetate fraction	144.25 ± 0.97
n-Butanol fraction	63.11 ± 2.60
n-Hexane fraction	102.45 ± 6.78
Aqueous fraction	16.92 ± 0.34

Data are expressed as mean ± S.E.M (n = 3).

Table 5: Acute Toxicity Test of Crude Ethanol Extract of *Solanum erianthum* in Mice.

Dose (mg/kg Body Weight)	Number of Animals	Mortality
First Phase		
10	3	0/3
100	3	0/3
1000	3	0/3
Second Phase		
1600	3	0/3
2900	3	0/3
5000	3	0/3

Table 6: Membrane Stabilizing Activities of Crude Ethanol Extract and Fractions of *S. erianthum* on Bovine Red Blood Cell.

Extract/Fraction Conc. (mg/ml)	C EE	EAF	n-BF	AqF	n-HF	Diclofenac
			Percentage Stability			
0.05	9.23 ± 0.22	10.10 ± 0.37	8.04 ± 0.40	8.12 ± 0.42	2.13 ± 0.65	9.68 ± 0.30
0.10	8.55 ± 0.29	15.38 ± 0.74	8.76 ± 0.78	11.59 ± 0.23	3.20 ± 1.37	12.11 ± 1.46
0.15	17.30 ± 0.66	19.97 ± 0.28	10.04 ± 0.29	10.14 ± 0.51	1.99 ± 0.56	17.06 ± 0.20
0.20	22.28 ± 1.86	21.10 ± 0.47	15.53 ± 0.29	18.84 ± 0.12	4.73 ± 0.48	19.48 ± 1.30
0.25	22.49 ± 0.22	22.44 ± 1.45	13.64 ± 0.38	17.39 ± 0.53	3.66 ± 0.25	23.82 ± 1.03
0.30	33.97 ± 0.47	29.17 ± 0.19	21.02 ± 0.29	24.64 ± 0.81	8.95 ± 0.40	27.42 ± 0.30

Data are expressed as Mean ± SEM, (n = 3). CEE = Crude ethanol extract, EAF = Ethyl acetate fraction, n-BF = Butanol fraction, AqF = Aqueous fraction, n-HF = Hexane fraction, Standard drug = Diclofenac and Conc. = Concentration.

In the DPPH assay, ethyl acetate fraction gave the highest activity with an IC_{50} of 0.33 ± 0.00, indicating that the activity increases with the increase in concentration (i.e. the activity was concentration dependent). Other fractions and crude ethanol extract gave the IC_{50} of 0.53 ± 0.01, 0.48 ± 0.01, 1.60 ± 0.05, 1.39 ± 0.10 mg/ml for crude ethanol extract, n-butanol fraction, aqueous fraction and n-hexane fraction respectively.

The ferric reducing antioxidant power (FRAP) assay result shows a concentration dependent change when the FRAP values of the crude extract and fractions were determined. The plant extract and fraction showed that the *S. erianthum* had 76.59 ± 2.88, 144.25 ± 0.97, 63.11 ± 2.60, 102.45 ± 6.78 and 16.92 ± 0.34 mg AAE/g for crude ethanol leaf extract, ethyl acetate, n-butanol, n-hexane and aqueous fractions respectively with ethyl acetate (144.25 ± 0.97) having the highest activity, and aqueous residues (16.92 ± 0.34) having the lowest activity as shown in Table 4.

The results of the acute toxicity test are presented in Table 5 while the membrane stabilizing activity of the extract and fractions of *S. erianthum* on bovine red blood cell exposed to both heat and hypotonic induced lyses are shown in Table 6. The effect of lead and crude ethanol extract and fractions of *S. erianthum* on average body weight of adult wistar rats in the first and last week of administration are shown in Table 7. There was significant increase in the percentage change in body weight of the rats in the control group, and there was significant decrease in the percentage change in toxicant groups.

Table 7: Effect of *Solanum erianthum* on Average Body Weight.

Group	Initial Weight (g)	Final Weight (g)	Percentage Change in Weight (%)
A	152.5 ± 15.34	190.0 ± 13.54	24.59
B	182.0 ± 4.64	214.0 ± 6.78	17.58
C	180.0 ± 6.52	228.0 ± 5.83	26.67
D	156.0 ± 2.45	177.0 ± 5.83	13.46
E	148.0 ± 4.90	184.0 ± 10.65	24.32
F	175.0 ± 3.16	196.0 ± 9.14	12.00
G	166.0 ± 3.67	200.0 ± 10.95	20.48

Keys: A = Control
B = Toxicant Alone (Lead 10 mg/kg body weight)
C = Extract Alone (100 mg/kg body weight)
D = Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
E = Pre Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
F = Post Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
G = Lead (10 mg/kg) + Vitamin E (100 mg/kg body weight)

The effects of lead intoxication and treatment with extract and fractions of *S. erianthum* on the excretory organs are shown in Table 8. There was slight difference in their weight. The toxicant treated groups showed decreased relative organs' weight.

Table 8: Effect of *S. erianthum* on Relative Weight of Kidney and Liver of Adult Wistar Rats.

Group	Liver (g)	Right Kidney (g)	Left Kidney (g)
A	3.15 ± 0.23	0.31 ± 0.02	0.31 ± 0.01
B	3.30 ± 0.12	0.28 ± 0.01	0.30 ± 0.01
C	3.12 ± 0.09	0.26 ± 0.01	0.25 ± 0.01
D	3.42 ± 0.04	0.32 ± 0.01	0.31 ± 0.01
E	3.28 ± 0.11	0.31 ± 0.01	0.31 ± 0.01
F	3.08 ± 0.08	0.34 ± 0.01	0.30 ± 0.01
G	3.23 ± 0.11	0.32 ±0.01	0.30 ± 0.01

Keys: A = Control
B = Toxicant Alone (Lead 10 mg/kg body weight)
C = Extract Alone (100 mg/kg body weight)
D = Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
E = Pre Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
F = Post Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
G = Lead (10 mg/kg) + Vitamin E (100 mg/kg body weight)

Table 9: Effect of *Solanum erianthum* on Creatinine, Urea and Total Protein Levels of Adult Wistar Rats.

Group	Creatinine in Plasma (mg/dl)	Urea in Plasma (mg/dl)	Total Protein in Kidney (mg/ml)
A	1.38 ± 0.66	39.15 ± 2.70	2.31 ± 0.07
B	2.44 ± 0.87	57.71 ± 3.31[a]	2.25 ± 0.24
C	1.51 ± 0.30	39.81 ± 4.13[b]	1.74 ± 0.18
D	1.33 ± 0.55[b]	37.04 ± 7.05[b]	1.73 ± 0.11
E	1.31 ± 0.31[b]	35.18 ± 13.6[b]	1.11 ± 0.14[a,b]
F	1.57 ± 0.50	30.55 ± 10.25[b]	1.47 ± 0.19
G	1.73 ± 0.26	37.18 ± 6.70[b]	1.24 ± 0.30[a,b]

[a] = significantly different from the control group at $p < 0.05$
[b] = significantly different from lead-treated group at $p < 0.05$
[c] = significantly different from extract-treated group at $p < 0.05$

Keys: A = Control
B = Toxicant Alone (Lead 10 mg/kg body weight)
C = Extract Alone (100 mg/kg body weight)
D = Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
E = Pre Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
F = Post Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
G = Lead (10 mg/kg) + Vitamin E (100 mg/kg body weight)

The effects of lead, crude ethanol extract and fractions of *Solanum erianthum* on the activities of creatinine, urea and total protein are shown in Table .9. The effects of vitamin E, lead, crude ethanol extract and ethyl acetate fraction of *Solanum erianthum* on the bilirubin and albumin levels of adult wistar rats are shown in Table 10 while the effects of lead and ethyl acetate fraction of *Solanum erianthum* on ALT and AST of adult Wistar rats are shown in the Table 12.

Table 10: Effect of *Solanum erianthum* on Bilirubin and Albumin Levels of Adult Wistar Rats.

Group	Total Bilirubin in Plasma (mg/dl)	Total Albumin in Plasma (g/dl)
A	0.87 ± 0.30	4.05 ± 0.49
B	1.12 ± 0.12	4.77 ± 0.67
C	1.08 ± 0.13	4.11 ± 0.17
D	1.07 ± 0.09	3.75 ± 0.20
E	1.18 ± 0.13	3.77 ± 0.21
F	1.19 ± 0.03	4.11 ± 0.37
G	1.32 ± 0.16	3.50 ± 0.40

Keys: A = Control
B = Toxicant Alone (Lead 10 mg/kg body weight)
C = Extract Alone (100 mg/kg body weight)
D = Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
E = Pre Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
F = Post Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
G = Lead (10 mg/kg) + Vitamin E (100 mg/kg body weight)

Table 11: Effect of *Solanum erianthum* on Total Protein Levels of Adult Wistar Rats.

Group	Total Protein in Plasma (mg/ml)	Total Protein in Liver (mg/ml)
A	3.01 ± 0.26	2.55 ± 0.59
B	2.75 ± 0.29	1.94 ± 0.05
C	2.33 ± 0.17	3.25 ± 0.39
D	2.69 ± 0.15	2.23 ± 0.37
E	2.71 ± 0.22	2.68 ± 0.51
F	2.45 ± 0.14	4.16 ± 0.26[b]
G	2.63 ± 0.15	4.45 ± 0.19[a,b]

[a] = significantly different from the control group at $p < 0.05$
[b] = significantly different from lead-treated group at $p < 0.05$
[c] = significantly different from extract-treated group at $p < 0.05$

Keys: A = Control
B = Toxicant Alone (Lead 10 mg/kg body weight)
C = Extract Alone (100 mg/kg body weight)
D = Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
E = Pre Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
F = Post Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
G = Lead (10 mg/kg) + Vitamin E (100 mg/kg body weight)

Table 12: Effect of *Solanum erianthum* on AST and ALT Levels of Adult Wistar Rats.

Group	ALT in Plasma (U/L)	AST in Plasma (U/L)	AST in Liver (U/mg Protein)
A	2.01 ± 0.50	55.59 ± 18.30	145.40 ± 2.91
B	8.25 ± 1.07[a]	90.61 ± 2.82[a]	83.77 ± 2.26[a]
C	3.98 ± 0.47[b]	43.26 ± 10.27[b]	154.20 ± 1.20[b]
D	4.46 ± 1.17	74.10 ± 7.82	159.00 ± 3.99[b]
E	5.13 ± 1.03	45.66 ± 5.26[b]	121.80 ± 19.88[b]
F	2.48 ± 0.77[b]	53.02 ± 3.23[b]	130.10 ± 2.23[b]
G	3.20 ± 0.37[b]	49.32 ± 2.63[b]	134.00 ± 3.74[b]

[a] = significantly different from the control group at $p < 0.05$
[b] = significantly different from lead-treated group at $p < 0.05$
[c] = significantly different from extract-treated group at $p < 0.05$

Keys: A = Control
B = Toxicant Alone (Lead 10 mg/kg body weight)
C = Extract Alone (100 mg/kg body weight)
D = Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
E = Pre Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
F = Post Lead (10 mg/kg) + Ethyl Acetate Fraction (100 mg/kg body weight)
G = Lead (10 mg/kg) + Vitamin E (100 mg/kg body weight)

Additionally the histomorphological changes in the kidneys and liver of test animals are shown in Plate 1 and Plate 2 respectively.

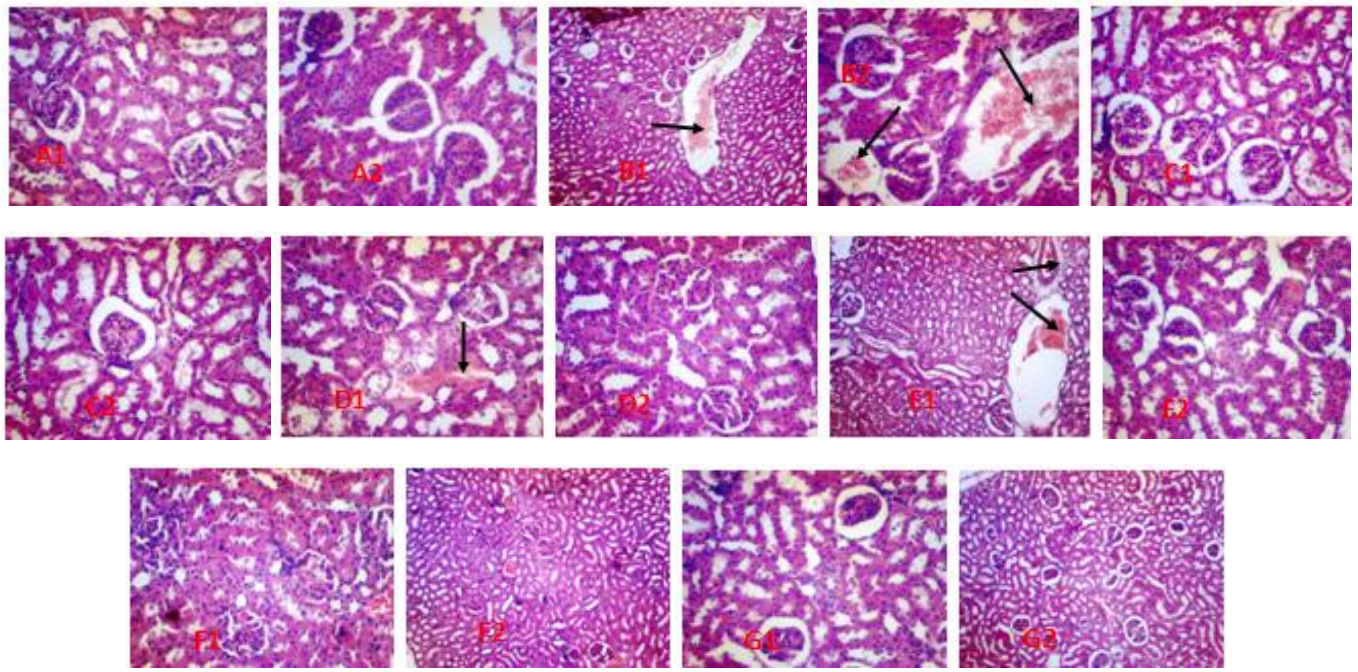

Plate 1: Photomicrographs of the uriniferous tubules of groups A, B, C, D, E, F and G showing glomerulus and Bowman's capsules while the arrows showing affected parts Stain H&E. Mag. X400.

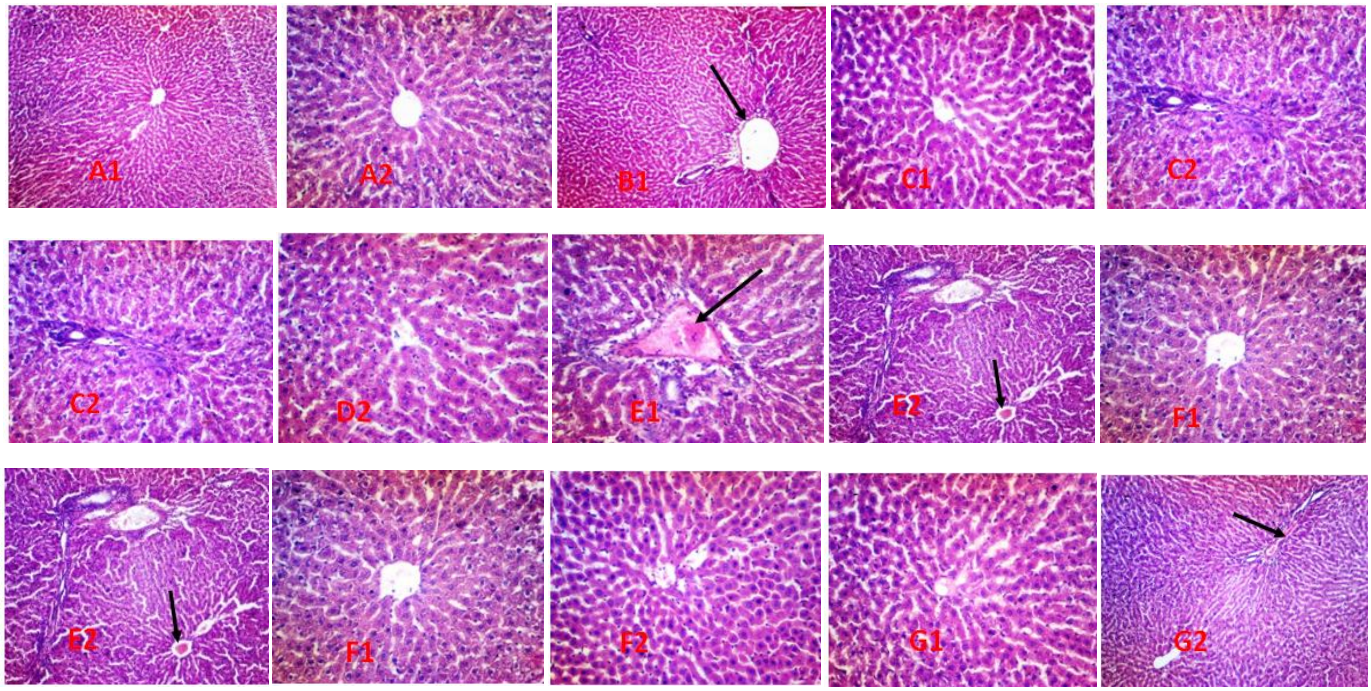

Plate 2: Photomicrographs of liver tubules of groups A, B, C, D, E, F and G showing different liver sinusoids while the arrows showing affected parts Stain H&E. Mag. X400.

DISCUSSION

The non biodegradable nature of lead is the prime reason for its prolonged persistence in the environment and this has led to a manifold increase in the occurrence of free lead in biological systems and the inert environment (Flora *et al*., 2012). Lead causes generation of reactive oxygen species (ROS) which results in critical damage to various biomolecules like DNA, enzymes, proteins and membrane based lipids, while simultaneously it impairs the antioxidant defense system. It has also been reported that lead increases the level of lipid peroxidation (Upasani *et al*., 2001). Oxidative stress has been found to be more pronounced and much more severe in various molecular, cellular and intercellular mechanisms proposed to explain the toxicological profile of lead. Various naturally occurring antioxidants (nutrient antioxidants) like vitamins, flavonoids and herbal antioxidants have been reported for the prevention and treatment of lead induced toxicity and oxidative stress in particular. They have the ability to scavenge ROS at molecular level and chelate lead ions, thereby reversing the toxic effects of lead (Flora *et al*., 2012).

The phytochemical screening of the crude ethanol extract and fractions of *S. erianthum* showed the presence of the following secondary metabolites: alkaloids, cardiac glycoside, flavonoids, saponins, tannins, triterpenes and steroids and this is in agreement with the phytochemical screening reported on the same plant by Bhargavi *et al*. (2012), Archana *et al*. (2013) and Sujatha *et al*. (2013). All the above mentioned secondary metabolites were present in the crude ethanol extract.

The antioxidant potential and screening of *S. erianthum* ethanol extract and fractions were assessed using various biological parameters and compared with the standard antioxidants. In this study, ethyl acetate fraction of *S. erianthum* contained the highest total flavonoid concentration while aqueous fraction contained the least flavonoid concentration. This was perfectly in agreement with the report of Sujatha *et al*. (2013). It has been established that flavonoids from medicinal plants possess high antioxidant potentials due to their hydroxyl groups and protect more efficiently against free radical related diseases like hepatotoxicity, cardiovascular diseases, kidney diseases, arteriosclerosis, etc (Kris-Etherton *et al*., 2002; Vaya *et al*., 2003). Flavonoids are also involved in scavenging of oxygen derived free radicals (Nijveldt *et al*., 2001). The major phenolic compounds (flavonoids and tannins) play major roles as antioxidant capacity of plants and biological activities of plants may be related to their antioxidant potentials, tannins contributed a major role as antihaemorrhagic, antihypercholesterol, hypotensive and cardiac depressant agent (Price *et al*., 1987), steroids, terpenoids and saponins were reported to have analgesic, hypocholesterolemic, anti-diabetic properties (Rupasinghe *et al*., 2003; Sayyah *et al*., 2004; Malairajan *et al*., 2006). It is therefore possible that the presence of flavonoids and tannins in the plant extract/fractions might be responsible for the free radical scavenging effects observed, since flavonoids and tannins are the major phenolic compounds that act as free radical scavengers. In the study, ethyl acetate fraction contained the highest concentration of phenol content while n-hexane fraction contained the least concentration of phenol content. Phenolic compounds are different in molecular structure, and are characterized by hydroxylated aromatic rings (Balasundram *et al*., 2006).

Free radical scavenging potential of *S. erianthum* extract and fractions at different concentrations was evaluated by the DPPH method. Antioxidant reacts with DPPH, which is a stable free radical, and converts it to 1, 1-diphenyl-2-picrylhydrazine. The highest scavenging activities (or percentage inhibition) were observed in ethyl acetate fraction. The strong inhibition displayed on DPPH radicals could be linked to polyphenolic compounds which are capable of donating electrons or transferring hydrogen atoms to neutralize free radicals (Huang *et al*., 2005) and thus, could be a promising therapeutic agent to address stress induced pathological conditions.

The FRAP assay (ferric reducing ability of plasma) evaluates total antioxidant power and is chosen to assess the presumable effects of medicinal plants (Szollosi and Varga, 2002). FRAP method is sensitive in the measurement of total antioxidant power of the fresh biological fluids, such as plant homogenates and pharmacological plant products (Szollosi and Varga, 2002; Rattanachitthawat *et al*., 2010). In the present study, the highest ferric reducing power activity was observed in ethyl acetate fraction. This suggests that the presence of reductants within the ethyl acetate fraction of *S. erianthum* play an important role in scavenging the free radicals i.e. the reducing ability of polyphenolic compounds within the ethyl acetate fraction that exhibit antioxidative potentials in breaking the free radical chain and donating a hydrogen atom may be responsible for their scavenging power.

The results of the acute toxicity studies showed that the LD_{50} is greater than 5000 mg/kg body weight and the crude ethanol extract of *S. erianthum* is therefore safe at a dose lower than 5000 mg/kg. The result obtained here is in agreement with that of Archana *et al*. (2013) on the same plant. This suggests that the extract at the limit dose is therefore non-toxic and safe in oral formulations.

Exposure of red blood cells to injurious substances such as a hypotonic medium results in lysis of its membrane accompanied by haemolysis and oxidation of haemoglobin (Augusto *et al*., 1982). Lysosomal hydrolytic enzymes are released during inflammation into the sites which cause damage to the surrounding organelles and tissues with attendant variety of disorders (Sadique *et al*., 1989; Oyedapo *et al*., 2010). The haemolytic effect of hypotonic solution is related to excessive accumulation of fluid within the cell resulting in the rupture of its membrane. Injury to red blood cell membranes will further render the cells more vulnerable to secondary damage through free radical-induced lipid peroxidation (Augusto *et al*., 1982; Ferrali *et al*., 1992). This mean that break down of bio-membranes leads to the formation of free radicals which in turn enhances cellular damage (Maxwell, 1995). It is therefore expected that compounds with membrane-stabilizing properties, should offer significant

protection to cell membrane against injurious substances (Liu *et al*., 1992; Maxwell, 1995; Shinde *et al*., 1999). Since the viability of cells depends on the integrity of their membranes (Ferrali *et al*., 1992), therefore, the anti-inflammatory action of *S. erianthum* on red blood cell (RBC) membranes stabilization was carried out in order to establish its anti-inflammatory potentials. The ethanol extract exhibited and provided highest protection against induced lyses and all the fractions and the crude ethanol extract showed dose dependent membrane stabilizing activity across the concentration ranges. The mode of response of the erythrocyte was biphasic. This was followed by ethyl acetate fraction and the mode of response of the erythrocyte was monophasic. Hexane fraction gave the least membrane stabilizing potential of all the fractions. The results indicated that all the fractions contained principles that protect and stabilize the erythrocyte effectively. The activities of the crude ethanol extract and that of ethyl acetate fraction were higher than the standard drug (diclofenac) used, even at lower concentration ranges. Moreover, the stabilization of lysosomal membrane is crucial in reducing or limiting the inflammatory response by preventing the release of the activated neutrophil, which can cause tissue damage upon extra cellular release (Oyedapo *et al*., 2004). Since erythrocyte membrane is analogous to the lysosomal membrane, its stabilization means that the extract may stabilize the lysosomal membrane too.

Liver plays a major role in metabolism and has a number of functions in the body which includes glycogen storage, decomposition of red blood cells, plasma protein synthesis, and hormone production, metabolism of xenobiotics and excretion of waste materials. Most injected agents pass through the liver before entering the general circulation (Matoni *et al*., 1993). Kidneys on the other hand, remove waste products, many of which are toxic, from the blood and also play a major role in controlling blood volume, the concentration of ions in the blood, and the pH of the blood. The kidneys are also involved in the control of red blood cells production and vitamin D metabolism. Liver damage could be confirmed by changes in the activities of hepatic enzymes in serum or plasma by their increased or decreased synthesis, released from damaged cells and extra-hepatic tissue (Chawla, 1999). Significant changes in the activities of plasma and liver albumin, bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels are indices good for detecting liver damage (Boelsterli, 2003). Chronic exposure of kidney to lead may cause nephrotoxicity characterized by glomerular sclerosis, interstitial fibrosis and proximal tubular nephropathy (ATSDR, 2007).

In the present study, oral administration of lead (10 mg/kg body weight) caused a marked decrease in percentage change in weight of lead-treated groups as compared with that of controls and extract alone.

Plasma creatinine concentration was significantly high in group treated with lead alone. Bazari (2007) reported that high creatinine level than normal might be due to kidney dysfunction while lower than normal levels indicates late muscular dystrophy and myasthenia gravis. The changes observed in plasma creatinine levels of rats treated with lead alone may suggest kidney damage. There was significant elevation in the plasma urea activities of the rats treated with lead alone which is an indication of renal impairment (Murray *et al*., 2003). The elevation in the plasma urea level might probably be due to impairment in the excretory function of the kidney possibly as a result of ingested lead.

There was significant decrease in the levels of kidney total protein in pre-treatment and positive control groups as compared to other groups. Measurement of total bilirubin includes both unconjugated and conjugated bilirubin. High levels of total bilirubin in lead-treated groups as compared to other groups were observed occasioned by the treatment with lead which suggests inability of the liver to metabolize bilirubin further confirming liver dysfunction, which might have been caused by haemolysis of red blood cells (Chawla, 1999).

Albumin is the major protein of the plasma and is responsible for the transportation of the fatty acids and bilirubin through the bloodstream to the liver. The synthesis of albumin is depressed in a variety of diseases, particularly those of the liver (Murray *et al*., 2003). Since albumin levels in group treated with lead alone were abnormally higher than other groups, it means that the transportation of materials within the blood stream might have been affected as well as the liver integrity.

There was a decrease in both the liver and plasma total protein concentrations in lead treated rats compared with control rats. It could be inferred that significant increase in plasma total protein levels as can be seen in intervention groups (i.e. groups D through G, table 3.11) might be the means through which the treated rats compensated for the production of enzyme or protein lost as a result of tissue necrosis or means to meet increase demand to detoxify the lead toxicity. This observation was in line with the results of Hassanin (1994) and El-Zayat *et al*. (1996) who found a decrease in hepatic total protein content in response to lead intoxication. They attributed that to a decreased utilization of free amino acids for protein synthesis. Pagliara *et al*. (2003) showed that lead-induced liver hyperplasia followed by apoptosis mediated by oxidative stress in kupffer cells. Also, it induced apoptosis in the germ cells within the seminiferous tubules (Adhikari *et al*., 2001) and in rod photoreceptors (He *et al*., 2003). Iavicoli *et al*. (2001) demonstrated that the induction of apoptosis contributes to the lead-induced inhibition of cell proliferation in rat fibroblasts. While the observed marked decrease in liver total protein concentration in group treated with lead alone could be attributed to inability of protein synthesizing machinery to be able to function properly as occasioned by higher concentration of lead in lead treated group. The moderate decrease observed in the levels of plasma total protein (table 3.11) might be a deliberate insult on the liver since all conditions that affect the liver, such as hepatitis, etc will cause the protein level in the blood to decrease. This is due to the fact that the liver is the organ that is responsible for producing protein.

In the study, the plasma alanine aminotransferase (ALT) activity increased significantly ($p \leq 0.05$) in group treated with lead alone. Change observed in plasma transaminase activities in

the treated rats is speculated to be a reflection of liver damage occasioned by ingestion of lead. The post-lead treated group favourably competed with the positive control (vitamin E). Similarly, there was a significant increase in plasma AST in group treated with lead alone than any other group. It was also seen here that the post-lead treated group favourably competed with the positive control group. Significant changes in the activities of plasma and liver aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels are indices good for detecting liver damage (Boelsterli, 2003).

The histology evidence from the study indicated the occurrence of a progressive degeneration of the liver and kidney tissues most especially in group treated with lead alone. However, histological study of the kidney and liver showed well arranged uriniferous tubules and hepatic sinusoids with distinct interstitial in control rats. Although, there were histology abnormalities; varying degree of cellular degeneration within the renal and hepatic tubules in rats challenged with lead which was obvious in rats treated with lead alone. There was also marked destruction of hepatic cells and uriniferous tubules in rats treated with lead and ethyl acetate fraction of *Solanum erianthum* with little or partial restoration of the peripherial tissues. This damage was characterized by necrosis and destruction of the uriniferous and hepatic tubules indicating the reduced ability of the kidneys to function properly to eliminate water-soluble chemicals that are removed from the blood by the process of reverse filtration, with complete restoration in post lead and positive control (vitamin E) treated groups.

In conclusion, marked degeneration of liver and kidney tissues could be attributed to ingestion of lead (10 mg/kg body weight) which were recovered by the use of the plant extract in reversing the altered biochemical variables that could be useful in enhancing endogenous antioxidant levels as can be seen in the histology evidence that confirmed the protective role of *S. erianthum* on various lead-induced histopathological injuries in the rat liver and kidney. Hence it could be surmised that the ethyl acetate fraction of *S. erianthum* exhibits very high mitigating potentials in lead associated nephrotoxicity and hepatotoxicity.

Nevertheless, further investigations on this fraction are hereby suggested to decode the specific phytochemical constituent(s) responsible for the antioxidant activities of the plant.

Financial support and sponsorship: Nil.

Conflict of Interests: There are no conflicts of interest.

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How to cite this article:

Agbi AJ, Badiora AS, Areola JO, Babalola OO. Protective Effects of *Solanum Erianthum* D. Don Leaf Extract on Lead-Induced Toxicity in Adult Wistar Rats. J App Pharm Sci, 2016; 6 (10): 113-123.