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Talinum trangulare (Waterleaf) Stem Extract Has Reno-Hepato Protective Potentials than Ameliorative Effects on Acetaminophen Toxicity in Sprague-Dawley Rats

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Abstract

Acetaminophen intoxication is not uncommon globally while herbs are increasingly utilized to counter many synthetic adverse drug reactions over time. It is against this concept that we investigated renal and hepatic protective/ameliorative potentials of *Talium trangulare* stem extract on acetaminophen toxicity in rats. In-bred Sprague-Dawley rats of both gender, 12-15 weeks old and weighed 188-202g were grouped (A to F, n=4) in a sanitized facility, wire-gauzed, and bedded with wood-dust. They adapted to facility temperature (25 ± 5ºC), humidity (45± 5%) and photoperiods (12:12hr day/night) for 14 days. Pelletized feeds® and water were provided while animal weights were measured before and after treatment. Control (group A) was untreated; group B administered 500 mg/kg b.w. *T. trangulare L. extract* while, Group C received 500 mg/kg b.w. acetaminophen. Group D treated with 500 mg/kg b.w. extract and 500 mg/kg b.w. acetaminophen. Group E administered 500 mg/kg b.w. acetaminophen and 500 mg/kg b.w. extract. Group F administered mixture of 500 mg/kg b.w. and 500 mg/kg b.w. acetaminophen. All rats were treated by oral intubation for 40 days at two days interval and sacrificed by cervical dislocation. Blood sample was collected through cardiac puncture to determine kidney and liver functions while related organs were processed histologically. Group C, E and F showed gross reductions in weight but marked in group C. Histopathology revealed varying degrees of deleterious effects in group C with abnormal hepatic and renal parameters ($p \leq 0.05$). In conclusion, the present extract has protective potentials against acetaminophen intoxication in renal and hepatic cells than reversal effects.

Keywords: Acetaminophen, *T. trangulare,* waterleaf stem, renal and hepatic toxicity

Introduction

The liver remains the major site for metabolism and excretion with a wide range of functions, including detoxification, protein synthesis, and biochemical productions that are necessary for digestion (Angelico *et al.* 2005; Ahsan *et al.* 2011; Kalantari *et al.,* 2015). The kidneys in turn are vastly specialized organs with a primary function of maintaining the composition of the body fluids at a balanced level including removal of toxic and excreted wastes substance from the body (Odigie *et al.,* 2015). Kidney and liver diseases have become so rampart these days such that they result in avoidable loss of human lives. Renal toxicity and hepatocellular defects due to indiscriminate consumption of medicaments appeared to be increasingly obvious in our society (Bhawna and Kumar, 2009). Aside numerous medications that are thought to be abused constantly are across the counter medicines, and paracetamol has been reported to be a leading medication that is constantly being abused as non-prescription drugs (Odigie and Achukwu, 2015). It is well tolerated and interacts well with other medications, and is mostly conjugated with glucuronic acid and sulfate producing water-soluble and non-toxic metabolites (Ita *et al.,* 2009). Acetaminophen overdose often results in acute centrilobular hepatic necrosis in humans and animal model

(Ita *et al.,* 2009). On the other hand, natural medicine has been an important source of hepatic and renal protective drugs involving different herbs in single or mixed form and its derivative (Ram, 2001). It was estimated that far above 700 single or mixture of herbs derivative have been used as constituents in tablets and capsules from different plants that forms the basis for clinical medications (Ram, 2001). Despite numerous herbal products in circulation, Talium triangulare (Jacg) Wild, popularly known as waterleaf has been reported to have varying medicinal properties and constitute a vital part of vegetable meals in many household diets globally (Enete and Okon, 2010). Waterleaf stem, which is the major focus for the present study appears thick and hairy with shining green coloration, and retains terminal inflorescences measuring between 7cm to 15cm in length (Aja *et al.,* 2010). *T. triangulare* has been reported to have potentials capable of relieving stomach aches and can readily be used as purgative, stooling and gastro-intestinal disorders and for managing varying heart diseases, stroke and excess body fat (Aja *et al.,* 2010). In many scientific studies, waterleaf was reported to inhibit proliferation of cancerous cells, reduce tumors growth, combat insomnia, and possess the ability to demonstrate cerebral-protective plausibility (Enete and Okon, 2010). *The* stem, root and leaf have healing properties and are reportedly used in the treatment of internal organs (Swarna and Ravindhran, 2013). After reviewing the potentiality of *T. triangulare* coupled with the devastating effects posed by paracetamol poisoning world-wide, it becomes imperative to deduce whether this plant can protect internal organs or ameliorate paracetamol offensives bearing in mind that renal and hepatic cells are the first point of contact for drugs interaction after ingestion (Odigie, 2013). It is against this evidence that we investigated *T. triangulare* stem protective potentials/ameliorative properties against acetaminophen induced toxicity in renal and hepatic cells and tissues in rats knowing that the livers and kidneys are exposed to acetaminophen intoxication regularly.

Materials and Methods

Collection of Plant materials

Samples of fresh plant of *T. triangulare* were uprooted from Obazuwa community in Benin City; Edo State where the plant was cultivated in abundance. Plant was identified and authenticated by an expert taxonomist in the Department of Plant Biology and Biotechnology, Faculty of Life Science, University of Benin. It was assigned a voucher number: UBH_T381 while a sample was deposited at the herbarium section of the Department.

Preparation and Extraction Process

The stem of *T. triangulare* were detached from the stalk and washed thoroughly with tap water. It was shade dried under normal atmospheric condition for a period of two weeks. The dried stem was pulverized into uniform powder using a house hold blender and sieved to obtain a pure fine powdered particle weighing 442.5g. The aqueous extract was prepared after measuring 440g of fine powdered particles with a weighing balance into a sterile conical flask. One and half liter (1.5L) of water was measured and added to it with the aid of a standard measuring cylinder. Heat was applied for 3minutes using the household gas cooker. The heated, boiled mixture was transferred to the GFL shaker (No 3017 MBH, Germany) and mechanically agitated for 10 hours. The mixture was filtered using Whatman no 1 filter paper while the filtrate evaporated with a Vacuum Rotary Evaporator under reduced pressure at 50°C. The yield was concentrated into uniform paste with the aid of a Bucchi Rotavapor and stored in a desiccator prior to use.

Drug Purchase and Preparation

Acetaminophen was obtained from a government approved pharmaceutical stores opposite University of Benin Teaching Hospital, Ugbowo Road, Benin City; Edo State with NAFDAC Registration Number: 04-0411. Manufacturer: Emzor Pharmaceutical Industries Ltd. Block A, Aswani Market Road, off Oshodi-Apapa Express Way, Isolo; Lagos. Acetaminophen was diluted to appropriate concentrations using commercially purchased UNIBEN table water with NAFDAC no 01-4597. It was dissolved in the table water at 70°C, and then cooled to 37°C for administration.

Lethal Dose Determinations (LD_{50})

Acute toxicity study (LD_{50}) was conducted on waterleaf stem extract using an adaptation to Lorke's method by Ogeyemhe *et al.* (2020) to ascertain the lethal dose that will serve as a guide in administering the required dosage to animals. On the other hand, chronic toxicity study was carried out on acetaminophen using the same method earlier described. Twenty rats were selected into six groups and a control (n=3), while extrapolated doses from previous studies were administered: 400 mg/kg b.w., 800 mg/kg b.w. and 1200 mg/kg b.w. daily for 12 weeks (waterleaf) and 24 weeks for acetaminophen. All rats were closely observed for abnormal signs within the initial 4 hours after treatment (water leaf and acetaminophen) followed by 24 hours sporadic observations.

Experimental animals

Twenty-four in-bred Sprague-Dawley male and female rats of 12-15weeks old weighing 188 - 202 g respectively were selected according to body weights and assigned to six groups of 4 rats per cage labeled group A to F. Rats were housed in a sanitized wire gauze cages with wood-dust underneath. Animals acclimatized for 14 days in an environment with temperature (25 ± 5ºC), humidity (45± 5%) and day/night periodicity (12hr/12hr) with adequate provision of pelletized feeds and drinking water *ad libitum*. Policies outlined in the Guide for the Care and Use of experimental animals, published by the US National Institute of Health (NIH Publication No. 85-23, revised 1996) where followed appropriately in this study.

Experimental Measurements

All experimental rats before and after experimentation were weighed with a digital Mettler weighing balance (Mettler Toledo Type BD6000, Mettler-Toledo GmbH, Greifensee, Switzerland). Differences after in reference to weight before treatment were calculated per group. Animals were monitored sporadically on daily basis for physical signs of abnormality both in behavior and activity for the entire period.

Experimental Protocol

Group A were untreated for 40 days

Group B served as negative control and received 500 mg/kg b.w. *of extract for 40 days*

Group C served as positive control administered 500 mg/kg b.w. of acetaminophen for 40 days.

Group D took 500 mg/kg extract for 20 days and 500 mg/kg b.w. acetaminophen for 20 days

Group E administered 500 mg/kg acetaminophen for 20 days and 500 mg/kg extract *for* 20 days.

Group F received a mixture of 500 mg/kg extract and 500mg/kg acetaminophen for 40 days.

All rats were treated by oral intubation for 40 days at two days interval (Table 1). At termination of experiment, all animals fasted overnight and were sacrificed by cervical dislocation.

Collection of Blood Samples

Four (4) ml of blood was collected through cardiac puncture and emptied into a sterile 5 ml plain container without anticoagulant with tab gel and centrifuged (Broadbent, UK) at 3000 rpm for 5 minutes to obtain the serum content to determine the biochemistry profile (kidney and liver function test) of animals and was stored at -20°C until it was needed for biochemistry tests.

Liver Function Test (LFT)

Actions of hepatic enzymes: Serum Aspartate and Alanine Transferase were assessed using the method described by Reitman and Frankel (1957) in which 0.2 ml of serum was measured with a micropipette and added to 1 ml of phosphate buffer, which contained a substrate. The mixture was incubated for 30 min peculiar to alanine aminotransferase (ALT) and 60 min for aspartate aminotransferase (AST). This was conducted at 37°C, before dispensing 1 ml of dinitrophenylhydrazine into the mix and again incubated for another 20 minutes at room temperature. Thereafter, 10 ml of 0.4% sodium hydroxide was dispensed into the mix, which was properly mixed for 5 minutes and was read spectrophotometrically at 550 nm against sample blank. AST and ALT values were calculated using a sequence of standardized curves.

Kidney Function Tests

Serum electrolyte (sodium, potassium, bicarbonate and chloride) levels were measured with the chemistry analyzer (Erba Chem 5X Analyzer, India). Serum creatinine was analyzed using commercially available kits (HUMAN Diagnostics, Germany) and read with the spectrophotometer (Buck Scientific 210 VGP, China) at 490 nm wavelength whereas; urea was estimated using the urease-Berthelot reaction, measured at 570 nm wavelength.

Grossing and Histopathology

Kidney and liver were excised, washed in normal saline, grossed accordingly and samples taken were preserved in 10% neutral buffered formalin for histopathology processing using an automatic tissue processor for dehydration, clearing, and impregnation, including embedding with an embedding machine. Tiny tissue sections were cut at 3-5microns with a digital rotary microtome (German hertz mode) to produce serial ribbons. Stained sections were according to H&E techniques while slides were examined using Swift(R) Binocular Microscope in which a lighting system was in-built to white films through an Olympus photomicroscope® (Opticshot- 2; Nikon, Tokyo, Japan) at x400 magnification.

Data processing and analysis

Data analysis was done using IBM Statistical Package for Social Sciences (SPSS) version 20.0 (Inc Chicago, Illinois, USA). Data were analyzed using ANOVA while outcome was presented in Means ± S.E.M. Duncan post hoc test was used for pairwise comparison between groups while significance was determined at ($p \leqq 0.05$).

Results

All rats in group C that received only acetaminophen solution were observed to show behavioral signs of acute toxicity like protracted sleep, lifelessness and limited activities. Body weight showed gross reduction in groups C, E and F treated animals but was particularly marked in group C (198.48 ± 1.2 reduced to 181.23 ± 1.1). Rat's weights in group B and D were slightly elevated compared to group A (Table 1). Grossly, organs showed no variation in colour, size and consistency except rats in group C. Mean weight of rat's liver in group (A) 0.45±1.1g (B) 0.45±1.3g (C) 0.43±9.2g (D) 0.45±2.6g (E) 0.45±1.1g and (F) 0.44±6.1g were within normal sizes but with little shrinkage in group (C). Cut surfaces of the liver was smooth and shiny (Group A) with reddish brown color. The cut surface for group B was also smooth like control group A but appeared glistening while Group C slightly differed from A and B with dull appearances. Group D was reddish and showed less glistening compared to group B. Groups E and F showed reddish dull coloration with rough patches particularly in group F. All kidney tissues (left and right) appeared similar in colour, weight, size and consistency except for the left kidney, which was slightly bigger in size; otherwise, all kidneys matched with the control. Renal function test revealed that all parameters (K, Na, CL, HC03, urea and creatinine) were within normal range. Though parameters for group C treated with acetaminophen alone was significantly increased compared to controls signaling renal toxicity (Table 2). On the other hand, parameters for liver function test (TB, CB, TP, ALB, AST, ALT and ALP) were normal and significant across board ($p \leqq 0.05$) using one-way Anova while values in Group C were out of range indicating hepatotoxicity (Table 3). Histopathology findings revealed varying degrees of deleterious effects in animals marked group C showing features like: focal hepatocyte necrosis and severe vascular congestion in the liver while the kidney showed moderately active interstitial congestion (Figure 3 and 9). However, animals in group F were slightly affected with moderate congestion within the central canal of the liver (Figure 6). Other results are in keeping with normal histology of the liver and kidney respectively (Figure 1, 2, 4, 5, 7, 8, 10, 11 and 12).

Table 1: Toxicity Analysis of Animals Treated for 40 Days At 2days interval

Groups	Treatment plan	Mean weight before treatment	Mean weight after treatment	Weight loss /gain	Physical activities
A	0 ml/kg	189.25± 1.4	201.12± 1.1	↑	+
B	500mg/kg b.w extract	192.40± 1.1	206.60± 0.3	↑	+
C	500 mg/kg acetaminophen	198.48± 1.2	181.23 ± 1.1	↓	-
D	500mg/kg b.w. extract + 500 mg/kg acetaminophen	200.58± 0.3	205.17 ± 1.4	↑	±
E	500 mg/kg acetaminophen + 500mg/kg b.w. of extract	201.51± 1.3	193.30 ± 1.1	↓	±
F	500 mg/kg acetaminophen mixed with 500mg/kg b.w. extract	201.66± 2.4	195.17 ± 1.3	↓	±

Key: Increase in weight (↑); slight increase in weight (↑); slight weight loss (↓); Presence of activities (+); Intermediate activities (±); marked presence of activities (++); Absence of activities (-); severe weight loss (↓);

Table 2: Renal Test (Electrolyte and Urea/ Creatine) in Both Treated and Untreated Rats After 40 days

Indices	Group A	Group B	Group C	Group D	Group E	Group F	P-value
K	4.00±0.07	4.45±0.01	9.07±0.01*	4.45±0.01	4.07±0.01	7.91±1.68	0.006
Na	129.01±0.37	129.12±0.02	149.35±1.53*	129.12±0.02	130.35±1.53	133.20±3.25*	0.001
Cl	96.50±3.39	97.11±1.32	121.01±0.37**	97.11±1.32	98.01±0.37	101.35±1.53	0.006
HCO3	17.80±2.09	17.53±0.54	26.05±0.92*	17.53±0.54	17.00±0.91	19.00±0.91	0.002
Urea	23.09±0.01	22.07±5.09	40.90±0.05**	23.07±5.09	23.90±0.05	27.50±2.12*	0.001
Cr	0.39±0.07	0.39±1.042	0.49±1.32*	0.39±1.042	0.40±0.02	1.30±0.00	0.001

All values expressed as mean ± standard error of the mean for 4 rats per group with varying treatment plans Values with asterisk significantly varied at P ≤0.05 (One way Anova). Acetaminophen (aceta) Bicarbonate (HCO3); Chloride (Cl); Sodium (Na); Potassium (K). Extract = *T. triangulare*

Table 3: Liver Function Test (Enzymes) in Both Treated and Untreated Rats After 40 days

Indices	Group A	Group B	Group C	Group D	Group E	Group F	P-value
TB	0.11±0.07	0.10±1.23	0.23±0.00*	0.10±1.23	0.13±0.04	0.13±0.04	0.008
CB	0.07±0.04	0.07±0.04	0.13±0.00*	0.07±0.04	0.06±0.12	0.06±0.12	0.086
TP	4.55±0.35	4.73±0.35	11.40±0.28*	4.73±0.35	4.32±0.42	6.32±0.42	0.003
Alb	1.80±0.71	1.80±0.71	7.65±0.49*	1.80±0.71	1.93±0.80	3.93±0.80	0.244
AST	40.50±0.7	40.50±0.7	66.50±1.09	43.52±1.27	43.52±1.27	45.02±4.04	0.001
ALT	16.50±2.12	16.01±1.51	29.50±2.12**	16.01±0.72	16.72±0.01	18.72±0.01	0.041
ALP	19.03±1.41	19.22±0.91	33.00±1.07*	20.08±0.22	19.22±0.91	21.22±0.91	0.002

All values expressed as mean ± standard error of the mean for 4 rats per group with varying treatment plan Values with asterick significantly varied at $P \leq 0.05$ (One-way Anova). Acetaminophen (aceta) total bilirubin (TB), albumin (Alb), conjugated bilirubin (B), aspartate transaminase (AST), alanine transaminase (ALT), total protein (TP), alkaline phosphatase (ALP).

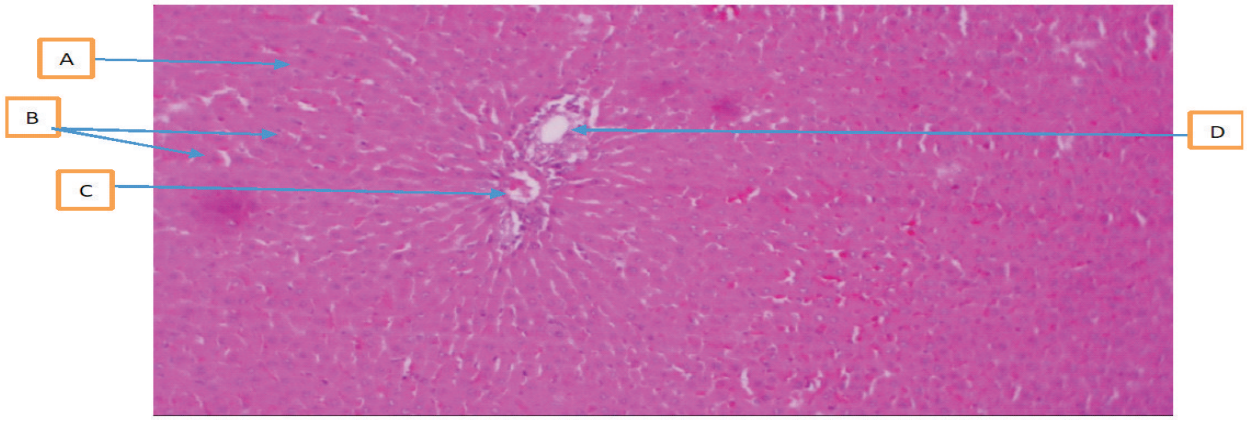

Figure 1: Group A (control): Rat's liver composed of A- hepatocytes, B- sinusoids, C- portal vein and D- bile duct (H&E x100)

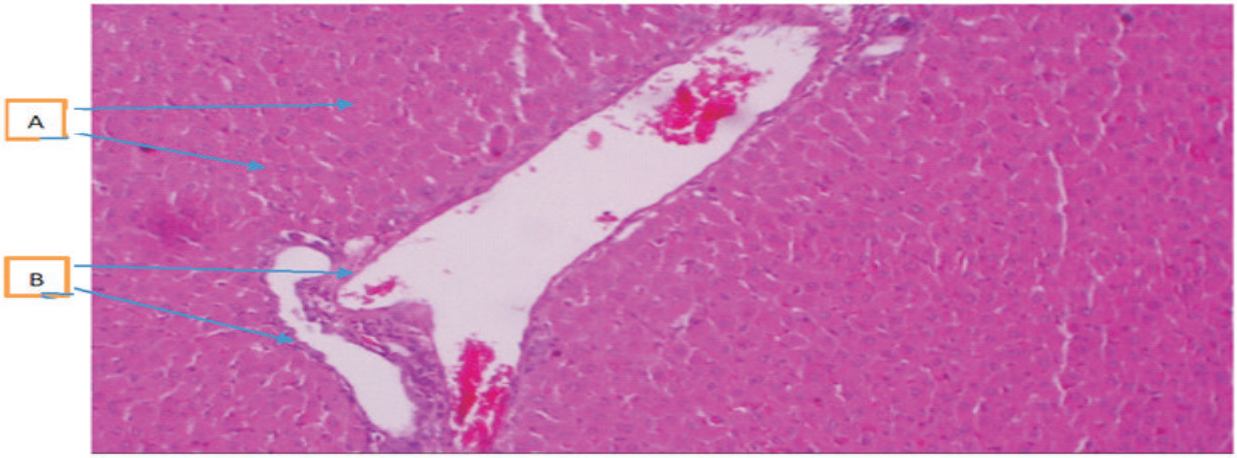

Figure 2: Group B (negative control): Rat's liver administered 500mgkg b.w. extract showed; A- normal hepatocytes and B- normal vascular architecture (H&E x100)

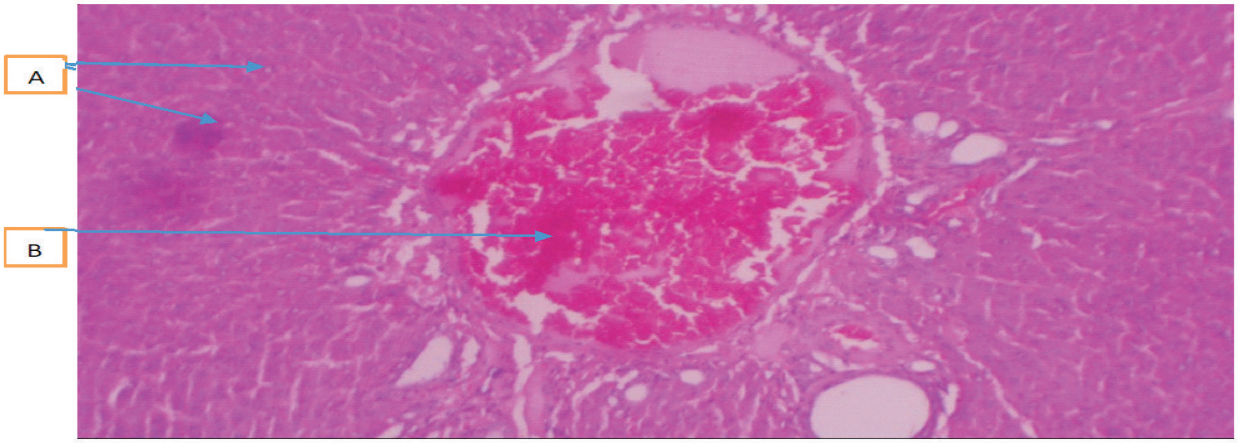

Figure 3: Group C (positive control): Rat's liver administered 500mg/kg b.w. acetaminophen showed A- fairly normal hepatocytes and B- severe vascular congestion (H&E x100).

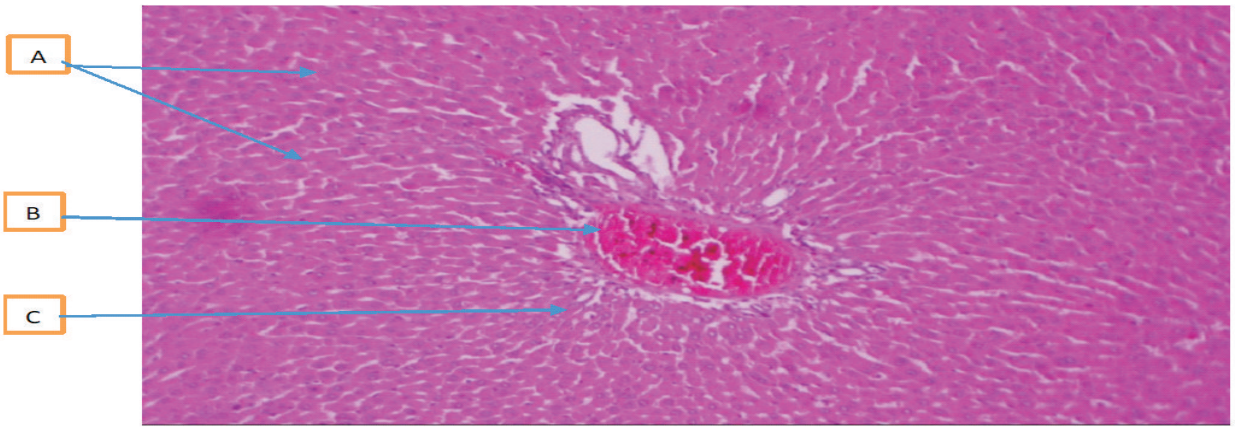

Figure 4: Group D: Rat's liver administered 500mg/kg b.w. extract for 20 days followed by 500mg/kg b.w. acetaminophen for another 20 days showed; A- normal hepatocytes and B- normal vascular architecture (H&E x100).

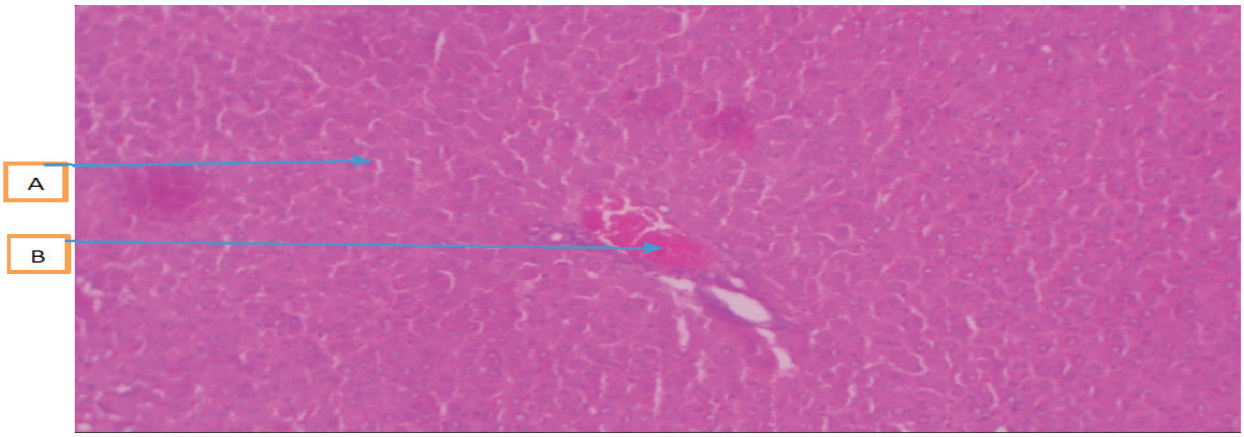

Figure 5: Group E: Rat's liver administered 500mg/kg Acetaminophen followed by 500mg/kg b.w. extract showed; A- fairly normal hepatocytes and B- mild active congestion (H&E x100).

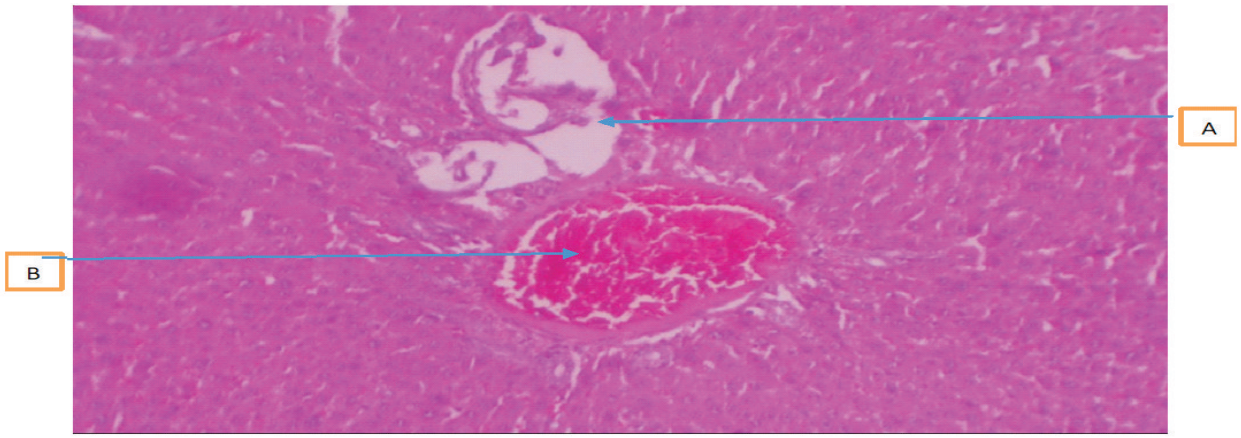

Figure 6: Group F: Rat's liver administered mixture of 500mg/kg b.w. extract with 500mg/kg b.w. acetaminophen showed A- focal hepatocyte necrosis and B- moderate congestion (H&E x100)

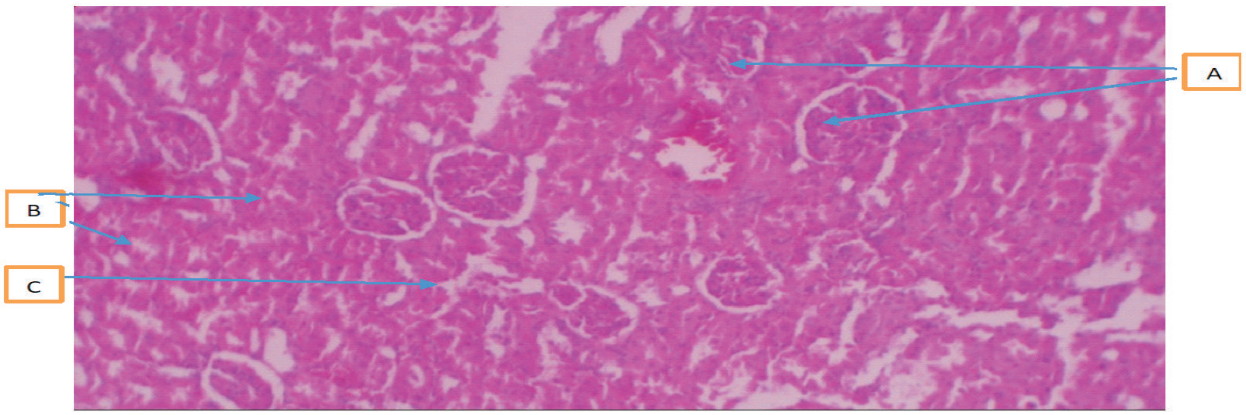

Figure 7: Group A (control): Rat's kidney composed of A- glomeruli, B- tubules and C- interstitial space (H&E x100).

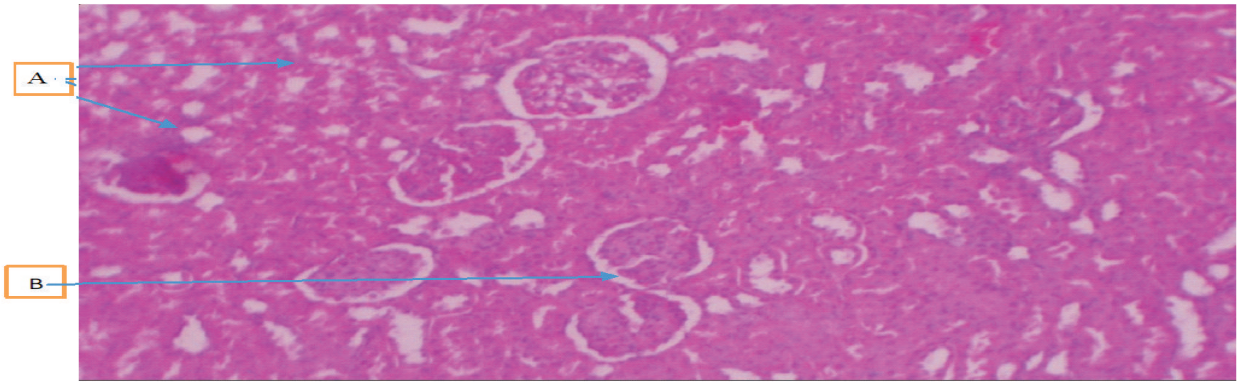

Figure 8: Group B (negative control): Rat's kidney administered 500mg/kg b.w. extract showed; A- normal tubules and B- glomeruli (H&E x 100).

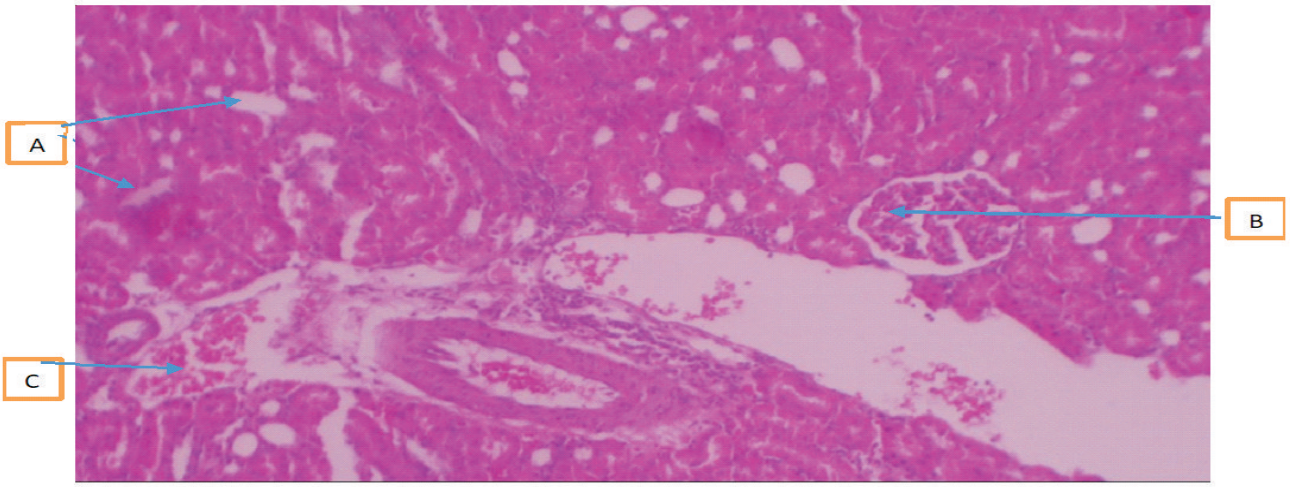

Figure 9: Group C (positive control): Rat's kidney administered 500mg/kg b.w. acetaminophen only showed; A- normal tubules, B- glomeruli and C- moderately active interstitial congestion (H&E x100).

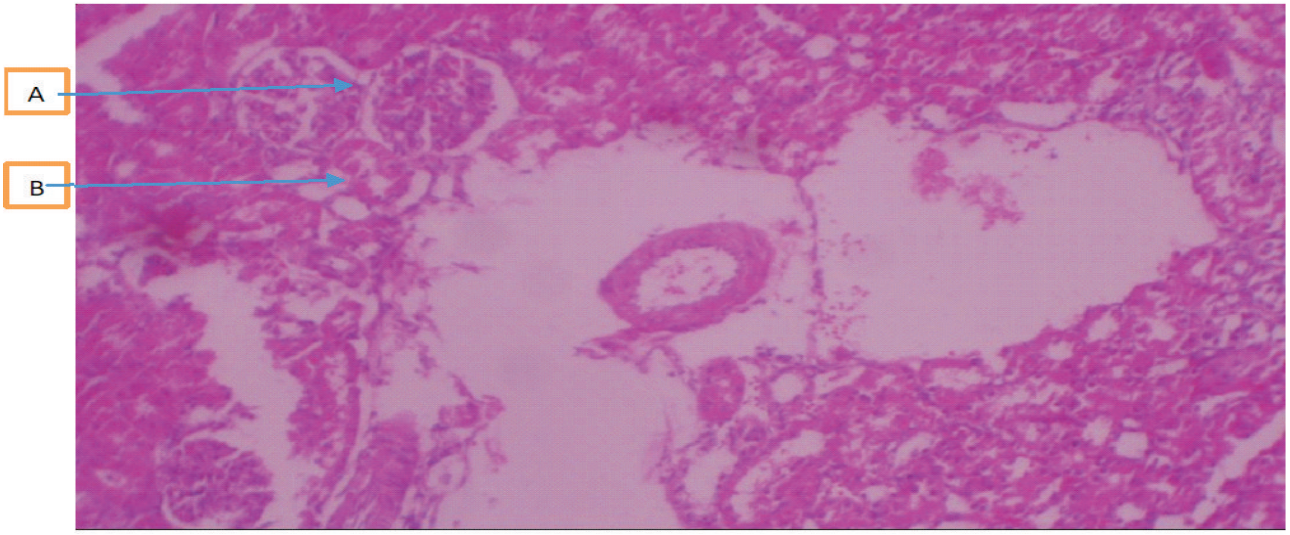

Figure 10: (Group D): Rat's kidney administered 500mg/kg b.w. extract followed by 500mg/kg b.w. acetaminophen showed; A- normal glomeruli and B- tubules (H&E x100).

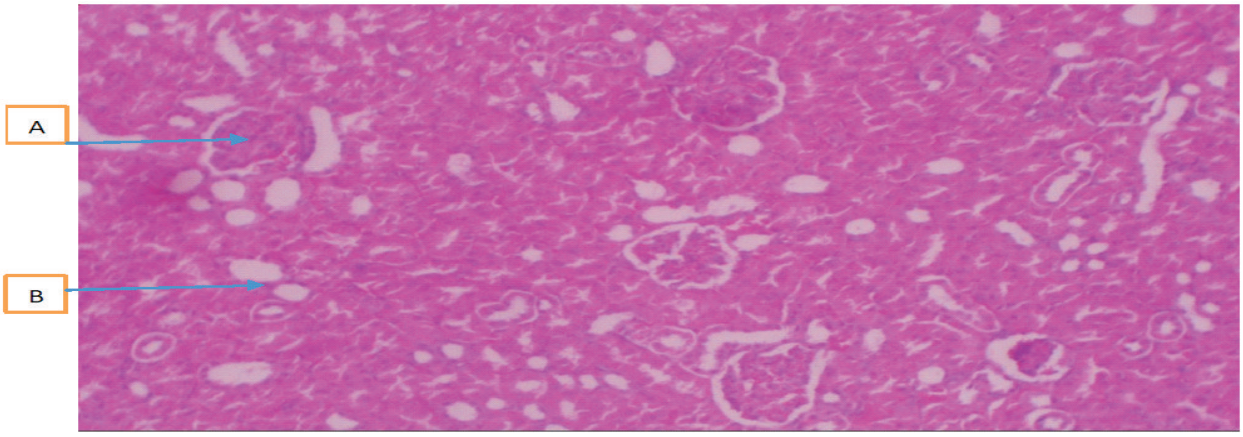

Figure 11: Group E: Rat's kidney administered 500mg/kg acetaminophen followed by 500mg/kg b.w. extract showed; A- normal glomeruli and B- tubules (H&E x100).

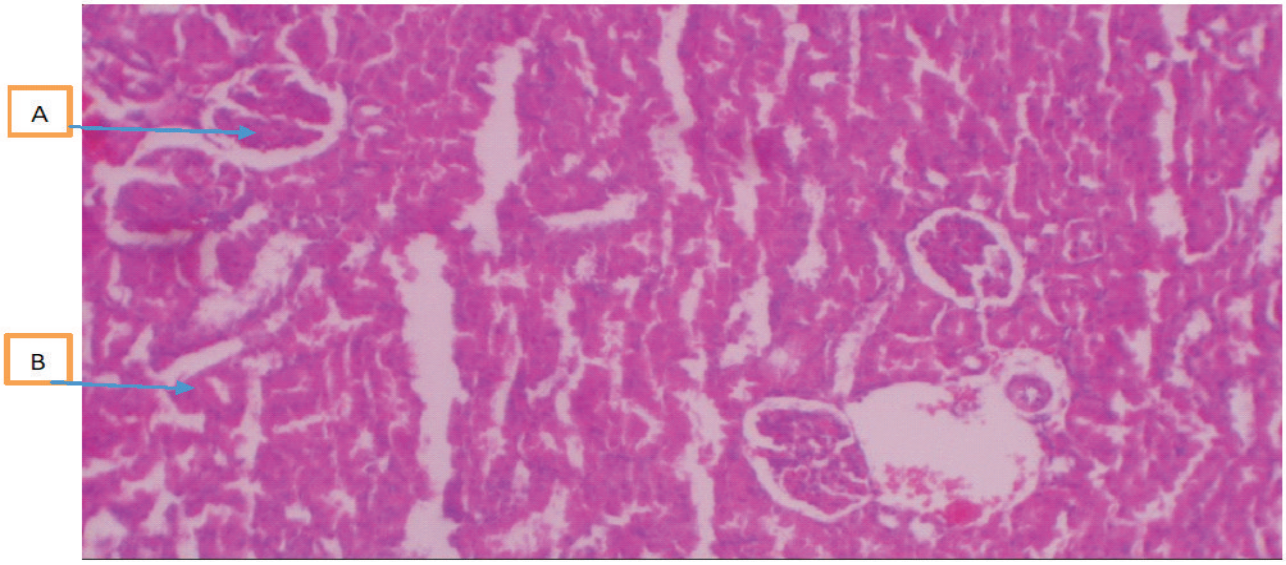

Figure 12: Group F: Rat's kidney administered mixture of 500mg/kg b.w. extract with 50mg/kg b.w. acetaminophen showed A- normal glomeruli and B- tubules (H&E x100).

Discussions

Herbal preparations are attracting the interest of researchers investigating their potentials with pharmacological activities for treating varying diseases (C´assia *et al.,* 2013). Meanwhile, protection against acetaminophen induced toxicity has been used as a test for a potential hepatoprotective agent by several investigators (Singh and Handa, 1995). An earlier study suggests that *T. trangulare* has different biological activities including hepatoprotective effects (Eyo *et al.,* 2001). This particular effect was demonstrated in this study considering the results from histopathology and liver enzymes (Table 3). Histopathology showed significant activity of *T. trangulare* stem extract as evident in the severity of damages observed only in acetaminophen treated animals (group C). Attenuating effects of the present extract demonstrated that it possesses hepatocellular mitigating properties in the face of acetaminophen intoxication, which corroborates the report by Eyo *et al.* (2001). This observation however buttresses a report, which suggests that *T. triangulare* can protect the liver against hepatocellular destruction traced to oxidative stress (Adefolaju *et al.*, 2008). This study collaborates the pharmacognosis claims accorded to *T. triangulare's ability to withstand intoxicants directed at the liver and kidney (*Swarna and Ravindhran*, 2013). The reasons may be partly attributed to abundant phytochemical properties embedded in the plant's stem, which c*onsisted of primary and secondary metabolites collectively assisting in general protection of organs responsible for drug metabolism and elimination. Sharma *et al.* (2009), reported that *T. trangulare* stem is rich in proteins, carbohydrate and amino acids, which are primary metabolites. Swarna and Ravindhran*, (2013)* revealed that primary metabolites are actively involved in three basic sustenance of life: growth improvement, reproductive processes and systemic development arising from the cellular level. On the other hand, secondary metabolites: saponins, steroids, tannins, terpenoids alkaloids, and flavonoids, *which are vastly distributed in varying parts of T. trangulare including the stem are responsible for its* pharmacological effects (Kokate 1997; Swarna and Ravindhran*, 2013)*. However, specific functions of secondary metabolites have been reported to include defense mechanism against external influences and bacteriological invasions (Otto *et al.,* 1999). From the ongoing, we realize that the healing activities of *T. trangulare* stem extract as medicinal intervention may just be as a result of the existence of numerous secondary metabolites capable of defending the kidneys and livers from external stimuli (Shanthi *et al.,*

2012). The above claims have been summarily demonstrated in this study going by positive results obtained via appreciable hepatic and renal function test parameters including normal histology respectively, which are consequent to *T. trangulare* hepato and reno protectiveness. This regularity has been established particularly in groups administered *T. trangulare* extract alone (group B), and those initially administered *T. trangulare* extract before consuming acetaminophen (group F) compared to the other treatment groups. This study further showed that *T. trangulare* validly protect the liver and kidney if administered regularly, which is to say, consumption must be prior to intoxication otherwise the attenuating effects are not excellently pronounced unlike the protective actions, which corroborate the report by Liang *et al.* (2011). It was also observed that the pathological effects indicated in this study were particularly attributed to the liver alone compared to the kidneys from the same animals in group C that remained unaffected after treatment. This observation may relate to the functional ability of the kidneys, which majorly eliminate drugs and its metabolites through physiological processes vastly involving glomerular filtration, followed by proximal tubular secretion, before distal tubular reabsorption of the drugs (Miners *et al.* 2010; Miners *et al.* 2011). It also accounted for the reason in which the liver was severely affected leaving the kidneys undistorted because the liver is always at the receiving end as it main function is drug metabolism (Knights *et al.,* 2013). This particular observation has been demonstrated previously in experimental rats (Odigie and Achukwu, 2015; Kalantari *et al.,* 2015). Therefore, this study suggests that oral intake of *T. triangulare* aqueous stem extract has strong protective potentials against acetaminophen intoxication in renal and hepatic cells. We conclude that the present extract possesses reduced potentiality in overriding acetaminophen injuries and thus acts as a protective agent to renal and hepatic cells than an ameliorative agent. We however recommend that waterleaf should be a major part of human diets as it is capable of protecting internal organs from unexpected paracetamol poisoning.

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Author's Contributions
Authors named in this paper declare that the research was undertaken solely by them and that all authors participated fully in the work to warrant authorship. We read and approved the final draft copy of this manuscript. Dr. E.B. Odigie is to communicate with the editorial team of SJMLS from this point onward.

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