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Assessment of the Sub-acute Toxicity Effects of *Thaumatococcus danielli* on the Liver and Kidney of Male Wister Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

This study investigated the toxic effect of aqueous extract of *Thaumatococcus danielli* leaves using morphological and functional changes in the liver and kidney of *Wistar* rats as indicators.The extract was orally administered to three groups of six animals (n=6) B, C, D at doses of 1.414 g/kg, 2.828 g/kg and 4.242 g/kg body weight respectively whilecontrol group (group A) received 2ml of distilled water for 28 days. Body weights were measured weekly throughout the experimental period. At the end of the experiment, organ weights, activities of alanine and aspartate amino transaminases, serum creatinine and urea levels were analysed using standard protocol. Additionally, liver and kidneys were excised in the animals and processed for morphological examination.

Dose dependent and significant ($P<0.05$) increase in body weight, activities of Alanine and Aspartate amino transaminases, serum creatinine and urea levels, as well as significant decrease in organ weight was observed in groups C and D. Distortion, congestion of central vein and proliferation of collagen fibres were observed in the liver while distorted glomeruli, bowman capsule, dilated renal tubules with presence of necrotic cells were observed in the kidney of group C and D. These parameters in group B showed no significant ($p>0.05$) difference compared with the control

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group. No variation was observed in the renal and liver histology of the group B when compared with the normal control.
From this study,the aqueous leave extract of*T. danielli*was only toxic at 2.828 g/kg and 4.242 g/kg body weight. Thus, the use of the leaves especially in food wrapping will be safe at low dose since the toxic dose is unlikely for food wrappings.

Keywords: Thaumatococcusdanielli; nylon; food; wrap; kidney; liver; function tests; morphology.

1. INTRODUCTION

Thaumatoccocus danielli (Benn.) Benth which belongs to the family of Marantaceae, is a plant species from West Africa known for being a natural source of thaumatin, an intensely sweet protein which is of interest in the development of sweeteners [1]. It is a forest under-storey herb in the Marantaceae native to equatorial Africa, where its leaves are locally used to wrap food and as material for roofing and woven mats [2]. It grows throughout the hot, humid, tropical rain forest and coastal zone of West Africa [3-14]. The sturdy leaf petioles are used as tools, building materials and as wrapper for food (Chinedu, 2014). The fruit of the plant is used as a laxative, the seeds as an emetic and for treating pulmonary problems [15]. The leave sap is used in traditional medicine as antidote against venoms, stings, and bites [16-17]. Leave and root sap are used as sedative and for treating psychiatric problems [28]. Large quantities of the fruits are collected by local people to sweeten over fermented palm wine and sour foods [29]. The plant is significant such that the leaves have locally been used for wrapping and boiling foods in Ghana and Nigeria [30,31-42]. The antibacterial, antioxidant, and insecticidal activities of essential oil of the plant have been reported (Adeola *et al.,* 2015; Adeyemi *et al.,* 2014; Anthony *et al.,* 2013). Acute toxicity studies revealed that the LD_{50} of *T. danielli* is greater than 5000 mg/kg whereas the extract demonstrated nephro protective effects in streptozotocin induced diabetic rats [43]. Fadahunsi et al. [44] extensively reviewed various pharmacological activities of *T. danielli* and showed its potentials in providing benefits to human health. Because *T. danielli* is widely and effectively used by the locals for wrapping and preservation of food, it could be a replacement for nylon which is known to have carcinogenic effect. In this current study, we evaluated the safety of the aqueous leaf extract of *T. danielli* in rats by determining the effects on the body weight, organ weights, liver, and kidney function after sub-acute exposure.

2. METHODOLOGY

2.1 Experimental Animals

Twenty-four (24) adult Male Wistar rats (200-250g) were acclimatized to the experimental room having temperature 25 ± 1^0C, controlled humidity conditions (65%) and 12:12h light; Dark cycle. The experimental animals were housed in standard plastic cages, fed with standard diet (pelletized grower mash) and water. All experimental procedure and materials were approved by the Animal care and use committee of College Medicine Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.

2.2 Plant Collection

Freshly harvested leaves of *T. danielli* was collected around Sabo area Ogbomoso, Oyo State and was identified at the Biology Department (LAUTECH) Nigeria for authentication with voucher No. LHO 407. The collected leaves were air dried at the room temperature ($25\text{-}30^0$C) for four weeks before extraction. The aqueous extract was prepared as reported by [45].

2.3 Preparation of Extract

The air-dried leaf was pulverized using grinding machine (2.5 kg) and soaked for 72 h in 26 L of distilled water. The mixture was then filtered using a Whatman filter paper and the filtrate freeze-dried. The concentrate formed was taken to an oven at 50ºC for 1 hour the final residue of about 480 g was a dark green mass, which was stored at room temperature.

2.4 Determination of the LD_{50}

2.4.1 Acute toxicity test

Acute toxicity test was carried out according to the modified Lorke method, (1983). A total of 13 Wister Rats were used; in the initial phase, animals were assigned randomly into 3 groups of

3 mice each. Animals in each group were administered intraperitoneal injection of extract at 10, 100 and 1000 mg/kg body weight following which they were observed for signs of toxicity and death in the first 24 hours. In the second phase, another set of 4 mice were randomly assigned into four groups of 1 mouse each and administered the extract intraperitoneally at 1600, 3200, 5000, and 6400 mg/kg based on the result of the first phase. The LD50 was calculated to be 5656.9 mg/kg.

2.5 Experimental Design

The Wister rats were divided into four groups of six animals each (n=6), Group1 animals received 2mls of distilled water (control group), Group2 animals received 25% of LD50 of *Thamatococcusdanielli* leaf extract (1.414 g/kg), Group3 animals received 50% of LD50 of *Thamatococcusdanielli* leaf extract (2.828 g/kg), Group4 animals received 75% of LD50 of *Thamatococcusdanielli* leaf extract (4.242 g/kg). The treatment was done for four weeks. The weight of the animals was monitored weekly, while the food and water intake was monitored on the daily basis [46] (Hill et al., 2001; Eteng et al., 2009).

2.6 Sample Collection and Biochemical Analysis

At the end of the administration, blood sample was collected into plane bottles through cardiac puncture after an overnight fasting. Blood was allowed to clot and serum separated by centrifugation at 4000 rpm for 10 minutes using a centrifuge (JICA, Japan). The serum was assayed either immediately or stored at –20^{o}C. Alanine and Aspartate transaminase (ALT, AST) levels were determined by the spectophotomeric method described by (Berg Meyer and Bernt, 1974), Serum creatinine was determined by a colometric reaction (Jaffe's Method), (Jaffe, 1886, Slot 1965), using an autoanalyser (Astra 8 autoanalyzer; Beckman Instruments, Fullerton, CA) serum urea was measured using a colometric reaction (DAM Method) (Fearon, 1937, Wybenga, 1971).

2.7 Histological Analysis

The histological procedure was carried out by the method described by Biswas *et al*. (2010) with some modifications. The kidney from both the treated and control groups was processed with automatic tissue processor (STP 120) by tissue processing method as described by Galen and Gambino (1975). Histology of tissues 4 µm sections was prepared with the help of Microtome (Leica, RM 2145). These sections then de-paraffinated in xylene, dehydrated through a graded ethanol series, and stained with haematoxylin and cleared in xylene I and xylene II and these organs were preserved for microscopic examination. The slides prepared by this process were observed under microscope (Model Nikon Labophot. 223425 Japan) and photographed through Nikon labophot Advanced Research Microscope, Model 223425 Japan, with Sony Digital 12.1 MEGA PIXELS.

2.8 Data Analysis

Data obtained are expressed as Mean ± Standard error of mean. The data was subjected to one-way analysis of variance (ANOVA) and differences between means were determined using the Graph Pad Prism 5 (Graph Pad Software Inc., San Diego, CA). The level of significance was set at $p<0.05$.

3. RESULTS

3.1 Effect of *T. danielli* on Body Weight

During the experimental period all animals in the normal control group and the group of the animals that receives 25% LD50 of the extract remained alive while one animal each was lost in the groups of the animals that received 50%LD50 and 75% LD50 of the extract. The animals in control group and 25%LD50 of the extract group appeared healthy, active and gained body weight while there was little instability in weight of the groups of the animals that received higher doses of the extract (50% and 75% LD50 of the extract).

The body weight in rats treated with 25% LD50, 50%LD50 and 75%LD50 was significantly increase in weight ($P<0.05$) when compare with the control group during the whole experimental period except during week 3 and week 4 in the group of animals that received 50% and 75% LD50 of extract where there was significant decrease in weight ($P<0.05$) but with no significant difference in week 3 and week 4 of the group treated with 25% LD50 of extract (Fig. 1).

3.2 The Effect of *T. danielli* on Relative Organ Weight

There were no visible changes in the gross morphology of the liver and kidney. The relative organ weight of the liver in the control, 25%, 50%, and 75%LD50 groups were:2.795±0.043, 2.840± 0.040, 2.964± 0.006 and 2.985± 0.005 g respectively with no significant differences (P>0.05) between the control and the 25%LD50 (Fig. 2A).

The relative organ weight of the kidneys in the control, 25%, 50%, and 75%LD50 groups were:2.597± 0.0234, 2.733± 0.1750, 2.818± 0.2264 and 2.838± 0.1092 g respectively with no significant differences(P>0.05) when comparison was between the control and treated groups (Fig. 2B).

3.3 The effect of *T. danielli* on Liver Transminases (ALT, AST) Activities

The effect of *T. danielli* on the activities of alanine amino transaminase and aspartate amino transaminase in treated rats is revealed in Fig. 3D and E respectively. No significant differences (P>0.05) was observed between the 25%, LD50 groupcompared with the control whereas statistically significant (P<0.05) increase was observed in the 50%LD50 and 75%LD50 groups when compared with the control.

3.4 The Effect of *T. danielli*on Serum Urea and Creatinine

Fig. 3E and F shows the mean levels of serum urea and creatinine of the control, 25%, 50%, and 75%LD50 groups. No significant differences (P>0.05) was observed in the urea and creatinine concentration of the control and the lowest dose(25%LD50) group whereas statistically significant (P<0.05) increase in the 50%LD50 and 75%LD50 when compared with the control.

3.5 Liver Histopathology (Haematoxylin and eosin (H&E) stain) and Massion Trichrome

Slides made from sections of liver from group A animals revealed normal liver architecture with radially arranged cords of hepatocytes around terminal hepatic venule. There were intervening sinusoidal spaces between each cord and plate of hepatocytes; normal central veins were also seen. These are in keeping with normal hepatic histology while liver slides from groups B animals showed mild loss of normal liver architecture with numerous radially arranged cords of hepatocytes with normal prominent nuclei, a few hepatocytes with either pale or deeply staining nuclei. Result of slides from group C animals also showed mild loss of normal liver architecture with numerous well-arranged cords of hepatocytes with normal prominent nuclei, a few hepatocytes with pale staining nuclei. There was also little dilatation of sinusoids and central vein. In addition, slides from group D animals also showed loss of normal liver architecture: with numerous distributed cords of hepatocytes with normal prominent well staining nuclei. There was also dilatation of the sinusoids and central vein filled with bleeding probably due to inflammation (Fig. 4). The massiontrichromestain in control slides showed from group A presents normal liver architecture with well distributed cords of hepatocytes with normal prominent well staining nuclei, sinusoids and central vein. Also, the slides from group B animals showed normal liver architecture with well-arranged hepatocytes, well sized sinusoidal space and normal central vein. Group C animals revealed some level of disorganized liver architecture with moderatewith presence of congested central vein, hepatocytes with dillated nuclei also presence ofvacuolisation at the parenchymal aspect of the tissue and dillation at the sinusoidal space. The results of the slides from group D demonstrates some degree of distortionMT staining presentingwith pale nuclei with congested central vein, hyalin changes and necrosis (Fig. 5).

3.6 Kidney Histopathology(Haematoxylin and eosin (H&E) stain) and Massion Trichrome

Slides taken from sections of the kidney of animals in group A and group B showed normal kidneys with well demarcated cortex and medulla. Glomeruli, bowman capsules, renal tubules and blood vessels all appeared normal within the renal cortex while sections from group C showed disorganized kidney architecture and dilated renal tubules with little distorted glomeruli and the bowman capsules. Furthermore, Group D revealed some level of disorganized structures in the kidney architecture with distorted glomerulus, bowman capsule and dilated renal tubules (Fig. 6). Massion trichrome showed sections of the kidney of animals in group A and group B demonstrated normal kidneys with well-arranged structure (glomeruli, bowman capsules,

renal tubules and blood vessels all appeared normal within the renal cortex). Slides taken from sections of the kidney of animals from the group C and D showeddistortion, which reveals shrunken glomeruli and bowman capsule with dllated renal tubules and necrotic cells (Fig. 7).

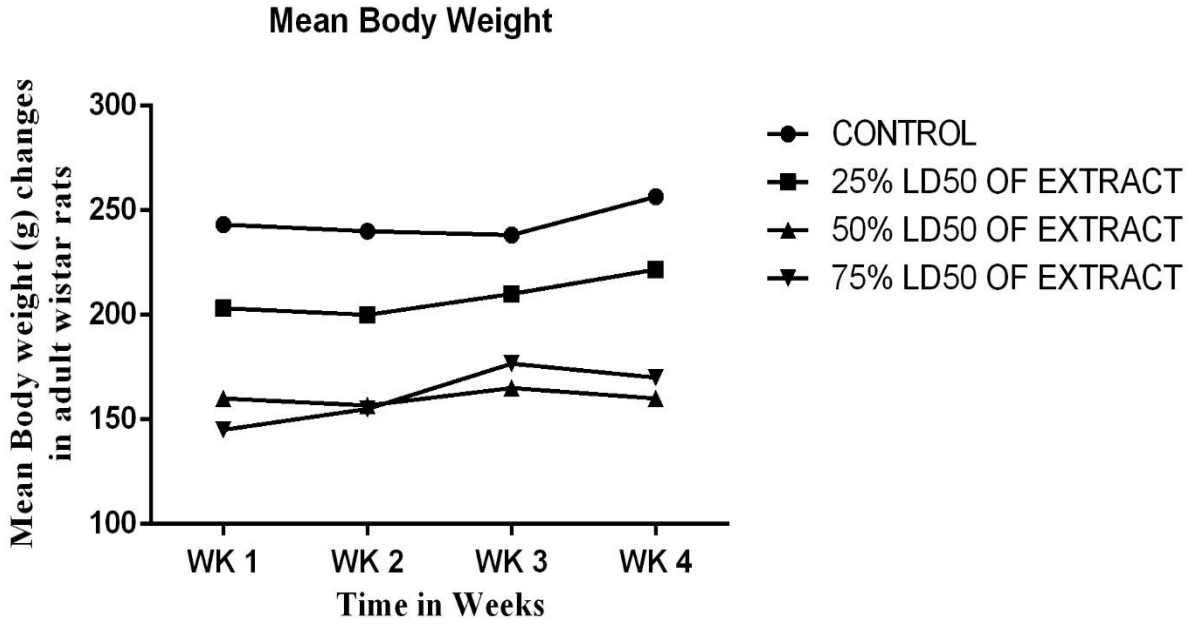

Fig. 1. Shows trend in the mean body weight of experimental Wistar rats throughout the period of the experiment. The mean body weights were on downward trends in the groups treated with 50% and 75% of LD_{50} after week 3 while an upward trend was observed in the control group and the 25% of LD groups in beyond week 3

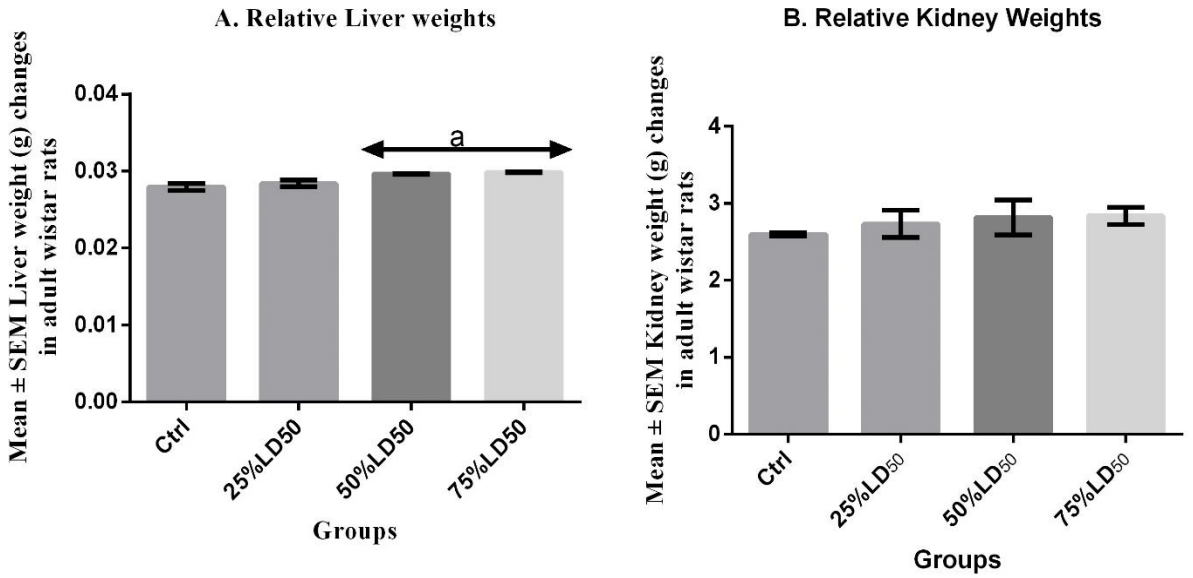

Fig. 2 shows the effects of *T. daniellio*n relative organ weight. Graphs A and B show the effect on organ weight after sacrifice, Organ weight (y-axis) plotted against groups: control, 25%LD50, 50%LD50, 75%LD50 of thaumatococcusdanielli leaf. Statistically significant increase in the relative liver weight (p< 005) was observed in the 50%and75% of LD_{50} treatment groups compared to the control. There were no changes observed in the relative kidney weight throughout the experiment

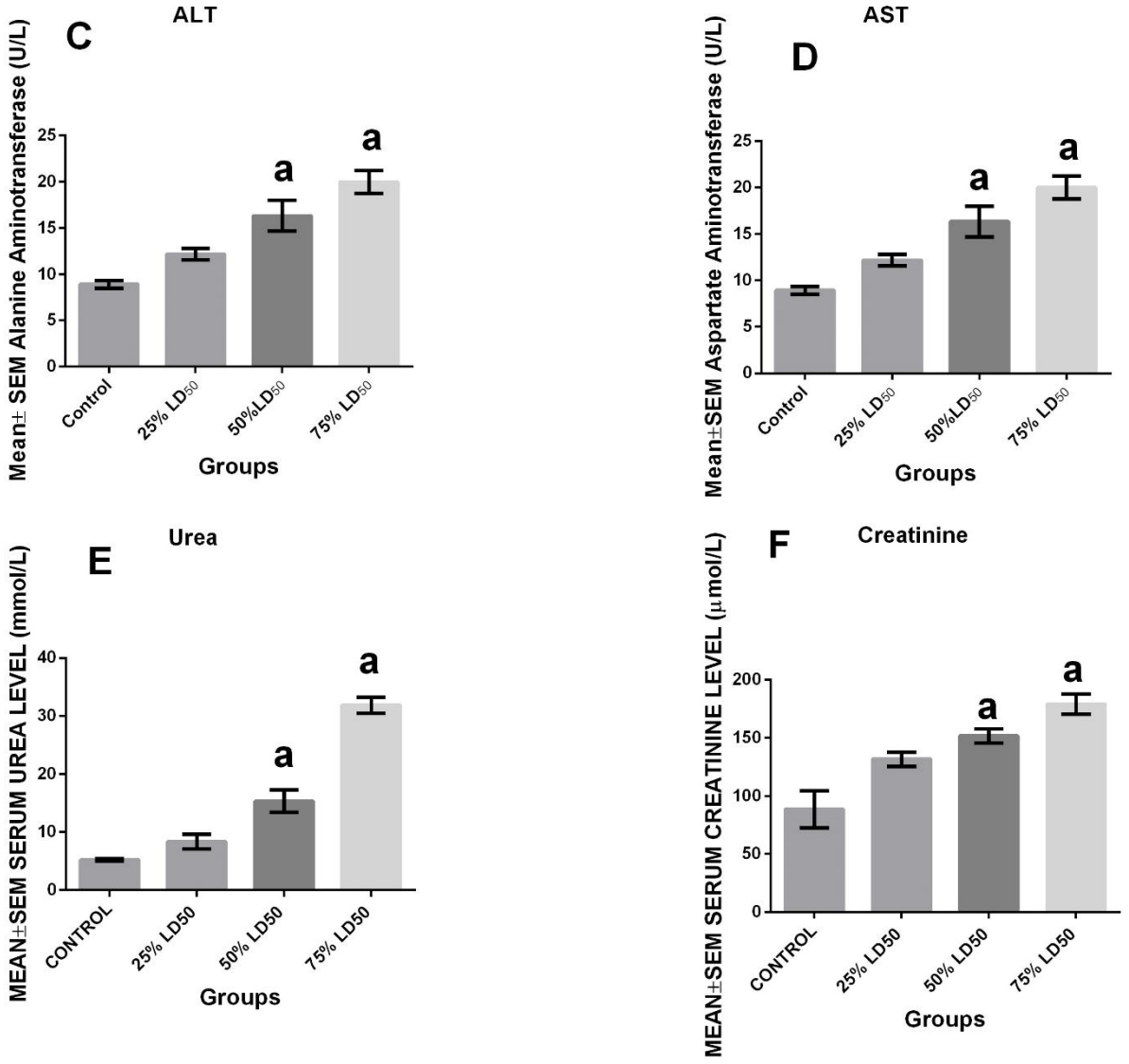

Fig. 3. shows the effects of *T. daniellio*n Liver function and Kidney function. Graph C-F show the effects of oral administrationof aqueous extract of *T. daniellio*leaves on Liver Transaminases (ALT and AST) and serumurea and creatinine in the different experimental animal groups which revealed statistical significant increase [a] P<0.05 at high doses (50%LD50 and 75%LD50)

4. DISCUSSION

The use of plants with medicinal properties for the treatment, cure and prevention of diseases as well as for traditional purposes is one of the oldest medicinal methods known in history [47]. The renowned usefulness of plant for various medicinal and biological purposes is premised on the ready availability, cheapness and perceived safety**.** This present study investigated the morphological and functional changes in the liver and kidney of *Wistar* rats treated with aqueous leaves extract of *T.danielli*, a biological useful plant.

Acute toxicity assessment is a preliminary step in the evaluation of the toxicity of a substance [48], it provides knowledge of the dose of a test substance that might be lethal to the test subject. The acute toxicity dose of *T. danielli* reported in this study was greater than 5000 mg/kg/bwt. At this dose, no lethal effect was observed on the rats.

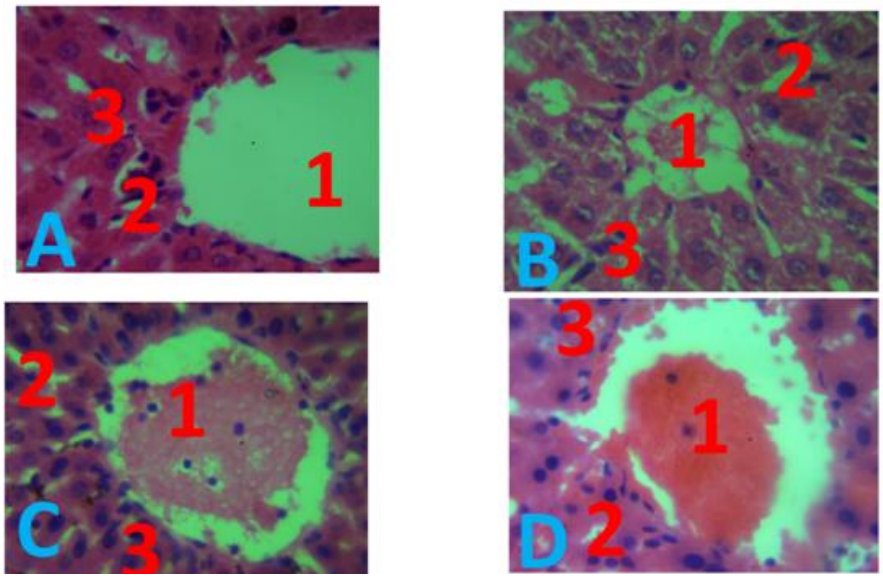

Fig. 4. Photomicrograph showing the distribution of liver architecture: Plate A.(Control) and B.(25%LD50 of *Thaumatococcus daniell)* showed 1=cleared central vein; 2=sinusoids; 3=hepatocyte with normal prominent nuclei. Plate C and D (50% LD50 and 75% LD50 of Thaumatococcus danielli): Disorganized liver architecture. 1=Congested central vein with ruptured epithelium; 2=partial dilated sinusoids; 3= necrotic cells.. H&E stain. Mag. X400

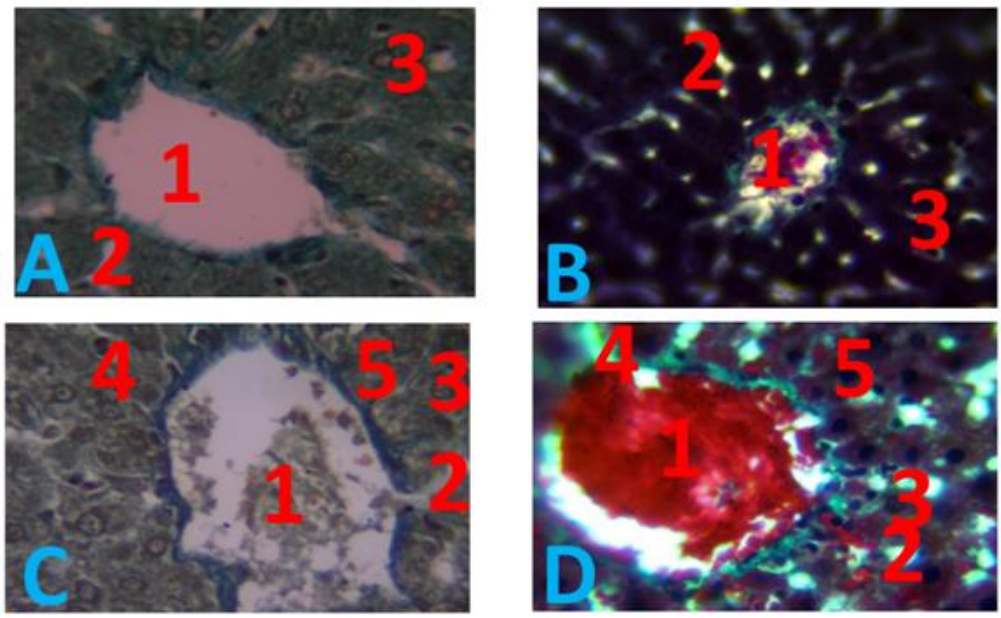

Fig. 5. Photomicrograph showing the distribution of liver architecture A. (Control): 1= central vein; 2= sinusoids; 3= hepatocytes with well distributed nucleus. B. (25% LD50 of Thaumatococcus danielli): 1= Congested central vein with scattered fibrotic tissues in the parenchyma; 2= sinusoids; 3= hepacytes with pale nuclei. C. 50% LD50 of Thaumatococcus danielli): 1= Congested central vein with scattered fibrotic tissue in the parenchyma; 2= sinusoids; 3= hepatocytes with dillated nuclei i.e necrotic hepatocyte; 4= vacuolisation. D. (75% LD50 of Thaumatococcus danielli): Disorganized liver histoarchitecture 1= dillated congested central vein with blood and scattered fibrotic tissue seen around the parenchyma; 2=dillated sinusoids. 3=necrotic hepatocytes with pale nuclei (2 and 3) ; 4= vacuolisation; 5= fibrotic tissue. MT stains. Mag. X400

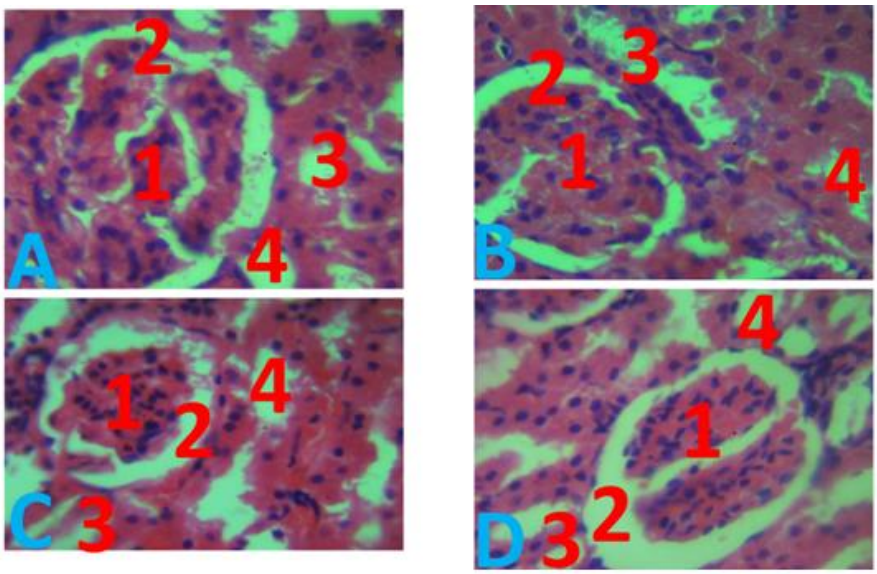

Fig. 6. Photomicrograph showing the distribution of kidney architecture A. (Control): 1= normal glomeruli with prominent nuclei; 2= bowman capsule; 3= proximal convolute tubules; 4= distal convoluted tubules. B. (25% LD50 of Thaumatococcus danielli):1= normal glomeruli with prominent nuclei; 2= bowman capsule; 3= proximal convoluted tubules; 4= distal convoluted tubules. C. (50% LD50 of Thaumatococcus danielli):1= shrunken glomeruli with prominent nuclei; 2= bowman capsule; 3&4= dillated renal tubules D. (75% LD50 of Thaumatococcus danielli):1 = normal glomeruli with prominent nuclei; 2= bowman capsule; 3&4= dilated renal tubules, mononuclear cell infiltration. H&E stain. Mag. X400

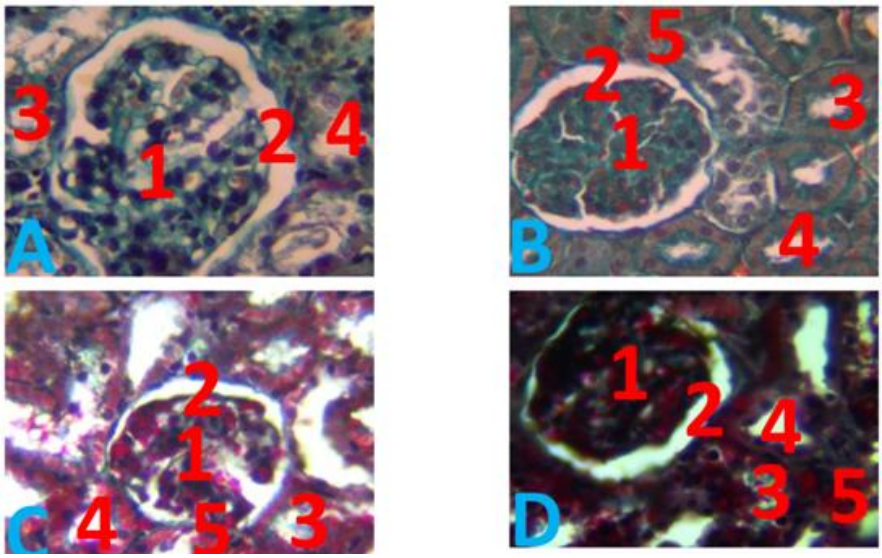

Fig. 7. Photomicrograph showing the distribution of kidney architecture A. (Control): 1= normal glomeruli with prominent nuclei; 2= bowman capsule; 3= proximal convolute tubules; 4= distal convoluted tubules; B. (25% LD50 of Thaumatococcus danielli):1= normal glomeruli with prominent nuclei; 2= bowman capsule; 3= proximal convoluted tubules; 4= distal convoluted tubules. C. (50% LD50 of Thaumatococcus danielli):1= Congested and shrunken glomeruli with pyknotic nuclei; 2= shrunken bowman capsule; 3&4dillated renal tubules; 5= necrotic cells. D. (75% LD50 of Thaumatococcus danielli):1 = Collapsed necrotic glomeruli with pyknotic nuclei; 2=shrunken bowman capsule; 3&4= dilated renal tubules; 5= necrotic cells. MT stains. Mag. X400

Liver is responsible for the metabolism of xenobitoicsand often the major affected organ due to exposure toxic substance. Biochemical parameters including the alanine aminotransferase (ALT),and aspartate aminotransferase (AST), are key markers in the assessment of functional integrity of the liver [49]. Changes in the activity of AST, and ALT, singly or in combination may suggest physiological changes in response to toxic plant extracts or materials [50,51]. In this study, alteration in the activity of AST and ALT at the highest doses of *T. danielli*infers the toxic effects on the liver of rats. Ogoloma et al. [52] had previously reported a slight change in these biochemical markers after 4 weeks exposure in rats. Similarly, changes in the biochemical parameters and liver architecture of rats fed with the extract of *T. danielli* as reported by Okafor et al. [53] revealed the hepatotoxic nature of the plant and informed the need for caution in it use for biological and medicinal purpose.

The kidney is the major organ involved in getting rid of metabolic waste that are either ingested or generated from the detoxification process of the liver. In lieu of this, the kidney is predisposed to damages upon accumulation of these toxic metabolites or chemicals [54]. In this study, the renal function biochemical parameters monitored are sufficient markers for the assessment of functional capacity of the kidney. Both the result of the organ weight and the chemical makers reported showed that the aqueous extracts of *T. danielli* is toxic at high dose.

Both the concentration of urea and creatinine could give an insight into the effects of plant extract onthe tubular andglomerular functions of the kidney [48]. Normal renal function depends on a normal filtration rate. Through glomerular filtration, creatinine from the blood is excretedin the urine without reabsorption by the tubules to any significant extent. In addition, when the blood level becomes elevated above normal, tubular excretion could also occur. By implication, the serum creatinine level in renal disease generally does not increase until the renal function is substantially impaired [55]. More so, high serum urea and creatinine level may be an indication of renal failure [56]. The result of the renal histology supports the findings reported regarding the biochemical parameters, range of histological changes observed upon administration of high dose of *T. danielli* further establish the toxic nature of the plant. Although Olorunnisola *et al*. [43] previously showed the nephroprotectrive effects of *T. danielli* in diabetic rats, reverse might be the case when *T. danielli* is administered in non-pathological state. Other studies have also reported the toxic nature of the plant and our result agrees with their findings.

CONCLUSION

Findings from this study suggested that *T. danielli*leave extract is toxic at high doses, although when used in food wrapping, it is unlikely to obtain such the toxic dose. Therefore, *T. danielli*leaf can be safe for food wrapping at the lowest dose used in this study.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

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

NOTE

The study highlights the efficacy of "traditional medicine" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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