

## Research Paper:

# Protective Role of *Adansonia digitata* Extract Against Glyphosate-induced Hepatorenal Toxicity in Adult Male Wistar Rats



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## ABSTRACT

**Background:** Glyphosate is the most widely used herbicide, and it poses numerous health risks to the environment and living organisms. This study aimed at assessing the protective role of *Adansonia digitata* (*A. digitata*) on glyphosate-induced hepatorenal toxicity in a Wistar rat model.

**Methods:** Twenty-five rats were randomly divided into five groups of five animals each. The first group did not receive glyphosate and served as the control group. The second group received a single daily dose of only glyphosate (375 mg/kg). The treatment groups 3 and 4 were given a single daily dose of glyphosate (375 mg/kg) together with 250 mg/kg and 500 mg/kg of *A. digitata* extract, respectively. Group 5 was administered glyphosate (375 mg/kg) with Ascorbic Acid (200 mg/kg) as a comparison. At the conclusion of the study, blood serum samples from the rats were used for biochemical analysis. Then, the liver and kidneys were removed for histological examinations.

**Results:** In comparison to the control rats in group I, those in group 2 that were given glyphosate had increased liver enzymes biomarkers, urea, creatinine and malondialdehyde levels, but their superoxide dismutase, catalase, and glutathione peroxidase levels decreased ( $P < 0.05$ ). Groups 3 and 4 rats that received fruits of *A. digitata* did not show the upsurge of liver enzymes biomarkers creatinine, urea and malondialdehyde. Furthermore, the extract of the fruits increased endogenous antioxidant biomarkers. *A. digitata* protected the glomeruli from degeneration and prevented histological liver steatosis.

**Conclusion:** This study's findings suggest that the pre-treatment of rats with *A. digitata* extract provides a hepatorenal protective effect against glyphosate toxicity.

**Keywords:** *A. digitata*, Ascorbic acid, Glyphosate, Kidneys, Liver

## Introduction

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lyphosate is among the herbicides, commonly used in many countries, that is implicated in numerous health hazards in both living and environmental organisms [1]. This chemical compound is widely

used to control a variety of weeds, and plantation crops, such as rice and soya beans [2]. Glyphosate is used together with surfactants as commercial improve the herbicide's effectiveness by increasing the plants' toxicity and absorption tendencies of the glyphosate [3]. Both living organisms and humans get exposed to this xenobiotic agent daily, through the remains of the glypho-

sate residue on foodstuffs as grains, vegetables, animal products, water as well as the air we breathe [4]. The daily exposure of this glyphosate to humans might lead to many complications and health challenges [5]. It has been reported that glyphosate exposure to humans and mammals induces oxidative stress by upregulating the production of reactive species and malondialdehyde [6]. This reactive oxygen species generated by the glyphosate can deplete the endogenous antioxidant parameters like superoxide dismutase and catalase within mammals, hence inducing hepatic injury [7]. Glyphosate has also been implicated to have a side effect on some enzymes in the cytochrome P-450 superfamily within the mitochondria, which a significant role in the proper functioning of the liver [8]. It also decreases the activity of complex II and III within the electron transport chain of the mitochondria and the membrane potentials of the mitochondria [9]. Myers et al. [10] reported that glyphosate could diffuse into many other tissues like the kidney via its systemic circulation within the bloodstream.

*Adansonia digitata* L. (Baobab) is an indigenous plant to most countries in Africa, and it is of significant interest among other plants as it was claimed to be rich in ascorbic acid and minerals [11]. Its fruit pulp is used in several parts of Sub-Saharan Africa for medicinal reasons against some body disorders: fever, diarrhoea, constipation, and many other ailments [12]. The fruit pulp is known to be consumed in Europe because of its various health benefit and its novel food ingredient, as its consumption was authorized by the European parliament and council [13]. Furthermore, there are a growing number of pieces of literature with evidence that *A. digitata* improves the metabolism of lipid and carbohydrates [14, 15]. It was reported that the leaves of the *A. digitata* has hepatoprotective and antioxidant potential attributed its high content of flavonoid, Polyphenols, and vitamin C [16, 17]. Despite the above-mentioned medicinal properties of *A. digitata* fruit pulp, the protective potential of the pulp against glyphosate has been poorly examined. Therefore, the present study aimed to evaluate the protective potential of *A. digitata* fruit pulp against glyphosate-related hepatorenal toxicity in adult Wistar rats.

## Materials and Method

Glyphosate (Bushfire®, Monsanto Europe SA), 44% purity glyphosate crystal form, was obtained from Steve Moore Laboratory Chemical store, Emanto Zaria, and was used as a toxicant for liver and kidney. Ascorbic Acid (tablet) was used as a commonly prescribed antioxidant drug. Ketamine hydrochloride (PVT Ltd, India) was the anaesthetic agent used in the study. Also, alanine

aminotransferase, alkaline phosphatase, aspartate transaminase, urea, and creatinine colorimetric diagnostic kits (Randox kits) were used. Antioxidant enzyme activities, such as superoxide dismutase, catalase, glutathione peroxidase and malondialdehyde content in blood serum were assessed using laboratory diagnostic kits (Biodiagnostic Co., Cairo, Egypt).

## Plant collection and authentication

The fruits of *A. digitata* were sourced from a Samaru-based farm, Sabo Gari, Kaduna, Nigeria. The fruit was verified at the Herbarium of Ahmadu Bello University (ABU), Zaria, Nigeria (Specimen number, 5578).

## Extraction

*A. digitata* fruit pulp was ground and extracted using a soxhlet apparatus for 10 hours with distilled water.

## Experimental animals

In this study, 25 healthy Wistar rats were utilized, weighing 150-190 g obtained from Ahmadu Bello University Zaria's Department of Pharmacology. The rats were allowed two weeks to acclimate to the animal house environment before the experiments began. The animals had free access to rat food pellets and water ad libitum. The study was approved by the Ethics Committee on Animal Use and Care at Ahmadu Bello University (Registration Code: ABUCAUC/2019/071). All ethical guidelines were carried out effectively upon the rats' arrival in the laboratories where experiments were conducted.

## Experimental design

Five groups of rats were created (n=5 each) randomly. Table 1 summarizes the animal groupings and administration of the aqueous extract of *A. digitata* fruits, glyphosate, and ascorbic acid.

## Biochemical analyses

At the end of the 56-day period, the rats were euthanized, and blood samples from each rat were collected in a plain tube by cardiac puncture. The blood samples were centrifuged at 3000 rpm for 5 minutes. The sera were used to determine the levels of superoxide dismutase, catalase, glutathione peroxidase, malondialdehyde, alanine aminotransferase, alkaline phosphatase, aspartate transaminase, creatinine, and urea.

**Table 1.** Summary of experimental design

Rat Groups	Administrations	Duration (day)
1	Distilled water at 2 ml/kg	56
2	glyphosate at 375 mg/kg	56
3	<i>A. digitata</i> at a dose of 250 mg/kg+glyphosate at 375 mg/kg	56
4	<i>A. digitata</i> at a dose of 500 mg/kg+glyphosate at 375 mg/kg	56
5	Ascorbic Acid at 200 mg/kg+glyphosate at 375 mg/kg	56 d

### Histopathological study

The harvested liver and kidneys were fixed in neutral buffered formalin, then dehydrated in graded alcohol, embedded in paraffin wax, cleared in xylene, sectioned at 5 microns, and stained with Haematoxylin and Eosin (H&E). The demonstration of hepatic reticular fibres was achieved with Gordon and Sweet stains.

### Statistical analyses

GraphPad Prism, version 9.2 software was used to perform a one-way Analysis of Variance (ANOVA) followed by a Tukey's post-hoc test. The data were displayed as the Mean±SE, and  $P<0.05$  was chosen as the level of statistical significance.

## Results

### Liver function enzymes

When glyphosate-treated rats were compared to control rats and *A. digitata*-treated rats and ascorbic acid, alanine aminotransferase, alkaline phosphatase, and aspartate transaminase levels increased significantly ( $P<0.0001$ ) (Figure 1). *A. digitata* treatment at 500 mg/kg was found to be more effective. alanine aminotransferase, alkaline phosphatase, and aspartate transaminase levels did not differ significantly ( $P>0.05$ ) between control rats and rats treated with *A. digitata* (500 mg/kg) and ascorbic acid (Figure 1).

### Renal function parameters

Urea and creatinine levels in the serum of rats treated with only glyphosate increased significantly ( $P<0.0001$ ) when compared to control and *A. digitata*/Ascorbic Acid-treated rats (Figure 2). Creatinine levels did not differ significantly ( $P>0.05$ ) between control and *A. digitata*-treated rats (500 mg/kg) and Ascorbic Acid (Figure 2).

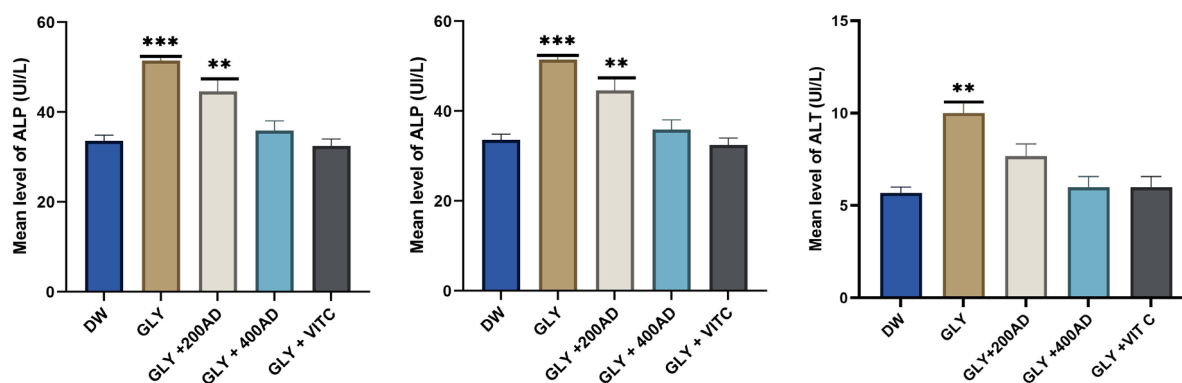
### Oxidative stress biomarkers

The levels of catalase, superoxide dismutase, and glutathione peroxidase significantly decreased ( $P<0.0001$ ) in the serum of glyphosate control rats when compared to control and *A. digitata*-treated rats (Figure 3). The *A. digitata* treatment at 500 mg/kg was found to be more effective. There was no significant variability ( $P>0.05$ ) in superoxide dismutase, catalase, and glutathione peroxidase levels between control and *A. digitata* (500 mg/kg) treated rats (Figure 3). For malondialdehyde, a significant increase ( $P<0.05$ ) was observed in the glyphosate control rats compared to rats cotreated with *A. digitata* (500 mg/kg) and Ascorbic Acid.

### Histopathological study

Normal hepatocytes, central veins, and sinusoids were visible in the photomicrographs of the livers from healthy control rats (Figure 4a). The liver of rats exposed only to glyphosate exhibited remarkable degenerate hepatocyte, steatosis, and fat hepatocellular vacuoles (Figure 4b). The livers from rats treated with glyphosate (375 mg/kg) and *A. digitata* extract at doses of 250 and 500 mg/kg, respectively, concurrently revealed mild steatosis (arrow) and some micro-vesicular fatty droplets (Figure 4c & 4d). The glyphosate (375 mg/kg) and ascorbic acid (200 mg/kg) treatments resulted in mild dilatation of the liver sinusoids in the rats (Figure 4e). The liver samples from the control group revealed normal reticular fibres distributed in the parenchyma (Figure 5a), while those from the rats exposed only to glyphosate exhibited marked depletion of the reticular fibres (Figure 5b).

**Combined glyphosate & extract:** The livers of rats treated with both glyphosate at 375 mg/kg and *A. digitata* at a 250 mg/kg and 500 mg/kg concurrently revealed mild and remarkable restoration of reticular fibers, respectively (Figure 5c & 5d). Glyphosate (375 mg/kg) and Ascorbic (200 mg/kg) treatment resulted in mild restoration of the reticular fibers (Figure 5e). The kidneys



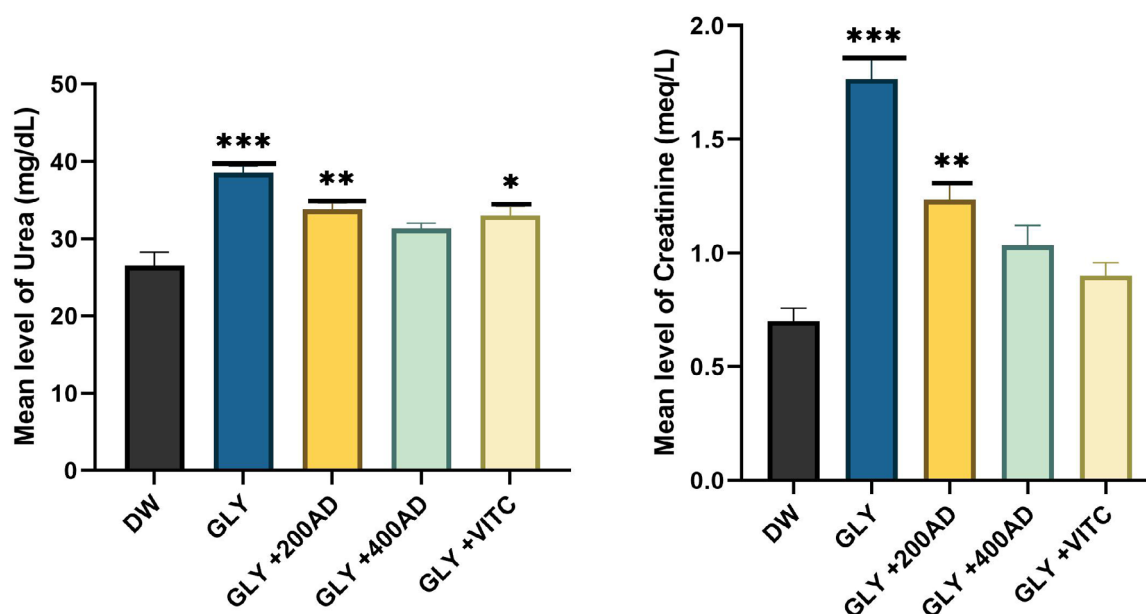
**Figure 1.** Charts of parameters of liver enzymes (a) ALP, (b) AST, and (c) ALT, of the study, comparing the treated and the control groups

One-way ANOVA was used to examine the data, followed by a Tukey post hoc test. with \* $P < 0.033$ ; \*\* $P < 0.002$ ; \*\*\* $P < 0.0001$  for the experimental tests groups (DW). For each group, the data are the Mean $\pm$ SEM, with  $n=5$  rats.

from normal control rats revealed a typical histological structure, with normal renal tubules and glomeruli (Figure 6a). The kidneys from the glyphosate-treated rats revealed focally retracted and degenerated glomeruli (Figure 6b). The kidneys of the rats treated with glyphosate (375 mg/kg) and *A. digitata* extract at doses of 250 and 500 mg/kg revealed mildly retracted glomeruli and normal glomerulus mild, respectively (Figure 6c, 6d). The kidneys from the rats treated with glyphosate and ascorbic acid exhibited obliterated forms of glomeruli (Figure 6e).

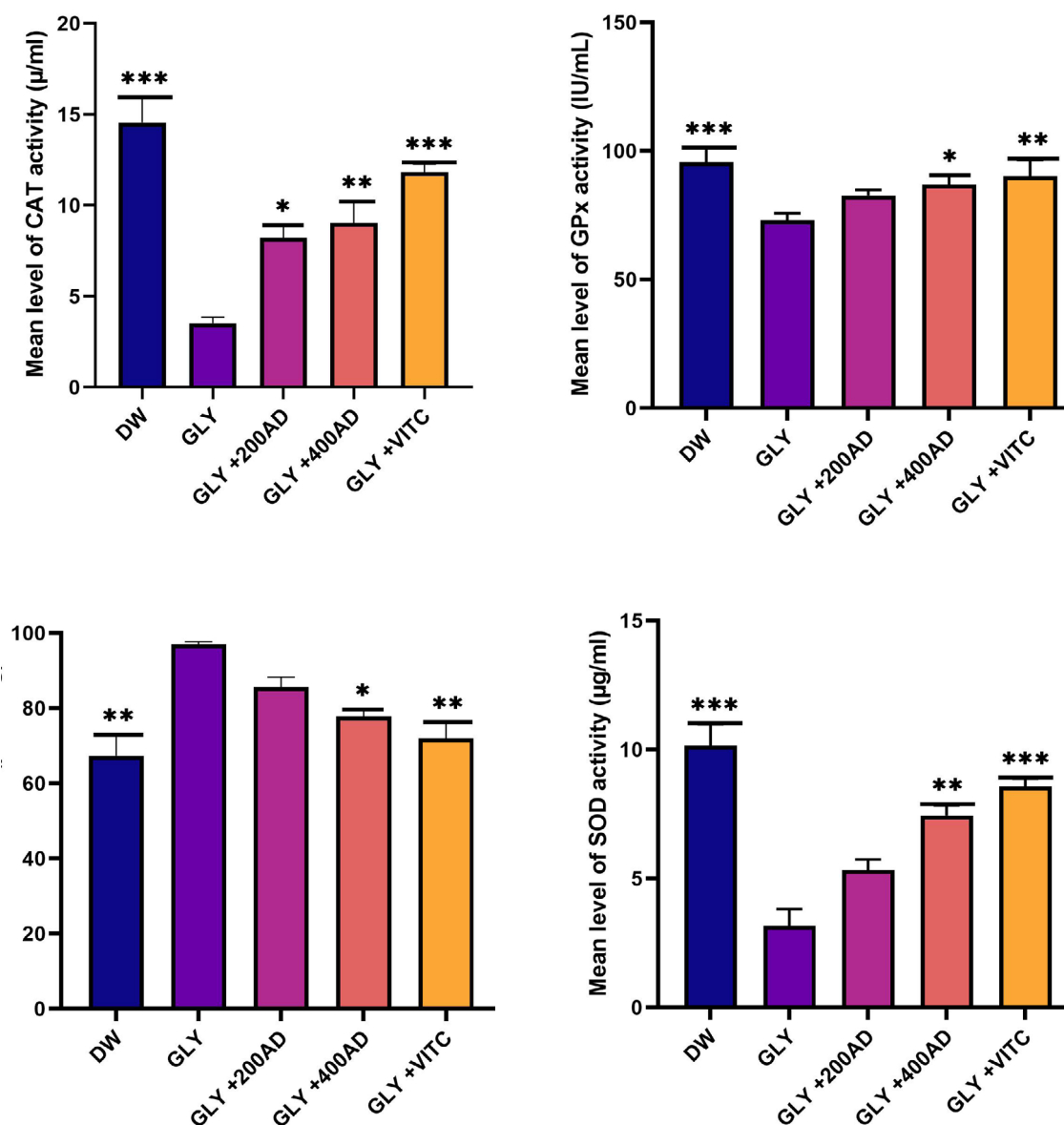
## Discussion

This study investigated the hepatorenal protective effects of *A. digitata* aqueous extract against the toxicity of glyphosate exposure in Wistar rats. Generally, increases in alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase liver enzyme levels were linked to hepatic toxicity [18]. The increased creatinine and urea concentrations in the blood serum were often associated with the impairment of the kidneys due to the



**Figure 2.** Charts of kidney function parameters (A) Urea, and (B) Creatinine of the study, comparing the treated and the control groups

One-way ANOVA was used to examine the data, followed by a Tukey post hoc test. with \* $P < 0.033$ ; \*\* $P < 0.002$ ; \*\*\* $P < 0.0001$  for the experimental tests groups (DW). For each group, the data are the Mean $\pm$ SEM, with  $n=5$  rats.



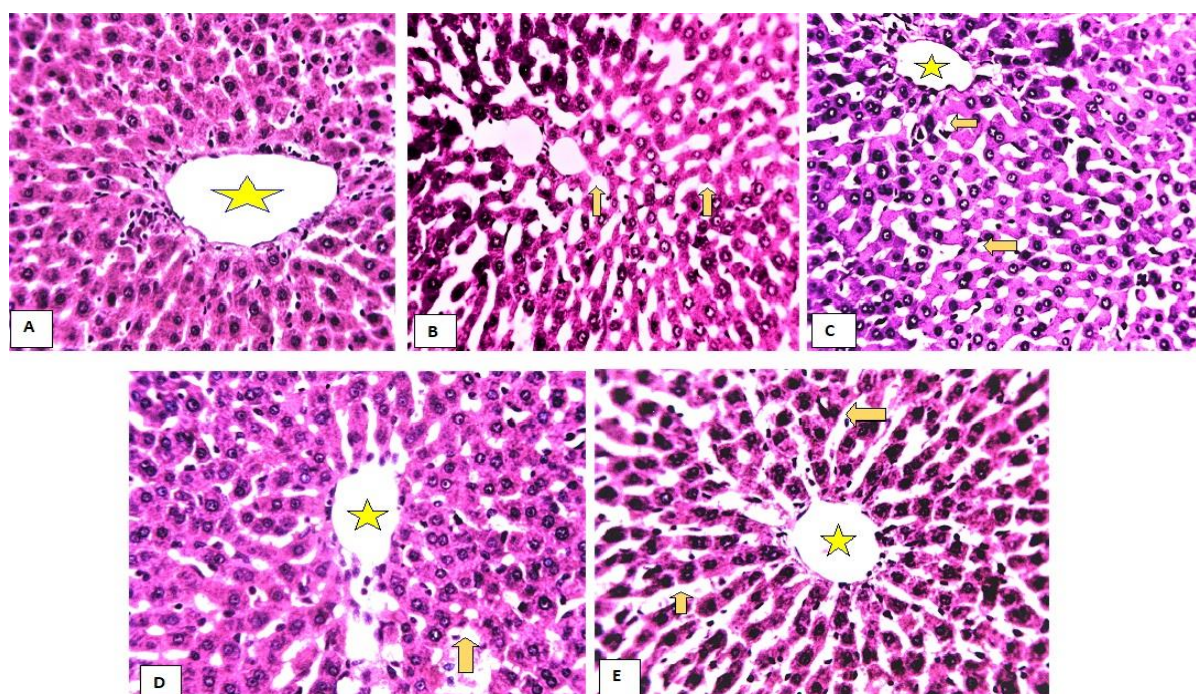
**Figure 3.** Charts of oxidative stress parameters (A) SOD, (B) CAT, (C) GPx and (D) MDA of the experimental study, comparing the treated and the control groups

One-way ANOVA was used to examine the data, followed by a Tukey post hoc test. with \* $P < 0.033$ ; \*\* $P < 0.002$ ; \*\*\* $P < 0.0001$  for the experimental tests groups (DW). For each group, the data are the Mean $\pm$ SEM, with  $n=5$  rats.

failure of glomeruli to reabsorb and prevent the leakage of proteins and urea into the blood [19].

The results of this study demonstrated that rats' exposure to glyphosate caused significant increases in the serum levels of liver enzymes, creatinine and urea levels. The findings are consistent with similar reports from previous studies [7, 20]. The marked increases in the liver enzymes and serum urea and creatinine levels found in the glyphosate administered rats (Figure1a-c and Figure2a & b) could be due to the adverse effect of glyphosate on the cells in both the liver and kidneys.

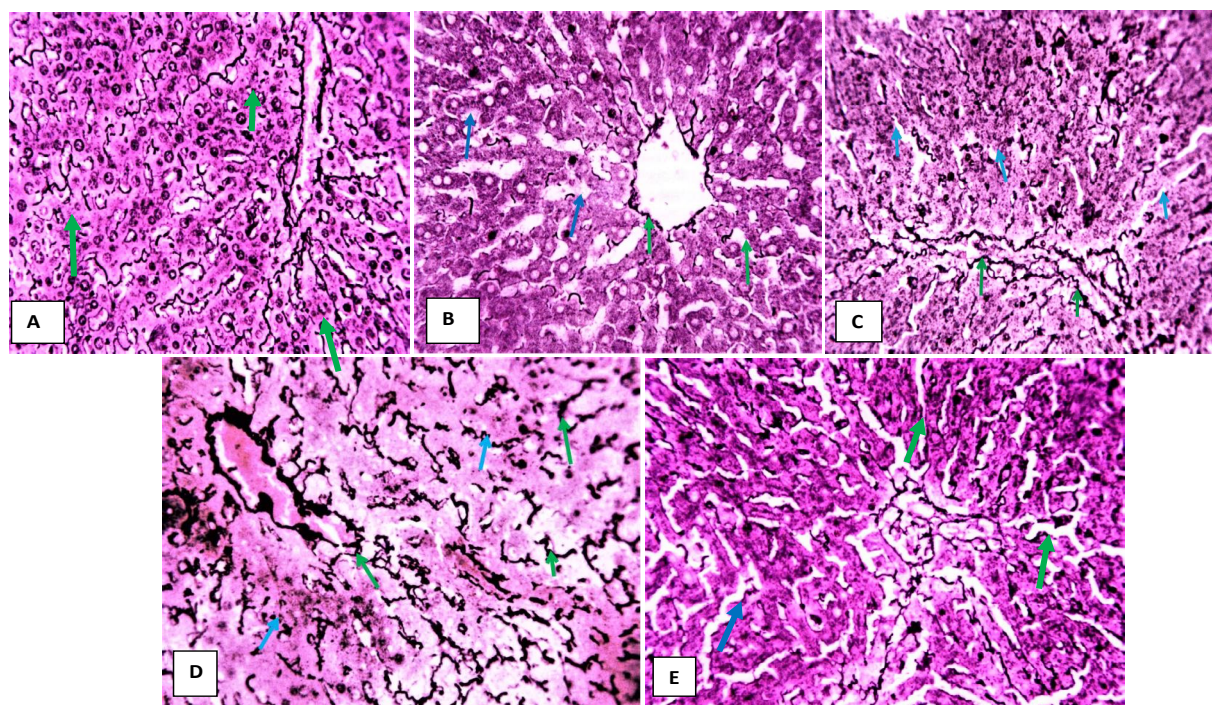
This could explain that glyphosate disrupts the liver cell membranes and kidneys glomeruli [21, 22]. The treatment with *A. digitata* fruit extract remarkably inhibited the upsurge of the serum alanine aminotransferase, alkaline phosphatase, and aspartate transaminase, urea, and creatinine. These findings suggest that the fruit extract prevented and/or protected from liver and kidneys toxicity induced by either a xenobiotic agent or heavy metals, as reported by previous studies [23, 24]. These might be due to the antioxidant and scavenging activities of the *A. digitata* fruits extract [25, 26]. *A. digitata* has been well documented to have high antioxidant properties [27].



**Figure 4.** Photomicrographs of the liver in control and experimental treated rats

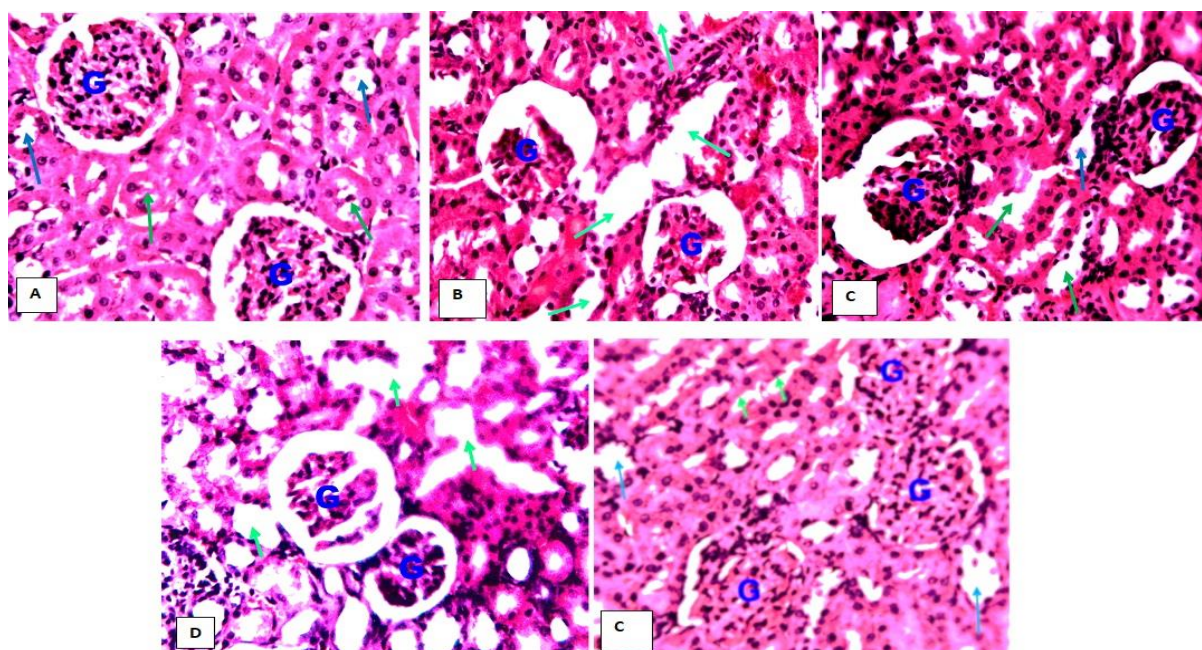
Showing normal hepatocytes in a, exhibited remarkable fat degenerating hepatocytes, and hepatocellular vacuoles in b, mild steatosis (yellow arrow) and some micro vesicular fatty alteration in c, & d, and mild dilatation of the sinusoid in the liver of rats in e. H&E x250.

a=normal control; b=glyphosate control; c=375 mg/kg glyphosate+250mg/kg *A. digitata*; d=375 mg/kg glyphosate+500 mg/kg *A. digitata*; e=375 mg/kg glyphosate+200mg/kg Ascorbic Acid.



**Figure 5.** Composite photomicrographs of liver of control and experimental treated rats revealed normal distribution of reticular fibres in a, liver exhibited marked depletion of reticular fibres (blue arrow) in b, liver shows mild and remarkable restoration of reticular fibres (green arrow) in c, d, & e. Gordon & Sweet Silver Stain x 250.

a=normal control; b=glyphosate control; c=375 mg/kg glyphosate+250mg/kg *A. digitata*; d=375 mg/kg glyphosate+500 mg/kg *A. digitata*; e=375 mg/kg glyphosate+200mg/kg Ascorbic Acid.



**Figure 6.** Composite photomicrographs of kidney of control and experimental treated rats

Showing a normal glomerulus and renal tubules in a, exhibited focal retracted and degenerated Glomerulus (G) in b, a mild retracted glomerulus, and a normal glomerulus respectively in c, & d, and exhibited obliterative form of Glomerulus (G) in e. H&E x250.

a=normal control; b=glyphosate control; c=375 mg/kg glyphosate+250mg/kg *A. digitata*; d=375 mg/kg glyphosate+500 mg/kg *A. digitata*; e=375 mg/kg glyphosate+200mg/kg Ascorbic Acid.

The results achieved by the present study revealed significant decreases in catalase, superoxide dismutase, and glutathione peroxidase activities due to glyphosate toxicity (Figure 2a-d). The decline in these endogenous antioxidants were associated with rises in free radicals and lipid peroxidation levels (malondialdehyde). These antioxidant parameters, i.e., Superoxide dismutase, Catalase and Glutathione Peroxidase (SOD, CAT and GPx), play significant roles in regulating the cells' metabolic activities and protect the cells against free radical-induced tissue injury [28]. The depressed catalase, superoxide dismutase, and glutathione peroxidase levels might be associated with glyphosate ability to induce the mechanism of oxidative stress [1].

The administration of *A. digitata* fruit extract to rats showed significant elevations in the activities of superoxide catalase, dismutase, glutathione peroxidase and decreased malondialdehyde. These findings suggest that the *A. digitata* fruit extract has the potentials to serve as free radicals' inhibitor. Alternatively, the extract can scavenge against free radical accumulation, which might mitigate the free radical-induced tissue damages [29]. The antioxidant activity of the *A. digitata* extract against xenobiotic agents, such as glyphosate might be linked to the action of various components in the fruits' extract. As previously reported, the *A. digitata* fruit extract has

high concentrations of ursolic acids, vitamin C and sitosterol [30]. Plants with high antioxidant activities have a positive effect in protecting against the induced toxicity either by their heavy metals or xenobiotic compounds [31]. Hence, *A. digitata* fruit extract's protective role against glyphosate induced hepatorenal damages, as evident by the findings of this study.

The distortions caused by glyphosate in the histology of the liver and kidneys samples confirmed the biochemical results of the present study and support the generation of free radicals by glyphosate [7, 32]. Rats administered with glyphosate revealed a severe depletion of hepatic reticular fibers and formation of fatty droplets plus the renal glomeruli atrophy. The outcomes are in line with those reported by previous research [20]. The histopathological outcomes observed in rats co-treated with *A. digitata* fruits extract revealed a marked restoration of the cytoarchitecture of the liver and kidney tissues. This study provided evidence that *A. digitata* extract is rich in antioxidants, which can protect against the hepatorenal toxicity induced by glyphosate. Hence, treatment with *A. digitata* extract preserved the normal cytoarchitecture of both the liver and kidneys by lowering the hepatic steatosis and formation of fatty droplets in the macro/microvasculature, thus preventing reticular fibre's degradation.

## Conclusions

Glyphosate caused increased hepatic and renal biomarkers, oxidative stress and aberrations in the histological structure of the liver and kidney in the glyphosate-treated rats, according to the findings of this study. Regardless of dose, co-treatment with *A. digitata* fruit extract showed antioxidant properties of the extract by reducing glyphosate-induced abnormalities due to *A. digitata*'s chelating activities (Figures 1-6). The results show that the fruit's potent antioxidant potentials may be the primary mechanism driving the protective benefits. Finally, because of its protective potential and wide pharmacological safety margin, *A. digitata* could be developed as a natural antioxidant drug for the protection/prevention/treatment of glyphosate toxicity.

**Limitations of the study:** The hepatorenal protective role of *A. digitata* fruit extract is believed to be stem from its antioxidant potential. However, this study did not assess the associated gene expression and/or disruption, and the interference with mitochondrial metabolism at the end of the experiments.

**Recommendations for future research:** We recommend that the status of apoptotic gene expression associated with the fruit extract be further investigated in rats or other experimental animal models.

## Ethical Considerations

### Compliance with ethical guidelines

All animal-related experimental protocols have received the institutional ethical clearance (Registered No.: ABU-CAUC/2019/071) from the Ethics Committee on Animal Use and Care at Ahmadu Bello University, Zaria, Nigeria.

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## Authors' contributions

Conceptualization and design: All authors; Provision of study materials: Addai Terna Ini, Wusa Makena, and Aisha Aminu; Data collection: Ibe Michael Usman Addai Terna Ini and Wusa Makena; Data interpretation and analysis: All authors; Manuscript's initial draft: Wusa Makena, Madu Nom Gadzama, and Addai Terna Ini. Critical review of the manuscript: Wusa Makena, Ibe Michael, Aisha Aminu, Aisha Aminu and Madu Nom Gadzama; Final approval of manuscript: All authors.

## Conflict of interest

The authors declared no conflicts of interests.

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