

Anti-inflammatory and anti-oxidative activities of *Xylopiya aethiopica* stem-bark extract on glyphosate-induced hepatotoxicity

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ABSTRACT

Toxicity posed by exposure to pesticides is known to be a major threat to public health, and phytochemicals have been suggested to confer ameliorative effects against pesticide toxicity. Hence, this work is designed to explore the anti-inflammatory and anti-oxidative activities of *Xylopiya aethiopica* stem-bark (XASE) on glyphosate-induced hepatotoxicity. A total of 36 male albino rats weighing between 150-200 g were randomly assigned into six groups. Group 2 received 150 mg/kg b.wt of glyphosate; group 3 received 150 mg/kg b.wt of glyphosate and 126.49 mg/kg b.wt of XASE (1/10th LD₅₀ of XASE) after 2 hours; group 4 received 250 mg/kg b.wt of vitamin C after 2hrs of treatment with 150 mg/kg b.wt of glyphosate; group 5 & 6 received 126.49 mg/kg b.wt of XASE and 250 mg/kg b.wt of vitamin C respectively while group 1 served as control. The administration was done orally for a week. Activities of Aspartate and Alanine aminotransferases; total and conjugated bilirubin, and total protein levels were measured in the serum, while the level of oxidative stress markers like malondialdehyde, nitric oxide, reduced glutathione, glutathione peroxidase, catalase, superoxide dismutase, and Inflammatory markers C-reactive proteins, Interleukin-6, and Tumor necrosis factor- α levels in the liver homogenate were measured. Results show that treatment with XASE significantly modulates the incidence of oxidative stress, inflammation, and hepatotoxicity induced by glyphosate ($p < 0.05$). Likewise, the histopathological analyses of liver tissue result affirmed the hepatoprotective effect of XASE. Hence, *X. aethiopica* could confer protective effects against glyphosate-induced hepatotoxicity and inflammation.

Keywords: Glyphosate, hepatotoxicity, inflammation, oxidative stress, and *Xylopiya aethiopica*.

1.0 INTRODUCTION

Toxicities posed by exposure to pesticides to humans and aquatic animals have been a major concern for public health. Glyphosate, a major active ingredient in the commonly used herbicide roundup, has been linked to several toxicities (Soares *et al.*, 2021; Klátyik *et al.*, 2025). Pandey *et al.* (2019) have reported multi-organ toxicity, inflammation, oxidative stress, lipid peroxidation, metabolic enzymatic level dysregulation, and endocrine disruption. Chemically, Glyphosate is an N-(phosphonomethyl) glycine-based herbicide, sold under a different trade name such as Roundup, Roundup Pro, Glypro, etc. It is used as a nonselective and broad-spectrum weed control chemical in food crops and fruit plantations, horticulture, viticulture, roadsides, playgrounds, and many more (Aoun *et al.*, 2025). Humans and animals come in contact with this herbicide through inhalation, contaminated water, fruit, crops, and vegetables. Occupational and accidental exposure are additional sources. Both glyphosate and aminomethylphosphonic acid (its metabolites) have been documented to be found in contaminated water and food crops, and

these were reported to pose toxicity in living organisms (Drechsel *et al.*, 2024). The mechanism of glyphosate and its metabolites' toxicity in plants has been validated to cause inhibition of 1-5-enolpyruvylshikimate-3-phosphate synthase, which is required for the formation of 5-enolpyruvylshikimate-3, an intermediate that produces chorismic acids as a precursor for the formation of aromatic amino acids (Phe, Tyr & Trp), thus interfering with the formation of amino acids (Kanissery *et al.*, 2019). Although the proposed mechanism of toxicity in humans and animals has been complicated, nonetheless, some studies have suggested the disruption of the cellular antioxidants system, lipid peroxidation, and oxidative stress (Locatelli *et al.*, 2022); uncoupling of oxidative phosphorylation (Wang *et al.*, 2022) endocrine disorders (Muñoz *et al.*, 2021); systemic inflammation (Pandey *et al.*, 2019; Tang *et al.*, 2020) multi-organ inflammation, upregulation of the enzymes prostaglandin-endoperoxide synthase and adverse effects metabolic process in liver and adipose (Pandey *et al.*, 2019) and development of non-alcoholic fatty liver (NAFL) (Romualdo *et al.*, 2023). Common

side effects associated with exposure to this herbicide in both animals and humans include skin irritation, dizziness, diarrhea, nausea, body tremors, throat and mouth burning, impaired vision, numbness, and fatigue (Rawat *et al.*, 2023). Glyphosate's lethal dose LD₅₀ has been estimated as 4900 mg/kg b.wt for rodents (Pandey *et al.*, 2019). Glyphosate can linger for a very long time in soil and water bodies; its half-life in water bodies and soil has been estimated to be between 3 to 19 weeks and 1 to 174 days, respectively (Rawat *et al.*, 2023). Upon cellular uptake, Glyphosate eventually stops several metabolic reactions that are vital to the survival of living things, such as respiration, protein synthesis, nucleic acid synthesis, and photosynthesis (Locatelli *et al.*, 2022).

Oxidative stress and inflammation have been mostly implicated in pesticide toxicological mechanisms (Sule *et al.*, 2022). Overwhelm of the cellular antioxidant defense system by Reactive oxygen or nitrogen species (ROS/RNS) and other very reactive molecules results in an oxidative attack on lipids, proteins, DNA, and other macromolecules, leading to cellular structural damage, impaired metabolism, and bioenergetics. Inflammation itself is a body's natural reaction to the invasion of xenobiotics, but can also be employed to protect the site of an injury and infection (Kumari and Kumar, 2022). This process is often associated with oxidative stress and may or may not cause pain. Increased blood flow and capillary permeability, neutrophil recruitment, and macrophage migration are all caused by inflammatory reactions. Interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β), collectively called Pro-inflammatory cytokines, are secreted by neutrophils and trigger inflammatory reactions. Additionally, cytokine production is enhanced, endothelial gene expression is altered, and chemotaxis, leukocyte adherence, and fibroblast activation are all happening in the target tissue (Sproston and Ashworth, 2018).

Plant-based chemicals, over time, have been considered to be safer means of lessening herbicide-induced toxicity due to their medicinal properties and very low toxicity (Jablonska-Trypuc and Water, 2022). Negro pepper or African plant (*Xylopia aethiopica*) is one of the medicinal plants known to have therapeutic actions. *X. aethiopica* belongs to a member Annonaceae family. This perennial plant is grown mostly in tropical and subtropical African rainforests (Anyamele *et al.*, 2023). Also, the negro pepper obtained from these plants is used as a spice in preparing local soup and as a local remedy for combating inflammatory diseases like bronchitis, asthma, rheumatism, and arthritis, chronic

pain, and other diseases like diarrhea, epilepsy, and dysentery (Evuen *et al.*, 2022).

Therapeutic potentials of the bioactive compounds in this plant have been reported to exhibit free radical scavenging (Adewale *et al.*, 2023); anticarcinogenic capacities (Soni *et al.*, 2024); ameliorate ovarian oxidative attack (Japhet *et al.*, 2024), and inhibit I,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and maintain Fe²⁺/Fe³⁺ homeostatic level (Yusuf *et al.*, 2018). Phytochemicals screening report on this plant extract reflected the presence of cardiac glycosides, steroids, terpenes, alkaloids, flavonoids, and saponins (Adewale *et al.*, 2023), which are essential compounds reported to exhibit beneficial properties to counter the effect of oxidation and inflammatory processes (Santiago *et al.*, 2021; Ndoye *et al.*, 2024). The lethality dose (LD₅₀) of the fruit and stem-bark extracts had been reported to be 3,464 mg/kg b.wt and 1264.9111 mg/Kg b.wt (Akinloye *et al.*, 2019; Babatunde *et al.*, 2025). Likewise, a report from GC-MS investigation shows the presence of the coumarin family named scoparones, which exhibit free radical scavenging and antitumor activities, and neurostimulants named amphetamines, which exhibit neuroprotective effects against attention deficit (Adewale *et al.*, 2023). Also, HPLC-DAD profiling accounted for the presence of polyphenols like ferulic acid, vanillic acid, salicylic acid, caffeic acid, coumaric acid, anthocyanins, and gallic acid in the plant (Omoba *et al.*, 2019; Okpoghono *et al.*, 2023). Other studies have reported the plant's neuroprotective (George *et al.*, 2019; Nneka *et al.*, 2021); nephroprotective (Babatunde *et al.*, 2025); antimicrobial (Yusuf *et al.*, 2018); anti-infertility (Chibuogwu *et al.*, 2022), hypoglycaemic (Asanga *et al.*, 2025) and anti-hypertensive effects (Ogbuagu *et al.*, 2020).

However, to date, there has been no information on the protective effect of *X. aethiopica* on the hepatotoxicity actuated by pesticides. This is important since the liver is an important organ, mainly concerned with detoxification, and it is highly susceptible to injury posed by exposure to xenobiotics. Also, the xenobiotics are usually concentrated in the liver since the blood conveying dissolved materials arrives directly via the portal veins from the gastrointestinal tract. These compromised liver metabolic pathways lead to liver dysfunction, disease, and failure in the long run (Wang, *et al.*, 2025). Therefore, this work aim to investigate the hepatoprotective potential of *X. aethiopica* against glyphosate-induced toxicity.

2.0 MATERIALS AND METHODS

2.1 Chemicals and reagents

Herbicide Roundup with 480 g of glyphosate per /Liter manufactured by Monsanto Company (Mumbai, India) was utilized for this study. Radox ALT and AST kits with Cat.No AL8304 and AS8306 were procured from Radox Laboratories Limited (U.K.), while rat IL-6 (CSB-E04640r), rat CRP (CSBE07922r), and rat-TNF- α (CSE-E1187r) were procured from e-Bioscience, Inc. Other laboratory bench reagents, like Na₂CO₃ and NaHCO₃, used were of analytical grade.

2.2 Collection and Authentication

A fresh stem bark of *X. aethiopicum* was obtained from Oba-Ile Village forest situated along Ikirun-Offa road, Osun state. Authenticated at the Department of Plant Biology, University of Ibadan, and specifically at the Herbarium unit of this department. UIH-22944 was the authentication voucher number allotted to the plant. Upon authentication, the same plant stem bark was obtained for this study.

2.3 Plant extract preparation

The above-mentioned stem bark sample was chopped into bits and ground into a powder after being allowed to air dry for two weeks. The resulting powder was macerated in 50 % ethanol for three days, with frequent morning and evening shaking. After 72 hours, the extract was filtered and condensed with a rotary evaporator to produce an adequate amount of extract. After being lyophilized and freeze-dried, the extracted

material was kept refrigerated until needed again. A yield of the extract of about 35 % was achieved.

2.4 Qualitative Phytochemical Screening

To affirm the presence of the phytochemicals present, qualitative phytochemical screening was done to test the presence of steroids, saponins, flavonoids, alkaloids, tannins, phenolics, and cardiac glycosides following the method described by Odebiyi and Sofowora (1978).

2.5 Experimental animals

Apparently healthy male albino Wistar rats (*Rattus norvegicus*) of thirty-six (36) with a weight ranging from 150 – 200 g were used for this study. The animal was sourced from Osun State University, Osogbo's Central Animal House, College of Health Sciences. For acclimatization, the animals were housed in transparent and spacious polypropylene cages and placed in the animal house of the department for a week. The animals were subjected to a 12-hour light/dark cycle, relative humidity of 45–55 % and temperature of about 25 \pm 2°C. The animals were daily fed with standard laboratory rat chow and allowed free access to cleaned water regularly. The NIH Guide for the Care and Use of Laboratory Animals was followed when handling and using the animals. Also, with the issued ethical permission number UNIOSUN/HREC/2021/003C, the ethics committee of Osun State University's College of Health Sciences in Osogbo awarded ethical approval.

2.6 Experimental Design

The animals were randomly divided into six groups and treated as follows;

Table 1: Experimental design

Group	Treatment
1	Negative control (fed with normal rat chow and freshwater)
2	Treated with 150 mg/kg Glyphosate [1/48 LD ₅₀] (Turkmen <i>et al.</i> , 2020)
3	Treated with 150 mg/kg Glyphosate + 126.49 mg/kg of XASE after 2 hrs
4	Treated with 150 mg/kg Glyphosate + 250 mg/kg Vitamin C after 2 hrs
5	Treated with 126.49 mg/kg of XASE [$\frac{1}{10}$ th of LD ₅₀] (Babatunde <i>et al.</i> , 2025)
6	Treated with 250 mg/kg Vitamin C (Adewale <i>et al.</i> , 2023)

The administration of the extract was done orally and treatment lasted for a week.

2.7 Tissue Collection and Processing

After 24 hours following the last administration, the animals were fasted overnight, anesthetized, and sacrificed. Collection of blood samples was performed using heart puncture into a sterile plain container as follows. After 10 mins of blood clotting, the samples were then centrifuged at 3000 rpm for 10 minutes in order to remove blood cells, leaving the serum behind. The serum obtained for each sample was stored at - 20°C. Also, for each group, the rat liver was excised,

rinsed, and subjected to a homogenization process using an ice-cold sucrose buffer (0.25 M, pH 7.4). To obtain the post-mitochondrial fraction, the tissue homogenates obtained were centrifuged at 10,000 rpm for about 10 min at 40°C in accordance with the method of Adebisi *et al.* (2022) and Adewale *et al.* (2023). Thereafter, the supernatant was obtained, collected, and stored for biochemical assays. Some liver samples were kept for histopathological examination by fixing using 10 % formalin.

2.7.1 Determination of liver function markers levels

The serum hepatic functional biomarkers, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities, were determined following their kit protocol. Also, the concentration of the total and direct bilirubin, as well as total protein level in the serum, was determined following the method of Reitman and Frankel (1957)

2.7.2 Measurement of liver oxidative stress and antioxidant markers

The Catalase enzyme activity in the liver homogenate was determined by employing hydrogen peroxide (H_2O_2) as substrate and the loss in absorbance upon splitting of H_2O_2 was determined estimated at a wavelength of 240 nm following Claiborne's method (1985). while superoxide dismutase (SOD) activity was measured following the protocol of Misra and Fridovich (1972), which specifically involved measurement of the rate of inhibition of epinephrine auto-oxidation. Glutathione peroxidase (GPx) activity in the liver homogenate was determined via its reductive catalytic action on H_2O_2 using GSH as described earlier by Rotruck *et al.* (1973), while the concentration of reduced glutathione (GSH) present was quantitatively measured at a wavelength of 412 nm in accordance with the protocol of Beutler *et al.* (1963).

2.7.3 Determination of liver lipid peroxidation and nitric oxide levels

Malondialdehyde (MDA-lipid peroxidation product formed) level was measured following the method of Farombi *et al.* (2000), established to quantify the degree of liver lipid peroxidation and expressed as micromoles of MDA per milligram protein. The nitric oxide level in the samples was measured using the Griess reaction as specified by the method of Green *et al.* (1982).

2.7.4 Quantitative measurement of C-reactive protein level

Using the method outlined in the instructional manual for rat C-reactive protein (CRP) ELISA Kit, the C-proteins (CRP), which is one of the most keen indicator of systemic inflammation, were quantified using sandwich enzyme-linked immunosorbent assay (ELISA) methodology.

2.7.5 Quantitative measurement of Tumor necrosis factor-alpha level

The concentration of Tumor necrosis factor-alpha ((TNF- α) in the liver was quantitatively measured using a sandwich ELISA method as specified ELISA kit instructional manual obtained from CUSABIO.

2.7.6 Quantitative estimation of Interleukin-6 level

The pro-inflammatory cytokine named Interleukin-6(IL-6), known also to be an indicator of cellular and systemic inflammation, was quantified by measuring its concentration in the liver homogenate using sandwich ELISA techniques. This was done by following the protocol in its ELISA kit's instructional manual.

2.8 Histopathology

The formalin solution (10 %), which had been buffered, was used for the fixation of the liver samples for 3 days. Every day, the solution was changed to reduce shrinkage and the existence of artefacts. For microscopic examination, the tissue was sectioned and stained with hematoxylin and eosin in accordance with the earlier procedure described by Fischer *et al.* (2008). Tissue sections of 4-5 μ m were cut for imaging and examination using an Amscope microscope (Amscope camera: 5-megapixel resolution) at magnification X400 by a pathologist.

2.9 Statistical Analysis

The statistical software named Graph Pad Prism version 5.0, for Windows (Graph Pad Software, San Diego, CA), was used for the analysis of data obtained in the study. Data analysis was done using One-way analysis of variance (ANOVA), this then followed by Tukey's multiple comparisons for analyzing the differences between their means and data values, with p-values less than 0.05 considered statistically significant. All results obtained were presented as mean \pm standard deviation.

3. RESULTS

3.1 Qualitative phytochemical screening result of XASE

The *X. aethiopica* phytochemicals composition tested for was outlined in Table 2. The results showed the presence of the following bioactive compounds: saponins, tannins, phenolics, flavonoids, glycosides, steroids, and alkaloids were present in the plant extract.

Table 2: Qualitative Phytochemical Profile of *X. aethiopica* Stem bark ethanol extract

Phytochemical	Status
Saponin	+
Tannin	+
Phenolics	+
Flavonoids	+
Glycoside	+
Steroid	+
Alkaloid	+

+ Indicate the presence of the bioactive compound

3.2 Effect of treatment of *X. aethiopica* extract on the body weight of rats upon exposure to glyphosate

The body weight of rats treated with glyphosate only and those administered *X. aethiopica* extract upon exposure to glyphosate are present (Table 3). As shown

below, exposure to glyphosate only significantly decreased the body weight gain of the rats when compared to the control ($p < 0.05$). However, treatment with *X. aethiopica* extract or vitamin C after exposure to glyphosate significantly modulates the rat body weight gain.

Table 3: Effect of treatment of *X. aethiopica* extract on the body weight of rats upon exposure to glyphosate

Group	Final body weight(g)	Initial body weight(g)	Body weight gain(g)
Group 1	180.6 \pm 1.50	159.2 \pm 3.84	34.60 \pm 4.37
Group 2	181.8 \pm 3.07	169.6 \pm 3.11	12.01 \pm 0.45 ^a
Group 3	181.2 \pm 1.66	160.6 \pm 3.67	32.60 \pm 3.56
Group 4	183.2 \pm 3.15	159.8 \pm 2.82	32.40 \pm 2.64
Group 5	194.2 \pm 2.42	165.0 \pm 2.98	29.20 \pm 0.75
Group 6	199.2 \pm 1.86	169.2 \pm 2.38	30.00 \pm 1.10

Data are displayed as the mean \pm standard deviation (n=5) for each group. Superscript ^a values are significantly different ($p < 0.05$) from the control group.

3.3 Effect of *X. aethiopica* on liver function markers level in Glyphosate-Induced Hepatotoxicity

Results obtained revealed that exposure to glyphosate caused significant ($p < 0.05$) elevation in the activities of hepatic functional biomarkers, AST and ALT, in the blood serum of Wistar rats as compared to the control group (Table 4). However, co-treatment with either *X. aethiopica* extract or vitamin C (Standard drug) alone upon exposure to glyphosate significantly ($p < 0.05$) modulated the activities of these hepatic enzymes when compared to the group treated with glyphosate only. Also, the serum level of conjugated and total bilirubin was significantly increased ($p < 0.05$) upon exposure to glyphosate in comparison to the control group, but co-

treatment of rats with either *X. aethiopica* extract or vitamin C alone with or without exposure to glyphosate in combination significantly ($p < 0.05$) modulate the level of the molecules when compared to the group exposed to glyphosate only as shown in Table 4.

3.4 Effect of *X. aethiopica* on Total Protein Level in Glyphosate-Induced Liver Toxicity

As depicted in Table 4, exposure of rats to glyphosate significantly ($p < 0.05$) decreased the level of total proteins in the serum of rats when compared to the control group; however, co-treatment of rats with *X. aethiopica* extract or ascorbic acid significantly modulates the levels of serum.

Table 4: Impact of *Xylopiya aethiopica* on hepatic functional biomarker levels in the serum of rats exposed to glyphosate

Group	AST(U/L)	ALT(U/L)	Total Protein(U/L)	Total Bilirubin (mg/dl)	Conjugated Bilirubin (mg/dl)
1 (Control)	63.84 \pm 2.23 ^a	58.37 \pm 3.10 ^a	17.63 \pm 0.46 ^a	1.49 \pm 0.31 ^a	0.56 \pm 0.46 ^a
2	91.68 \pm 1.56 ^b	92.98 \pm 0.57 ^b	6.63 \pm 0.40 ^b	2.56 \pm 0.31 ^b	1.54 \pm 0.55 ^b
3	65.68 \pm 2.16 ^{a,c}	63.63 \pm 1.44 ^{a,c}	16.23 \pm 1.40 ^{a,c}	1.80 \pm 0.05 ^{a,c}	0.92 \pm 0.09 ^{a,c}
4	65.84 \pm 2.20 ^a	61.61 \pm 2.52 ^a	15.92 \pm 1.21 ^a	1.59 \pm 0.20 ^a	0.81 \pm 0.03 ^a
5	64.68 \pm 3.36 ^a	60.98 \pm 1.50 ^a	14.91 \pm 0.87 ^a	1.88 \pm 0.27 ^a	0.88 \pm 0.09 ^a
6	65.79 \pm 1.06 ^a	59.44 \pm 3.02 ^a	13.74 \pm 1.03 ^a	1.94 \pm 0.17 ^a	0.85 \pm 0.10 ^a

ALT-Alanine aminotransferase; AST-Aspartate aminotransferase; Data are presented as the mean \pm standard deviation (n = 5) for each group. Values with superscripts ^{a, b & c} were those that were significantly different ($p < 0.05$)

3.5 Effect of *X. aethiopica* extract on antioxidant enzymes and GSH in glyphosate-induced liver toxicity

In this study, exposure of rats to glyphosate leads to oxidative stress and inhibition of enzymes as reflected by significant declines ($p < 0.05$) in the activities of the enzymatic antioxidants CAT, SOD, and GPx when compared with the control group. Albeit, treatment with *X. aethiopica* extract and vitamin C each alone upon exposure to glyphosate significantly modulate their activities by increasing the activities of SOD and CAT enzymes in comparison to the control group (Fig. 1). Co-treatment of glyphosate exposed rats with extract or vitamin C significantly increased the GPx activity as compared to those administered glyphosate only (i.e. group 2), although the improvement this antioxidant enzymes activity is up to the control group but it was far greater than that of the group 2.

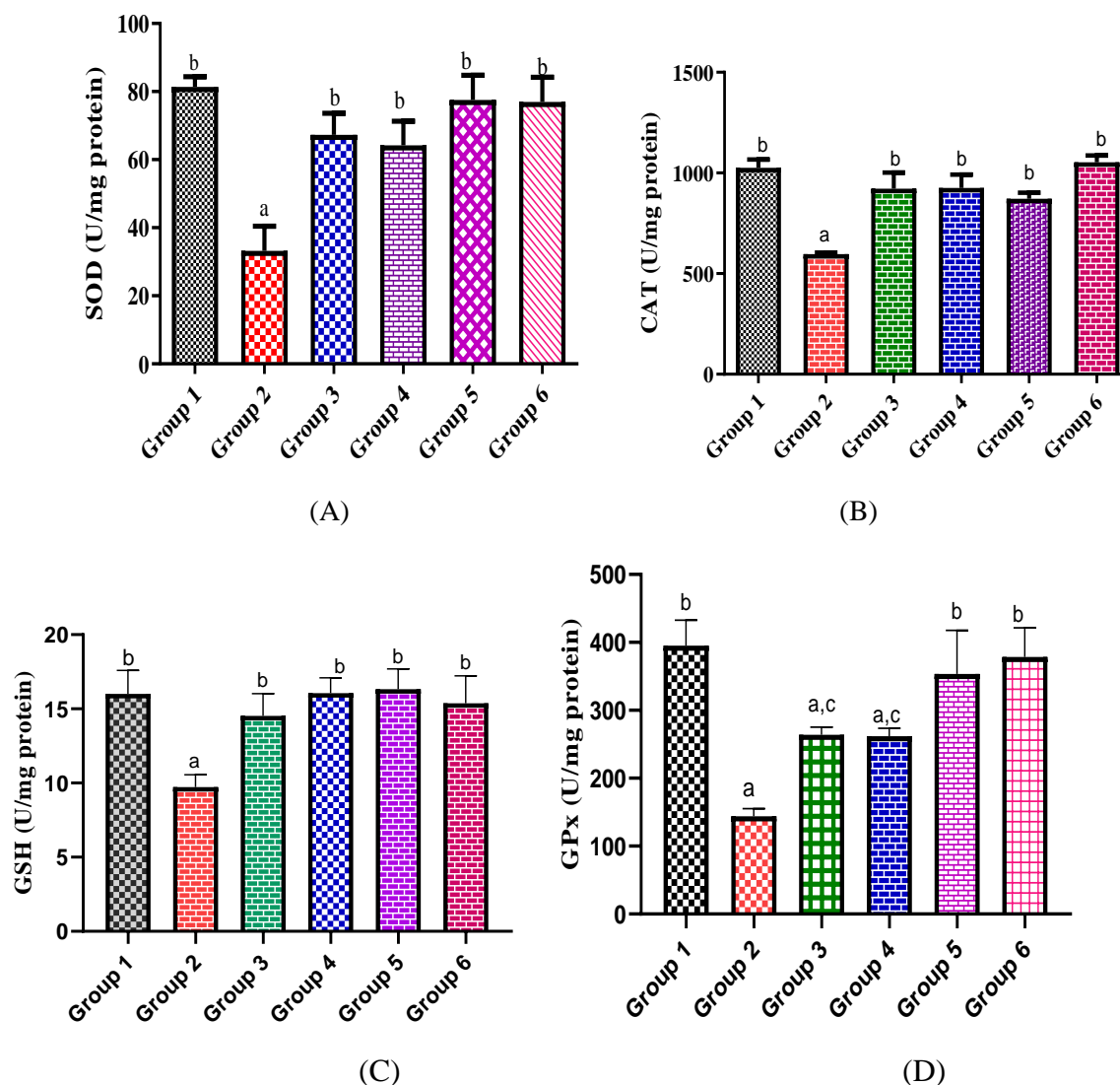


Fig. 1: Effect of *Xylopiya aethiopica* extract on antioxidant enzymes and GSH in glyphosate-induced hepatotoxicity. Data are presented as the mean \pm standard deviation ($n=5$) for each group. Superscripts ^{a, b & c} values were those that are significantly different ($p < 0.05$). SOD: superoxide dismutase (A); CAT: catalase (B) GSH: reduced glutathione (C) and GPx: glutathione peroxidase (D)

3.6 Impact of *Xylopiya aethiopica* extract on nitric oxide and malondialdehyde levels in the liver homogenate of rats exposed to glyphosate

To determine further the depth of oxidative stress, we measured the level of nitric oxide and lipid peroxidation product “malondialdehyde” in the tissue homogenate. The result revealed that glyphosate exposure elicits a significant increase ($p < 0.05$) in the level of nitric oxide and malondialdehyde, as shown in Fig. 2; however, treatment with *X. aethiopica* extract alone, separately, and upon exposure to glyphosate significantly modulates the concentrations of these molecules when compared to the negative control group.

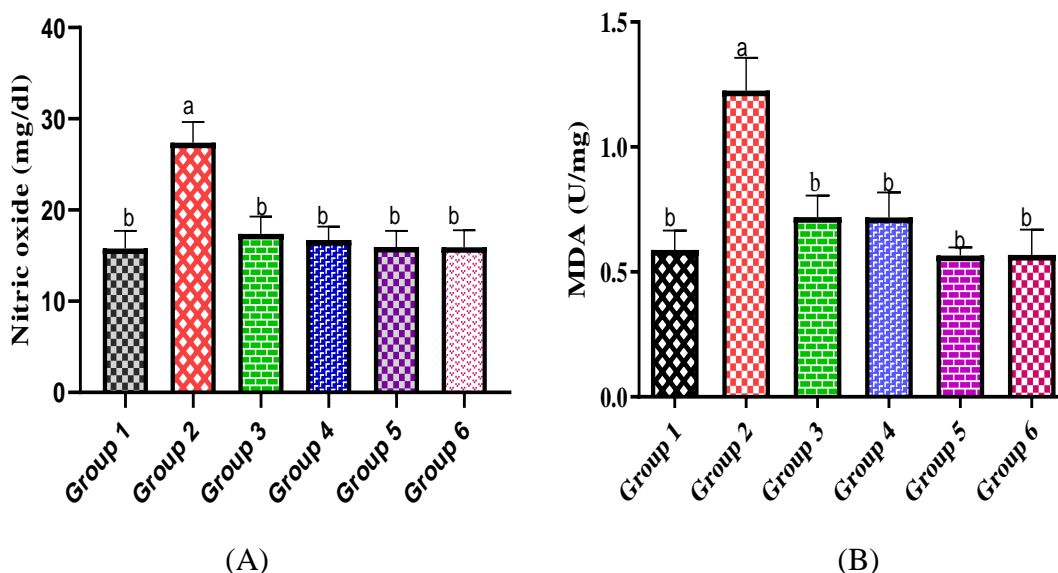
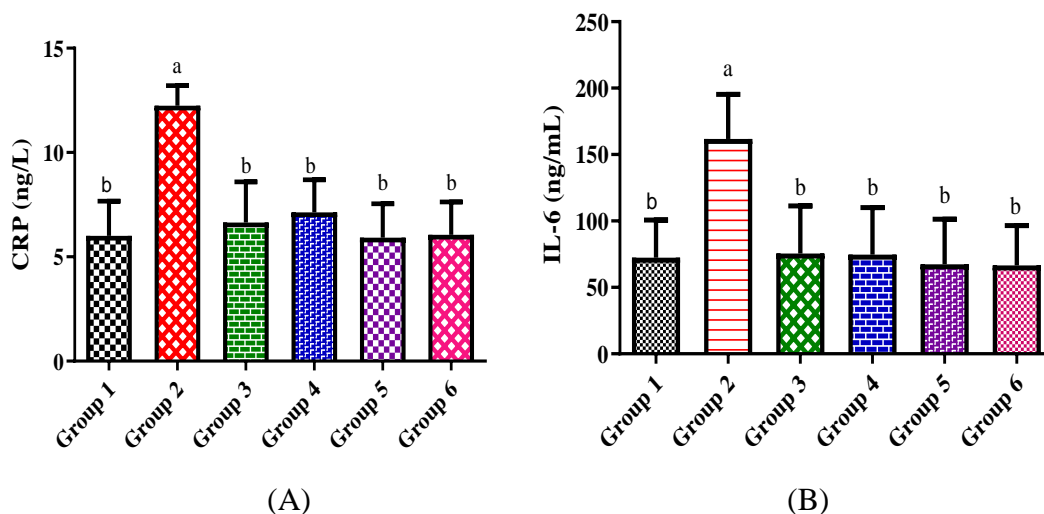
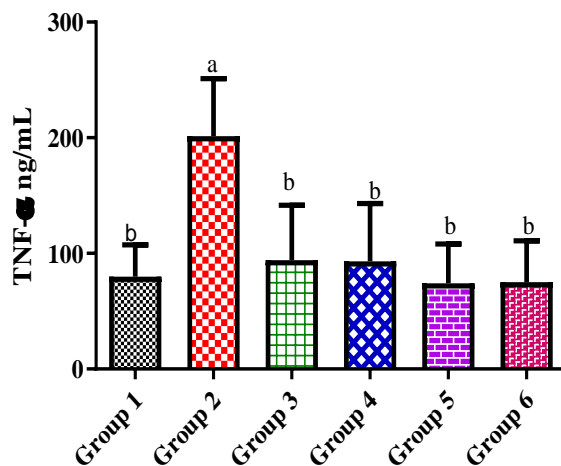


Fig 2: Effect of *Xylopiya aethiopica* extract on Nitric oxide and Malondialdehyde in the liver homogenate of rats exposed to glyphosate. Data are presented as the mean \pm standard deviation ($n=5$) for each group. Superscripts ^a & ^b values were those that are significantly different ($p < 0.05$). NO: Nitric oxide (A); MDA: Malondialdehyde (B)

3.7 Effect of *Xylopiya aethiopica* extract on inflammatory markers in glyphosate-induced hepatotoxicity

In this study, an assessment of the level of C-reactive protein, tumor necrosis factor- α , and interleukin-6, which are inflammatory markers, was carried out. Results of our findings revealed that exposure of rats to glyphosate only significantly ($p < 0.05$) elevated the expressions of these cytokines and proteins when compared with the control group (Fig.3). Albeit, treatment of rats with *X. aethiopica* extract and vitamin C upon exposure to glyphosate and treatment of rats with the extract or vitamin C alone significantly modulate the levels of these inflammatory markers when compared to the group treated with glyphosate-only ($p < 0.05$).





(C)

Fig 3: Effect of *X. aethiopica* extract on inflammatory markers in glyphosate-induced hepatotoxicity

Data are presented as the mean \pm standard deviation (n=5) for each group. Superscripts ^a & ^b values were those that are significantly different (p<0.05). C-reactive protein (CRP), interleukin 6 (IL-6), and Tumor necrosis factor alpha (TNF- α).

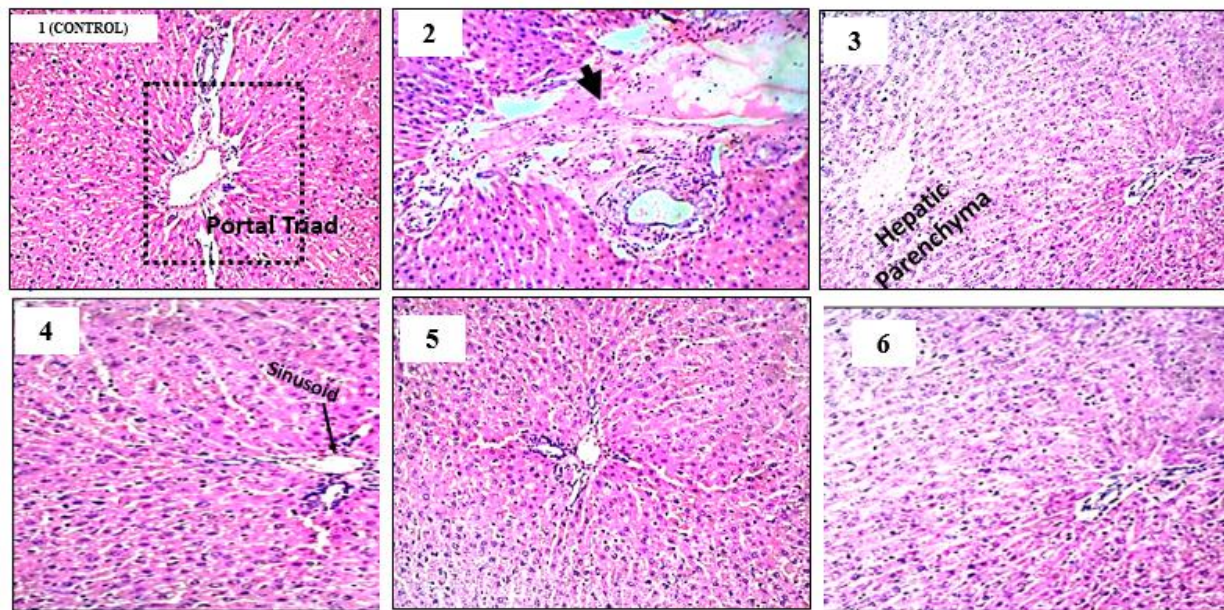


Plate 1: Photomicrographs of the liver tissue at magnification X400.

Group 1: (Control) showed no visible pathological alterations; **Group 2:** rats showed cellular degeneration of hepatocytes and multiple foci of hepatocellular necrosis with infiltration by lymphocytes and macrophages. Remarkable improvement was observed in hepatocyte architecture at different areas around the central veins and portal tract in **group 3** upon co-

treatment with *X. aethiopica* extract. **Group 4** rats showed normal hepatocyte architectural morphology, with their sinusoids appearing normal and not infiltrated upon treatment with vitamin C only. **Group 5** rats showed no morphological alterations and congestion upon treatment with *X. aethiopica* extract only. **Group 6** rats showed liver cells (hepatocytes)

morphology appearing normal, with no significant observable pathological lesions.

4.0 DISCUSSION

The risk associated with glyphosate exposure has raised concerns due to the toxicity posed to humans and animals. Recent research toxicity of glyphosate has shown it altered mitochondrial activity by uncoupling oxidative phosphorylation, and deregulation of metabolic pathways leading to oxidative stress, systemic inflammation, and organ injury (Pandey *et al.*, 2019; Klátyik *et al.*, 2025). Some additional reports have also linked its exposure to a higher possibility of developing cancer (Panzacchi *et al.*, 2025) because many of these molecular mechanisms mediate the development of cancer. Therefore, there is a need for safer means to eliminate this toxicological effect naturally; hence, phytotherapy is an alternative form of preventive or ameliorative medicine to combat pesticide toxicity.

In our present study, we set out to accentuate the beneficial potential of *X. aethiopica* on glyphosate-induced hepatotoxicity in rats. *X. aethiopica* is among the medicinal plants that have been reported to exhibit pharmacological effects in treating many diseases in humans. Studies have proven the presence of phytochemicals such as alkaloids, cardiac glycosides, saponins, flavonoids, steroids, anthraquinones, and tannins in this plant which enable its conferred several therapeutic roles (Alagbe *et al.*, 2023; Ndoye *et al.*, 2024). For instance, *X. aethiopica* has shown antioxidant, anti-inflammatory, antimicrobial, anti-allergic, anti-hypertensive, and cancer-preventive activities (Ogbuagu *et al.*, 2020; Adewale *et al.*, 2023; Babatunde *et al.*, 2025). In this present study, qualitative phytochemical screening of *X. aethiopica* also unveiled the presence of active phytochemical compounds like saponins, tannins, phenolics, flavonoids, glycosides, steroids, and alkaloids in the plant extract (Table 2).

On the body weight, exposure to glyphosate only significantly reduced the body weight gain of rats upon comparison to the control groups and others (Table 3), which might occur due to a rise in the concentration of potentially toxic compounds in the blood plasma, which can impair metabolism. This result supports earlier reports of oral exposure to glyphosate formulations at low doses (Pandey *et al.*, 2019; Teleken *et al.*, 2019; Mutwedu *et al.*, 2021). However, administration of either vitamin C or *X. aethiopica* alone or in concurrent treatment with glyphosate significantly modulates the declines in rats' body weight gain when compared to the control group.

Also, the serum or plasma levels of ALT and AST are liver-specific enzymatic biomarkers used to assess the structural integrity of the hepatocytes and early hepatic acute injury/damage and leakage of the hepatic content. In this present investigation, the exposure of rats to glyphosate only caused a significant increase in the activities of AST and ALT (Table 4). This could arise as a result of cytolysis, leading to leakage of the hepatocyte cytosolic enzymes into the bloodstream when injury occurs (Patel and Windon, 2020). However, co-treatment with XASE or vitamin C alone upon exposure to glyphosate significantly modulates the hepatic enzyme activities when compared with the glyphosate-treated group only. This result is in accordance with the earlier report of Ngozika *et al.* (2022), who reported that XASE is more hepato-protective and reno-protective than other plant extracts considered ethanol-induced toxicity. Serum Bilirubin level, a degradative end products of hemoproteins is another principal marker of liver injury or hepatocyte loss. Exposure to organophosphate pesticides has been linked to building of this toxic end product, leading to liver function impairment and damage (Huang *et al.*, 2025). Evidence of these was observed in this study, as glyphosate exposure notably increased total and conjugated bilirubin levels compared to controls. However, co-treatment with XASE normalized the bilirubin level to a level similar to that of the control group.

One of the most common pathological mechanisms implicated in hepatotoxicity, liver injury, and failure is Oxidative stress (Kumari and Kumar, 2022). The body cell defends itself against this oxidative attack by free radicals and ROS via an antioxidant system, which includes SOD, CAT, GPx, GST, and GSH. The action of SOD and CAT serves as the first line of cellular protection against oxidative damage. The SOD helps to convert superoxide radicals generated endogenously to hydrogen peroxide, while CAT helps to convert destructive peroxide radicals into harmless forms such as oxygen and water (Rao *et al.*, 2025). In our present study, exposure to glyphosate only significantly decreased the enzymatic activities of SOD and CAT as compared to the control (Fig.1 A-B). The occurrence of these exists due to either oxidative destruction of the enzymes (proteins) or additive inhibition of the enzyme's defensive activity by the toxicant. In contrast, administration of either *X. aethiopica* extract or vitamin C upon exposure to glyphosate significantly modulates the activities of these enzymes when compared to the control group. The ethnopharmacological potential of this extract to restore the anti-oxidative activities of SOD and CAT might be due to the presence of

phytochemicals qualitatively identified above, i.e., flavonoids and tannins, as well as scoparones (which belong to the family of coumarins), as suggested in a previous study (Adewale *et al.*, 2023). Yu *et al.* (2021) and Adewale *et al.* (2023) earlier reported that flavonoids, tannins, and scoparones exhibit antioxidant properties to enhance the synthesis of SOD and CAT enzymes directly or indirectly via the supply of their cofactors. Likewise, treatment of rats either with Vitamin C or extract alone modulates the activities of these antioxidant enzymes.

The antioxidant molecule GSH, which is a secondary line of cellular defense utilized by glutathione peroxidases (GPx), glutathione-s-transferases, and Peroxiredoxins (Prdx) against cellular attack by reactive molecular species and for the detoxification process by phase II metabolizing enzymes (Elias-Assmann *et al.*, 2020; Averill-Bates *et al.*, 2023). Results from the present investigation demonstrated that exposure to glyphosate significantly decreased the level of GSH (Fig. 1C) and activity of GPx (Fig. 1D) which might be due to its overutilization by these antioxidant enzymes. However, treatment with either *X. aethiopica* extract or vitamin C upon exposure to glyphosate significantly elevates the level of GSH and GPx activity as compared to the group treated with glyphosate, which may occur due to the ability of the bioactive compounds in the *X. aethiopica* to enhance the production of GSH. Modulatory control in the level of GSH was also observed upon treatment of rats with either *X. aethiopica* extract or Vitamin C alone. The modulatory activity of *X. aethiopica* and vitamin C against alteration in the level of cellular GSH observed in this study is similar to findings in previous reports on the brain (Adikwu and Ehigiator, 2020).

Nitric oxide (NO) is one of the ROS known to be a pro-inflammatory mediator. Under abnormal cellular conditions, such as exposure to radiation, pesticides, or during cellular injury and defense against pathogens, NO is generated in excess by the action of inducible nitric oxide synthase, leading to an enhanced inflammation process (Scioli *et al.*, 2020). As for the group treated with glyphosate only, their NO level was significantly increased as compared to the control group (Fig. 2A). This might probably occur as a result of additional reaction of NO with superoxide anion, generating more destructive nitrite anion, causing damage to the liver (Lashgari *et al.*, 2024). In this present study, administration of either *X. aethiopica* extract or vitamin C alone or in combination with glyphosate significantly modulates the level of NO when compared to the control group.

The ability of *X. aethiopica* extract to modulate the level of NO might be due to the antioxidant capacity of the phytochemicals.

Lipid peroxidation product MDA is an important index for estimating the level of oxidative attack on cellular polyunsaturated fatty acids. The high susceptibility of the cell membrane to oxidative attack is due to the presence of polyunsaturated fatty acids in its structure. Its biochemical quantitative assessment is based on interaction with thiobarbituric acid. It is used as a biomarker for cell membrane injury, oxidative stress, asthma, cardiovascular diseases, tumors, and cancer (Zheng *et al.*, 2024). Several reports have implicated oxidative stress and lipid peroxidation as part of the mechanisms by which pesticides exact their toxicity (Ndonwi *et al.*, 2019; Sule *et al.*, 2022). Results from this study also support lipid peroxidation as a pathological process implicated in pesticide toxicity, because the toxicant group expressed a significantly up-regulated level of MDA in comparison to the control group (Fig.2B). However, treatment with *X. aethiopica* extract upon exposure to glyphosate significantly modulates the level of MDA. Also, treatment with either vitamin C or *X. aethiopica* extract alone produces no significant alteration in the MDA level. This is an indication that the *X. aethiopica* extract has modulatory potential in suppressing oxidative stress and lipid peroxidation as previously described by Ibiam *et al.* (2024)

Systemic and organ inflammation are physiological mechanisms associated with pesticide toxicity and employed in disease pathogenesis (Lopesferreira *et al.*, 2023). Result obtained from our study shows that exposure to glyphosate significantly increased ($p < 0.05$) the level of inflammatory indicators cytokines (TNF- α , IL-6) and C-reactive proteins (Fig. 3A-C), which is consistent to the report of Pandey *et al.* (2019), however treatment with *X. aethiopica* extract and the standard drug (vitamin c) alone upon exposure glyphosate exhibit modulatory effect by decreasing the level of expression of the inflammatory markers to a level closer to that of the control. Additionally, compared to the control group, treating rats with the extract or vitamin C alone without exposure to glyphosate modulates the level of these indicators. This outcome is consistent with our earlier research (Adewale *et al.*, 2023). Interestingly, at different phases of inflammation, cytokines (proteins) and chemokines generated are transported to the injury site (Megha *et al.*, 2021). Among these, IL-1 β , TNF- α , and IL-6 constituted the pro-inflammatory cytokines,

while IL-4, IL-11, IL-13, and IL-10, among others, constituted the anti-inflammatory cytokines.

Our findings from a histopathological study of the liver of rats exposed to glyphosate only showed a marked architectural cellular degeneration of hepatocytes, characterized by multiple foci of hepatocellular necrosis with infiltration by lymphocytes and macrophages. These results further affirmed the cytotoxicity of the glyphosate (Plate 1). These histopathological changes were similar to earlier finding of Agbohessi *et al.* (2023). However, in groups treated with either *X. aethiopica* extract or vitamin C upon exposure to glyphosate, remarkable showed visible improvement was shown in hepatocyte architecture with respect to different areas studied around the central veins and portal tract, while other groups showed no visible morphological alterations and congestion.

5.0 CONCLUSION

Taking account of all these together, we conclude that *X. aethiopica* possess some useful phytochemicals capable of combating free radical generation, oxidative stress, inflammation, and organ damage associated with glyphosate-induced hepatotoxicity.

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AUTHORS' CONTRIBUTIONS

EOA: Conceptualization, methodology, writing-Original draft preparation, Investigation. **IOB:** Methodology, investigation, review, study design, and re-editing. **ABA:** Methodology, investigation, review, and editing. **ATA:** data analysis and reviewing; **HIA:** data analysis, review, and editing; **OOA:** Supervision, Investigation, Writing, review, and editing. All authors have read and approved the final version of the manuscript.

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