HISTOPATHOLOGICAL EVALUATION OF PHYLLANTHUS MUELLERIANUS ROOT EXTRACTS: PROTECTIVE EFFECTS ON TISSUES IN LETROZOLE-INDUCED RATS

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Abstract. The histopathological evaluation of kidney, liver, and heart tissues was conducted to investigate the protective and toxicological effects of aqueous and ethanolic root extracts of Phyllanthus muellerianus in rats administered letrozole (LTZ). LTZ-induced damage was characterized by hemorrhagic changes, necrosis, and inflammatory cell infiltration in the kidney, liver, and heart tissues. Treatment with 30 mg/kg body weight of both aqueous and ethanolic extracts showed marked restoration of normal histological features, particularly in the kidney and heart, with reduced cellular degeneration and inflammation. However, higher doses (60 mg/kg and 120 mg/kg) exhibited variable outcomes, including focal necrosis, hemorrhagic lesions, and inflammatory aggregates, particularly in the liver and kidney tissues. These findings highlight the dose-dependent therapeutic and toxicological effects of P. muellerianus root extracts, with lower doses demonstrating significant protective potential against LTZ-induced organ damage. The study underscores the importance of dose optimization in harnessing the therapeutic benefits of P. muellerianus while minimizing potential toxicities. Further research is recommended to elucidate the mechanisms underlying these effects and their implications for clinical application.
Keywords: *therapeutic, histopathology, toxicity, aqueous extract, ethanolic extract*

Introduction

The use of letrozole to enhance follicle development may be in vain, considering its usage in current infertility treatments due to the fact that it leads to various adverse toxic effects on the kidney, liver, heart, embryo, and ovary (Mukherjee et al., 2022). Hence, the process may result in apoptosis, fibrosis, and necrosis, which ultimately lead to the death of cancerous cells (Mukherjee et al., 2022). Phyllanthus muellerianus, a notable species from the Phyllanthaceae family, has a long-standing history of traditional use in various therapeutic practices, particularly for the treatment of kidney, liver, and cardiovascular diseases. This plant's applications in ethnopharmacology have garnered increasing interest as recent scientific studies validate its potential as an effective natural remedy for a range of health conditions (Ofokansi et al., 2023).

Review of literature

Research has particularly highlighted the nephroprotective effects of P. muellerianus. For example, Mbosso et al. (2010) conducted a study demonstrating that the aqueous extract of this plant significantly mitigated gentamicin-induced nephrotoxicity in rats. The protective effects were assessed through the monitoring of serum creatinine and urea levels, which are used as common indicators of kidney function. The findings suggest that the plant's bioactive compounds could play a crucial role in safeguarding renal health, providing a natural alternative for kidney protection (Mbosso et al., 2010). Moreover, Nayak et al. (2013) expanded on these findings by investigating the methanolic extract of P. muellerianus and its nephroprotective properties against cisplatin-induced nephrotoxicity in a rat model. This research further corroborated the plant's efficacy in preventing kidney damage, highlighting its potential as a supportive treatment for conditions that often lead to renal impairment (Nayak et al., 2013). In addition to its renal benefits, P. muellerianus has been recognized for its hepatoprotective properties. Suryakumar and Gupta (2011) illustrated this in their study, where they reported that the aqueous extract effectively protected against carbon tetrachloride-induced hepatotoxicity in rats. The protective effects were evidenced by significant reductions in serum levels of alanine transaminase (ALT) and aspartate transaminase (AST), enzymes commonly elevated during liver damage (Suryakumar and Gupta, 2011). In a related study, Dalla-Bona et al. (2015) found that the methanolic extract of P. muellerianus also demonstrated hepatoprotective activity against acetaminophen-induced liver toxicity, suggesting its role as a potential therapeutic agent for liver-related ailments (Dalla-Bona et al., 2015).

The cardioprotective effects of P. muellerianus have also been rigorously examined. Sugimoto et al. (2015) researched the plant's efficacy and found that the aqueous extract offered significant protection against isoproterenol-induced cardiotoxicity in rats. This cardioprotection was measured through decreased levels of serum creatine kinase (CK) and lactate dehydrogenase (LDH), both of which are markers indicative of cardiac injury (Sugimoto et al., 2015). In a subsequent study, Kazmi et al. (2018) explored the methanolic extract's effectiveness against doxorubicin-induced cardiotoxicity, reinforcing the plant's potential as a natural therapy for preventing heart damage during chemotherapeutic treatments (Kazmi et al., 2018). Overall, the diverse pharmacological effects of P. muellerianus-including its nephroprotective, hepatoprotective, and cardioprotective capabilities-position it as a promising candidate for natural health remedies aimed at addressing a variety of health issues. Continued exploration could lead to new insights into its applications in modern medicine. This study aims to gather insights into the histological examination of Phyllanthus muellerianus root extracts in treating letrozole-induced changes in rat tissues (kidney, liver and heart) to improve understanding and inform future interventions.

Materials and Methods

Female Wistar rats used for this study were procured from the animal facility of Ahmadu Bello University, Zaria. The animals were housed for acclimatization under standard laboratory conditions with free access to rat chow and drinking water ad libitum. The animals were acclimatized for one week before the commencement of the treatments. They were caged in well-ventilated wooden cages, maintained at a temperature of 27 ± 1°C with a twelve-hour light-dark cycle. Female rats with normal estrus cycles were selected and divided into eight groups. The control group received an

oral administration of vehicle (0.9% NaCl solution) once daily. The second group was orally administered letrozole (1 mg/kg/day) dissolved in 0.9% NaCl for twenty-one days, enough to cause alterations in the kidney, liver and heart tissues of rats. This group were then divided into six groups and treated orally for fourteen days with P. muellerianus root extracts at doses of 30, 60, and 120 mg/kg/day. At the end of the fourteen days of treatment, a rat from the control groups (normal rat and letrozole-induced rat) and representative rats from the letrozole (LTZ)-treated groups were randomly selected for euthanasia. Histological analyses were also conducted to confirm the alterations in the tissues of rats.

After fourteen days of treatment, the rats were weighed and euthanized via cervical dislocation under halothane anaesthesia. Following euthanasia, representative tissues (kidney, liver and heart) were carefully excised, cleaned, weighed, and fixed in formaldehyde solution for histological examination. Each representative tissues were processed step by step through 10% neutral formalin fixation (24 h), paraffin embedding, and longitudinally and serially sectioned at 4 μm with a microtome. The samples were stained with hematoxylin and eosin and read under a microscope according to the slightly modified methods described by Boakye et al. (2018).

Results and Discussion

The result of the histological examination of LTZ-induced alterations in rats and treated with the root extracts of P. muellerianus were presented in Table 1 with Figure 1, Figure 2 and Figure 3 (Plate A-X).

Table 1. *The LTZ-induced alterations in rats and treated with the root extracts of P. muellerianus.*

Plate	Category	Description
A	Photomicrograph of kidney from a rat that was not induced (Control) (H&E x250).	The renal cortex shows apparently normal renal corpuscle of the glomerulus (G), proximal (P) and distal (D) convoluted tubules with partly hemorrhagic cells (arrow).
B	Photomicrograph of kidney from a rat administered with LTZ (H&E x250).	The section is hemorrhagic (circle) with partly damaged cells (arrow).
C	Photomicrograph of kidney from a rat administered 30 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The renal cortex shows normal histological features of proximal (P) and distal convoluted tubules (D). Some of the glomerulus (G) appeared slightly shrunken with wider Bowman's space (arrowhead).
D	Photomicrograph of kidney from rat administered 60 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The section is marked by heavy degenerated renal cells (circle).
E	Photomicrograph of kidney from rat administered 120 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The section is hemorrhagic (blue arrow). The glomerulus (G) is partly surrounded by inflammatory cells (black arrow).
F	Photomicrograph of kidney from rat administered 30 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The renal cortex shows apparently normal renal corpuscle of proximal and distal convoluted tubules (P and D) with slightly degenerated glomerulus (G) and focal aggregate of inflammatory cells (arrows).
G	Photomicrograph of kidney from a rat administered 60 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The renal cortex shows damaged renal corpuscle presented by empty bowman's capsule (EBC), hemorrhagic (blue arrow) and necrotic cells (circles).
H	Photomicrograph of kidney from a rat administered 120 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The renal cortex shows apparently normal renal corpuscle of proximal and distal convoluted tubules (P and D) and glomerulus (G). There is with slightly focal aggregate of inflammatory cells (circle).
I	Photomicrograph of liver from a rat that was not induced (Control) (H&E x250).	The section presents normal histological features of hepatocytes (green arrow) and sinusoids (blue arrow) with scanty focal aggregates of mononuclear cells (circle).

J	Photomicrograph of kidney from a rat administered with LTZ (H&E x250).	The section shows degenerative changes of the hepatocytes along the central vein (CV) with focal aggregates of inflammatory cells. (arrows).
K	Photomicrograph of liver from a rat administered 30 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The section presents normal features of hepatocytes (blue arrow) with slight Kupffer cells hyperplasia (black arrows) and scanty aggregate of mononuclear cells (circle).
L	Photomicrograph of liver from rat administered 60 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The section shows normal histological features of hepatocytes (blue arrow), with a dilated and congested central vein (CV) surrounded by mononuclear cells (arrows).
M	Photomicrograph of liver from rat administered 120 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The section is marked with a focal area of necrotic hepatocytes and inflammatory cells (circles).
N	Photomicrograph of liver from rat administered 30 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The section shows hepatic changes and luminal thrombosis of the central vein (CV) surrounded by inflammatory cells along the portal triad.
O	Photomicrograph of liver from a rat administered 60 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The section shows normal histological features of hepatocytes (blue arrow), with a dilated central vein (CV) surrounded by mononuclear cells (arrows).
P	Photomicrograph of liver from a rat administered 120 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The section is hemorrhagic, marked by dilated and congested central veins (CV) with many bi-nucleated hepatocytes (black arrows).
Q	Photomicrograph of heart from a rat that was not induced (Control) (H&E x250).	The longitudinal section (LS) is showing apparently normal histological features. The myocytes have acidophilic sarcoplasm (blue arrow) and deeply stained nuclei (green arrow).
R	Photomicrograph of heart from a rat administered with LTZ (H&E x250).	The LS is marked by hemorrhagic (circle) and disarranged muscle fibres (green arrow).
S	Photomicrograph of heart from a rat administered 30 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The LS presented features of normal histology (green and blue arrow).
T	Photomicrograph of heart from a rat administered 60 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The LS presents normal histological features of cardiac myocytes (green and yellow arrows).
U	Photomicrograph of heart from rat administered 120 mg/kg bwt of aqueous extract of Phyllantus muellerianus (H&E x250).	The LS shows an apparently normal histological appearance of cylindrical branches of cardiac myocytes with an acidophilic sarcoplasm (blue arrow) and single oval vesicular nuclei (green arrow).
V	Photomicrograph of heart from rat administered 30 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The LS shows slightly disarranged myocytes' histological features (blue and green arrow).
W	Photomicrograph of heart from a rat administered 60 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The LS presented a focal aggregate of inflammatory cells (circle). The myocytes appeared normal (blue and green arrow).
X	Photomicrograph of heart from a rat administered 120 mg/kg bwt of ethanolic extract of Phyllantus muellerianus (H&E x250).	The LS shows an area of disarranged muscle fibres with scanty inflammatory cells (green arrow). The myocytes presented normal acidophilic sarcoplasm (yellow arrow) and single oval central vesicular nuclei (blue arrow).

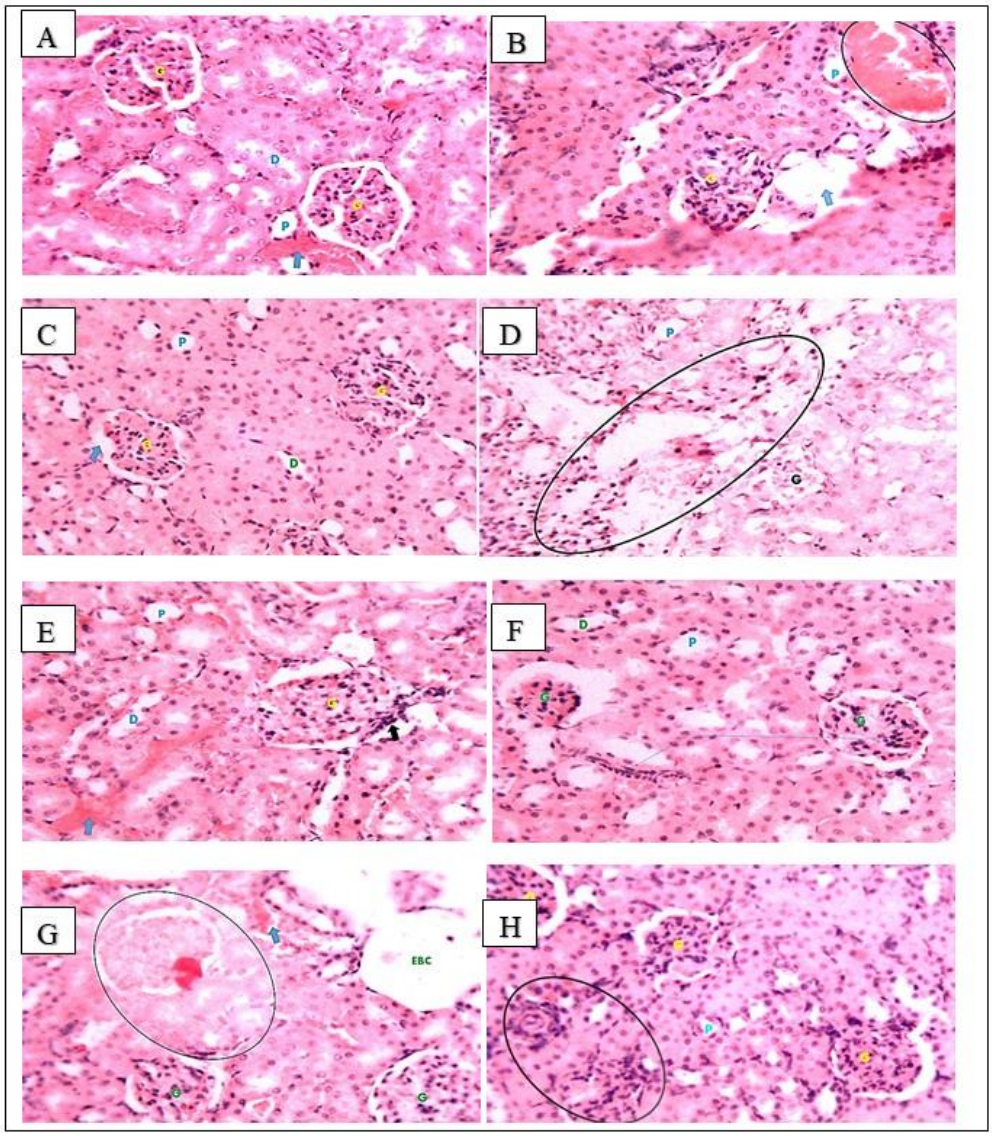

Figure 1. *Photomicrographs of kidney of rats.*

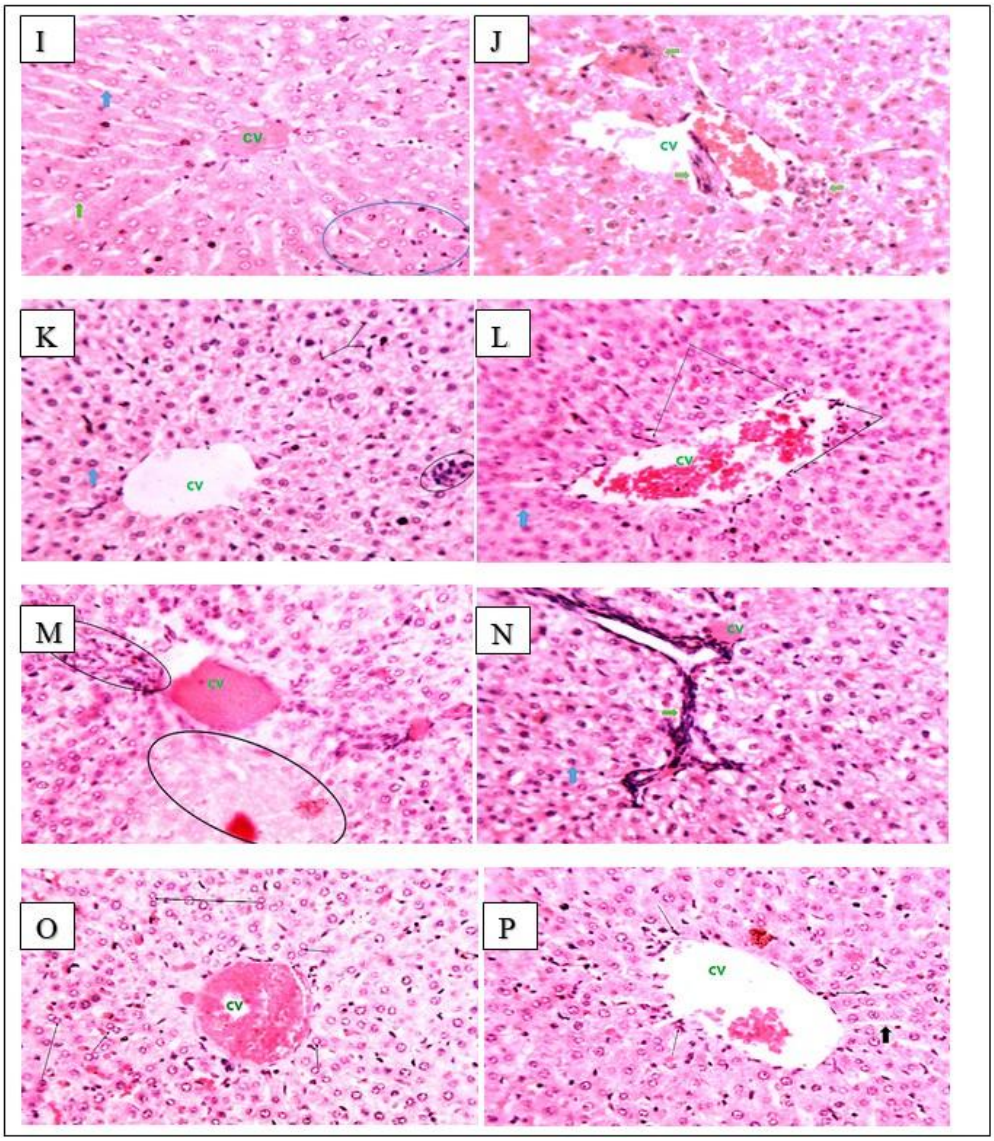

Figure 2. *Photomicrographs of liver of rats.*

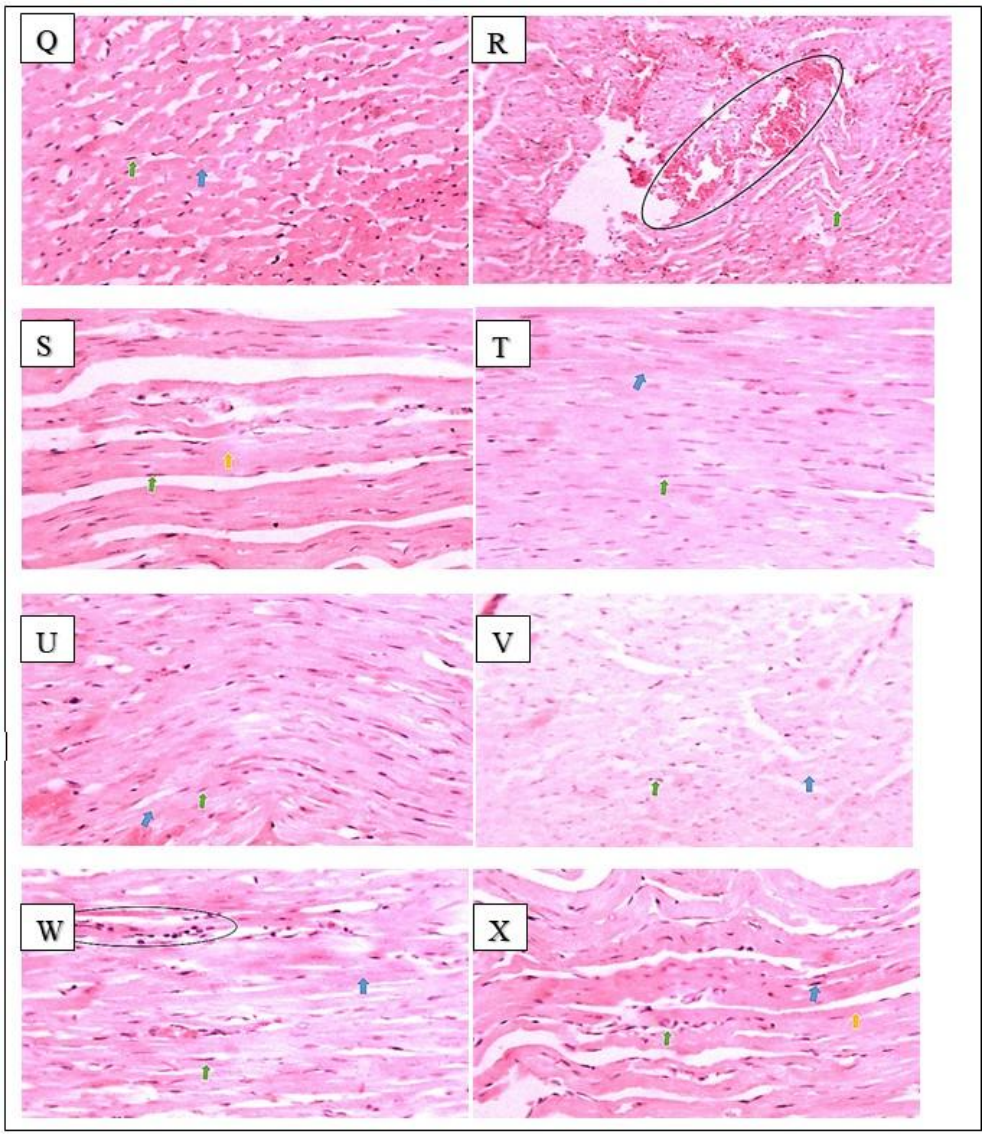

Figure 3. *Photomicrographs of heart of rats.*

The findings of this study provide insights into the effects of Phyllanthus muellerianus root extracts on histoarchitectural changes in the kidney, liver and heart of LTZ-induced alterations in rats, with a focus on histological analysis of these tissues. The results suggest that both aqueous and ethanolic roots extracts of P. muellerianus have potential therapeutic effects in ameliorating the histological alterations caused by LTZ in rats. The histopathological examination of the kidneys, liver, and heart in this study revealed significant structural alterations caused by letrozole (LTZ)-induced PCOS and the therapeutic effects of Phyllanthus muellerianus root extracts.

Kidney histopathology

The control group (Plate A) demonstrated normal renal architecture, including intact glomeruli and proximal and distal convoluted tubules. However, LTZ administration (Plate B) caused marked structural damage, such as hemorrhage and partly damaged renal cells, indicative of nephrotoxicity. This is consistent with previous studies demonstrating LTZ's nephrotoxic effects via oxidative stress and inflammation (Puri et

al., 2020). Treatment with aqueous and ethanolic extracts showed varying levels of protection and damage depending on the dosage. The 30 mg/kg aqueous extract (Plate C) exhibited nearly normal renal histology with slightly shrunken glomeruli, while higher doses (60 mg/kg and 120 mg/kg; Plates D and E) caused significant degeneration, haemorrhage, and inflammation, suggesting potential dose-related toxicity. Similarly, the ethanolic extract at 30 mg/kg (Plate F) showed relatively preserved renal architecture with minimal degeneration, but higher doses (60 mg/kg and 120 mg/kg; Plates G and H) led to haemorrhage, necrosis, and inflammatory cell infiltration, aligning with findings from other phytotherapeutic studies where higher doses induced toxicity (Anywar et al., 2021).

Liver histopathology

The control group (Plate I) exhibited normal liver architecture, including intact hepatocytes and sinusoids. LTZ induction (Plate J) resulted in degenerative changes, including inflammatory cell infiltration and hepatocyte damage, indicating hepatotoxicity. This is consistent with the known hepatotoxic effects of LTZ, which induce hepatotoxicity in rats without causing oxidative stress (Gharia et al., 2017; Aydin et al., 2011). The aqueous extract demonstrated a dose-dependent response. At 30 mg/kg (Plate K), liver histology was nearly normal, with slight Kupffer cell hyperplasia and minimal inflammation. At 60 mg/kg (Plate L), there was evidence of congestion and dilation of the central vein surrounded by mononuclear cells, while 120 mg/kg (Plate M) caused necrotic hepatocytes and inflammation, suggesting toxicity at higher doses. Similarly, the ethanolic extract at 30 mg/kg (Plate N) caused luminal thrombosis and inflammatory infiltration, while 60 mg/kg (Plate O) showed normal hepatocyte architecture with mild inflammation. However, the 120 mg/kg dose (Plate P) resulted in hemorrhagic and congested central veins with bi-nucleated hepatocytes, indicating potential hepatotoxicity at higher doses. These observations align with phytochemical studies suggesting that overconcentration of bioactive compounds may induce cellular stress and hepatotoxicity (Kamel et al., 2023).

Heart histopathology

The control group (Plate Q) showed normal cardiac myocytes with intact sarcoplasm and nuclei, while LTZ-induced rats (Plate R) exhibited haemorrhage and disorganized muscle fibres, indicating cardiotoxicity. These findings are similar to studies that associate LTZ administration with systemic oxidative damage (Pilutin et al., 2024). Treatment with aqueous and ethanolic extracts largely preserved cardiac architecture. All doses of the aqueous extract (Plates S, T, and U) maintained normal histological features of the cardiac myocytes with no significant damage, suggesting a protective effect. The ethanolic extract at 30 mg/kg (Plate V) caused slight disorganization of muscle fibres, while higher doses (60 mg/kg and 120 mg/kg; Plates W and X) resulted in focal inflammatory cell infiltration and minor disarrangements of cardiac fibres. These findings support the cardioprotective properties of bioactive compounds in P. muellerianus, such as flavonoids and saponins, known for their antioxidant effects (Gnaléi et al., 2019).

General observations

The histological findings demonstrate the protective effects of P. muellerianus root extracts, particularly at lower doses, in mitigating LTZ-induced damage. The aqueous extract showed a more consistent protective effect, especially in the kidneys and heart, but higher doses caused notable toxicity in the liver and kidneys. The ethanolic extract also exhibited protective properties, but higher doses led to greater histopathological alterations. These results suggest that while P. muellerianus root extracts hold therapeutic potential in addressing LTZ-induced histopathological damage, careful dose optimization is critical to minimize potential toxicity and maximize therapeutic efficacy. Further studies should investigate the mechanisms underlying the dose-dependent effects and validate these findings in clinical settings (Anywar et al., 2021; Nyirenda et al., 2021; Gnaléi et al., 2019).

Conclusion

The histopathological analysis of the kidneys, liver, and heart revealed the therapeutic potential of Phyllanthus muellerianus root extracts in mitigating organ damage induced by LTZ. Lower doses of both aqueous and ethanolic extracts (30 mg/kg) demonstrated significant protective effects, with near-normal histological features observed in the kidneys, liver, and heart. However, higher doses (60 mg/kg and 120 mg/kg) resulted in varying degrees of organ toxicity, including hemorrhagic changes, necrosis, and inflammatory cell infiltration, particularly in the liver and kidneys. These findings suggest that P. muellerianus root extracts exhibit dose-dependent effects, with lower doses showing promise as a therapeutic agent for managing LTZ-induced organ damage. However, higher doses may pose a risk of toxicity, emphasizing the need for careful dose optimization. Further studies are warranted to elucidate the mechanisms underlying these effects and to explore the potential clinical applications of P. muellerianus.

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Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

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