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Tissue Residue Profiles and Histopathological Alterations induced by Enrofloxacin and Ciprofloxacin in Albino Rats

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Abstract
The widespread use of veterinary antibiotics, particularly fluoroquinolones like enrofloxacin and ciprofloxacin, has raised serious concerns about tissue residue accumulation and toxicological effects in animal products consumed by humans. This study investigated the tissue residue levels and histopathological effects of enrofloxacin and ciprofloxacin in the liver and kidney of albino rats. Fifteen (15) female albino rats (weighing 120 to 160 g) were obtained from a certified animal breeding center in the University of Ibadan, Oyo State. Tissue residue levels of Enrofloxacin and Ciprofloxacin were quantified using High-Performance Liquid Chromatography (HPLC). The fixed tissue samples (liver and kidney) were processed through standard histological procedures. Result revealed that high-Performance Liquid Chromatography showed that enrofloxacin accumulated more in the liver (1.92 ± 0.23 µg/g) than the kidney (0.88 ± 0.15 µg/g), while ciprofloxacin accumulated more in the kidney (2.41 ± 0.25 µg/g) than the liver (1.27 ± 0.19 µg/g), with all treated groups significantly different from controls ($p < 0.05$). Histologically, treated rats exhibited vascular congestion, hepatocellular necrosis, fatty change, glomerular atrophy, and tubular epithelial necrosis, whereas controls showed normal architecture. Based on the findings, it was therefore recommended that veterinary practitioners should regulate the dosage and duration of fluoroquinolone use in animals to minimize hepatic stress and prevent toxic accumulation in the liver. Farmers should strictly adhere to drug withdrawal periods before slaughtering animals to ensure that harmful antibiotic residues are cleared from liver tissues.

Keywords: Enrofloxacin, Ciprofloxacin, Antibiotic residues, Veterinary drug metabolism, Toxic pathology

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Introduction

Antibiotics are widely used in veterinary medicine to manage bacterial infections in both livestock and laboratory animals. Their administration serves preventive, curative, and metaphylactic purposes, particularly in intensive animal production systems where diseases can spread rapidly (Ahmed *et al.*, 2023). The widespread use of antibiotics ensures animal health and productivity, yet it also brings growing concerns about antimicrobial resistance and drug residues in food products (Munanura *et al.*, 2023). Among the most commonly used antibiotics in veterinary settings are fluoroquinolones, especially Enrofloxacin and Ciprofloxacin **(**Abate and Birhanu, 2025**)**. These drugs are effective against a wide range of Gram-positive and Gram-negative bacteria due to their ability to inhibit bacterial Deoxyribonucleic acid (DNA) gyrase and topoisomerase IV—essential enzymes required for DNA replication (Shariati *et al.*, 2022). Their potency, broad-spectrum activity, and favorable pharmacokinetics make them a preferred option in treating infections in poultry, cattle, fish, and laboratory animals like albino rats. This also

extends to their use in clinical research and drug efficacy studies (Zhang *et al.*, 2024).

Enrofloxacin, a synthetic fluoroquinolone, is exclusively formulated for veterinary use, while Ciprofloxacin is its active metabolite and is used in both veterinary and human medicine (Moghadam *et al.*, 2018). After administration, Enrofloxacin is metabolized in animal systems into Ciprofloxacin, which may then circulate and accumulate in various tissues, including the liver, kidneys, and muscles (Shan *et al.*, 2022). The pharmacokinetic properties of fluoroquinolones—including rapid absorption, wide tissue distribution, and slow elimination—contribute to residue accumulation, especially when withdrawal periods are not observed. This represents a public health concern for consumers (Rodrigues & Silva, 2025). Residues of Enrofloxacin and Ciprofloxacin in edible tissues have been linked to adverse health effects, such as allergic reactions, disruption of gut microbiota, and contribution to antibiotic-resistant bacterial strains (Oladeji *et al*., 2025). Therefore, monitoring these antibiotics in animal tissue is crucial for safeguarding public health and maintaining confidence in food safety (Govind *et al.*, 2023).

Tissue residue refers to traces of pharmaceutical substances that remain in animal tissues such as muscle, liver, kidney, and heart—after the therapeutic use of a drug (Pratiwi *et al.*, 2023). These residues can persist long after the cessation of treatment and may enter the human food chain if the animals are slaughtered without respecting proper withdrawal periods (Khalifa *et al.*, 2023). In the case of Enrofloxacin and Ciprofloxacin, these residues are particularly persistent in liver and muscle tissues, which are frequently consumed (Moghadam *et al.*, 2018). This accumulation poses significant toxicological and immunological risks. For example, consumption of meat containing antibiotic residues has been associated with disturbances in human immune function and allergic responses. Moreover, persistent exposure contributes to antimicrobial resistance (AMR), a growing global threat that renders common infections harder to treat (Munanura *et al.*, 2023). In Uganda, residue levels of Enrofloxacin and Ciprofloxacin were detected above internationally acceptable limits, highlighting a lack of proper regulation and monitoring (Munanura *et al.*, 2023). International agencies like Codex Alimentarius, World Health Organization (WHO), and Food and Agriculture Organization (FAO) have established Maximum Residue Limits (MRLs) to reduce public exposure to such risks. These limits dictate the maximum concentration of a drug legally allowed in edible animal tissues (Sawyer *et al.*, 2024). However, in many developing nations, enforcement is weak, and surveillance systems are underfunded, allowing for excessive or inappropriate antibiotic use (Govind *et al.*, 2023).

Histopathology, the microscopic examination of tissue in order to study the manifestations of disease, remains a critical scientific method for evaluating toxicological impacts of pharmaceuticals on biological systems. When applied to antibiotic research, especially on fluoroquinolones like Enrofloxacin and Ciprofloxacin, histopathology offers insights into tissue-level damage that cannot be observed through external examinations alone (Ahmed *et al.*, 2023). Prolonged exposure to fluoroquinolones has been shown to induce organ-level toxicity, particularly in the liver and kidney, due to their metabolic transformation and persistence in these organs (Ahmed *et al.*, 2023; Genid *et al.*, 2022). Enrofloxacin, often metabolized into Ciprofloxacin in vivo, tends to persist in tissues for extended periods, particularly when withdrawal times are not adequately observed. According to Zhang *et al.* (2024), these antibiotics caused histological alterations in liver tissues of aquatic species, including hepatocellular degeneration and inflammation, confirming their systemic toxicity. In experimental mammalian models, including albino rats, histopathological examinations conducted by Genid *et al.* (2022) demonstrated cellular degeneration,

necrosis, and inflammatory damage in fluoroquinolone-exposed tissues.

The increasing use of fluoroquinolone antibiotics in animal production poses serious public-health concerns because these drugs can accumulate as residues in edible tissues and may cause organ toxicity in exposed animals. In Nigeria, poor adherence to recommended withdrawal periods and weak enforcement of veterinary drug regulations increases the likelihood of antibiotic residues entering the food chain. Studies such as Zhang *et al.* (2024) and Ahmed *et al.* (2020) reported residue levels above permissible limits, indicating a persistent safety challenge. Furthermore, fluoroquinolones have been linked to tissue damage in laboratory animals, yet limited local research has examined both residue levels and histopathological alterations simultaneously. Therefore, this study investigates the tissue residue profiles and associated liver and kidney histopathological changes induced by enrofloxacin and ciprofloxacin in albino rats, providing evidence that can guide veterinary drug safety policies.

Moghadam *et al.* (2018) conducted a comprehensive assessment of enrofloxacin and ciprofloxacin residues in broiler chicken tissues using Dispersive Liquid–Liquid Microextraction (DLLME) followed by High-Performance Liquid Chromatography (HPLC). A total of 250 liver, skin, muscle, heart, and gizzard samples were collected from slaughterhouses in Tabriz, Iran. The study found that enrofloxacin residues occurred most frequently in liver (52%) and skin (20%), while ciprofloxacin residues appeared in 30% of liver samples and 6% of skin samples. These findings highlight the liver as a primary reservoir for fluoroquinolone accumulation due to its central metabolic functions. Interestingly, muscle and other edible tissues showed no detectable residues, demonstrating that drug distribution varies considerably across organs. The study also confirmed the efficiency of DLLME in extracting trace residues from biological tissues, supporting its suitability for routine monitoring in food safety investigations. Furthermore, the detection of residues in liver and skin reinforces the importance of enforcing proper withdrawal periods before animal slaughter to prevent consumer exposure to veterinary drug residues.

Hou *et al.* (2022) evaluated the reproductive toxicity of ciprofloxacin (CIP) and enrofloxacin (ENR) in zebrafish and adolescent mice to understand how these antibiotics affect endocrine and reproductive development. The study showed that CIP exposure reduced spermatogonial mass, impaired sperm-forming tissues, and significantly lowered testosterone levels in male zebrafish. It also decreased the expression of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) genes, indicating hormonal disruption. In adolescent mice, ENR exposure inhibited the proliferation of Sertoli and Leydig cells and altered the transcription of genes essential for normal testicular development. Histological analysis revealed clear structural degeneration of testicular tissue after 30 days of treatment, confirming that prolonged fluoroquinolone exposure can harm reproductive organs. These findings demonstrate that fluoroquinolones may act as endocrine disruptors capable of affecting both hormonal pathways and reproductive morphology. The study underscores the broader toxicological implications of antibiotic overuse, especially in animals exposed to repeated or high doses.

Arunsi *et al.* (2025) investigated the hepatotoxic effects of chlorpyrifos—a commonly used agricultural insecticide—by analyzing liver histopathology in albino rats exposed to varying doses. Rats were divided into dose groups ranging from 0.01 to 0.05 ml/kg, and liver sections were examined for structural damage. The control rats showed normal hepatic architecture, whereas all treatment groups exhibited clear signs of liver injury. Low doses produced mild hepatocellular swelling and early fatty degeneration, while higher doses induced severe hepatic lesions, including necrosis, vacuolization, distorted hepatic cords, and dilated central veins. The most severe group (0.03 ml/kg) showed extensive cellular

damage and increased fat deposition, providing strong evidence that chlorpyrifos can induce dose-dependent hepatotoxicity. The changes were statistically significant ($p < 0.05$), confirming the toxic effects of repeated chemical exposure on mammalian liver tissue. The study highlights the vulnerability of liver tissue to xenobiotic substances and reinforces the relevance of histological assessment when evaluating chemical safety.

Materials and Methods

Experimental Animals

Fifteen healthy female albino rats (*Rattus norvegicus*) were obtained from the Animal Breeding Unit, University of Ibadan, Oyo State. Female albino rats were used because they are generally calmer, easier to handle, and exhibit lower levels of aggression than males, reducing stress-related physiological variations during experiments. Additionally, female rats show more stable body-weight patterns, which supports consistency in dose calculation. Their use is widely recommended in toxicological and residue-based studies for improved uniformity. The animals were aged 6–8 weeks and weighed between 120–160 g at the start of the experiment. They were housed in clean, well-ventilated cages with wood shavings as bedding under controlled environmental conditions (temperature 25 ± 2°C, 12-hour light/dark cycle). The animals were provided with commercial rat feed and clean water ad libitum. They were allowed to acclimatize for 7 days prior to the commencement of the experiment. Ethical approval for animal use was obtained from the Institutional Animal Ethics Committee (Approval No.: 241/IAEC/2025).

Experimental Design

The animals were randomly divided into three (3) groups of five (5) rats each:

- **Group A (Control)**: Received 1 mL of distilled water orally.
- **Group B (Enrofloxacin-treated)**: Received 10 mg/kg body weight of Enrofloxacin orally.
- **Group C (Ciprofloxacin-treated)**: Received 20 mg/kg body weight of Ciprofloxacin orally.

The administration of the drugs was done via oral gavage once daily for 7 consecutive days using calibrated feeding needles. The dosage of 10 mg/kg for enrofloxacin was selected based on veterinary therapeutic ranges documented in prior toxicological studies, where this dose produced measurable tissue responses without causing acute lethality. Ciprofloxacin was administered at 20 mg/kg because it has lower bioavailability in rats, and higher doses are required to achieve comparable systemic exposure. Rats were treated once daily for 7 days, following standard repeated-dose toxicity protocols. All drugs were diluted in distilled water and administered via oral gavage to simulate natural oral exposure similar to livestock medication practices.

Histopathological Preparation

All animals were anesthetized humanely using intraperitoneal injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). Once fully sedated, the animals were sacrificed, and tissues including the liver and kidney were carefully excised, rinsed in normal saline, and weighed. Each tissue sample was divided into two portions: one portion was preserved at -20°C for tissue residue analysis, and the other was fixed in 10% neutral buffered formalin for histopathological examination. The animals were not infected because the study focused on drug-induced tissue alterations rather than antimicrobial efficacy. Treatment commenced after a 7-day acclimatization period. Enrofloxacin and ciprofloxacin solutions were freshly prepared each day and administered orally using calibrated gavage needles once daily for 7 consecutive days. After the final administration, animals were fasted for 12 hours before anaesthesia, followed by tissue collection for residue quantification and histopathology

Tissue Residue Determination

Tissue residue levels of Enrofloxacin and Ciprofloxacin were quantified using High-Performance Liquid Chromatography (HPLC). Method validation was performed following standard chromatographic procedures. Calibration curves for

enrofloxacin and ciprofloxacin showed linearity ($R^2 > 0.998$) (Kassab *et al.*, 2005). Limits of detection (LOD) and quantification (LOQ) were established using signal-to-noise ratios of 3:1 and 10:1 respectively. Recovery tests using spiked tissue samples produced values between 85% and 98%, confirming the accuracy and precision of the HPLC method. About 1 gram of each tissue (liver and kidney) was homogenized in a solution of acetonitrile and centrifuged. The supernatant was filtered and injected into the HPLC system equipped with a C18 column and UV detector set at 278 nm. The mobile phase consisted of a mixture of acetonitrile and water (in specified ratios). Residue concentrations were calculated based on standard calibration curves obtained using known concentrations of Enrofloxacin and Ciprofloxacin.

Histopathological Examination

The fixed tissue samples (liver and kidney) were processed through standard histological procedures (Gurina & Simms, 2023). The tissues were dehydrated in ascending grades of ethanol (70% to 100%), cleared in xylene, and embedded in paraffin wax. Thin tissue sections (5 µm) were obtained using a rotary microtome and mounted on glass slides. These sections were stained with hematoxylin and eosin (H&E) to observe cellular and structural changes. Stained slides were examined under a light microscope, and photomicrographs were taken for documentation and analysis.

Statistical Analysis

All results were calculated and reported as mean ± standard deviation. Data was analyzed using SPSS software version 26. One-way ANOVA was used to check for differences between the groups.

Results

Table 1 showed that liver samples from the control group showed mild degeneration and inflammation, typical of normal hepatic stress. However, Enrofloxacin and Ciprofloxacin induced more pronounced effects such as vascular congestion, fatty change, hepatocyte binucleation, and Kupffer cell hyperplasia. The observed damage, particularly necrosis and congestion, suggests potential hepatotoxicity, possibly due to drug metabolism in the liver.

Table 1: Histopathological Effects of antibiotics (Enrofloxacin and Ciprofloxacin) on the Liver

Sample	Necrosis/Degeneration	Vascular Changes	Inflammation	Fibrosis	Others
C1	Multifocal thinning of hepatic cords	Mild central vein congestion	Mild mixed-cell periportal inflammation	No lesion	No lesion
C2	Hepatocellular vacuolation and binucleation	Mild congestion	Mild midzonal inflammation	No lesion	No lesion
C3	Coagulative necrosis with sinusoidal widening	Mild central vein congestion	Moderate periportal inflammation with Kupffer cell hyperplasia	No lesion	No lesion
C4	Coagulative necrosis and fatty change	Mild congestion	Centrilobular & periportal inflammation with Kupffer hyperplasia	No lesion	No lesion
B1	No lesion (2/2)	No lesion (2/2)	No lesion (2/2)	No lesion	No lesion
B2	No lesion	Marked central vein congestion	No lesion	No lesion	Mild bile ductular reaction

B3	Nil	Mild congestion with hemosiderosis	No lesion	No lesion	No lesion
B4	Coagulative necrosis and fatty change; binucleation	Moderate congestion	Mild periportal and midzonal inflammation	No lesion	No lesion
B5	Diffuse mild microvacuolation around central vein	Mild congestion	Mild Kupffer cell hyperplasia	No lesion	No lesion

Keys:
B: Enrofloxacin **C:** Ciprofloxacin

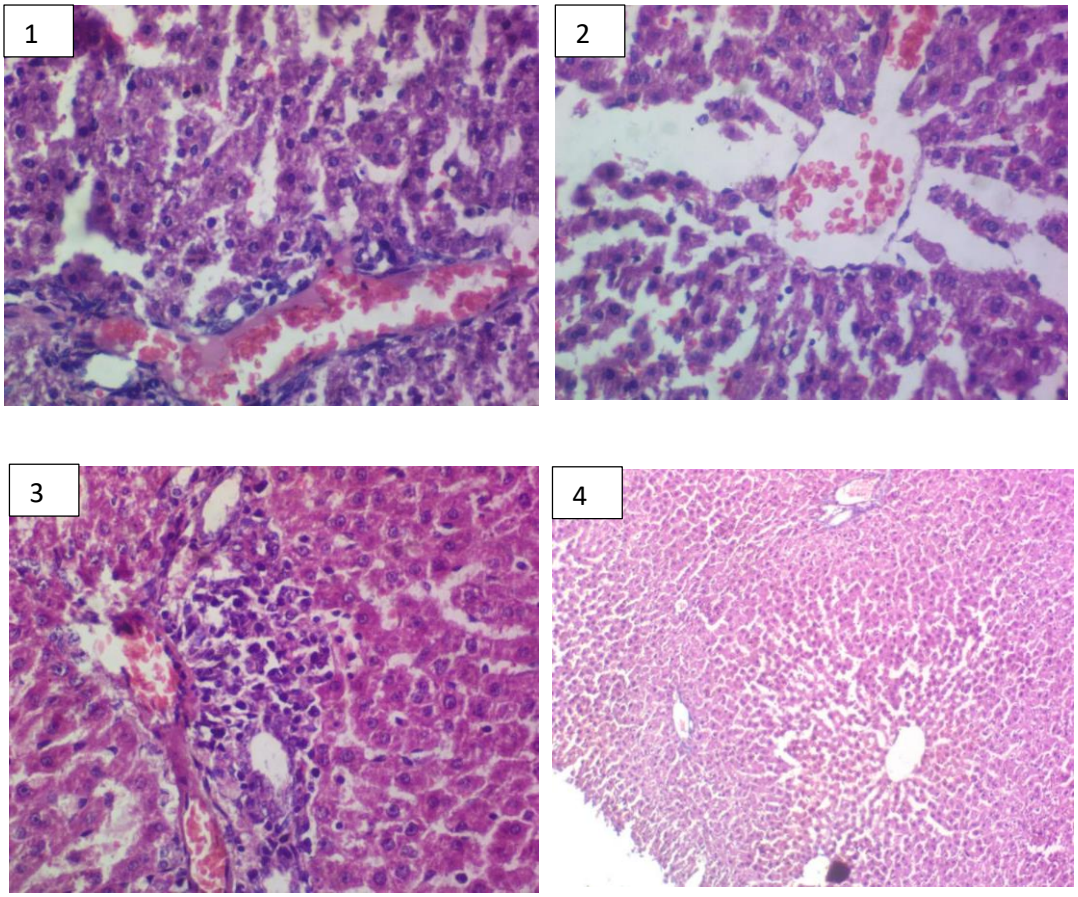

Figure 1: Microphotographs of section of albino rat liver of Ciprofloxacin treated group

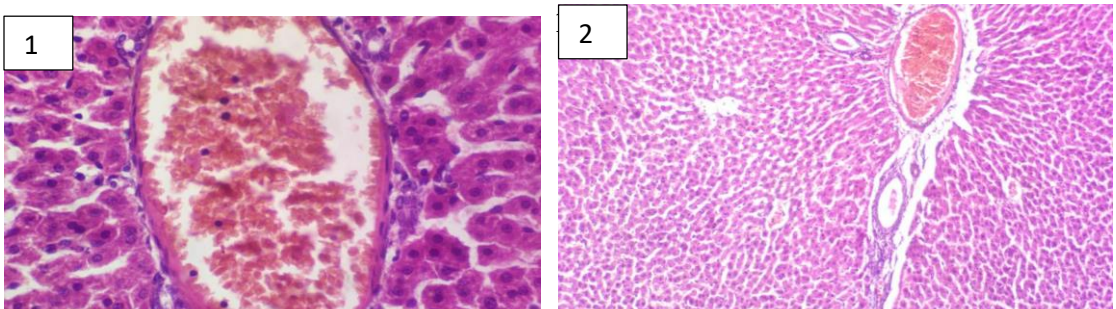

Figure 2: Microphotographs of section of albino rat liver of Enrofloxacin treated group

Result in Table 2 showed that the kidneys from control rats showed minimal pathology. However, Group B (Enrofloxacin) samples, particularly B2 and B3, revealed mild degenerative and vascular changes, such as glomerular atrophy and congestion. Some tubular necrosis and epithelial hyperplasia were also observed, which may indicate early signs of nephrotoxicity from antibiotic residues.

Table 2: Histopathological Effects of antibiotics (enrofloxacin and ciprofloxacin) on the Kidney

Sample	Glomerular Changes	Tubular Changes	I ıation & Type	Cast Formation	Vascular Changes	Remarks

C1	No lesion	Intact tubules	-	-	Congested cortical sinusoids	Normal
C2	Nil	Nil	Nil	Nil	Nil	Apparently normal architecture
C3	Nil	Focal tubulo-epithelial necrosis	Mild interstitial inflammation	Inapparent	Nil	-
C4	Nil	Single epithelial necrosis	Mild cortical lymphocytic inflammation	-	Marked sinusoidal ectasia	-
B1 (A&B)	No lesion	Intact tubules	Nil	Nil	Congested sinusoids	Sample B thicker (artefact)
B2	Focal glomerular atrophy	Vacuolar degeneration	Nil	Nil	Mild congestion	-
B3	Nil	Single-cell necrosis	Nil	Inapparent	Nil	-
B4	Nil	Nil	Nil	Nil	Nil	-
B5	Nil	Nil	Nil	Nil	Nil	-

Keys: B: Enrofloxacin **C:** Ciprofloxacin

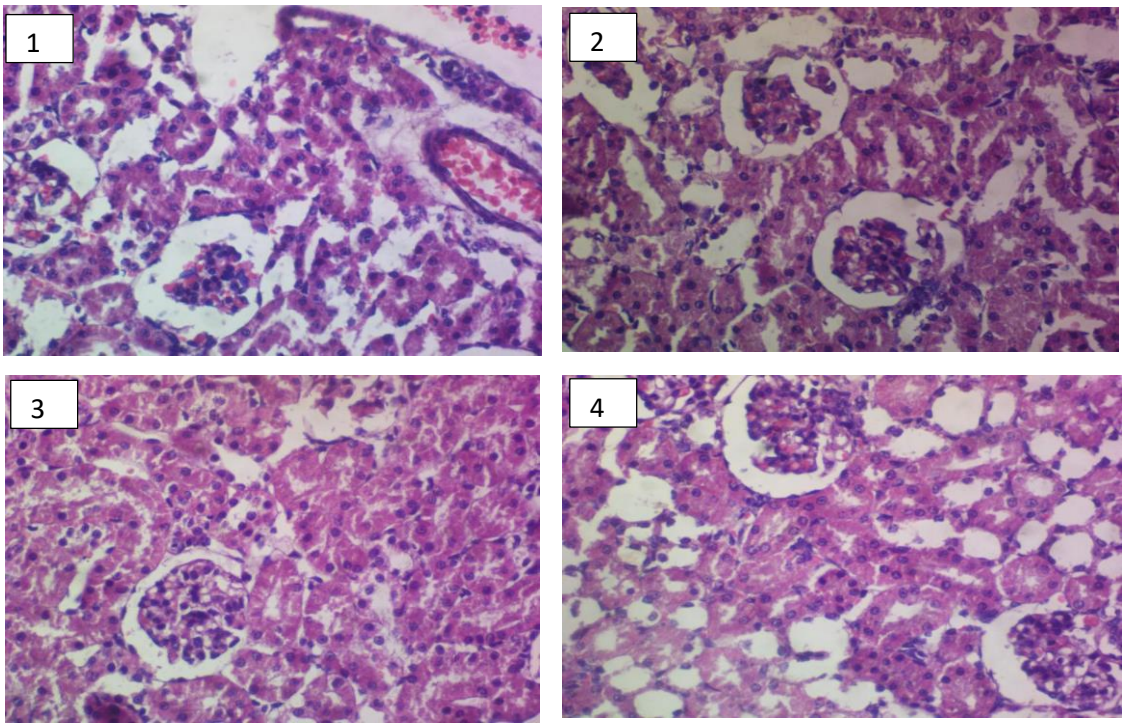

Figure 3: Microphotographs of section of albino rat kidney of Ciprofloxacin treated group

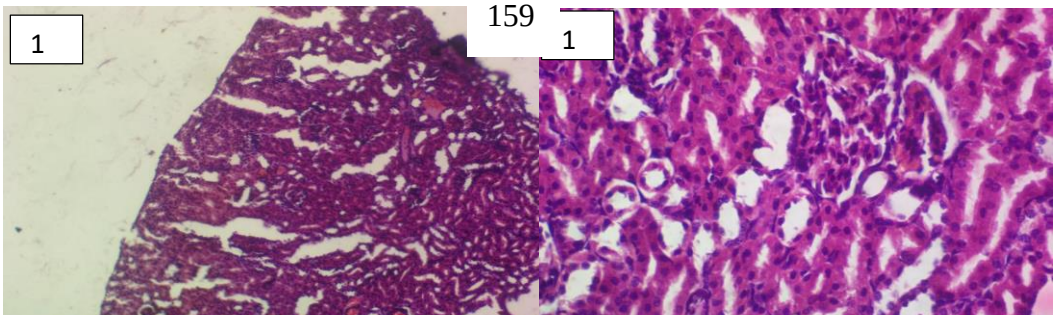

Figure 4: Microphotographs of section of albino rat kidney of Enrofloxacin treated group

Result in Table 3 showed that the control group showed no detectable residues in the liver and kidney, confirming the absence of background drug contamination. Rats treated with enrofloxacin (10 mg/kg) had measurable residues in both the liver and kidney, with higher levels in the liver (1.92 ± 0.23 µg/g) than the kidney (0.88 ± 0.15 µg/g). In contrast, rats treated with ciprofloxacin (20 mg/kg) showed higher accumulation in the kidney (2.41 ± 0.25 µg/g) compared to the liver (1.27 ± 0.19 µg/g). Hence, enrofloxacin residues were higher in the liver tissue, whereas ciprofloxacin residues were greater in the kidney tissue.

Table 3: Levels of Tissue Residues of Enrofloxacin and Ciprofloxacin in Albino Rats

Group / Treatment	Tissue	Detected Residue (µg/g)
Control	Liver	ND (no residues detected)
Control	Kidney	ND (no residues detected)
Enrofloxacin (10 mg/kg)	Liver	1.92 ± 0.23
Enrofloxacin (10 mg/kg)	Kidney	0.88 ± 0.15
Ciprofloxacin (20 mg/kg)	Liver	1.27 ± 0.19
Ciprofloxacin (20 mg/kg)	Kidney	2.41 ± 0.25

Note: ND = Not Detected (below HPLC detection limit)

Discussion

The current study reported tissue residue accumulation and histopathological changes in the liver and kidney of Albino rats induced with Ciprofloxacin and Enrofloxacin drugs. The study showed that the liver of control rats

showed only mild stress, while rats treated with Enrofloxacin and Ciprofloxacin had severe liver damage such as vascular congestion, fatty changes, and cell death. This suggests that both antibiotics may cause liver toxicity due to how they are processed in the liver. This finding aligns with the study of Abdelgadir *et al.* (2021), who asserted that the liver plays a central role in metabolizing fluoroquinolones like enrofloxacin and ciprofloxacin, making it vulnerable to hepatocellular injury due to the reactive metabolites produced during biotransformation. This finding is supported by Zhang *et al.* (2024), who documented hepatic dysfunction in soft-shelled turtles exposed to high doses of enrofloxacin. Likewise, Al-Sayed *et al.* (2018) observed hepatocellular necrosis and sinusoidal congestion in rats treated with fluoroquinolones, attributing the damage to oxidative stress induced by the drugs. These findings indicate that fluoroquinolone exposure can lead to clinically significant liver and kidney damage, suggesting that these organs are major targets of toxicity. The accumulation of residues alongside organ injury highlights the need for strict regulation of veterinary antibiotic use to protect both animal health and consumer safety.

The study revealed that the kidneys of control rats appeared normal, but induced with Enrofloxacin and Ciprofloxacin showed histopathological changes such as glomerular atrophy, bleeding, and tubular cell damage. This points to possible early kidney damage caused by both antibiotics used. This finding aligns with the study of Aseel *et al.* (2020) who reported that ciprofloxacin led to notable renal injuries such as tubular necrosis and glomerular degeneration in experimental rats, with observable vacuolization and epithelial damage. This finding also supports the report by Genid *et al.* (2022), who found that ciprofloxacin caused glomerular atrophy, epithelial necrosis, and mitochondrial swelling in renal tissues of albino rats. The stu reported that these histological changes we evident within 14 days of drug administration, and partial recovery was possible with antioxidant co-treatment. Likewise, Amin *et al.* (2019) noted that high doses of fluoroquinolones result in irreversible nephrotoxicity, marked by tubular damage and inflammatory infiltration in kidney sections.

The study showed that enrofloxacin residues were higher in the liver tissue, whereas ciprofloxacin residues were greater in the kidney tissue. This finding tally with the study of Moghadam *et al.* (2018) who asserted that enrofloxacin residues are most frequently retained in the liver due to its central role in drug metabolism. Similarly, Munanura *et al.* (2023) reported that enrofloxacin was more concentrated in poultry liver compared to muscle, further confirming that the liver serves as a major reservoir for drug accumulation. This finding is also in line with Zhang *et al.* (2024) who observed that enrofloxacin induced dose-dependent hepatic alterations, indicating that the liver is more exposed to residue buildup. On the other hand, ciprofloxacin accumulation in the kidney agrees with Genid *et al.* (2022) who demonstrated that ciprofloxacin exposure led to renal cortical damage, highlighting its nephrotoxic tendency. Furthermore, the present result supports the report of Hou *et al.* (2022) who showed that ciprofloxacin significantly affected renal and testicular tissues in animal models, suggesting higher retention in excretory organs.

Conclusion

This study demonstrated that repeated oral administration of enrofloxacin and ciprofloxacin resulted in significant liver and kidney damage in albino rats, confirming their potential to induce hepatotoxicity and nephrotoxicity. HPLC analysis revealed that enrofloxacin accumulated predominantly in the liver, while ciprofloxacin showed higher retention in the kidney, aligning with organ-specific damage observed histologically. On the other hand, ciprofloxacin residues showed greater retention in kidney tissues, which indicates that ciprofloxacin is predominantly excreted through the renal pathway, leading to its accumulation in renal tissues. Such high residue levels in the kidney suggest potential nephrotoxic effects, especially with long-term or high-dose administration. Finally, enrofloxacin residues were higher in the liver tissue, whereas ciprofloxacin residues were greater in the kidney tissue. Hence, repeated or

high-dose exposure to enrofloxacin and ciprofloxacin can lead to significant liver and kidney damage in albino rats. Based on the findings of this research, it was recommended that veterinary practitioners should regulate the dosage and duration of fluoroquinolone use in animals to minimize hepatic stress and prevent toxic accumulation in the liver. Farmers should strictly adhere to drug withdrawal periods before slaughtering animals to ensure that harmful antibiotic residues are cleared from liver tissues. Routine kidney function monitoring should be conducted in animals treated with fluoroquinolones to detect early signs of nephrotoxicity and prevent irreversible renal damage. Animal health authorities should implement residue screening programs in meat products to detect nephrotoxic drugs and ensure food safety compliance. Veterinary practitioners should enforce strict withdrawal periods before slaughter to prevent transmission of hepatic residues into the food chain. Routine monitoring of enrofloxacin residues in animal liver tissues should be mandated to ensure consumer safety and minimize risks of antimicrobial resistance. Also, regulatory bodies should prioritize kidney residue testing in animals treated with ciprofloxacin to strengthen public health safety measures.

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