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EVALUATION OF *DENNETTIA TRIPETALA* (PEPPER FRUIT) ETHANOL EXTRACT AGAINST CIPROFLOXACIN-INDUCED CARDIOPULMONARY DAMAGE IN ALBINO RATS

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***Abstract*: Background: Ciprofloxacin belongs to the fluoroquinolone class of antibiotics, which are often prescribed to treat various bacterial infections, including those of the respiratory, urinary, and gastrointestinal tracts. Research has shown that *Dennettia tripetala* contains bioactive compounds which are known to possess strong antioxidant properties Aim: The primary aim of this study was to evaluate the protective effect of *Dennettia tripetala* (pepper fruit) against ciprofloxacin-induced cardiac and lung damage in albino rats. Methodology: The animals used were grouped into 5 comprising of 5 rats in each group and were acclimatized in a well ventilated iron cage for a period of 14 days prior to the commencement of the experiment. All groups except the baseline control (group 1) received 100mg/kg body weight of ciprofloxacin for 10 days. Group 2,3 and 4 received additional oral doses of *Dennettia tripetala* extract of (400, 600, 1000) mg/kg b.wt for 14 days respectively. Group 5 served as the negative control, and received only ciprofloxacin at a dose of 100mg/kg body weight for 10 days. On the last day of treatment, the rats were sacrificed under chloroform anesthesia, the hearts and lungs were carefully excised using a sterile surgical blade. The harvested organs were fixed, histologically processed and stained using H&E staining. Result: The findings suggested that *Dennettia tripetala* extract possesses significant protective potential, effectively mitigating ciprofloxacin-induced cardiopulmonary damage in albino rats**

***Keywords:* Ciprofloxacin, *Dennettia tripetala*, Cardiac, Pulmonary, Toxicity, Albino rats.**

1. INTRODUCTION

Antibiotics have revolutionized modern medicine by effectively treating bacterial infections that were once fatal (Ventola, 2015). Ciprofloxacin is a fluoroquinolone antibiotic used for respiratory, urinary, and gastrointestinal infections (Anderson et al., 2020). It works by inhibiting bacterial DNA gyrase and topoisomerase IV, enzymes crucial for bacterial DNA replication. (Collins *et al* 2024). Despite its efficacy, there is growing evidence that ciprofloxacin poses serious risks of toxicity on non- target organs, particularly the heart and lungs (Anderson *et al*., 2012; Sharma *et al*., 2017).

Ciprofloxacin has been linked to a range of adverse effects, from mild gastrointestinal disturbances to more severe conditions such as tendinitis, neuropathy, and, most concerning, cardiac and pulmonary toxicity (Smith *et al.*, 2021). Studies have also demonstrated that ciprofloxacin alters the expression of genes involved in inflammation and

apoptosis, contributing to lung tissue damage and fibrosis (Zhao *et al*., 2020). The study suggested that the inflammatory response was triggered by oxidative damage and mitochondrial dysfunction, similar to the mechanisms observed in cardiac tissue (Borger *et al*, 2024) Its has cardiotoxic effects include arrhythmias, QT prolongation, and myocardial damage, and in rare cases lead to sudden cardiac death (Porta *et al*, 2019; Efe & Husain, 2026). Studies indicate that prolonged use or high doses of ciprofloxacin can trigger oxidative stress, mitochondrial dysfunction, and apoptosis in cardiomyocytes and alveolar cells (Williams & LeBlanc, 2021). This imbalance promotes cellular damage, inflammation, and programmed cell death, particularly in metabolically demanding tissues such as the heart and lungs (Ahmed *et al.*, 2020).

Clinically, these effects manifest as cardiomyopathy, arrhythmias, and pulmonary fibrosis**,** restricting ciprofloxacin's use in vulnerable populations, including the elderly and patients with cardiovascular disease (Wang *et al*., 2020). The underlying mechanisms are thought to involve overproduction of reactive oxygen species (ROS)**,** which drive oxidative stress, inflammation, and tissue injury (Smith *et al.*, 2021). Experimental evidence supports by Raza *et al*. (2021) reported that high doses of ciprofloxacin induced significant oxidative stress and apoptosis in cardiac tissue, accompanied by myofibril degeneration and inflammatory cell infiltration. Such adverse reactions, particularly cardiotoxicity and pulmonary damage limit the drug's long-term application and raise ongoing concerns about its safety profile (Alomar, 2014).

Herbal remedies, long valued in traditional medicine, are increasingly recognized as viable options for mitigating the side effects of conventional drugs (Ekor, 2014). It is widely consumed in Nigeria, Ghana, and other West African countries for both nutritional and medicinal purposes (Oyemitan *et al*., 2008; Ndukwu *et al.*, 2020). These bioactive compounds exhibit antioxidant, anti-inflammatory, antimicrobial, and analgesic properties, making the fruit a valuable source of natural therapeutics (Eze *et al*., 2019).

Moreover, Research has shown that *Dennettia tripetala* contains bioactive compounds such as alkaloids, flavonoids, saponins, tannins and essential oil, all of which are known to possess strong antioxidant properties (Okwu & Morah, 2004; Ndukwu *et al.*, 2020). These compounds help neutralize free radicals; thereby reducing oxidative stress a key driver of drug- induced cellular damage (Onyenekwe *et al*., 2018). Beyond scavenging free radicals, they also modulate signaling pathways involved in inflammation and apoptosis, offering a dual protective mechanism against drug-induced toxicity (Gao *et al*., 2020).

Recent studies highlight the ability of *Dennettia tripetala* to protect vital organs from oxidative damage, particularly in tissues vulnerable to drug-induced injury such as the heart and lungs (Eze *et al*., 2019). This evidence underscores its potential role in mitigating the toxic effects of ciprofloxacin, supporting further exploration of pepper fruit as a natural adjunct in pharmacotherapy.

However, its specific role in mitigating ciprofloxacin-induced cardiac and pulmonary toxicity remains largely unexplored, thus present a significant research gap. Despite these concerns, there are currently few strategies to effectively mitigate these adverse effects. The search for safe and effective remedies has led researchers to explore natural products, given their availability and minimal side effects. Pepper fruit, due to its strong antioxidant and anti-inflammatory properties, is hypothesized to offer protection against the oxidative stress and tissue damage induced by ciprofloxacin. This study is designed to explore whether the bioactive components of *Dennettia tripetala* can provide a protective effect on the heart and lungs, thereby reducing the toxic impact of ciprofloxacin.

2. MATERIALS AND METHODS

Research Design

The study was conducted as a randomized controlled experimental investigation to evaluate the protective effect of *Dennettia tripetala* extract against ciprofloxacin-induced cardiac and lung damage in albino rats. The aim was to compare outcomes between treated and untreated groups to ascertain the efficacy of the pepper fruit extract in mitigating the adverse effects of ciprofloxacin.

Animals Procurement

In this work, 25 adult albino rats, aged 8 to 10 weeks were utilized. These rats were sourced from the animal house of Enugu State College of Medicine (ESUCOM). The animals were grouped into 5 comprising of 5 rats in each group and were acclimatized in a well ventilated iron cage for a period of 14 days prior to the commencement of the experiment.

Ethical Considerations

Prior to commencing the experiments, it was ensured that all procedures involving animal subjects were conducted in accordance with the ethical guidelines established by the Institutional Animal Care and Use Committee (IACUC). Ethical approval was obtained from the Animal Welfare and Ethics Committee [ESUT/AREC/0225/37/2019030190361MLS]. Measures were implemented to minimize any suffering experienced by the animals. The rats were housed under standard laboratory conditions with unrestricted access to food and water.

Materials and Equipment

Materials: *Dennettia tripetala* (pepper fruit) was sourced from Ogbede market, a local market in Igbo-Etiti local government area and authenticated by a botanist at the herbarium section of Department of Plant Sciences and Biotechnology, University of Nigeria, Nsukka [UNN/13032]. Then, the fruits were processed into an extract.

Ciprofloxacin hydrochloride manufactured by Fidson (pharmaceutical grade) was obtained from Veronica Plus pharmacy, a licensed pharmacy in GRA Enugu, Enugu state.

Preparation of *Dennettia tripetala* Extract

Fresh pepper fruits were washed, cleaned, and air-dried. The dried fruits were ground into a fine powder using a mechanical grinding machine. The powdered fruit underwent extraction via a cold maceration method, wherein approximately 100 grams of the powder was soaked in 500 ml of ethanol in a refrigerator for 48 hours, with periodic shaking. Following this period, the mixture was filtered through Cheese cloth and further filtered with filter paper Whatman No.1 and the resultant filtrate was concentrated using a rotary evaporator set at 55°C to obtain a semi-solid extract. Finally, the extract was stored in a refrigerator at 4°C until when needed.

Animal inducement

Study has shown that 50-100mg/kg/day for 5-14 days can cause cardiac and lung toxicity (Almeida *et al.*, 2017).

Experimental Groups

The rats were categorized into five distinct groups, each comprising 5rats, group 1 was designated as the baseline control group, and received food and water only. Group 2-4 received 100mg/kg b.wt of ciprofloxacin administration for 10 days followed by *Dennetia tripetala* extract (400, 600, 800) mg/kg body weight for 14 days respectively. Group 5 served as the negative control, and received only ciprofloxacin at a dose of 100mg/kg body weight for 10 days. Both the extract and ciprofloxacin were administered orally (ingestion). The rats were then closely observed to monitor the health and growth throughout the experiment.

Sample Collection

Data collection was conducted at the conclusion of the treatment period. On the 24th day, the rats were sacrificed under chloroform anesthesia, under which the heart and the lungs were identified and carefully excised using a sterile surgical blade.

Histopathological Examination:

Harvested heart and lung tissues were washed with physiological saline and immediately fixed in 10% neutral buffered formalin to avoid post-mortem changes. The samples collected were processed according to histological technique and stained with heamatoxylin and eosin (H&E) for histomorphological examination.

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3. RESULTS

LUNG PHOTOMICROGRAPHS

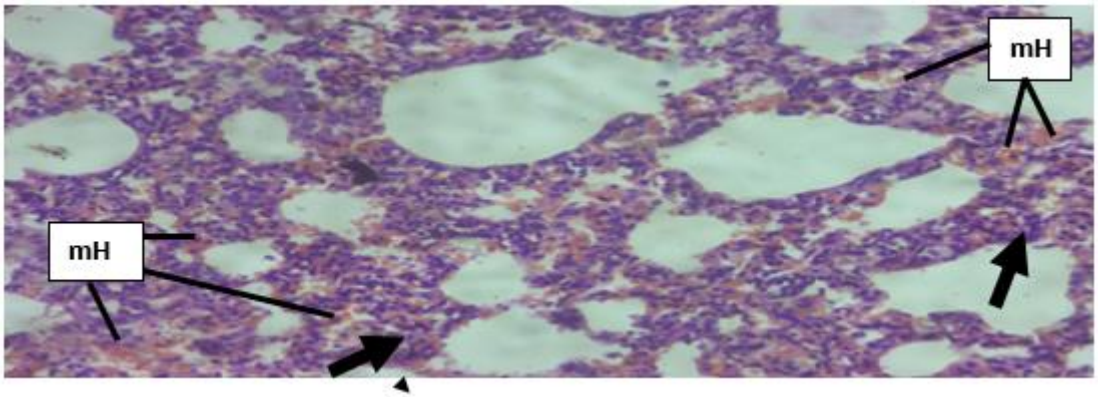

Figure I: - Light photomicrograph of lung section from rat in group 2 that received low dose (400mg/kg b.wt) of *Dennetia tripetala* extract before lung injury induction with ciprofloxacin showing mild structural alterations; there's presence of cellular infiltration (arrows) and micro-haemorrhage (mH) (Stain; Haematoxylin and Eosin: Mag x100).

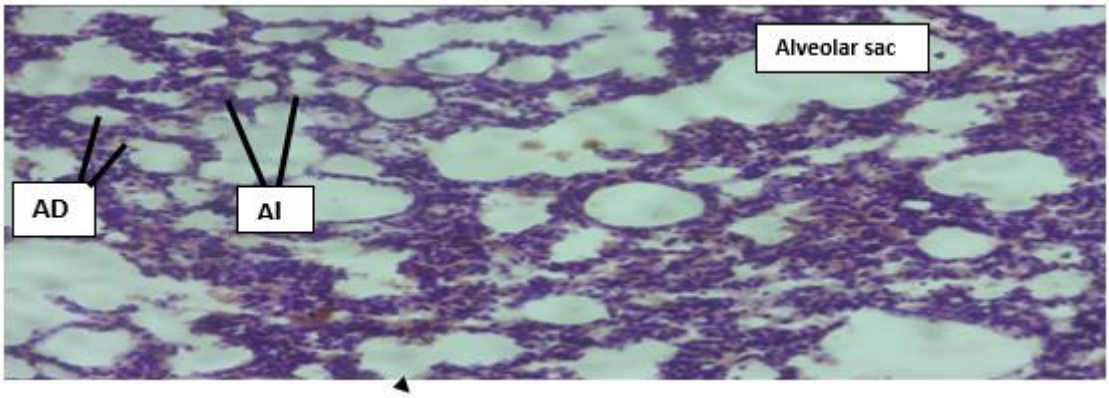

Figure II: - Light photomicrograph of lung section from rat in group 3 that received medium dose (600mg/kg b.wt) of *Dennetia tripetala* extract before lung injury induction with ciprofloxacin showing normal histological features, the Alveolar Duct (AD), Alveolar sac and alveoli (Al) appear normal. Indicating adequate protection of the lung tissue by 600mg/kg of *Dennetia tripetala* extract (Stain; Haematoxylin and Eosin: Mag x100).

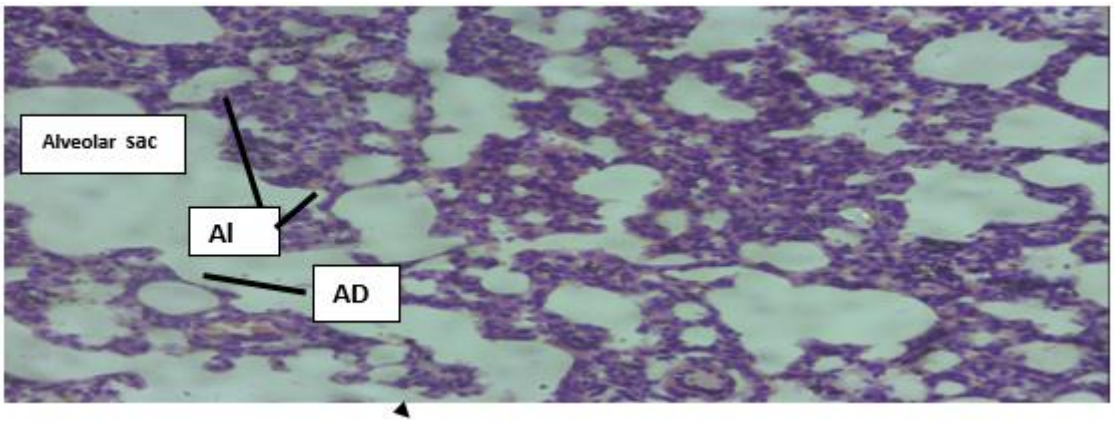

Figure III: - Light photomicrograph of lung section from rat in group 4 that received high dose (800mg/kg b.wt) of *Dennetia tripetala* extract before lung injury induction with ciprofloxacin showing normal histological features, the Alveolar Duct (AD), Alveolar sac and alveoli (Al) appear normal. Indicating adequate protection of the lung tissue by 800mg/kg of *dennetia tripetala* extract (Stain; Haematoxylin and Eosin: Mag x100).

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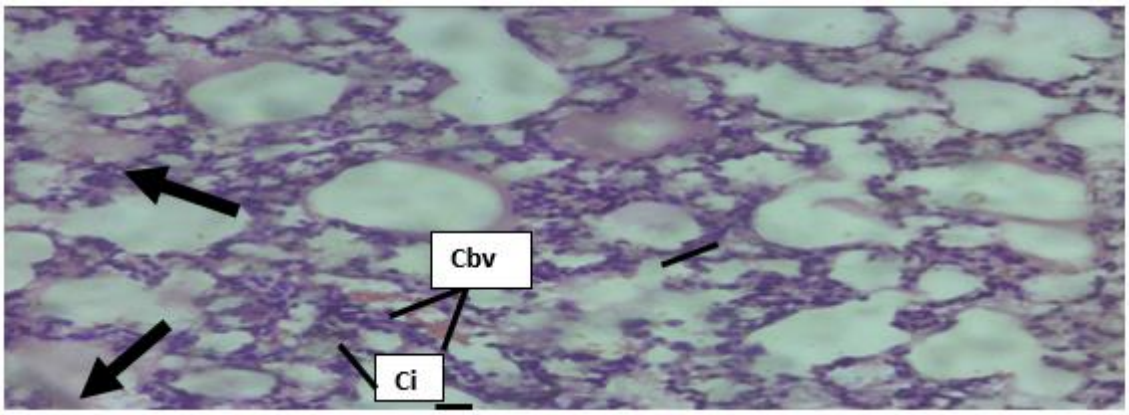

Figure IV - Light photomicrograph of lung section from rat in group 5 that received ciprofloxacin only (positive control). There are some obvious histomorphological alterations; features observed are degenerated alveolar duct (arrows), congested blood vessel (Cbv) and cellular infiltration (Ci). (Stain Haematoxylin and Eosin: Mag x100).

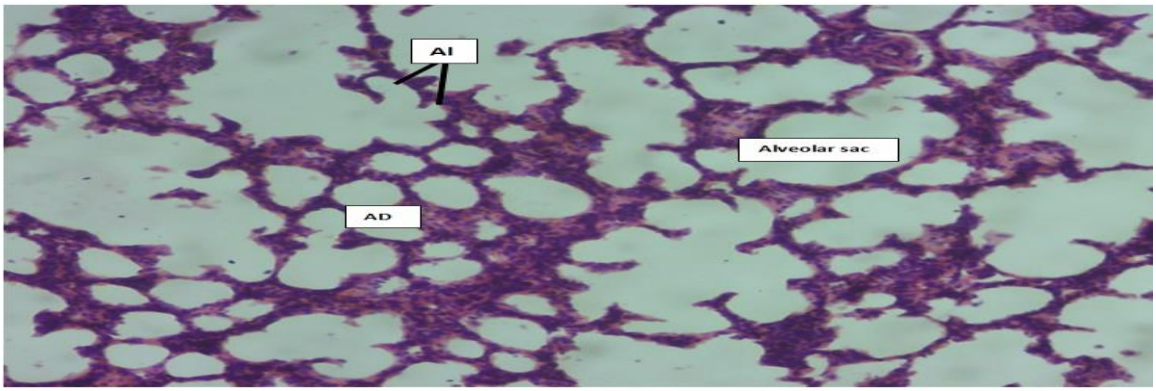

Figure V: - Light photomicrograph of lung section from rat in group 1 that received food and water only (negative/baseline control) showing normal histological features, the Alveolar Duct (AD), Alveolar sac and alveoli (Al) appear normal. (Stain Haematoxylin and Eosin: Mag x100).

HEART PHOTOMICROGRAPHS

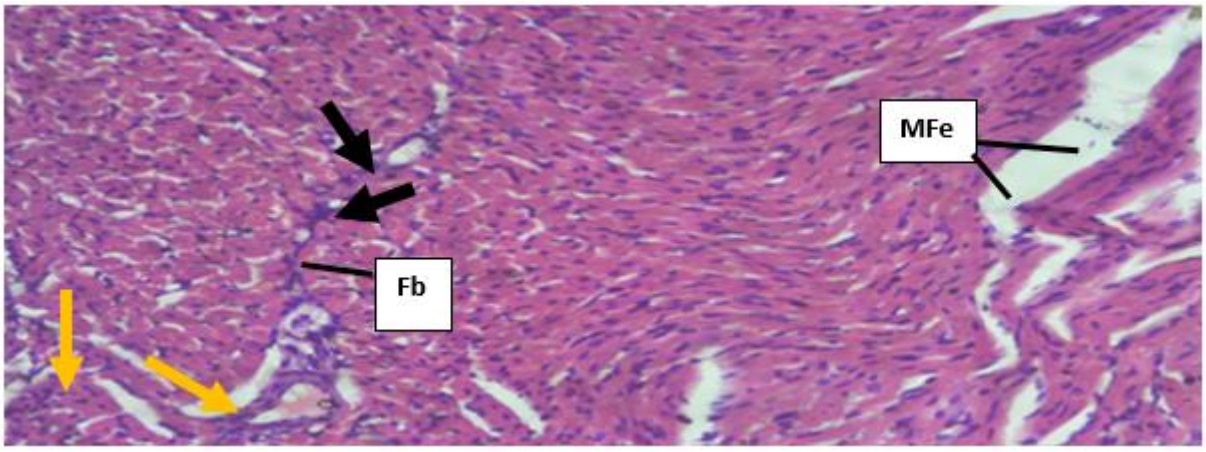

Figure VI: - Light photomicrograph of heart section from rat in group 2 that received low dose (400mg/kg b.wt) of *dennetia tripetala* extract before heart injury induction with ciprofloxacin showing obvious structural alterations; there's presence of cellular fibrosis (Fb), necrotic cells (black arrows), cellular infiltration (orange arrows) and area of myocardial fiber erosion (MFe) (Stain; Haematoxylin and Eosin: Mag x100).

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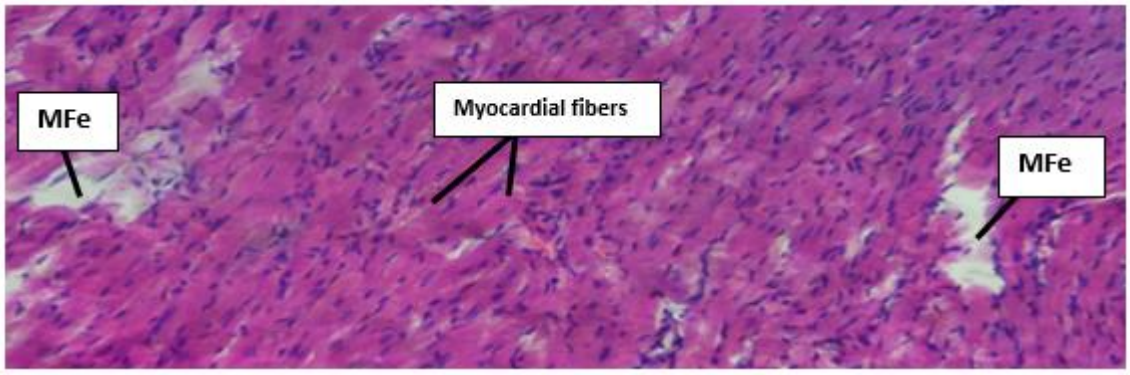

Figure VII: - Light photomicrograph of heart section from rat in group 3 that received medium dose (600mg/kg b.wt) of *Dennetia tripetala* extract before heart injury induction with ciprofloxacin showing improved histomorphology when compared with the negative control, the myocardial fibers appear normal with regular structural organization, however, there's presence of erosion of some regions of the myocardial fibers (Stain; Haematoxylin and Eosin: Mag x100).

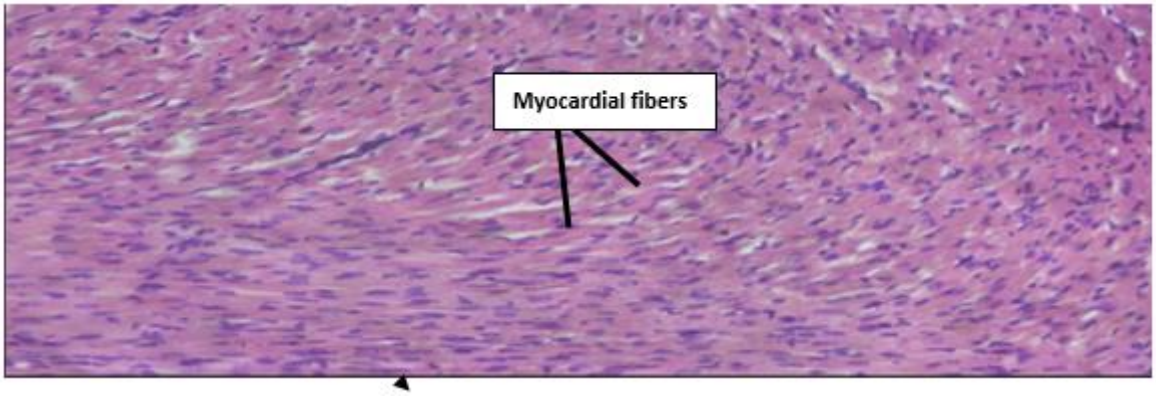

Figure VIII: - Light photomicrograph of heart section from rat in group 4 that received high dose (800mg/kg b.wt) of *Dennetia tripetala* extract before heart injury induction with ciprofloxacin showing improved histomorphology when compared with the negative control, the myocardial fibers appear normal with regular structural organization. Indicating adequate protection of the heart tissue by 800mg/kg of *Dennetia tripetala* extract (Stain; Haematoxylin and Eosin: Mag x100).

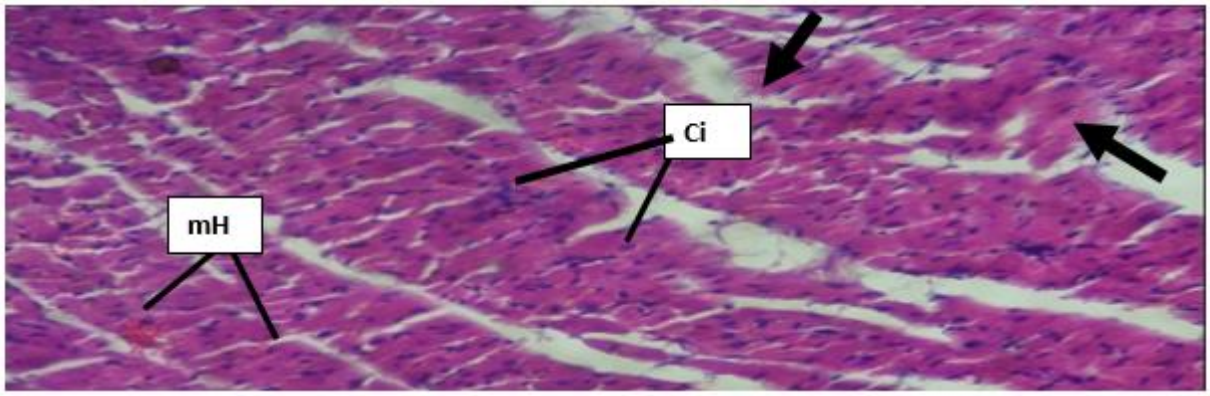

Figure IX - Light photomicrograph of heart section from rat in group 5 that received ciprofloxacin only (negative control). There are some obvious histomorphological alterations; features observed are marked irregular organization of myocardial fibers (arrows), micro-haemorrhage (mH) and cellular infiltration (Ci). (Stain Haematoxylin and Eosin: Mag x100).

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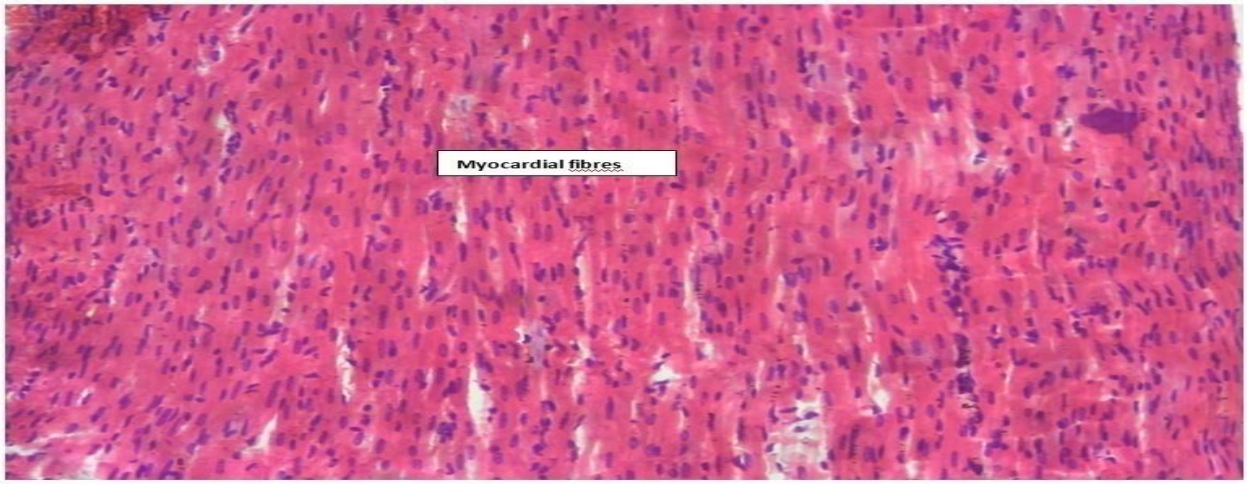

Figure X: - Light photomicrograph of heart section from rat in group 1 that received food and water only (baseline control) showing normal histological features, the myocardial fibers appear normal with regular organization. (Stain Haematoxylin and Eosin: Mag x100).

4. DISCUSSION

The study highlighted the damaging effects of ciprofloxacin on cardiac and plumonary tissues due to oxidative stress and inflammation, resulting in structural impairments. The pre-treatment with *Dennetia tripetala* extract demonstrated significant protective effects which is attributed to its phytochemical composition rich in antioxidants and anti-inflammatory agents like flavonoids and saponins. These bioactive compounds reduced oxidative stress, inhibited inflammation, and stabilized cellular membranes, thereby mitigating ciprofloxacin-induced organ injury.

Histological analysis revealed that the high-dose group which received (800mg/kg b.wt) of *Dennetia tripetala* extract exhibited normal histological features of the alveolar duct (AD), Alveolar sac and alveoli (AI). In the other hand, the morphology of the myocardial fibers also appeared normal with regular structural organization. These indicated absolute protection of both the heart and the lungs by the high dose of *Dennettia tripetala* extract.

The medium-dose group which received (600mg/kg b.wt) of the extract showed absolutely normal histological features of the Alveolar Duct (AD), Alveolar sac and alveoli (AI), indicating adequate protection of the lung tissue by 600mg/kg of *Dennetia tripetala* extract. Also, it showed improved histomorphology of the myocardial fibres, however, there was presence of erosion of some regions of the myocardial fibres. This indicated moderate protection of heart tissues by the extract.

Then, the low-dose group which received (400mg/kg b.wt) showed obvious structural alterations (no protection) against ciprofloxacin organ toxicity. In contrast, the ciprofloxacin only group (negative control) showed obvious histomorphological alterations, marked irregular organization of myocardial fibers (arrows), microhaemorrhage (mH) and cellular infiltration (Ci). This result is in alignment with the study by Yao *et al.* (2020); Wang *et al.* (2020); and Al-Zubaidi *et al.* (2022); whose studies highlighted the organ protective effects of flavonoids and saponins which are major components of *Dennettia tripetala* extract.

5. CONCLUSION

The findings confirmed that *Dennettia tripetala* extract effectively counteracted ciprofloxacin-induced cardiopulmonary damage in albino rats. Its protective properties were linked to its ability to reduce oxidative stress and inflammation, preserve tissue integrity, and prevent histological alterations. This positions *Dennettia tripetala* as a promising natural therapeutic agent for mitigating drug-induced organ toxicity.

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