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Original Research Article

Histological and Physiological Effects of the Anti-Inflammatory Treatment's Naproxen and Cefpodoxime on Lung Function in Male Albino Rats

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Abstract: This study was designed to evaluate the possible histological and physiological changes induced by naproxen (an NSAID) and cefpodoxime (a cephalosporin derivative) administration on lung function of male albino rats. The overall physiological results revealed a significant ($P \leq 0.05$) increase in packed cell volume (PCV), total white blood cells (WBCs) count, and lymphocyte count in all treated groups compared to control groups. In contrast, the results demonstrated a significant decrease in platelet (PLT). There were no significant differences in hemoglobin levels or red blood cell counts. Histological examination showed definite pathological lesions including thickening of alveolar walls, vascular congestion and infiltration of inflammatory cells. At higher doses, this drug ruptured the alveolar walls, caused fibrous masses and narrowed the bronchi. In conclusion, chronic or high-dose exposure to these drugs provokes abnormal physiological and histological responses in the lung which should warn against their therapeutic use.

Keywords: Naproxen, Cefpodoxime, NSAIDs, Cephalosporins, Pulmonary toxicity, Histopathology, Packed Cell Volume (PCV).

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics are common classes of medications to manage inflammation and infectious diseases in medical practice. Although these drugs have an impact on a wide number of therapeutic areas, long-term or high-dose use of these medications can result in adverse effects, including functional deficits and/or histological alterations in multiple organs such as the liver, kidneys and lungs. Therefore, it has become essential to study the physiological and histological effects of these drugs using animal models to understand their mechanisms of action and their biosafety (Kakumanu *et al*., 2006; Mujeeb & Pardeshi, 2011).

Naproxen is an NSAID derived from propionic acid and is widely used to treat pain and inflammation in various conditions, such as rheumatoid arthritis, osteoarthritis, and other inflammatory disorders. Naproxen belongs chemically to the arylacetic acid group. (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid sodium salt are the chemical names for naproxen and naproxen sodium, respectively (Ahmad *et al*., 2018). Its therapeutic effect is primarily based on the inhibition of cyclooxygenase enzymes responsible for prostaglandin synthesis. Naproxen inhibits cyclooxygenase 1 and 2 enzymes associated with prostaglandin E, which is responsible for pain and inflammation in the body (Walley *et al*., 2007).

Naproxen is used to relieve pain from various conditions such as headaches, muscle pain, tendonitis, and gingivitis (Mujeeb & Pardeshi, 2011). However, prolonged use or high doses may lead to toxic effects in various tissues due to oxidative stress or inflammatory changes in vital organs (Farooq *et al*., 2024). Naproxen may cause gastric ulcers, vomiting, diarrhea, and other abnormal physical symptoms (Mujeeb & Pardeshi, 2011; Ahmad *et al*., 2018). Several experimental studies have shown that NSAIDs can cause histological and functional changes in the lungs, with pathological changes in lung tissue and alterations in certain hematological and physiological parameters being recorded, suggesting that

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continuous exposure to these drugs may lead to adverse effects on the respiratory system and its vital functions (Lojo *et al*., 2016).

Cefpodoxime is a semi-synthetic, third-generation cephalosporin antibiotic with broad-spectrum activity against both Gram-positive and Gram-negative bacteria. It is a prodrug that is deesterified in the body to release the active component (free cefpodoxime acid). It exerts its inhibitory effect by interfering with bacterial cell wall synthesis through binding to penicillin-binding proteins (PBPs). The drug is bactericidal and resistant to hydrolysis by a wide range of penicillins and cephalosporins (Liu *et al*., 2005). This drug is widely used to treat respiratory, urinary tract, and skin infections (Balakrishna *et al*., 2014). It is also used to treat upper and lower respiratory tract infections such as sinusitis, bronchitis, and pneumonia, and data suggest it is a suitable treatment option for acute otitis media (Todd, 1994). Cefpodoxime has a high capacity for distribution within various body tissues, including lung tissue, where its concentrations reach levels close to those in the blood. However, this widespread distribution may, in some cases, be accompanied by physiological effects or changes in certain vital signs with prolonged use or at high doses (Pistos *et al*., 2004).

The lungs are vital organs responsible for gas exchange and maintaining the balance of oxygen and carbon dioxide in the blood. Any histological or physiological changes in this organ directly affect the efficiency of the respiratory system. Therefore, studying the histological and physiological effects of common drugs on the lungs is an important topic in experimental pathology and pharmacotoxicology (Elder *et al*., 1997; Balansky *et al*., 2016). Accordingly, this study aims to evaluate the histological and physiological effects of both naproxen and cefpodoxime on lung function in white rats, by analyzing histological changes in lung tissue and studying physiological indicators related to the respiratory system, thus contributing to clarifying the safety of using these drugs and their potential effects on lung tissue.

Materials and Methods

Five groups of male rats were divided, with each group consisting of six rats of similar weight. The groups were given to the rats at random. The animals were given the following dosages following two weeks of acclimation:

For thirty days, the control group was given distilled water. For 30 days, the naproxen group took naproxen orally at a regular dose of 8 mg/kg body weight (Paglia *et al*., 2021). For 30 days, naproxen (40 mg/kg body weight) was administered orally to the third group. For thirty days, the fourth group was given oral cefpodoxime (10 mg/kg body weight) (Mittal *et al*., 2023). The fifth group received cefpodoxime orally (50 mg/kg body weight) for 30 days.

Preparation of the Study Samples

a) **Serum Samples:** After the experiment, the inoculated male rats were anesthetized to obtain blood samples. Blood samples were collected and processed to isolate serum for biochemical analysis of oxidized components.
b) **Histological Preparation:** After lung tissue extraction, it was rinsed with water, fixed in 10% formalin for 24 hours, dried using increasing concentrations (70%, 80%, 95%, 100%, 100%), imbedded in paraffin after being filtered via xylene. After the lung tissue was dissected, all of these operations were carried out. Hematoxylin and eosin were used to stain lung tissue slices that had been paraffin-fixed and cut to a thickness of five millimeters. The samples were examined under a 400-fold light microscope (Anthony, 2016).

Medication Used

The medication used in this study was NP (naproxen), an NSAID, or nonsteroidal anti-inflammatory medicine. Sigma Chemicals (USA) provided it. It was given orally through a feeding tube after being dissolved in DMSO. The concentrations of DMSO used showed no toxicity or effect on animal viability.

Statistical Analysis

Analysis of variance (ANOVA) was used for statistical analysis. The results were evaluated for significance using Duncan's test with a significance threshold of $P < 0.05$.

Results

1. Physiological Results: The biochemical and hematological analyses performed on the total blood serum after the end of the experiment showed the following results:

Figure (1) revealed a significant increase ($p \leq 0.05$) in PCV levels in all groups that received therapeutic doses compared to the control group.

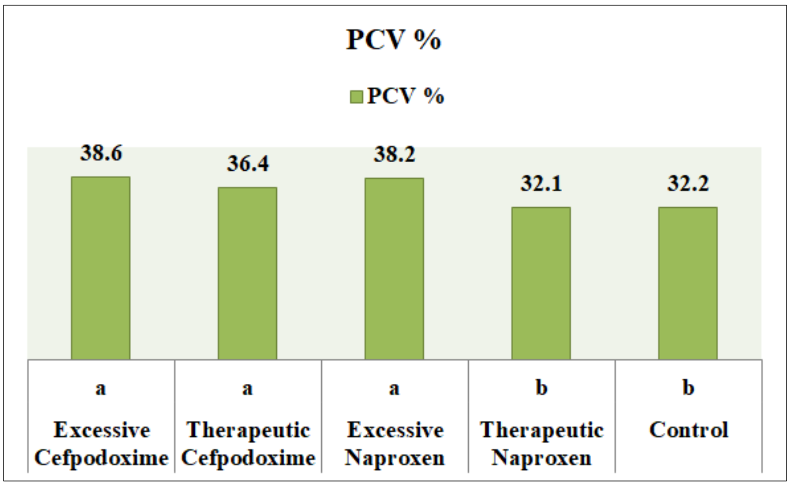

Figure 1: Shows that there is a significant increase ($p \leq 0.05$) in PCV levels in all treatment dose groups compared to the control group

The graphs in Figures (2) and (3) did not show any statistically significant differences in hemoglobin levels or red blood cell counts between the treated groups and the control group.

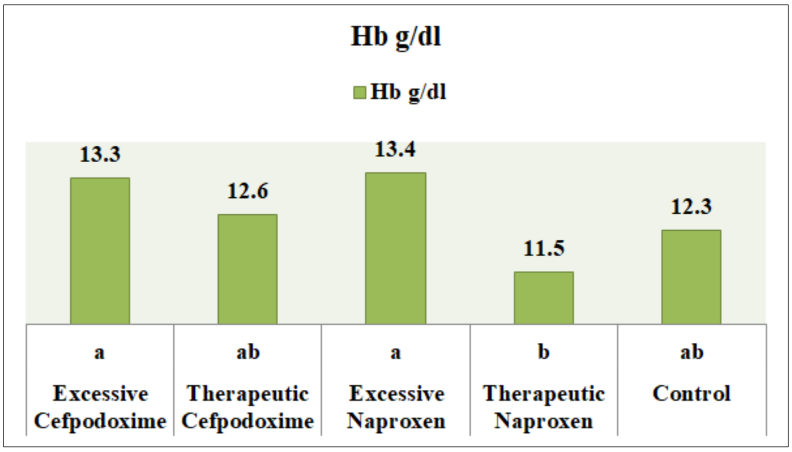

Figure 2: Shows that in Hb levels in all groups, no significant differences were observed compared to the control group

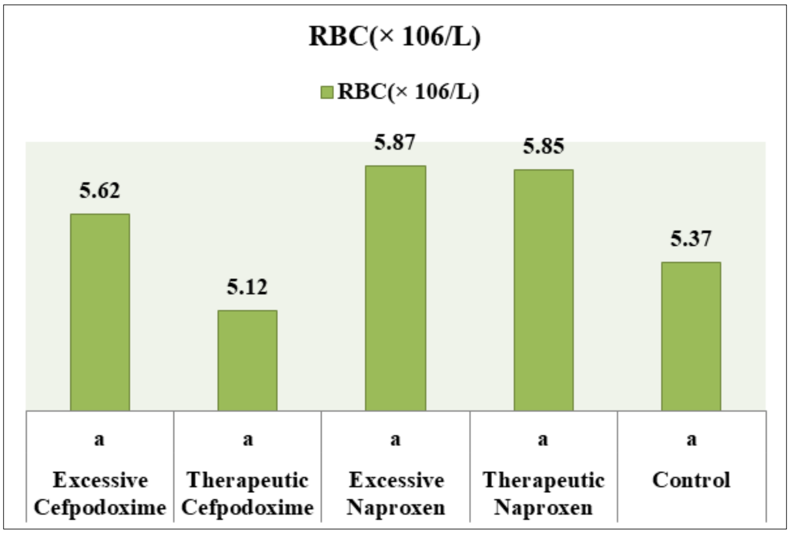

Figure 3: Shows that in RBC levels in all groups, no significant differences were observed compared to the control group

Figures (4) and (5) show a significant increase ($P \leq 0.05$) in the total number of white blood cells as well as lymphocytes in all treated groups, which may indicate an immune or inflammatory response resulting from the drugs used.

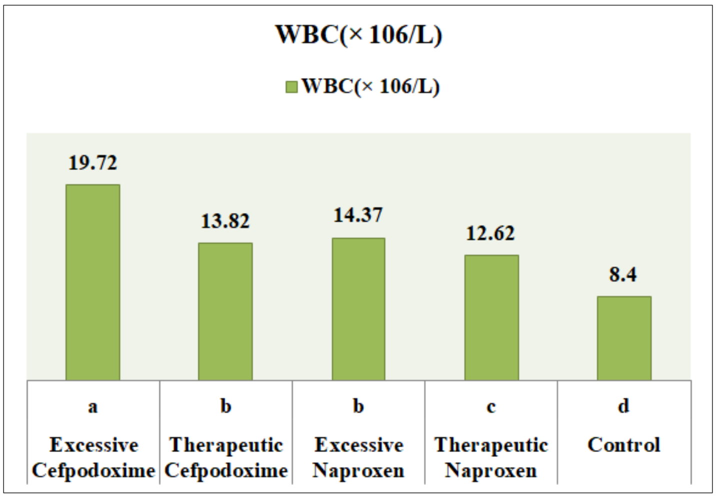

Figure 4: Shows that the WBC level showed a significant increase (P ≤ 0.05) in all treatment dose groups compared to the control group

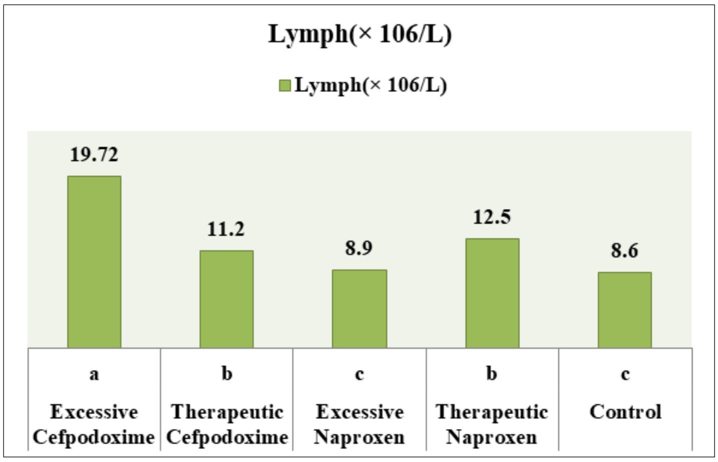

Figure 5: Shows that the Lymph cells level showed a significant increase (P ≤ 0.05) in all treatment dose groups compared to the control group

Figure (6) showed a significant decrease ($P \leq 0.05$) in platelet levels in the treated groups compared to the control group.

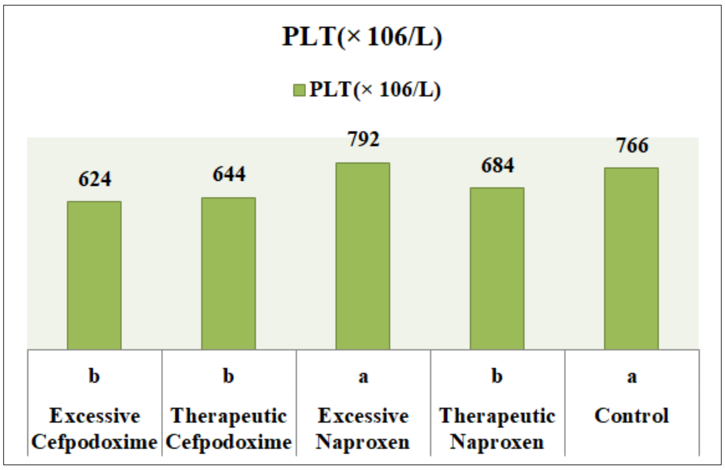

Figure 6: Shows that the PLT level showed a significant decrease (P ≤ 0.05) in all treatment dose groups compared to the control group

2. Histological Findings of Lung Tissue: The lung samples were examined microscopically after being fixed and stained with hematoxylin and eosin (H&E) at 400x magnification, and the images revealed the following changes:

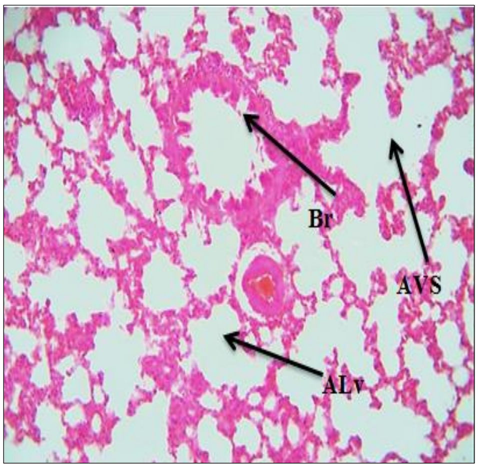

Image 1: Shows the lung sacs (AVS), alveoli (ALV), and bronchi (Br) in their normal form. Control group lung section. H & E 100 X.

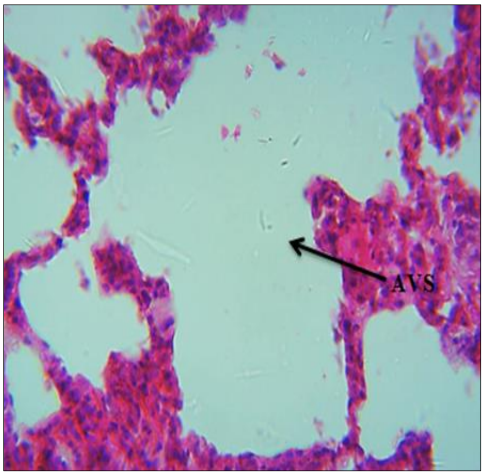

Image 2: A lung section showing the alveoli (AVS) in their normal form in the control group. 400X, H & E.

Images (1) and (2) illustrate the normal appearance of lung tissue in the control group, where the air sacs (AVS), alveoli (ALV), and bronchi (Br) appear with a healthy structure and free from any pathological lesions.

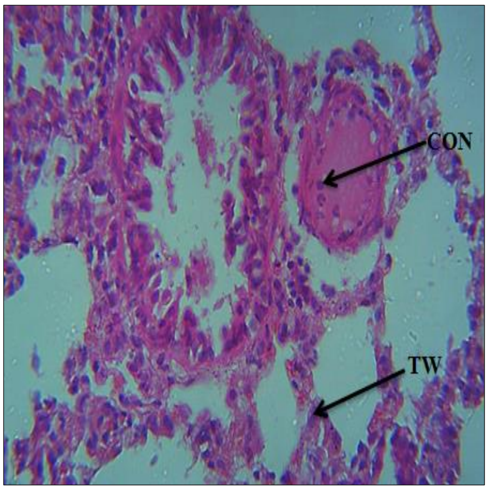

Image 3: A section of the lung of the group treated with therapeutic naproxen showing vascular congestion (CON) and thickening of the alveolar walls (TW).H & E, 400X

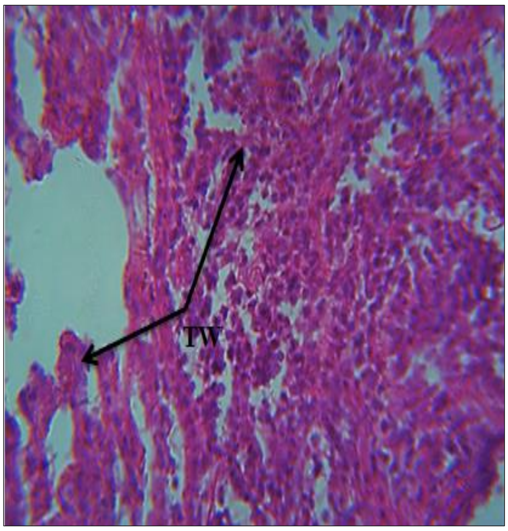

Image 4: A section of the lung of the group treated with naproxen, showing thickening of the alveolar walls (TW).H & E 400X.

Images (3) and (4) of the naproxen-treated group showed a clear effect on lung tissue, represented by thickening of the alveolar walls (TW) and vascular congestion (CON). With certain doses, image (5) revealed rupture of the alveolar walls (DA) with dense infiltration of inflammatory cells (IF), indicating drug-induced tissue damage.

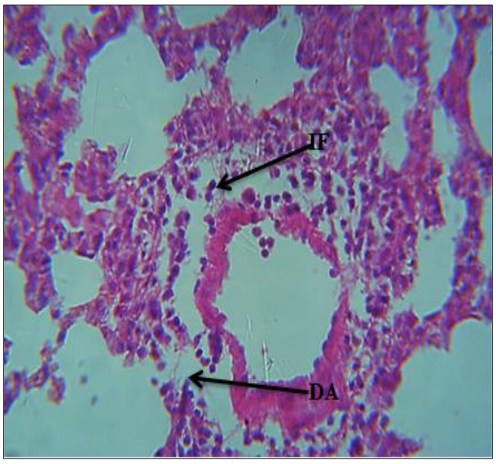

Image 5: A double-sided lung section of the naproxen-treated group showing inflammatory cell infiltration (IF) and rupture of the air sac walls (DA). H & E 400X.

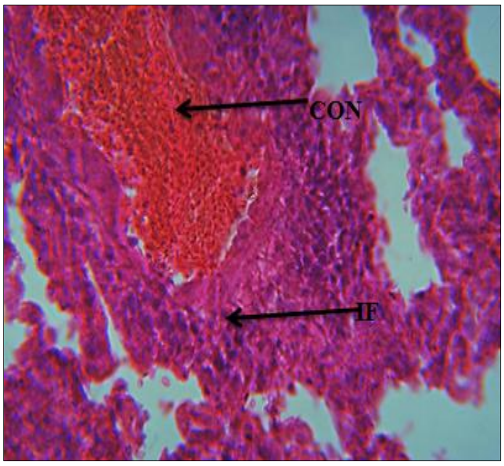

Image 6: Lung section of the group treated with therapeutic cefpodoxime showing inflammatory cell infiltration (IF) and hematologic congestion (CON). H & E 400X,

Image (6) of the cefpodoxime-treated lung tissue revealed inflammatory cell infiltration (IF) and congestion (CON). In the groups that received double doses of cefpodoxime, Image (7) and (8) showed progression of tissue damage including the formation of fibrous masses (FM) and bronchial constriction (Br) resulting from endothelial cell swelling.

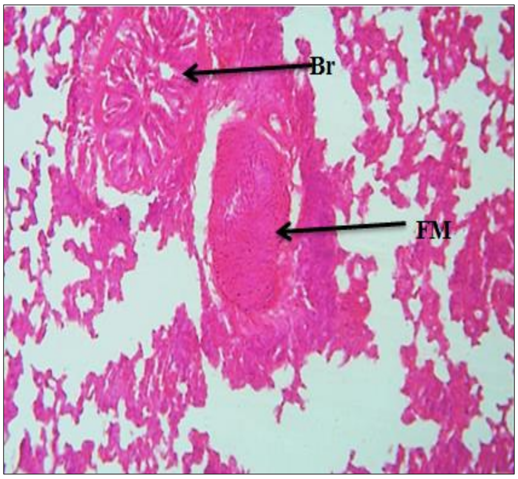

Image 7: Shows the formation of a fibrous mass (FM) and narrowing of the bronchial lining (Br) as a result of swelling of the endothelial cells in a section of the lung of the group treated with cefpodoxime doubled H & E 100X.

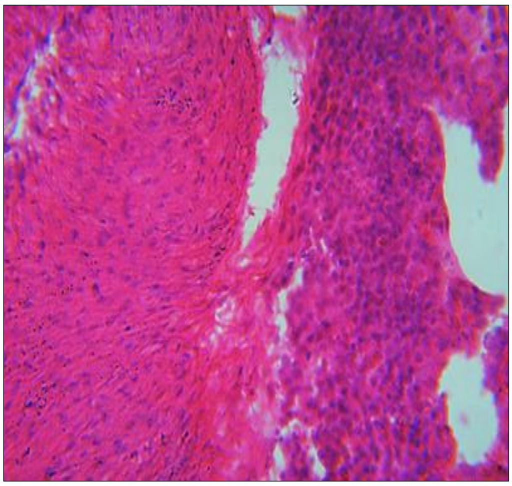

Image 8: Shows the formation of a fibrous mass (FM) in a section of the lung of the group treated with cefpodoxime doubled. H & E 400X.

Taken together, these results indicate that the use of naproxen and cefpodoxime, especially at high doses or for extended periods, leads to abnormal physiological responses in blood parameters and pathological histological changes in the lung, which calls for caution in their therapeutic use to ensure respiratory and vital safety.

DISCUSSION

The present study showed substantial hematological and histological changes in rat lungs following administration of naproxen and cefpodoxime. Dose-dependant toxic effect was confirmed by stronger effects having been seen in the higher (double) doses.

Concerning hematological parameters, red blood cell (RBC) counts revealed that there were no significant differences in between of all treated groups and control ones. Although Hb levels remained stable, a pronounced increases of PCV was found in each therapeutic dose group versus the control group. This rise may be explained by a compensatory physiological response or plasma volume alterations due to chronic administration of these drugs.

Moreover, there were marked increases in total white blood cell (WBC) and lymphocyte counts, especially in high-dose treatment groups. These finding is similar to the study (Ali *et al.,* 2014). Which indicated increased WBC (white blood cell) due to immune and inflammatory responses of tissue damaged following vehicle. That is a common indicator of lung injury and tissue inflammation caused by effects from the drug. This can be attributed to disturbances in hematological parameters due to drug toxicity, whereas a marked reduction in PLT levels was noted among treated groups.

In terms of histological changes, microscopic sections of the lungs in all two treated groups were characterized by severe vascular congestion and a significant augmentation in alveolar wall (TW) thickness. Results also showed a dense infiltration of inflammatory cells (IF), rupture of the alveolar walls (DA), fibrous masses (FM) and constriction of bronchi, especially with high doses of cefpodoxime. These findings are consistent with a study (Liu *et al*., 2005) that showed lung injury in rats is often associated with oxidative stress and tissue fibrosis resulting from drug accumulation. Analysis of the pharmacological properties shows that cefpodoxime has a high capacity for accumulation in lung tissue, which explains the severity of the observed changes such as fibrosis, endothelial cell swelling, and bronchiectasis when used at high doses. Naproxen, on the other hand, works by inhibiting COX enzymes, which can lead to a disruption of the balance between oxidants and antioxidants and tissue damage, thus explaining the acute congestion and inflammation observed in the lungs.

Comparing the two drugs, cefpodoxime appears to have a stronger effect in stimulating the chronic inflammatory response and the formation of tissue fibrosis, while naproxen's effect is more strongly associated with acute inflammatory changes and tissue rupture. Overall, this study is consistent with (Liu *et al*., 2005; Ahmad *et al*., 2018) which confirms that exposure to high doses of drugs leads to an increase in inflammatory cytokines and oxidative stress, manifested as congestion and thickening of the alveoli, findings that are entirely consistent with the histological sections observed in these studies.

CONCLUSIONS

The current study concludes that both naproxen and cefpodoxime, used in this study, have clear toxic effects on lung tissue and blood physiological parameters in male albino rats. The severity of these effects increases proportionally with increasing doses and exposure periods. Treatment with these drugs led to an inflammatory immune response, manifested in a significant increase in white blood cell and lymphocyte counts, resulting in disturbances in platelet levels and packed cell volume, as well as severe tissue damage including thickening of alveolar walls, blood congestion, pulmonary fibrosis, and bronchoconstriction, especially in the groups treated with high doses. In conclusion, considering these observations, the authors conclude that cautious therapeutic use of these drugs in prolong and high dose regimens is necessary with periodic assessment for respiratory function and blood markers as needed during patients follow up in this type of treatment protocols. This study has also opened a new avenue for future research to examine the efficacy of natural antioxidants used as an adjuvant, in impacting oxidative stress-mediated tissue injury caused by these drugs.

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