Research Article

An Investigation of Anti-inflammatory Effects of Famotidine in Rats by Evaluating Inflammatory Cells and Lung Histopathology: An Airway Model

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Abstract | Respiratory inflammatory disorders, including asthma and chronic obstructive pulmonary disease, are prevalent conditions affecting the airways. Current study aimed to investigate the impact of famotidine on respiratory inflammation in rats. Thirty adult male albino rats were segmented into five distinct groups, each group comprising six rats (n=6). A_group (Negative Control) rats received distilled water only, without any drug; B_group (Positive Control) rats underwent ovalbumin sensitization and challenge of the airways; C_group rats were treated orally with a dose of prednisolone (4.12 mg/kg/d) and subjected to ovalbumin sensitization of the airways; D_group rats received oral famotidine at a dose of 20 mg/kg/d with ovalbumin sensitization of the airways; and E_group rats were given oral prednisolone (4.12 mg/kg) and famotidine (20 mg/kg) with ovalbumin sensitization of the airways. The count of inflammatory cells in the broncho-alveolar lavage fluid was determined, as well as lung tissue histological analysis was conducted. The eosinophils, neutrophils, mononuclear cells, and total white blood cell count were all increased (P<0.05) in the positive control (B_group) when compared to the negative control group. Both D and E_groups, when treated with famotidine, showed a significant reduction (P<0.05) in the eosinophils, neutrophils, mononuclear cells, and total white blood cell count. Additionally, the histopathological examination revealed that both of these groups showed reduced accumulation of inflammatory cells within the lungs and dilation of the bronchiolar wall across the lung tissue. In conclusion, famotidine has a protective effect against airway inflammation by the reduction of inflammatory cells and improvement in the histopathological picture.

Keywords | Broncho-alveolar lavage fluid; Famotidine; Inflammatory cells; Ovalbumin; Pulmonary inflammation.

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INTRODUCTION

Persistent respiratory conditions like asthma and chronic obstructive pulmonary disease (COPD) remain significant global challenges for individuals and healthcare systems due to respiratory complications, prolonged hospitalization, and heightened mortality risks (Liccardi et al., 2012). Typically, asthma involves immune system activation, leukocytes infiltration, excessive mucus production, and remodeling of the airways (Boonpiyathad et al., 2019, Athari, 2019). Moreover, COPD has emerged as a significant contributor to mortality and has been classified as the third leading cause of death worldwide (Sritharan et al., 2021, Lee and Sin, 2022). Individuals with COPD face a heightened risk of infection, lung cancer, and sudden occurrences of acute pulmonary embolism (Lopez-Campos et al., 2014, Patel and Priefer, 2022).

Eosinophils exhibit a bi-lobed structure and serve as versatile cells within the innate immune system. They possess a variety of cell surface receptors that play a role in controlling both local immune reactions and inflammatory responses (Sharma et al., 2022). The recruitment of eosinophils effectively triggers a distinct immune response, subsequently resulting in airway hyper-responsiveness and remodeling. These phenomena are recognized as prominent indicators of chronic respiratory disorders (Lee et al., 2021). Prior studies have provided supporting evidence regarding the presence of eosinophilic infiltration within the respiratory system in cases of airway inflammatory diseases (Nagasaki et al., 2019, Aubier et al., 2018).

Neutrophils represent the predominant cellular component in human blood and play an important role as primary responders in the initial defense against pathogens (Rungelrath et al., 2020). In the context of pulmonary infections, these cells are mobilized to the site of inflammation, where they initiate the inflammatory process through the secretion of diverse pro-inflammatory chemokines and cytokines (Ham et al., 2022). Apart from eosinophils and neutrophils, the involvement of monocytes, as well as monocyte-derived and resident pulmonary macrophages, holds indispensable significance in the course of inflammation. Macrophages constitute a category of cells that facilitate responses within both innate and adaptive immunity (Kosyreva et al., 2021). During the inflammatory process, monocytes can differentiate into macrophages or dendritic cells upon stimulation by particular inflammatory cytokines (Takeda et al., 2018). Moreover, prior studies have demonstrated significant infiltration and activation of neutrophils and monocytes within the airways as a response to inflammation (Takeda et al., 2018, Gómez-Rial et al., 2020).

Presently, Corticosteroids are considered the preferred option for managing pulmonary inflammatory events (Ritchie and Wedzicha, 2020). Nonetheless, a significant percentage of individuals with asthma still struggle to achieve disease recovery (Buhl et al., 2018). Challenges in treating airway inflammatory diseases arise due to the absence of secure and effective disease-modifying therapies. Therefore, it is essential to prioritize the research objective of exploring alternative medical options.

Famotidine is an approved medication by the United States Food and Drug Administration for peptic ulcers and gastroesophageal reflux disease (GERD), belongs to the class of histamine-2 receptor (H2R) antagonists (Balouch et al., 2023). Famotidine is considered a cost-effective, and readily accessible medication, with excellent tolerability and minimally documented drug-drug interactions (Brennan et al., 2022). In addition, Famotidine has demonstrated safe usage across a broad spectrum of oral doses, ranging from 20 mg once daily to 160 mg four times daily (Janowitz et al., 2020). Its widespread use by millions of patients worldwide further supports its safety profile (Brennan et al., 2022). Histamine triggers the activation of protein kinase A, resulting in the (H+/K+) activation, which ultimately leads to elevated secretion of gastric acid (Seldeslachts et al., 2023). The H2R, which famotidine targets, extends beyond the stomach and is also present in other anatomical regions, including the pulmonary system (Mukherjee et al., 2021). Research findings indicate that famotidine achieves systemic concentrations capable of effectively antagonizing H2R on various cell types, including those present in inflammatory cells (Malone et al., 2021).

The primary objective of this study was to assess the efficacy of famotidine in treating airway inflammatory disease in rats. This evaluation involved examining its potential to suppress inflammatory cells and prevent pathological changes in lung tissue in rats that were sensitized with ovalbumin (OVA).

MATERIALS AND METHODS

Ethics Statement

Animal experiments were carried out in accordance with the ethical guidelines outlined in the European Union Directive (86/609/EEC) dated November 24, 1986, and received approval from the local ethical committee at the College of Pharmacy, University of Basrah.

Material

The medication, materials, and chemicals utilized in this research comprise famotidine from Medocheme Ltd-Cyprus, prednisolone from The State company for Drugs Industry and Medical pliances-Iraq, phenobarbital from IBN HAYYAN Pharmaceutical co.-Syria, OVA powder from RIEDEL-DEHAENAG, SEELZE-HANNOVER-Germany, aluminum hydroxide powder from MERK Darmstadt-Germany, 0.9% sodium chloride solution from Pharmaceutical Solution Industry-Saudi Arabia, and formaldehyde 37% from Aqua Medical-Turkey.

Animals

A total of thirty healthy adult male albino rats, aged between 2-3 months and weighing 150-200 grams, were used in this study. These rats were procured from the Biotechnology Research Center / Nahrain University, and were randomly housed in suitable cages at the Animal House of the Pharmacy College, University of Basrah.

To ensure proper adaptation, the rats were allowed to adapt to their new environment for 14 days. During this period, optimal conditions were maintained, including a temperature of 21 ± 4 degrees Celsius, a light-dark photoperiod of

12 hours of light and 12 hours of darkness, and efforts were made to minimize unnecessary stress. Throughout the experiment, the rats were provided with a commercial pellet diet and had access to clean tap water.

Animal grouping

A_group (Negative Control): Rats received distilled water only, without any drug, for 14 days.
B_group (Positive Control): Rats underwent OVA sensitization and challenge of the airways.
C_group: Rats were treated orally with a dose of prednisolone (4.12 mg/kg/d) and subjected to OVA sensitization of the airways (Ahmed et al., 2021).
D_group: Rats received oral famotidine at a dose of 20 mg/kg/d after OVA sensitization of the airways (Loffredo et al., 2021).
E_group: Rats were given both oral prednisolone (4.12 mg/kg) and famotidine (20 mg/kg) after OVA sensitization of the airways (Ahmed et al., 2021, Loffredo et al., 2021).

Experimental method

The method of inducing airway inflammation in rats through OVA-sensitization (applied to all groups except A_group) was modified from the approach used by previous researchers. During days 1-3 of the experiment, the rats were sensitized through intraperitoneal (IP) injections of a mixture containing 1 mg of OVA and 100 mg of aluminum hydroxide in 1 mL of N/S. This sensitization was administered once daily to the rats in the respective groups, except A_group. They were allowed to rest without any additional interventions. From days 6 to 8 of the experiment, the rats were subjected to another round of sensitization through IP injections. This time, the injection contained 100 mg of OVA and 100 mg of aluminum hydroxide in 1 mL of N/S. The sensitization was administered once daily during this period for the respective groups, except A_group. From days 9 to 14 of the experiment, the rats were challenged by being placed inside a glass chamber measuring 30 x 35 x 40 cm. This chamber was connected to a nebulizer that generated a 1% OVA aerosol, which consisted of 1 gm of OVA dissolved in 100 mL of N/S. The rats inhaled this aerosol for 30 minutes each day as part of the challenging process. On day 15, the rats were killed by an IP injection of (800 mg/kg) of sodium phenobarbital and sacrificed for further analysis and examination (Ahmed et al., 2021, Algaem et al., 2013, Alabdali and Ibrahim, 2023). In groups receiving prednisolone and famotidine, the drug doses were given 60 minutes before exposing the rats to airway sensitization with OVA. This pre-treatment was conducted to evaluate the impact of the drugs on the airway inflammation induced by OVA sensitization (Ahmed et al., 2021). The process of broncho-alveolar lavage involved infusing 3 mL of N/S through a catheter which was inserted into the rat's trachea. The broncho-alveolar lavage fluid (BALF) was then centrifuged at 3000 rpm for 4 min. The inflammatory cells present in the BALF were then quantified using an automated hematology analyzer (Alabdali and Ibrahim, 2023, Poitout-Belissent et al., 2021, Alabdali and Algaem, 2023).

The left lung was cut, rinsed with saline, and preserved in cups containing 10% formaldehyde for subsequent histopathological analysis (leukocytes count). The histology images of lung segments were carefully inspected and photographed using a light microscope at the amplification of X40. Inflammatory cells that infiltrated the bronchi and alveoli were assessed through a series of lung sections stained with H&E (hematoxylin and eosin) (Alabdali and Ibrahim, 2023, Ahmed et al., 2021).

Statistical analysis

In this study, mean ± SEM values were represented using bar graphs. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 20. The statistical differences were assessed using ANOVA, and a significance level of $P<0.05$ was set to determine statistical significance.

RESULTS

The Effect of Famotidine on Eosinophils Count/µL in the BALF of a Rat Model of Airway Sensitization

Following airway sensitization, the positive control group exhibited a significantly higher eosinophils count ($P<0.05$) compared to the negative control group (5.40±1.69 and 0.003±0.002), respectively. In contrast, the groups treated with prednisolone, famotidine, and both (prednisolone and famotidine) showed a significant decrease in eosinophils count ($P<0.05$) compared to the positive control group (0.002±0.002, 0.07±0.07 and 0.003±0.002), respectively. Furthermore, there was no significant difference between the famotidine, (prednisolone and famotidine) treated groups when compared with the prednisolone treated group, as illustrated in Figure 1.

The Effect of Famotidine on Neutrophils Count/µL in the BALF of a Rat Model of Airway Sensitization

The neutrophil count in the BALF of rats exhibited a significant increase (P<0.05) in the positive control group in comparison to the negative control group (19.05±10.34 and 0.218±0.039), respectively. Furthermore, the neutrophil counts in the airway OVA-sensitized rats treated with prednisolone, famotidine, and both (prednisolone and famotidine) showed a significant reduction ($P<0.05$) compared to the positive control group (0.633±0.210,

0.736±0.247, and 0.555±0.193), respectively. Moreover, no significant difference was shown between the famotidine, (prednisolone and famotidine) treated groups when compared with the prednisolone treated group, as illustrated in Figure 2.

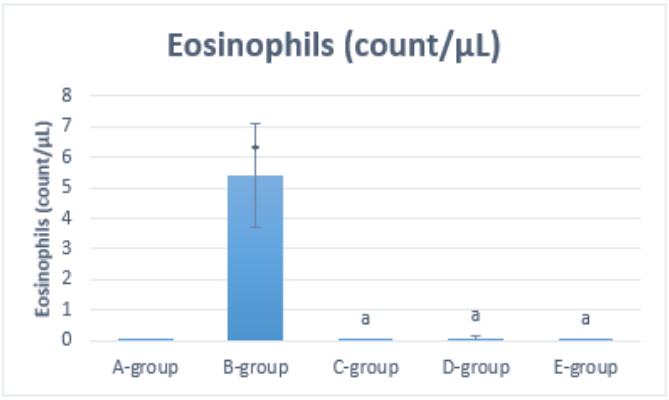

Figure 1: The effect of famotidine on the eosinophils count in the BALF of airway-sensitized rats. OVA-sensitization resulted in an increase in eosinophils count in the BALF, whereas treatment with famotidine reduced these counts. A_group, negative control; B_group, positive control (sensitized); C_group, prednisolone; D_group, famotidine; E_group, prednisolone and famotidine; *= denoting statistical significance (P<0.05) in comparison to A_group; a= denoting statistical significance (*P*<0.05) in comparison to B_group.

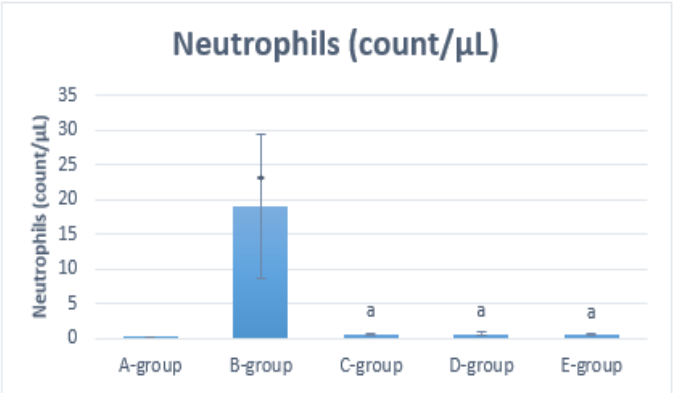

Figure 2: The effect of famotidine on the neutrophils count in the BALF of airway-sensitized rats. OVA-sensitization resulted in an increased neutrophil count in the BALF of rats, whereas famotidine treatment reduced this expression significantly. A_group, negative control; B_group, positive control (sensitized); C_group, prednisolone; D_group, famotidine; E_group, prednisolone and famotidine; *= denoting statistical significance (*P*<0.05) in comparison to A_group; a= denoting statistical significance (*P*<0.05) in comparison to B_group.

The effect of Famotidine on Mononuclear Cells Count/µL in the BALF of a Rat Model of Airway Sensitization

The count of mononuclear cells in the BALF of rats was significantly increased (*P*<0.05) in the positive control group when compared with that of the negative control group (21.42±6.47 and 0.218±0.061), respectively. Moreover, the counts of mononuclear cell in the D- and E_groups of OVA-sensitization that were treated with prednisolone, famotidine, and both (prednisolone and famotidine) demonstrated a significant reduction (*P*< 0.05) when compared to the positive control group (0.745±0.155, 1.33±0.526, and 0.441 ±0.184), respectively. In addition, no statistical significance was demonstrated between the Famotidine, (prednisolone and famotidine) treated groups when compared with the prednisolone treated group, as shown in Figure 3.

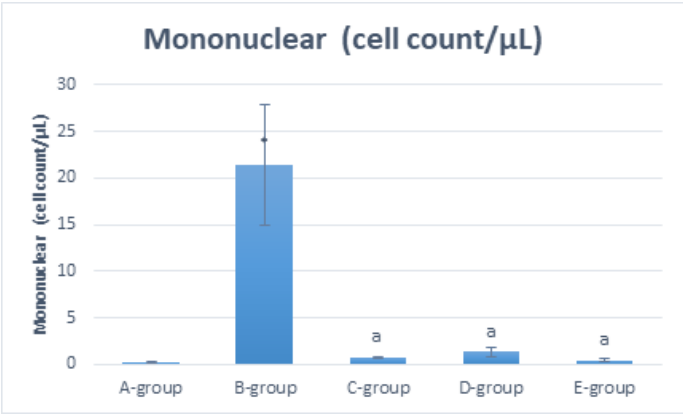

Figure 3: The effect of famotidine on the mononuclear cell count in the BALF of airway-sensitized rats. OVA-sensitization was associated with a significant elevation in mononuclear cell count present in the BALF, whereas treatment with famotidine led to their significant reduction. A_group, negative control; B_group, positive control (sensitized); C_group, prednisolone; D_group, famotidine; E_group, prednisolone and famotidine; *= denoting statistical significance (*P*<0.05) in comparison to A_group; a= denoting statistical significance (*P*<0.05) in comparison to B_group.

The Effect of Famotidine on Total WBC Count/µL in the BALF of a Rat Model of Airway Sensitization

The count of total WBC in the BALF of rats was significantly higher (*P*<0.05) in the positive control group when compared to the negative control group (42.17±16.75 and 0.463±0.076), respectively. Furthermore, the total WBC count in the airways of OVA-sensitized rats when treated with prednisolone, famotidine, and both (prednisolone and famotidine) showed a significant reduction (*P*< 0.05) when compared to the positive control group (1.39±0.358, 1.27±0.439, and 0.965±0.369), respectively. In addition

to that, no significant difference was shown between the famotidine and prednisolone plus famotidine treatment groups when compared with the prednisolone treatment group, as demonstrated in Figure 4.

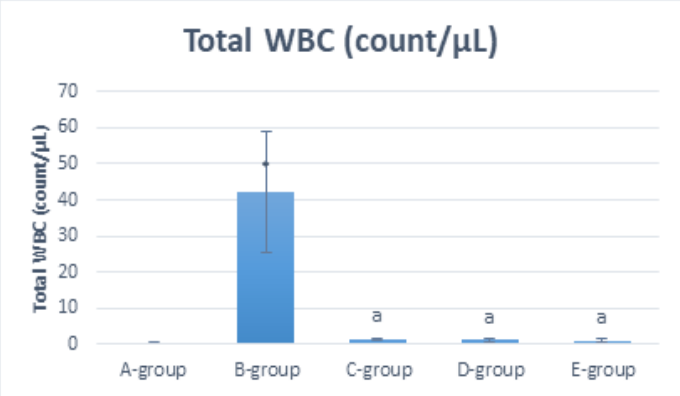

Figure 4: The effect of famotidine on total WBC count in the BALF of airway-sensitized rats. After OVA sensitization, there was a general increase in the number of inflammatory cells in the BALF. However, treatment with famotidine resulted in a significant reduction in the WBC count. A_group, negative control; B_group, positive control (sensitized); C_group, prednisolone; D_group, famotidine; E_group, prednisolone and famotidine; *= denoting statistical significance (P<0.05) in comparison to A_group; a= denoting statistical significance (P<0.05) in comparison to B_group.

The Effects of Famotidine on the Histopathology of Lung Tissue Following OVA-Sensitization of the Airway in Rats:

The histopathological examination of lung tissue from healthy rats in (A_group) revealed well-preserved bronchioles and alveoli. The bronchioles were dilated and demonstrated a normal architecture with an intact epithelial lining, and the alveoli appeared healthy, exhibiting normal wall thickness. Notably, no indications of inflammation or cellular infiltrates were observed within the alveolar spaces (Figure 5, A_group).

In (B_group), OVA-sensitization led to bronchoconstriction, resulting in the narrowing of the airways. Moreover, there was a clear inflammation of submucosal cells with leukocytes infiltration (mainly neutrophils and lymphocytes) detected by the exudate of such cells in bronchial lumen, suggesting an immune response with evident signs of damage and disruption. Furthermore, an increase in the alveolar macrophages population was observed. Alveolar wall thickness was increased in addition to the proliferation of alveolar cells within the damaged lung tissue (Figure 5, B_group).

Prednisolone treatment in (C_group) significantly improved the histopathological appearance. The bronchioles exhibited a more intact and organized epithelial lining with normal epithelial cell wall and lumen. Furthermore, there was an evident bronchodilation and no signs of bronchiolar call wall thickness. The reduction in leukocytes infiltrates within the bronchiolar walls indicated a notable decrease in inflammation. The alveoli revealed signs of wall restoration and total repair. However, the alveolar wall showed slight thickness with few scattered leukocytes within the alveoli (Figure 5, C_group).

Treatment with famotidine in (D_group) led to the reduction in cellular debris and inflammatory cell accumulation within the bronchioles except for minimal infiltration of macrophages. Bronchiolar cell walls were healthy with normally dilated bronchiolar lumen when compared to (B_group). The alveolar epithelial cells showed restoration towards their normal structure. A dilation of the alveolar lumen was noted, accompanied by a reduction in inflammatory cells, except for the presence of a few scattered macrophages within the alveolar spaces when compared to (B_group) (Figure 5, D_group).

Prednisolone with famotidine treatment in (E_group) also resulted in an overall improvement in lung histology. The histopathology of lung tissue revealed a slight dilation in bronchioles with normal structure of the cell walls. However, there was a detectable narrowing in the alveoli with infiltration of alveolar macrophages within the lung tissue when compared to (B_group) (Figure 5, E_group).

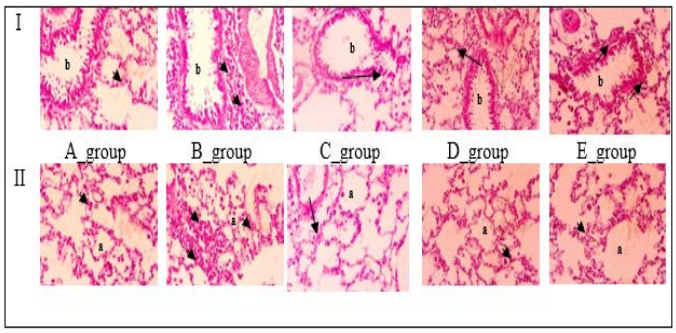

Figure 5: The effect of famotidine on the lung tissue histopathology. The process of OVA-sensitization resulted in a noticeable increase in the accumulation of leukocytes in lung tissue. However, in rats treated with famotidine, this accumulation was reduced, highlighting the anti-inflammatory effect of famotidine. Lung tissue photos were taken by light microscope, X-40, H&E stain. The arrows point to inflammatory cells; b, bronchioles; a, alveoli; A_group, negative control; B_group, positive control; C_group, prednisolone; D_group, famotidine; E_group, prednisolone and famotidine.

DISCUSSION

Pulmonary inflammation is a protective response of the

body by removing harmful substances such as irritants and damaged cells. Nevertheless, excessive inflammation can contribute to different lung disorders (Makris et al., 2017). Several findings indicate that famotidine can assist in alleviating inflammation triggered by histamine. Famotidine blood concentrations can reach sufficient levels to block histamine H2R present in several leucocytes (Mukherjee et al., 2021). A prior study showed that treatment with famotidine resulted in a more favorable clinical outcome in cases of severe Coronavirus Disease-2019 (COVID-19) (SÖZEN, 2023). Famotidine may also have an effect by scavenging reactive oxygen radicals, thus reducing secondary inflammation and damage (Yang et al., 2022).

Corticosteroids, including prednisolone, serve as the cornerstone of airway inflammation treatment. However, these medications come with a wide range of adverse effects, especially when used for prolonged periods (Williams, 2018, Cutrera et al., 2017).

In this study, the rat model sensitization was induced by OVA antigen and the aluminum hydroxide as an adjuvant, together they stimulated the rat's adaptive immune response (Casaro et al., 2019). The use of OVA has been employed in previous studies to induce respiratory inflammation in rats (Algaem et al., 2013, Hsu et al., 2012).

It is widely recognized that the allergic immune response begins with an initial phase known as sensitization, characterized by the production of antibodies directed against the allergen. The IP route has likely been the most conventional method for inducing sensitization. The subsequent phase is referred to as the challenge stage. Upon subsequent exposures to the same allergen, inflammatory cells in the airways become activated. Furthermore, these effector cells release inflammatory mediators (histamine), leading to edema, bronchospasm, and accumulation of mucous in the airways. The aerosol route is less invasive and does not require animal sedation. In addition, this route places the antigen directly in the respiratory system (Aun et al., 2017).

The ability of famotidine to alleviate eosinophil infiltration in the BALF suggests that famotidine, like prednisolone, has the potential to prevent eosinophil activation, leading to a reduction in eosinophil-caused inflammation in the lungs and airway remodeling. A previous research study has demonstrated that eosinophil functions are inhibited by H2R activation. The binding of histamine leads to a reduction in the release of eosinophil peroxidase, and at high concentrations, it blocks the eosinophil chemotaxis (Malone et al., 2021). Considering the findings from pharmacokinetic studies, which indicate that famotidine achieves blood concentrations capable of antagonizing histamine H2R present in neutrophils, mast cells, and eosinophils, these observations provide a rationale for famotidine's potential in modifying histamine-induced inflammation and cytokine release (Mukherjee et al., 2021).

When neutrophils are activated in the airways, they are associated with tissue damage and remodeling during the inflammatory process, potentially contributing to organ injury (Wang et al., 2018). Famotidine's significant reduction in neutrophils was attributed to its ability to counter the accumulation of leukocytes, resulting in a reduction in the magnitude of respiratory inflammation. Other studies corroborate these findings, demonstrating that famotidine treatment was associated with a reduction in neutrophils (Malone et al., 2021, Hosseini et al., 2023). One plausible explanation is that H2R activation in neutrophils inhibits their effector functions, including the release of O2- (Malone et al., 2021).

Histamine is known to exert a regulator, pro-inflammatory immune responses triggered by monocytes, including macrophages (Bernardino, 2021). In this study, famotidine's reduction in the accumulation of mononuclear cells suggests that famotidine has an inhibitory effect on inflammation of the airways, likely attributable to the decreased presence of mononuclear cells and the subsequent decrease in inflammatory molecules and cytokines that are produced by these cells.

The influence of famotidine on H2R can result in the modulation of immune system, leading to a reduction in airway inflammation, particularly through T-helper-1 lymphocytes (Hogan Ii et al., 2020). In this study, famotidine caused a reduction in the total WBC count in the BALF. This finding is consistent with a prior study that demonstrated a significant decrease in the WBC count for patients following treatment with famotidine when compared to placebo (Samimagham et al., 2021).

To be specific, famotidine treatment has been shown to inhibit the expression of Toll-like receptor 3 (TLR3) in COVID-19-infected cells, therefore reducing TLR3-dependent signaling processes. Leading to the modulation of interferon regulatory factor 3 (IRF3) and the transcription factor (nuclear factor kappa-light-chain enhancer of activated B-cells), known as NF-κB pathway activation, thereby controlling the inflammatory responses (Mukherjee et al., 2021). IRF3 stands as one of the extensively characterized transcription factors engaged in the regulation of innate-immune reactions to inflammatory events (Yanai et al., 2018).

Multiple preceding studies have established that airway inflammation is facilitated through the activation of NFκB

by inflammatory mediators. This, in turn, triggers gene transcription and the expression of various inflammatory mediators, culminating in the activation and infiltration of leukocytes (Lee et al., 2017, Sha et al., 2019).

Histopathological analysis in (A_group) showed normal architecture, indicating efficient gas exchange. The limited presence of macrophages suggested the absence of pathological processes. The healthy lung tissue of rats was similarly described by a previous study (Ezz-Eldin et al., 2020). In the OVA-sensitized rats (B_group), the submucosa was highly infiltrated with lymphocytes, which is consistent with the pathogenesis of OVA-induced lung inflammation. The proliferation of alveolar cells indicates potential damage to these cells due to the inflammatory response, ultimately leading to impaired lung function. These findings were consistent with prior research (Bai et al., 2019, Zainal et al., 2019).

The administration of prednisolone (C_group) resulted in reversed inflammatory events within the lung tissue. These results align with previous research in mice in which prednisolone treatment reversed leukocytes aggregation in lung tissue (Chiu et al., 2021). The administration of famotidine, in (D_group) and in combination with prednisolone in (E_group), significantly reduced leukocytes infiltration in bronchiolar walls, alveolar spaces and septa. In addition, a reduced alveolar wall thickness was noted, suggesting attenuation of edema and inflammatory changes. Collectively, famotidine treatment demonstrated lung tissue protection against the inflammatory process. In previous research, the histological damage and inflammation observed in the lungs of mice appeared to be reduced significantly through the administration of famotidine (Hattori et al., 2016).

CONCLUSION

Presently, corticosteroids widely regarded as the most efficacious medication in the management of airway inflammation, however, they are associated with various side effects. The findings from this present study indicate that famotidine, alone in group_D and when combined with prednisolone in group_E, exerts a protective effect against OVA-induced airway sensitization in rats by the reduction of inflammatory cell infiltration. In addition, famotidine has a protective effect against lung tissue remodeling. Consequently, famotidine holds promise as a potential prophylactic medication for inflammatory disease of the airways.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTION

The authors confirm their contribution to the paper as follows: study conception and design: Manal Abdulkhaliq. data collection: Wasan Ali; analysis and interpretation of results: Manal Abdulkhaliq, Wasan Ali. draft manuscript preparation: Manal Abdulkhaliq, Wasan Ali. All authors reviewed the results and approved the final version of the manuscript.

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