Original Article

Investigation of the Anti-Inflammatory Effect of Famotidine in Rats by Evaluation of IL-4, IL-6, TNF-α, and IL-10: Airway Model

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Abstract

Background: Lung inflammatory diseases (such as asthma and chronic obstructive pulmonary disease [COPD])) are widespread inflammatory airway illnesses that are characterized by cough, wheezing, chest tightness, and dyspnea, all of which are symptoms of airway obstruction. **Objective:** To investigate how famotidine influences pro-inflammatory cytokines (IL-4, IL-6, TNF-α, and IL-10) related to airway inflammation. **Materials and Methods:** Thirty healthy male albino rats weighing 150 and 200 g were divided into five groups of six rats each as follows: A Group: Control group—rats received distilled water for a period of 14 days. B Group: Positive control group—rats were exposed to airway sensitization. C Group: Rats were treated with oral prednisolone at a dose of 4.12 mg/kg, after exposure to airway sensitization. D Group: Rats received oral famotidine (20 mg/kg) after airway sensitization. E Group: Rats received oral prednisolone and famotidine (4.12 mg/kg and 20 mg/kg), respectively, after airway sensitization. Inflammatory cytokines of rats (IL-4, IL-6 IL-10, and TNF-α) were measured by ELISA after 14 days of study. **Results:** The levels of inflammatory cytokines such as IL-4, IL-6, and TNF-α were reduced after famotidine treatment, indicating that famotidine has anti-inflammatory properties. **Conclusion:** According to the current study, famotidine, as an antagonist of the histamine-2 receptor, has demonstrated anti-inflammatory properties in an airway model. This has been observed through decreased levels of crucial pro-inflammatory cytokines such as IL-4, IL-6, and TNF-α, in addition to an increase in IL-10 level. More research with famotidine could be conducted in future to prevent and treat other inflammatory respiratory illnesses.

Keywords: Airway inflammation, cytokines, famotidine, ovalbumin, prednisolone

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are widespread illness that affects people worldwide. They are distinguished by persistent inflammation of the airways caused by various trigger factors and reasons.[1] The mechanism of inflammation in these illnesses is marked by the activation of various cellular elements and the release of a wide range of pathogenic mediators.[2] Histamine is the most important mediator in these inflammations, and it is a small-sized and flexible biogenic amine that modulates cellular responses and performs various roles in physiological and pathological processes.[3]

Inhaled corticosteroids play a major role in the management of asthma or COPD.[3] The anti-inflammatory steroid approach has been successful in managing asthma or COPD, but despite this, it still just conveys symptoms in long-term treatment and is not always powerful.[4]

Famotidine is an FDA-approved drug for peptic ulcers and gastroesophageal reflux disease (GERD). It is a histamine-2 receptor antagonist that is inexpensive and widely available and has been safely used to decrease gastric acid production.[5] Histamine stimulates protein kinase A (PKA), causing the (H^+/K^+) pump to translocate to the

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plasma membrane and increase gastric acid secretion. Famotidine inhibits the specific action of acid secretion, thus lowering gastric acid in those with GERD.[6]

Cytokines are molecules consisting of polypeptides that are released by a range of cell types, such as inflammatory cells and pulmonary epithelium.[7] Cytokines play a crucial role in the development of airway inflammation and obstruction in both asthma and COPD.[2] One of the most important inflammatory mediators is interleukin-4 (IL-4) which serves various activities. It primarily stimulates T cell proliferation and B cell antibody production, but it can also stimulate the activation of fibroblasts, epithelial, and endothelial cells and increase the recruitment of inflammation-causing cells.[8] The cytokine IL-6 is pleiotropic in nature and is known for its diverse roles in many physiological processes, which include controlling inflammatory reactions. However, excessive IL-6 synthesis might cause cytokine production and systemic inflammatory responses.[9] Interleukin-10 (IL-10) is also called an inhibitory or regulatory cytokine with immunosuppressive and anti-inflammatory properties and is primarily generated by macrophages and T cells.[10] In addition, TNF-α is a significant pro-inflammatory mediator that attracts eosinophils and neutrophils to the site of inflammation and increases their cytotoxic action against endothelial cells.[11] The aim of this study is to examine the anti-inflammatory effect of famotidine on different pro-inflammatory cytokines in a rat model with ovalbumin powder (OVA) sensitization.

Materials and Methods

Materials

The drugs and compounds used in this investigation are famotidine (Medochemie Ltd, Cyprus), prednisolone (The State Company for Drugs Industry and Medical Appliances, Iraq), phenobarbital (Ibn Hayyan Pharmaceutical Co., Syria), OVA (Riedel-DeHaenag, Seelze, Hannover, Germany), aluminum hydroxide powder (Merk Darmstadt, Germany), 0.9% sodium chloride solution (Pharmaceutical Solution Industry, Saudi Arabia), and 37% formaldehyde (Aqua Medical, Turkey).

Animals

Thirty healthy male albino rats weighing 150–200 g were bought from the Biotechnology Research Center/Nahrain University. The rats were fed commercial pellets with distilled water after being housed in polypropylene cages (six rats per cage) under the normal conditions of humidity, light/dark photoperiod (12L/12D), and temperature (21 ± 4°C).

Experimental design

A Group: Negative control—the rats were administered distilled water only for 14 days without any drug. B Group: Positive control—the rats were subjected to OVA sensitization and challenge of the airways. C Group: The rats were treated with an oral prednisolone dose (4.12 mg/kg/d) and subjected to airway OVA sensitization. D Group: Rats were given oral famotidine (20 mg/kg/d) after OVA sensitization of the airways. E Group: Rats were given oral prednisolone and famotidine (4.12 mg/kg and 20 mg/kg),[12] respectively, after OVA sensitization of the airways. Inflammatory airway sensitization was achieved by (the inhalation of aerosolized ovalbumin) utilizing a modified airway inflammatory model developed by the previous researcher.[13,14] During the initial three days, rats underwent sensitization with (1 mg) ovalbumin and (100 mg) aluminum hydroxide dissolved in a 1 mL N/S. On the sixth day, the sensitization dose was escalated to 100 mg of ovalbumin and 100 mg of aluminum hydroxide mixed with 1 mL N/S. The challenge commenced on the ninth day using a glass container (measuring 30 cm × 35 cm × 40 cm) connected to a nebulizer containing 1% ovalbumin (1 gm ovalbumin in 100 mL solution of N/S), administered for 30 min daily for six consecutive days. In the treated groups, the drug doses were administered 60 min before sensitization. After 14 days, the rats were euthanized using 800 mg/kg sodium phenobarbital.[15]

Cytokine measurement

Serum cytokine levels of IL-4, IL-6, TNF-α, and IL-10 were measured using enzyme immunoassays in accordance with the manufacturer's procedure. Prior to the experiment, all reagents and samples were allowed to equilibrate at ambient room temperature.

Ethical approval

The study protocol was reviewed and approved by Basra University College of Pharmacy's local ethics committee. This approval was granted under document number Permissions: No.: 7/18/6081 on January 19, 2022.

Statistical analysis

The data of this study were represented as the mean value ± S.E. The SPSS statistical package was used for the statistical analysis. One-way ANOVA comparisons were employed to investigate differences between test groups. Statistical significance was determined by identifying differences with a P value < 0.05.

Results

The effect of famotidine on serum IL-4 in rats

The rats subjected to airway sensitization in the B group had significantly ($P < 0.05$) higher IL-4 levels (344.25 ± 111.99) (mean ± SEM) compared to rats in A, C, and E group (124.67 ± 28.97, 113.46 ± 51.32, and 79.30 ± 16.32), respectively. IL-4 levels were significantly

($P < 0.05$) decreased (113.46 ± 51.32) in the C group (prednisolone dose of 4.12 mg/kg/d) compared to the B group (344.25 ± 111.99). Furthermore, Table 1 and Figure 1 show that rats treated with 20 mg/kg famotidine had non-significantly different ($P < 0.05$) IL-4 levels (195.33 ± 43.17) compared to rats in all other groups. Rats treated with prednisolone and famotidine (4.12 mg/kg and 20 mg/kg), respectively, showed a significant ($P < 0.05$) lowering of IL-4 levels (79.30 ± 16.32) compared to the B group (344.25 ± 111.99).

The effect of famotidine on serum IL-6 in rats

The rats subjected to airway sensitization in the B group had significantly ($P < 0.05$) higher IL-6 levels (160.46 ± 20.79) (mean ± SEM) compared to rats in all groups. IL-6 levels were significantly ($P < 0.05$) decreased (103.28 ± 27.03) in the group treated with prednisolone (4.12 mg/kg) compared to the B group (160.46 ± 20.79). Furthermore, Table 1 and Figure 2 show that rats treated with 20 mg/kg famotidine had significantly ($P < 0.05$) decreased IL-6 levels (76.35 ± 12.28) compared to rats in B group (160.46 ± 20.79). Rats treated with prednisolone and famotidine (4.12 mg/kg/d and 20 mg/kg/d) showed a significant ($P < 0.05$) lowering of IL-6 levels (55.75 ± 17.65) compared to the B group (160.46 ± 20.79).

The effect of famotidine on serum TNF-α in rats

The rats subjected to airway sensitization in the B group had significantly ($P < 0.05$) higher TNF-α levels (241.48 ± 43.11) (mean ± SEM) compared to rats in all groups. TNF-α levels were significantly ($P < 0.05$) decreased (57.38 ± 15.25) in the C group (prednisolone dose of 4.12 mg/kg/d) compared to B and E group (241.48 ± 43.11 and 157.95 ± 26.77), respectively. Furthermore, Table 1 and Figure 3 show that the rats treated with 20 mg/kg famotidine had significantly ($P < 0.05$) decreased TNF-α levels (102.50 ± 13.15) compared to rats in the B group (241.48 ± 43.11). TNF-α had a significantly ($P < 0.05$) decreased in E group (prednisolone and famotidine) (157.95 ± 26.77) compared to A, B, and C group (43 ± 15, 241.48 ± 43.11, and 57.38 ± 15.25), respectively.

The effect of famotidine on serum IL-10 in rats

The rats subjected to airway sensitization in the B group (35.47 ± 13.62) had significantly ($P < 0.05$) decreased IL-10 levels compared to rats in A, C, and E group (205.63 ± 26.41,

Table 1: Serum level of IL-4, IL-6, TNF-α, and IL-10 in numerous groups of rats

Name of group $n = 6$	IL-4 in rats serum (means ± SEM)	IL-6 in rats serum (means ± SEM)	TNF-α in rats serum (means ± SEM)	IL-10 in rats serum (means ± SEM)
A (negative control)	124.67 ± 28.97[a]	30 ± 13.53 [a]	43 ± 15 [a]	205.63 ± 26.41 [a]
B (positive control)	344.25 ± 111.99[*]	160.46 ± 20.79[*]	241.48 ± 43.11[*]	35.47 ± 13.62[*]
C (prednisolone)	113.46 ± 51.32 [a]	103.28 ± 27.03 [a]	57.38 ± 15.25 [a]	182.26 ± 24.85 [a]
D (famotidine)	195.33 ± 43.17	76.35 ± 12.28 [a]	102.50 ± 13.15 [a]	72.95 ± 19.18
E (famotidine plus prednisolone)	79.30 ± 16.32 [a]	55.75 ± 17.65 [a]	157.95 ± 26.77 [a]	107.11 ± 16.46 [a]

The values are presented as means ± standard error of the mean (SEM)

[*] = significant differences (P value < 0.05) when compared to the negative control group. Values annotated with a superscript symbol (a) indicate significant differences (P value < 0.05) when compared to B group

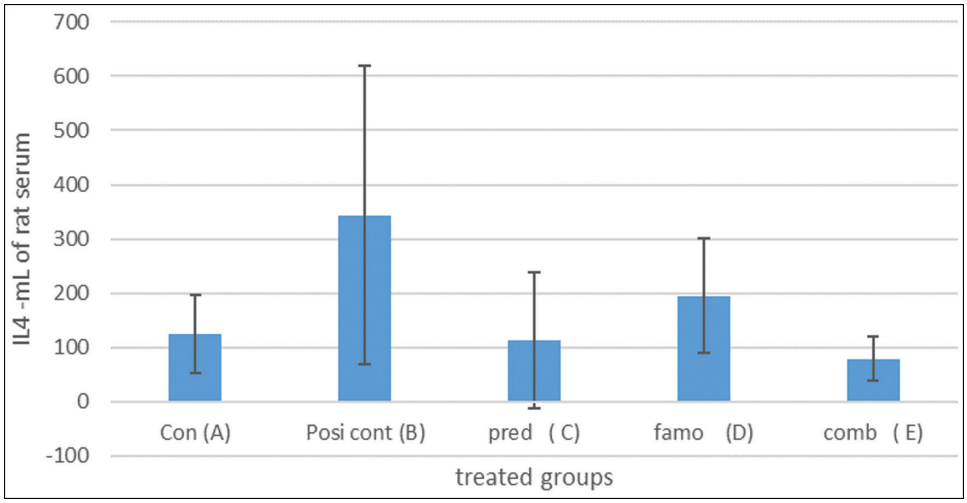

Figure 1: Serum IL-4 level of rats in treated groups

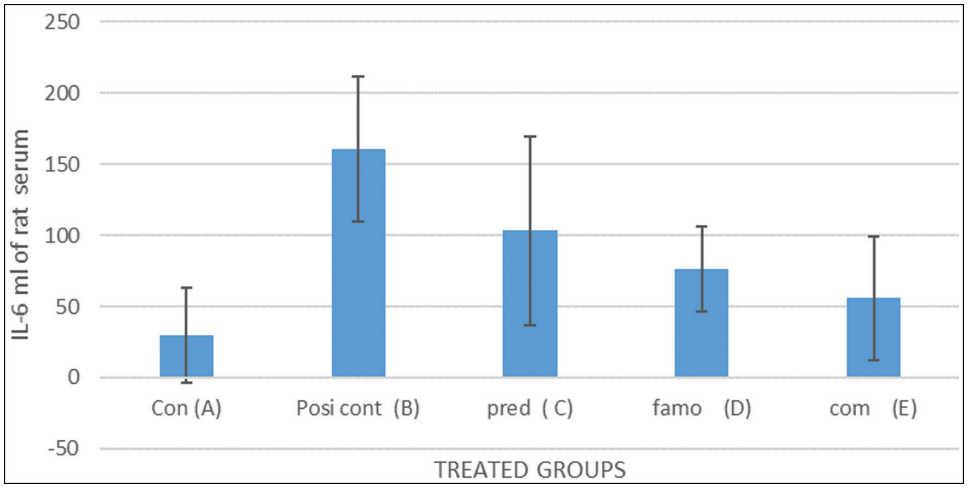

Figure 2: Serum IL-6 level of rats in treated groups

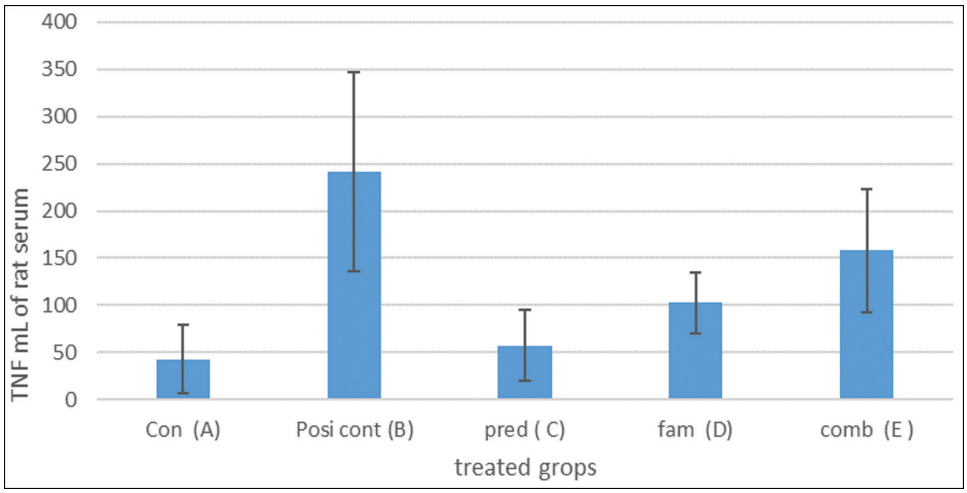

Figure 3: Serum TNF-α level of rats in treated groups

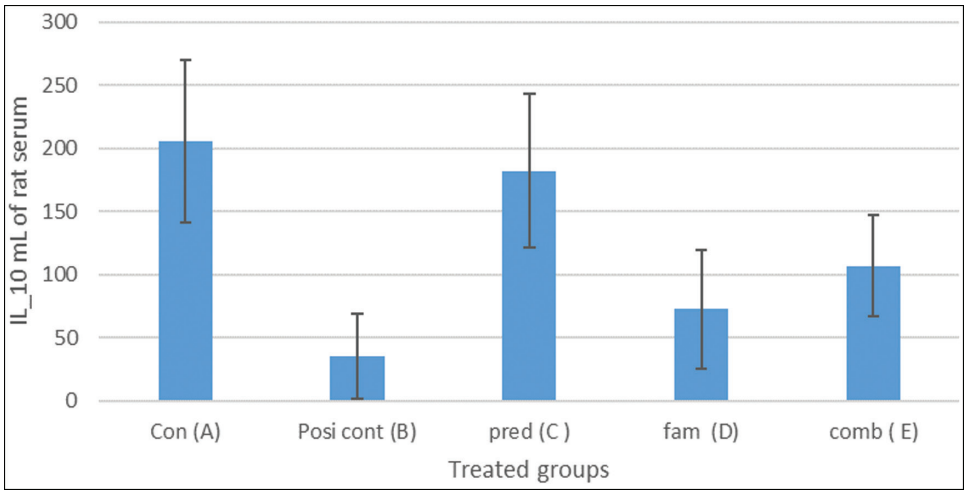

Figure 4: Serum IL-10 level of rats in treated groups

182.26 ± 24.85, and 107.11 ± 16.46), respectively. IL-10 levels were significantly ($P < 0.05$) increased in the group treated with prednisolone 4.12 mg/kg (182.26 ± 24.85) compared to B, D, and E group (35.47 ± 13.62, 72.95 ± 19.18, and 107.11 ± 16.46), respectively. Furthermore, Table 1 and Figure 4 show that rats treated with 20 mg/kg famotidine

had non-significantly ($P < 0.05$) increased IL-10 level (72.95 ± 19.18) compared to rats in A and C group (205.63 ± 26.41 and 182.26 ± 24.85), respectively. IL-10 level had significantly ($P < 0.05$) decreased (107.11 ± 16.46) in E group (rats were treated with prednisolone and famotidine (4.12 mg/kg and 20 mg/kg), respectively) compared to rats in A and C group (205.63 ± 26.41 and 182.26 ± 24.85) and significantly increased ($P < 0.05$) compared to rats in B group (35.47 ± 13.62).

Discussion

Lung inflammation is the defense mechanism of the body that begins the healing process through the elimination of harmful stimuli such as microbes, irritants, and destroyed cells. Immune defenses against respiratory infection must be precisely managed to allow pathogen clearance while sustaining organ function. Abnormal inflammation can limit gas exchange and contribute to many cases of lung illness. When pulmonary cells respond to infectious agents, the management of inflammation becomes particularly significant.[16]

Famotidine is an FDA-approved medication utilized for the treatment of GERD and peptic ulcers. In stomach parietal cells, it serves as a competitive antagonist of histamine.[17] Among the immunomodulators offered, famotidine has shown several promising benefits in addition to its role as an acid suppressor.[18] Famotidine may also have off-target effects, such as scavenging reactive oxygen radicals, which may reduce secondary inflammation and damage.[19] Famotidine can achieve blood concentrations that are effective in blocking histamine H2 receptors found in mast cells, eosinophils, and neutrophils. These observations explain how famotidine can help alleviate inflammation caused by histamine and reduce the release of cytokines.[17]

Cytokines are important mediators of inflammation in chronic inflammatory airway illnesses, including COPD and asthma. In response to stimuli, the airway epithelium can stimulate a more powerful pro-inflammatory cytokine production.[7] As a result, recognizing the importance of inflammatory mediators is vital in the development of numerous therapeutic approaches aimed at reducing inflammation and enhancing the quality of life in patients suffering from respiratory disorders. The aim of this study was to examine the effects of famotidine on different pro-inflammatory cytokines in a rat model with OVA sensitization. Prednisolone can be used to treat asthma and assist in improving asthma control in patients. In our study, prednisolone was used to compare the pharmacological effects of famotidine.

In this study, rats in the positive control (B group) exhibited longer ovalbumin sensitization than the negative control (A group), resulting in symptoms of airway inflammation. This outcome agrees with the results of Hsu *et al.* 2012 and Ahmed, Zalzala, and Ibrahim 2021.[11,20] According to our study's findings, famotidine causes a powerful suppression of pro-inflammatory cytokines and improves survival which was also documented in a study of Yang *et al.* 2022. The vagus nerve signaling is the mechanism through which famotidine reduces cytokine release.[19]

First, we monitored the pro-inflammatory mediator IL-4, which was shown to be considerably higher ($P < 0.05$) in sensitized rats (B groups) than in control rats (A group), as shown in Table 1 and Figure 1. These findings confirmed those of research by Zainab *et al.* (2021)[11] and Bagnasco *et al.* (2016),[21] which demonstrated that rats subjected to repeated OVA-experiment had significantly higher levels of IL-4 than the negative control group. Our data observed that serum IL-4 levels decreased after prednisolone treatment, which is in agreement with the study of Voo *et al.* 2022.[22] Prednisolone administration (C group) results in a decrease in airway inflammation as confirmed by a significant decrease in cytokines levels in comparison with B group, which was also demonstrated by a study of Hsu *et al.* 2012.[20]

Next, we also evaluated pro-inflammatory IL-6 generated after airway sensitization with OVA in a rat model. Literature suggested that the cytokine IL-6 is related to the development of asthma and is linked to unfavorable outcomes from treatment.[23] Table 1 and Figure 2 illustrated that prednisolone significantly decreases IL-6 serum level concentration in the current study ($P < 0.05$) when compared to the positive control group (B group), which was also reported in a study of Voo *et al.* 2022.[22] Famotidine administration in the D group resulted in decrease IL-6 level which is also recognized in a study of Yang *et al.* 2022.[19] Multiple clinical studies have provided evidence that famotidine could be beneficial in managing acute lung injury. It achieves this by reducing neutrophil migration, inhibiting histamine release from mast cells, and mitigating pulmonary edema.[18]

The cytokine TNF-α is the other significant pro-inflammatory parameter in lung damage. As indicated in Table 1, the serum levels of TNF-α in rats of B group (positive control) showed a significant ($P < 0.05$) increase compared to the A group (negative control). According to the study of Kumar *et al.* (2017), rats with induced airway sensitization have higher TNF-α levels compared to rats in the negative control group (A group), which is in agreement with our data.[24] As indicated in Table 1 and Figure 3], treatment with prednisolone dose of 4.12 mg/kg/d (C group) significantly lowered TNF-α levels when compared with the sensitization group (B group) ($P < 0.05$). This finding is consistent with the research of Rabaan *et al.* 2021 which showed that corticosteroids are useful strategies for suppressing the release of pro-inflammatory cytokines, including TNF-α and IL-6.[25] After airway sensitization, famotidine

treatment in the D group resulted in a decrease in TNF-α serum levels, indicating a reduction in inflammation; these findings were also reported in a study by Racca *et al.* 2022.[26]

IL-10 levels were observed to be reduced significantly ($P < 0.05$) in sensitized rats (B groups) compared to control rats (A group), this data are in agreement with the study of Huang *et al.* 2016 which reported that IL-10 is associated with a higher frequency of bronchial asthma and COPD. IL-10 activity is regulated by a particular cell surface receptor complex.[8] In this investigation, as illustrated in Table 1 and Figure 4, prednisolone significantly ($P < 0.05$) elevated IL-10 serum level concentration compared to the positive control (B group). This result was also previously reported by the study of Huang *et al.* 2016.[8]

According to this, famotidine's beneficial actions on human cells and the intracellular signaling that regulates host immune responses may be the cause of its positive effects.[17] It is important to highlight that H2R, the recognized molecular target of famotidine, is connected to the activation of many adaptive immune response mediators, including Th1 (helper cells) lymphocytes, which are linked to the generation of pro-inflammatory cytokines. Furthermore, it controls constriction of the bronchus, airway inflammation, and vasodilation.[27]

Conclusion

According to the current study, famotidine, an antagonist of the histamine-2 receptor, has demonstrated anti-inflammatory effects in a rat model of airway inflammation. This includes a decrease in the blood levels of crucial pro-inflammatory cytokines such as IL-4, IL-6, and TNF-α, in addition to increasing the level of IL-10. More research with famotidine could be conducted in future to prevent and treat other inflammatory respiratory illnesses.

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Conflicts of interest

There are no conflicts of interest.

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