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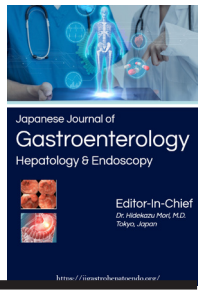

EpOME Regulates Staphylococcus Aureus-Induced Allergic Airway Inflammation by Targeting the NF-κB and MAPK Signaling Pathways

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ABSTRACT

Allergic airway inflammation (AAI) is a chronic disease caused by immune system dysfunction, leading to serious quality of life impairments such as allergic rhinitis and asthma, especially in children and newborns. Staphylococcus aureus is a common pathogen that plays a crucial role in exacerbating these inflammatory conditions by activating key immune pathways, including NF - κ B and MAPK. This study investigated the potential therapeutic effect of linoleic acid metabolite 9,10-epoxyoctadecenoic acid (EpoME) in regulating allergic airway inflammation induced by Staphylococcus aureus. There are studies suggesting that EpoME may regulate these inflammatory pathways to reduce inflammation, improve airway hyperresponsiveness, and repair epithelial cell damage. In in vivo experiments, we observed that EpoME treatment significantly reduced airway resistance and improved lung compliance in a mouse model, indicating an improvement in airway hyperresponsiveness. In addition, EpoME treatment reduced the levels of pro-inflammatory cytokines such as IL-6, TNF - α, and IL-1 β in serum, highlighting its role in reducing systemic and local inflammation. Western blot analysis confirmed that EpoME inhibits the activation of NF - κ B and MAPK signaling pathways, further supporting its anti-inflammatory effects. These results suggest that EpoME may become a potential therapeutic agent for treating allergic airway inflammation induced by Staphylococcus aureus by targeting these key inflammatory pathways. This study emphasizes the therapeutic potential of EpoME as an anti-inflammatory agent, particularly in cases involving Staphylococcus aureus induced airway inflammation. EpoME may provide a new approach for managing allergic airway diseases, which has great significance for newborns and other susceptible populations.

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INTRODUCTION

Allergic Airway Inflammation (AAI) is a chronic inflammatory disease caused by abnormal immune responses, typically manifesting as Allergic Rhinitis (AR) and Allergic Asthma (AA) [1-3]. These conditions significantly impact the quality of life of patients, with severe cases potentially leading to respiratory dysfunction. The onset of AAI is closely associated with IgE-mediated Type I hypersensitivity reactions, involving various immune cells and inflammatory mediators [4-6]. Additionally, recent studies suggest that microbial communities, particularly the dysbiosis of the upper airway microbiome, may play a crucial role in the development and progression of AAI [7-9].

Staphylococcus aureus, a common pathogenic microorganism, plays a significant pro-inflammatory role in various allergic airway inflammations. Research has found that Staphylococcus aureus activates the host's immune system, particularly through the NF-κB and MAPK signaling pathways, significantly promoting inflammatory responses and airway hyperresponsiveness. These signaling pathways regulate immune cell activation and cytokine release, exacerbating inflammation. The NF-κB signaling pathway is closely related to the expression of cytokines and is a key regulatory factor in many inflammatory diseases. The MAPK signaling pathway involves cell proliferation, differentiation, and stress responses, and its activation in allergic airway inflammation can trigger airway hyperresponsiveness and chronic inflammation [10-12].

Moreover, the role of 9,10-epoxyoctadecenoic acid (EpOME), a metabolite of linoleic acid, in inflammatory diseases has attracted considerable attention. EpOME is one of the products of linoleic acid metabolism and possesses significant biological activity, capable of modulating various immune responses. Studies have shown that EpOME interacts with several signaling pathways to regulate the body's inflammatory response. In particular, in allergic airway inflammation, EpOME may play a crucial role in Staphylococcus aureus-induced allergic airway inflammation by regulating the NF-κB and MAPK signaling pathways. However, the specific role of EpOME in Staphylococcus aureus-induced allergic airway inflammation and its regulatory mechanisms remain unclear, providing a basis for further exploration of its potential therapeutic effects [13-17].

This study aims to investigate how EpOME regulates *S. aureus*-induced allergic airway inflammation through targeting the NF-κB and MAPK signaling pathways in in vivo experiments. By analyzing the role of EpOME in immune regulation, this research aims to provide new theoretical insights and strategies for the treatment of allergic airway inflammation.

Methods

Allergic Airway Inflammation Mouse Model

The allergic airway inflammation mouse model will be induced using ovalbumin (OVA) to mimic allergic airway diseases, followed by infection

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with Staphylococcus aureus (*S. aureus*) to simulate the bacterial infection environment associated with AAI.Mice sensitized by intraperitoneal injection of 100 μg OVA emulsified in 100 μl aluminum hydroxide gel ($Al(OH)_3$) on Day 1 and Day 14. On Days 21–23, the sensitized mice will be exposed to aerosolized 1% OVA for 30 minutes each day to induce allergic airway inflammation. On Day 23, the mice will be infected with S. aureus by intranasal administration of 10^8 CFU/mouse in 30 μl saline solution. The bacterial infection will mimic the dysbiosis-induced exacerbation of AAI.

Experimental Groups

Animal Model Groups

(1) Control Group: Mice will receive saline solution only (no OVA or *S. aureus* exposure).

(2) OVA Group: Mice will be sensitized and challenged with OVA only.

(3) OVA + *S. aureus* Group: Mice will be sensitized with OVA and challenged with *S. aureus* infection.

(4) OVA + *S. aureus* + EpOME Group: Mice will be sensitized with OVA, challenged with *S. aureus*, and treated with EpOME (10 μM).

Cell Model Groups

(1) Control Group: Cells will be cultured in the absence of any treatment.

(2) *S. aureus* Infection Group: Cells will be exposed to *S. aureus* extract (10 μg/ml).

(3) *S. aureus* + EpOME Group: Cells will be exposed to *S. aureus* extract and treated with EpOME (1, 5, 10 μM).

Inflammatory Cytokine Detection

The levels of IL-6, TNF-α, and IL-1β in the serum and bronchoalveolar lavage fluid (BALF) will be measured using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's protocol. Cytokine levels will provide insight into the degree of inflammation in the mouse model.

Airway Hyperreactivity Measurement

Airway reactivity will be assessed using a non-invasive small animal plethysmograph (e.g., FinePointe™ or Buxco™). Mice will be subjected to inhalation of methacholine, a muscarinic agonist, and respiratory parameters, including airway resistance and lung compliance, will be measured. Increased airway resistance and reduced lung compliance indicate airway hyper responsiveness, a hallmark of allergic airway inflammation.

Western Blot Analysis

After treatments, tissues will be lysed with RIPA buffer containing protease and phosphatase inhibitors. The protein concentration will be determined using the BCA protein assay. Proteins (30 μg per lane) will be separated using SDS-PAGE, transferred onto PVDF membranes, and blocked with 5% non-fat milk. Membranes will be incubated with primary antibodies against NF-κB (p65, p-p65) and MAPK (p38, p-p38) signaling pathway proteins. The membranes will then be incubated with secondary antibodies and visualized using enhanced chemiluminescence (ECL). The relative expression levels of these proteins will be quantified using ImageJ software.

Statistical Analysis

Data Analysis: All data will be presented as mean ± standard deviation (SD). Statistical comparisons between groups will be performed using one-way ANOVA followed by Tukey's post-hoc test. A p-value of < 0.05 will be considered statistically significant.

Results

The effect of EpoME on body weight and IgE in AAI mouse models induced by S. aureus and OVA

The effects of EpoME on body weight and IgE levels in AAI mouse models induced by S. aureus and OVA were examined. The results showed that OVA and OVA+SA treatments significantly aggravated allergic reactions in mice, manifested as significant weight loss and significant increase in IgE levels. EpoME partially alleviated the trend of weight loss and reduced the levels of total IgE and OVA specific IgE, demonstrating a certain protective effect. The body weight of mice in the normal control group and EpoME treated group remained stable, while OVA and OVA+SA treatments significantly reduced body weight. The weight of the EpoME+OVA treatment group was significantly higher than that of the OVA group, indicating that EpoME has a certain protective effect on OVA induced weight loss (Figure 1A). Further analysis of weight changes showed that the OVA+SA group had the most significant weight loss, while EpoME treatment alleviated the weight loss trend (Figure 1B). The serum IgE level significantly increased in the OVA treatment group and reached its highest level in the OVA+SA group. EpoME treatment significantly reduced IgE levels (Figure 1C). The level of OVA specific IgE (OVA sIgE) was significantly increased in the OVA and OVA+SA groups. The OVA sIgE levels in the EpoME+OVA group were significantly lower than those in the OVA group, indicating that EpoME has a significant alleviating effect on OVA induced specific allergic reactions (Figure 1D).

The effect of EpoME on airway responsiveness and dynamic compliance in AAI mouse models induced by S. aureus and OVA

The effects of EpoME on airway responsiveness and dynamic compliance in AAI mouse models induced by S. aureus and OVA were examined. The results showed that OVA and OVA+SA treatments significantly increased airway resistance and decreased dynamic lung compliance. EpoME significantly alleviated these adverse changes, which may have anti airway inflammation and protective effects on lung function. OVA and OVA+SA treatment significantly enhanced airway resistance, especially at high doses (12.5-25 mg/mL). The airway resistance treated with EpoME was significantly lower than that of the OVA group, indicating its significant alleviating effect on airway inflammation (Figure 2A). The quantitative results showed that the airway resistance of the OVA+SA group was significantly higher than that of the other groups, and the EpoME treatment (EpoME+OVA group and EpoME+OVA+SA group) significantly reduced this indicator (Figure 2B). The dynamic lung compliance of OVA and OVA+SA groups was significantly reduced, indicating impaired lung tissue elasticity. The lung compliance of the EpoME+OVA group was significantly higher than that of the OVA group (Figure 2C). Quantitative data shows that EpoME treatment significantly improves the decreasing trend of lung compliance, indicating its protective effect on lung tissue (Figure 2D).

Effect of EpoME on Cytokine Levels in S.aureus and OVA Induced AAI Mouse Models *in vivo*

The effect of EpoME on cytokine levels in S.aureus and OVA induced AAI mouse models was detected using ELISA method. The results showed that OVA and OVA+SA treatments significantly promoted the secretion of various Th2 related inflammatory factors, indicating that they exacerbated allergic inflammatory reactions. EpoME demonstrated inhibitory effects on Th2 mediated inflammation by significantly reducing the levels of these inflammatory factors, further enhancing its anti-inflammatory potential.

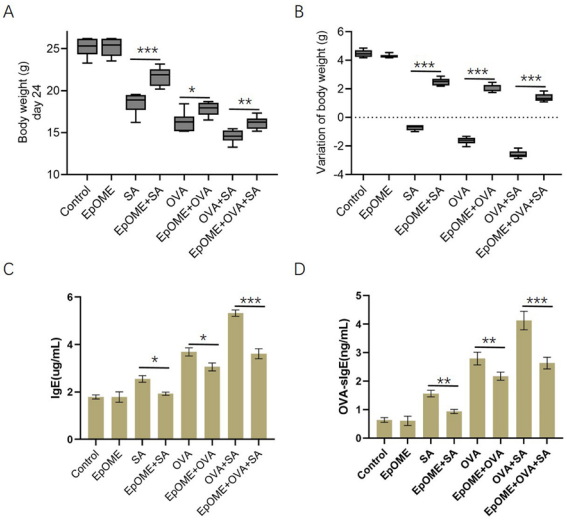

Figure 1: The effect of EpoME on body weight, IgE, and AHR in AAI mouse models induced by S. aureus and OVA is shown in Figure A (weight on day 24). (A) the body weight of AAI mouse model on day 24, (B) the variation of body weight of AAI mouse model on day 24, (C) the IgE level of AAI mouse model on day 24, (D) the OVA-sIgE level of AAI mouse model on day 24.

The IL-4 levels were significantly increased in the OVA and OVA+SA groups, indicating an enhanced Th2 cell-related inflammatory response. The IL-4 levels in the EpoME+OVA group were lower than those in the OVA group, indicating that EpoME may inhibit Th2 related inflammation (Figure 3A). The level of IL-5 was significantly increased in the OVA and OVA+SA groups, especially in the OVA+SA group, indicating an increase in eosinophil infiltration. The EpoME treatment group significantly reduced IL-5 levels, indicating that it may reduce the infiltration of inflammatory cells (Figure 3B). The level of IL-9 was significantly increased in the OVA and OVA+SA groups, closely related to airway remodeling. EpoME treatment reduced the expression of IL-9, indicating that it may have a certain inhibitory effect on airway remodeling (Figure 3C). IL-13 levels were significantly elevated in the OVA and OVA+SA groups, indicating an increased inflammatory response associated with airway hyperresponsiveness. The EpoME treatment group significantly reduced IL-13 levels (Figure 3D).

Effect of EpoME on the expression levels of NF - κ B and MAPK signaling pathway proteins in the AAI mouse model induced by S. aureus and OVA

Western blot was used to detect the effect of EpoME on the protein expression levels of NF - κ B and MAPK signaling pathways in the AAI mouse model induced by S. aureus and OVA. The results showed that OVA and OVA+SA treatment significantly activated the P38 and NF - κ B signaling pathways, indicating their important role in allergic inflammation. EpoME may exert its anti-inflammatory and protective effects by inhibiting the activation of these signaling pathways. The expression of p-P38 and p-P65 was significantly enhanced in the OVA and OVA+SA groups, indicating activation of inflammation related signaling pathways (MAPK and NF - κ B). The p-P38 and p-P65 levels in the EpoME treated group were lower than those in the untreated group, indicating a certain inhibitory effect. The quantitative results showed that the EpoME+OVA group significantly reduced p-P38 expression, suggesting that it may exert anti-inflammatory effects by inhibiting the MAPK pathway. The expression of p-P65 was strongest in the OVA+SA group, and EpoME treatment significantly reduced its expression, further supporting its regulatory effect on the NF - κ B signaling pathway (Figure 4).

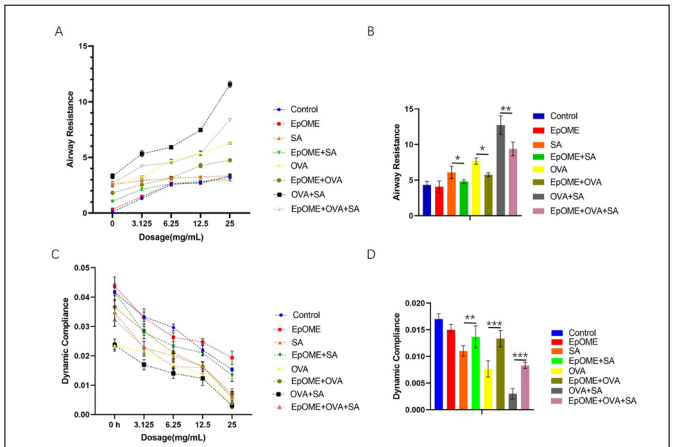

Figure 2: The effect of EpoME on airway responsiveness and dynamic compliance in AAI mouse models induced by S. aureus and OVA. (A, B) the Airway resistance of AAI mouse model, (C, D) the Dynaminc Compliance of AAI mouse model.

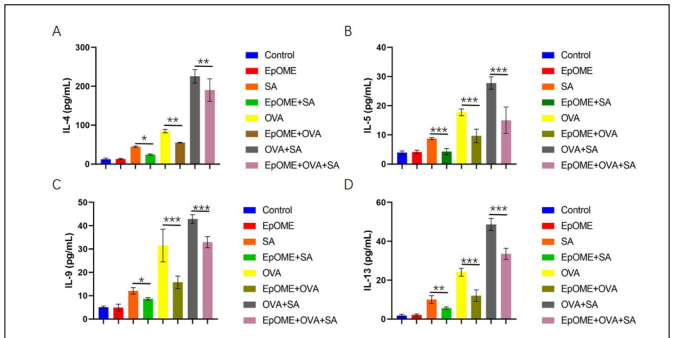

Figure 3: The effect of EpoME on cytokine levels in AAI mouse models induced by S. aureus and OVA. ELISA assay was used to test the IL-4 (A), IL-5 (B), IL-9 (C) and IL-13 (D) level in AAI mouse models.

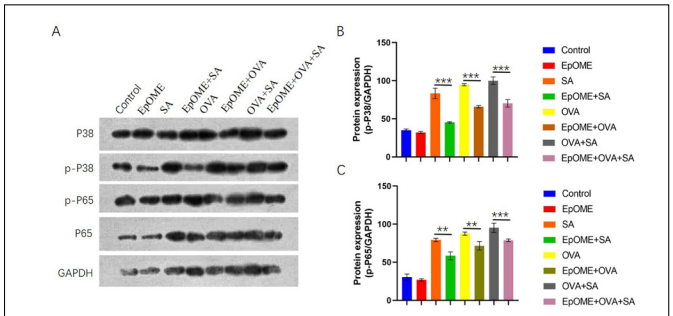

Figure 4: The effect of EpoME on NF - κ B and MAPK in AAI mouse models induced by S. aureus and OVA. (A-C) western blot assay was used to test the protein expression of P38, p-P38, P65 and p-P65.

Discussion

Allergic airway inflammation (AAI) is a chronic disease triggered by abnormal immune responses, severely affecting the quality of life of patients, particularly in children and neonates [18,19]. *S. aureus* plays a crucial role in the onset and exacerbation of allergic airway inflammation, yet effective therapeutic strategies targeting this pathological process remain limited [20,21]. Although conventional anti-inflammatory drugs and immunosuppressants have helped alleviate symptoms, their side effects and limitations make it essential to explore new and safer treatment strategies [22-26].

This study, by evaluating the role of EpOME in suppressing *S. aureus*-induced allergic airway inflammation, provides new theoretical evidence and practical guidance for developing novel anti-inflammatory treatments, particularly in reducing the release of inflammatory cytokines and repairing airway epithelial cell damage, with significant clinical potential.

The results of this study demonstrate that 9,10-epoxyoctadecenoic acid (EpOME) significantly alleviates allergic airway inflammation induced by *S. aureus* and OVA. Through a comprehensive analysis of the mouse model, we found that EpOME regulates the NF-κB and MAPK signaling pathways, significantly reducing the release of inflammatory cytokines, improving airway hyperresponsiveness, thus alleviating the symptoms of allergic airway inflammation.

First, airway hyperresponsiveness in the EpOME-treated group of mice was significantly improved, as evidenced by a marked reduction in airway resistance and increased lung compliance. Airway hyperresponsiveness is a critical feature of allergic airway inflammation, often associated with airway inflammation and constriction. EpOME alleviates the inflammation caused by *S. aureus* by improving airway compliance and reducing airway constriction. This result suggests that EpOME not only directly affects airway physiological functions, reducing airway hyperresponsiveness caused by immune activation, but also potentially modulates the immune response in the airways, thereby reducing excessive airway reactions.

In the analysis of inflammatory cytokine levels, EpOME significantly suppressed the release of IL-6, TNF-α, and IL-1β in mice serum, indicating that EpOME plays a vital role in reducing local and systemic inflammation. These inflammatory cytokines are key mediators of allergic airway inflammation, activating the immune system to cause tissue damage and inflammatory responses. By reducing the production of these pro-inflammatory cytokines, EpOME alleviated the excessive inflammatory response induced by *S. aureus*, thus mitigating damage to the airways and lungs.

Additionally, Western blot analysis showed that EpOME suppresses the activation of the NF-κB and MAPK signaling pathways, thereby reducing immune activation induced by *S. aureus*. The NF-κB and MAPK signaling pathways are critical regulatory pathways in inflammation, promoting the release of cytokines and inflammatory mediators. EpOME inhibited the activation of these pathways by downregulating the expression of p65, p-p65, and p-p38, thereby reducing the inflammation induced by *S. aureus*.

Overall, this study demonstrates that EpOME effectively reduces *Staphylococcus aureus*-induced allergic airway inflammation through multiple mechanisms. These mechanisms include inhibition of NF-κB and MAPK signaling pathways, reduction of inflammatory cytokine release, improvement of airway hyperresponsiveness and reduction of tissue inflammation. These findings provide strong experimental support for

EpOME as a potential therapeutic target for treating *S. aureus*-induced allergic airway inflammation. As a natural metabolite, EpOME exhibits significant anti-inflammatory effects, and its ability to regulate key immune signaling pathways offers a novel strategy for treating allergic airway inflammation. In the future, EpOME may become an effective intervention, particularly for neonates and other susceptible populations, and could potentially serve as a new therapeutic drug for allergic airway inflammation.

Conclusion

This study demonstrates that 9,10-epoxyoctadecenoic acid (EpOME) can effectively reduce *Staphylococcus aureus*-induced allergic airway inflammation by inhibiting the NF-κB and MAPK signaling pathways. EpOME improves airway hyperresponsiveness and alleviates tissue inflammation in the mouse model. This finding suggests that EpOME may become a potential therapeutic target for regulating *S. aureus*-induced allergic airway inflammation, particularly for neonatal-related inflammation, and may be used in the future to develop new anti-inflammatory drugs or interventions.

Author Contributions: XC and QX performed most of the experiments, analyzed the data, and drafted the manuscript. XC was mainly involved in data acquisition and article writing. XC and QX interpreted the data and participated in article revision. XC participated in the project design and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors have contributed to and approved the final manuscript. All authors participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflicts of interest.

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