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난백알부민으로 유발된 알러지성 천식모델에서 토후박의 기도염증에 대한 보호효과

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Protective Effects of *Machilus thunbergii* Siebold & Zucc on Airway Inflammation in Allergic Asthma Model Caused by Ovalbumin Inhalation

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ABSTRACT

Background: Asthma is a chronic pulmonary inflammatory disorder with a persistently increasing prevalence. Although many researchers have developed therapeutic agents to control asthma, their applications are limited because of their adverse effects. *Machilus thunbergii* Siebold & Zucc. has been used as a traditional herbal remedy to control various inflammatory conditions.
Methods and Results: In this study, we investigated the therapeutic effects of *M. thunbergii* ethanol extract (MTE) in an ovalbumin (OVA)-induced asthma model and lipopolysaccharide (LPS) treated RAW264.7 cells. MTE significantly decreased the inflammatory cell count, airway hyperresponsiveness, and cytokines in bronchoalveolar lavage fluid and OVA-specific immunoglobulin E in serum compared with those in asthmatic mice. Additionally, MTE decreased inflammatory responses and mucus production in asthmatic animals with decreases in NF-κB expression. These results are consistent with the results of *in vitro* experiments. MTE reduced cytokine and nitric oxide production in LPS treated cells, accompanied with reductions in NF-κB translocation into the nucleus.
Conclusions: MTE effectively suppressed asthma induced by OVA exposure, which was associated with the suppression of NF-κB. Therefore, our data suggest that MTE may be a potential therapeutic agent for the control of asthma.

Key Words: *Machilus thunbergii*, Allergic asthma, Cytokines, Nuclear factor kappa B

INTRODUCTION

The global incidence of allergic asthma has increased due to rising exposure to harmful environmental stimuli, such as fine dust, chemicals, and allergens (Smaller *et al.*, 2022).

Asthma typically manifests during childhood and is characterized by eosinophilic airway inflammation, airway hyperresponsiveness (AHR), and excessive mucus production, which result in symptoms including chest tightness, pain, and dyspnea (Martin *et al.*, 2022). During the pathogenesis of allergic asthma, a type 2 T-helper (Th2) immune response is triggered by allergen inhalation, releasing proinflammatory cytokines, including interleukin (IL)-4, IL-5, and IL-13.

These cytokines promote eosinophilic inflammation, mucus hypersecretion, and the production of allergen specific immunoglobulin (Ig)E, all of which are associated with the clinical manifestations of asthma (Jung *et al.*, 2020).

Currently, various pharmacological agents are used to manage allergic asthma, and ongoing research seeks to identify new therapeutic compounds (Lee e*t al.*, 2021). Commonly prescribed medications include beta-2 adrenergic receptor agonist (β2-agonist), leukotriene receptor antagonist, corticosteroids,

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and antibiotics.

However, these agents often have limitations, such as immune suppression, mood disorders, and the development of drug resistance (Pak *et al.*, 2022). Although β2-agonists effectively relieve AHR, they do not address the underlying cause of asthma development (Pak *et al.*, 2022). Consequently, there is a pressing need to discover novel therapeutic agents with anti-asthma and minimal adverse effects.

Machilus thunbergii Siebold & Zucc., widely distributed in South Korea, has long been used in traditional herbal medicine. *M. thunbergii* has been employed in treating edema, abdominal distension, and pain (Kim *et al.*, 2015).

Previous studies have demonstrated that *M. thunbergii* possesses anti-inflammatory and antioxidant properties (Yu *et al.*, 2000; Ryu *et al.*, 2003). Its pharmacological effects have been further evaluated in various experimental models (Lee *et al.*, 2009; Uhm *et al.*, 2010).

The bioactive constituents of *M. thunbergii* have shown potential therapeutic activities, suggesting its applicability in managing several diseases (Ma *et al.*, 2010; Kim *et al.*, 2013; Shin *et al.*, 2021). However, to date, no studies have investigated the therapeutic efficacy of *M. thunbergii* in allergic asthma.

Therefore, this study aimed to evaluate the therapeutic efficacy of *M. thunbergii* ethanol extract using an ovalbumin (OVA)-induced murine model of asthma and lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage cell and to explore its underlying mechanism of action via analysis of relevant protein expression profiles.

MATERIALS AND METHODS

1. Plant material

M. thunbergii was purchased from Naemome Dah Herbal Medicine (Ulsan Metropolitan City, South Korea) and its identity was confirmed via morphological analysis conducted by Dr. Goya Choi of the Korea Institute of Oriental Medicine (Daejeon, South Korea). A voucher specimen was deposited in the Korean Herbarium of Standard Herbal Resources (No.2-18-0158).

Dried plant material (500 g) was pulverized and extracted twice using 5 L of 70% ethanol with ultrasonic assistance for 1 h each. The extract was filtered through filter paper, concentrated using a rotary evaporator, and freeze-dried to yield a 70% ethanol extract [yield = 8.97% (w/w)]. Then extract stored at 4℃ until use.

2. Cell culture

RAW264.7 cells were cultured in Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum and antibiotics. Cells were maintained in a humidified CO_2 incubator at 37℃ with 5% CO_2. Cell viability was assessed using EZ-Cytox Cell Viability Assay Kit (DAELIL Lab, Seoul, Republic of Korea).

Cells were seeded in 96 well plates at a density of 1×10^4 cells/well and incubated for 24 h. Subsequently, fresh medium containing different concentrations of *M. thunbergii* ethanol extract (MTE) (6.25, 12.5, 25 and 50 ㎍/㎖) was added, and the cells were incubated for 24 h. EZ-Cytox reagent (10 ㎕) was added to each well, followed by a 4 h incubation. Absorbance was measured using a spectrophotometer (Bio-Rad Laboratories, Hercules, CA, USA).

3. Measurement of inflammatory mediators in LPS treated RAW264.7 cells

RAW264.7 cells were seeded into six-well plates at a density of 4×10^5 cells/well and treated with varying concentrations of MTE. After 1 h, LPS (1 ㎍/㎖) was added, and the cells were incubated for 24 h. Supernatants were collected, and the levels of nitric oxide (NO; iNtRON Biotechnology, Seongnam, Korea), IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α; R&D System, Minneapolis, MN, USA) were measured.

4. Analysis of NF-κB expression in LPS treated RAW264.7 cells

Double-immunofluorescence staining was performed to analyze NF-κB expression as previously described (Lim *et al.*, 2021).

An anti-NF-κB (ab32536, 1 : 100 dilution, Abcam, Cambridge, UK) was used. Samples were examined using confocal laser scanning microscope (LMS900, ZEISS, Dresden, Germany).

5. Experimental animals and protocol of the asthma model

Female BALB/c mice (Samtako, Osan, Korea) were housed in polycarbonate cages under standard conditions and given food and water *ad libitum*.

All procedures were approved by the International Animal Care and Use Committee of Chonnam National University (CNU IACUC-YB-2021-50).

The animals were randomly assigned into five groups (n = 5 per group): normal control (NC) group (phosphate-buffered saline (PBS) sensitization/inhalation and administration); OVA group (asthma model with PBS administration); DEX group (asthma model with dexamethasone administration); MTE 50 and MTE100 groups (asthma model with MTE administration at 50 and 100 ㎎/㎏, respectively).

The asthma model was induced as previously described (Lim *et al.*, 2021). On days 1 and 14, the mice were intraperitoneally injected with OVA (20 μg/mouse, Sigma-Aldrich, Burlington, MA, USA) mixed with aluminum hydroxide (2 ㎎/mouse).

From days 18 to 23, mice were exposed to 1% OVA aerosol for 1 h daily using a nebulizer (Omron, Tokyo, Japan). On day 24, AHR was assessed using FlexiVent system (SCIREQ, Montreal, QC, Canada) following a methylcholine (Sigma-Aldrich, St. Louis, MO, USA) challenge for 3 min.

6. Evaluation of bronchoalveolar lavage fluid (BALF) and serum

BALF was collected as previously described (Lim *et al.*, 2021). The supernatants were analyzed for IL-4 and IL-13 levels using ELISA kits (R&D Systems, Minneapolis, MN, USA).

BALF cell pellets were used to determine total and differential inflammatory cell count as previously described (Lim *et al.*, 2021). Blood samples were collected from the caudal vena cava, and serum was obtained by centrifugation. OVA-specific serum IgE levels were measured using an ELISA kit (BioLegend, San Diego, CA, USA).

Briefly, 96-well microtiter plates were coated overnight with 10 ㎍/㎖ of OVA in PBS-Tween 20. After the plate was washed and blocked, the samples were added to the plate, and the plate was incubated for 2 h. After the plates were washed, HRP-conjugated goat anti-mouse IgE antibody was added to the plates. After the plates were washed four times, 200 ㎕ of o-phenylenediamine dihydrochloride (Sigma-Aldrich, St. Louis, MO, USA) was added to each well.

The plates were incubated for 10 min in the dark, and then the absorbance was determined at 450 ㎚ using a microplate ELISA reader (Bio-Rad Laboratories, Hercules, CA, USA). The total IgE and OVA-specific IgE concentrations were calculated from a standard curve that was generated using 250 ng/㎖ recombinant IgE (Serotec, Oxford, England).

7. Histological analysis of lung tissue

The right lungs were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 4 μm, and stained with hematoxylin and eosin (H&E, Sigma-Aldrich, Saint Louis, MO, USA), and Periodic Acid Schiff (PAS, IMEB Inc., San Marcos, CA, USA).

The extent of inflammation and mucus secretion was quantified using an image analysis system (IMT i-Solution Inc., Vancouver, BC, Canada). For NF-κB expression, immunohistochemistry (IHC) staining was performed as described (Lim *et al.*, 2021) using a primary anti-mouse NF-κB antibody (1 : 200 dilution, Cell Signaling, Danvers, MA, USA).

8. Statistical analysis

Data were expressed as means ± standard deviation (SD). Statistical analysis was conducted using a one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparisons test. A P value < 0.05 and < 0.01 was considered statistically significant.

RESULTS

1. MTE suppressed the releases of inflammatory cytokines in LPS treated RAW264.7 cells

The highest concentration of MTE was determined as 50 μg/mL according to the result of cell viability (Fig. 1A). LPS treatment markedly increased the production of NO, IL-1β, IL-6, and TNF-α in RAW264.7 cells compared with the untreated cells (Fig. 1B, 1C, 1D and 1E, respectively). However, MTE treatment significantly decreased NO and cytokines production in a concentration-dependent manner compared with LPS-treated RAW264.7 cells.

2. MTE decreased the translocation of NF-κB into the nucleus in LPS treated RAW264.7 cells.

LPS treatment markedly increased NF-κB translocation into the nucleus compared with the untreated RAW264.7 cells (Fig. 2). Conversely, MTE treatment markedly inhibited NF-κB nuclear translocation induced by LPS stimulation.

3. MTE suppressed AHR in OVA sensitized/inhaled mice

The OVA group exhibited significantly elevated AHR compared with the NC group in response to increasing concentrations of methylcholine (Fig. 3). In contrast, the DEX group showed significantly decreased AHR compared with the

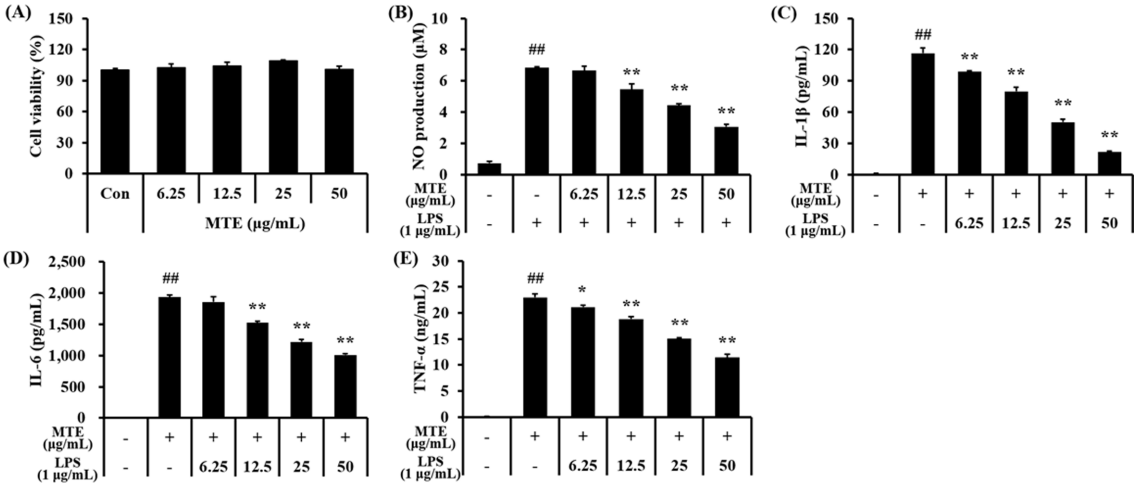

Fig. 1. Effects of MTE on NO and cytokine production in LPS-stimulated RAW264.7 cells. (A) Cell viability, (B) NO production, (C) IL-1β production, (D) IL-6 production, (E) TNF-α production. Values represent means ± SD (n = 3). Symbols indicate significant differences determined by the Dunnett's Multiple Comparison Test following one-way ANOVA. $^{\#\#}p < 0.01$ vs non-treated cell (CON); $^{*}p < 0.05$ and $^{**}p < 0.01$ vs LPS-treated cell, respectively.

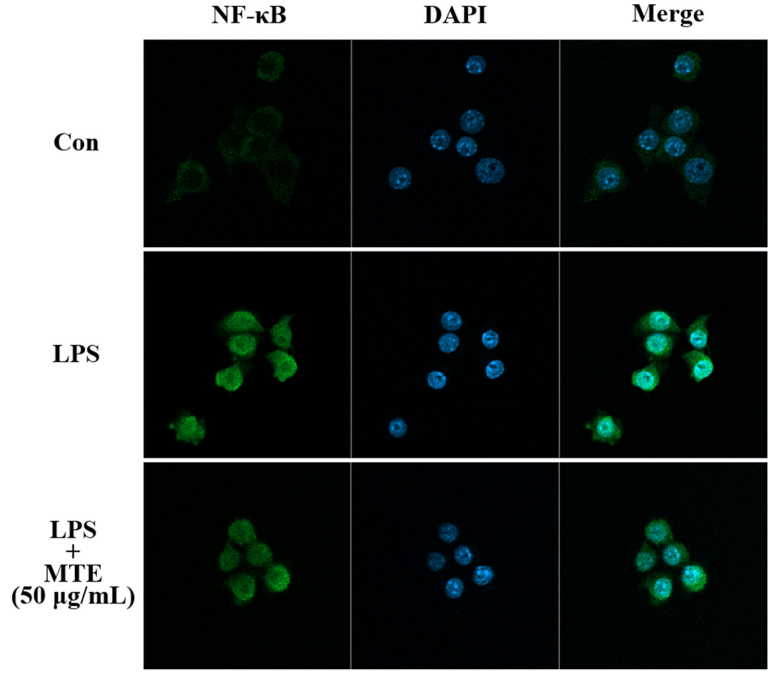

Fig. 2. Effects of MTE on NF-κB translocation into the nucleus in LPS-stimulated RAW264.7 cells. Representative immunofluorescence microscopy image showing NF-κB nuclear translocation.

OVA group. Similarly, the MTE groups demonstrated reduced AHR compared with the OVA group, which significantly decreased in the high dose group.

4. MTE reduced the number of inflammatory cells in BALF from OVA sensitized/inhaled mice

The OVA group showed a significant increase in total cell counts in BALF compared with the NC group (Fig. 4). Conversely, the DEX group exhibited a significant reduction in total cell counts compared with the OVA group. The MTE groups showed a dose-dependent decrease in total cell counts compared with the OVA group, with a marked reduction observed in the high dose group. Notably, the MTE groups showed a decrease in eosinophil counts compared with the

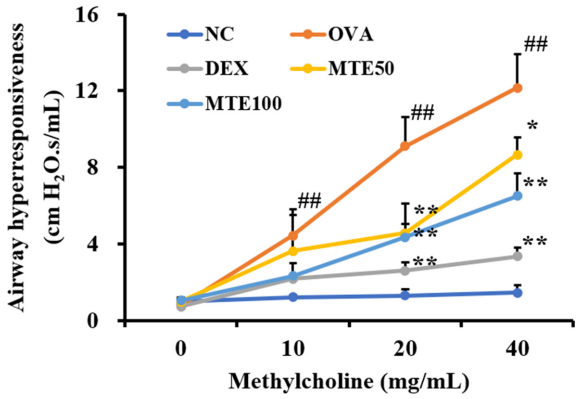

Fig. 3. Effects of MTE on AHR in OVA induced asthmatic mice. AHR was assessed using FlexiVent (SCIREQ) for 3 min following the methylcholine challenge. Values represent means ± SD (n = 5). Symbols indicate significant differences determined by the Dunnett's Multiple Comparison Test following one-way ANOVA. $^{\#\#}p < 0.01$ vs normal control (NC); $^{*}p < 0.05$ and $^{**}p < 0.01$ vs OVA group, respectively.

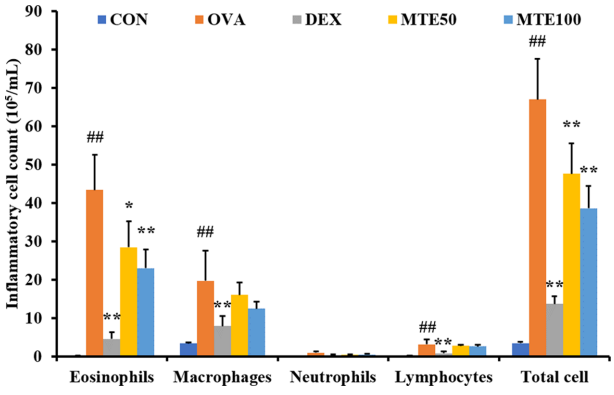

Fig. 4. Effects of MTE on inflammatory cell counts in BALF from OVA induced asthmatic mice. Total inflammatory cell counts were measured using Countess II and differential cell counts were evaluated by Diff-Quik staining. Values represent means ± SD (n = 5). Symbols indicate significant differences determined by the Dunnett's Multiple Comparison Test following one-way ANOVA. $^{\#\#}p < 0.01$ vs normal control (NC); $^{*}p < 0.05$ and $^{**}p < 0.01$ vs OVA group, respectively.

OVA group, with a more pronounced effect observed in the high dose group than in the low dose group.

5. MTE reduced inflammatory cytokines in BALF and OVA-specific IgE in the serum in OVA sensitized/inhaled mice.

The OVA group showed a marked increase in IL-4 and –13 levels in BALF compared with the NC group (Fig. 5A and 5B, respectively). Conversely, the DEX group exhibited a significant reduction in these cytokines compared with the OVA group. Similarly, MTE treatment reduced inflammatory cytokine levels in a dose-dependent manner compared with the OVA group, with a pronounced effect observed in the high dose group. Additionally, serum levels of OVA-specific IgE were significantly increased in the OVA group compared with the NC group (Fig. 5C). However, MTE treatment led to a dose-dependent decrease in the OVA group, with a significant reduction observed in the high dose group.

6. MTE alleviated pulmonary inflammation and mucus production in lung tissue from OVA sensitized/inhaled mice

The OVA group exhibited increased pulmonary inflammation, particularly in the perivascular and peribronchial regions, compared with the NC group (Fig. 6A and 6B). In contrast, the DEX group reduced inflammatory cell accumulation in lung tissue relative to the OVA group. MTE treatment also attenuated pulmonary inflammation in a dose-dependent manner, with the high dose group showing a statistically significant reduction. Furthermore, the OVA group demonstrated increased mucus secretion in the bronchi compared with the NC group, whereas the MTE group significantly reduced mucus secretion compared with the OVA group (Fig. 6A and 6C).

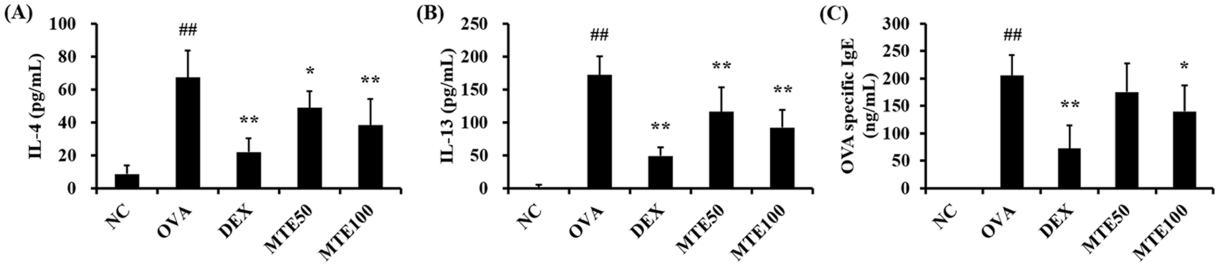

Fig. 5. Effects of MTE on cytokine levels and OVA-specific IgE in OVA induced asthmatic mice. (A) IL-4 level, (B) IL-13 level, (C) OVA-specific IgE level. Values represent means ± SD (n = 5). Symbols indicate significant differences determined by the Dunnett's Multiple Comparison Test following one-way ANOVA. $^{\#\#}p < 0.01$ vs normal control (NC); $^{*}p < 0.05$ and $^{**}p < 0.01$ vs OVA group, respectively.

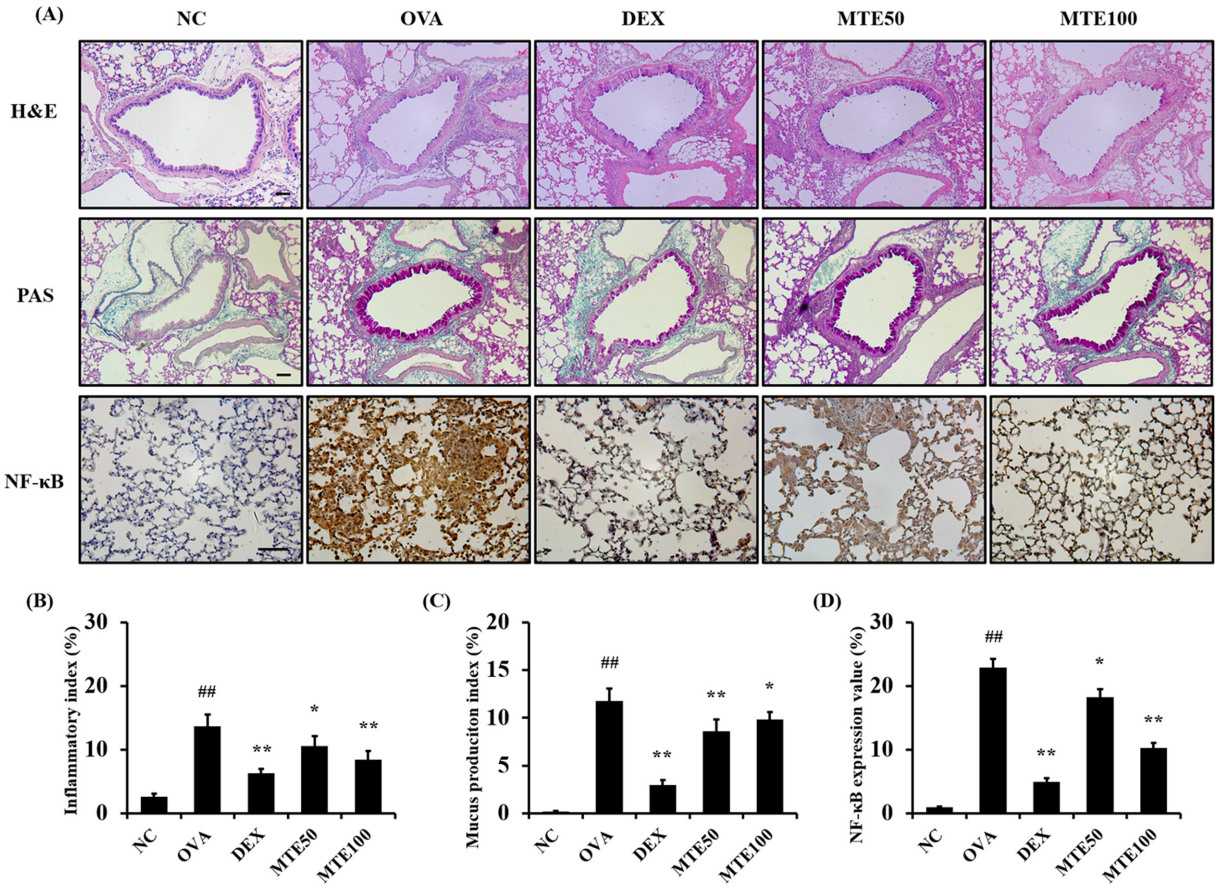

Fig. 6. Effects of MTE on inflammatory response, mucus production and NF-κB expression in OVA induced asthmatic mice. (A) Representative microscopy image of lung tissue stained with H&E, PAS, IHC, (B) Inflammatory index, (C) Mucus production index, (D) NF-κB expression quantification. Values are the means ± SD (n = 5). Symbols indicate significant differences determined by the Dunnett's Multiple Comparison Test following one-way ANOVA. Scale bar = 100 μm. $^{\#\#}p < 0.01$ vs normal control (NC); $^{*}p < 0.05$ and $^{**}p < 0.01$ vs OVA group, respectively.

7. MTE decreased the expression of NF-κB in lung tissue from OVA sensitized/inhaled mice

The OVA group demonstrated a significant increase in NF-κB expression in pulmonary tissue compared with the NC group (Fig. 6A and 6D). In contrast, the DEX group exhibited a notable reduction in NF-κB relative to the OVA group. Additionally, the MTE treatment decreased NF-κB expression dose-dependently, with a more pronounced reduction observed in the high dose group.

DISCUSSION

Allergic asthma is a significant respiratory disease that threatens human health. The increasing presence of air pollutants, allergens, and chemicals exacerbates allergic asthma. Although various pharmacological agents have been developed and are currently used to manage allergic asthma, their clinical use is limited due to side effects (Oriola and Oyedeji, 2022; Rahman *et al.*, 2022).

In this study, we investigated the protective effects of MTE on allergic asthma using an OVA induced asthma model and LPS stimulated RAW264.7 cells and explored the underlying mechanism. In the *in vivo* experiment, administration of MTE significantly decreased inflammatory cell count, cytokine levels, OVA-specific IgE, AHR, airway inflammation and mucus production compared with allergic asthmatic animals, concomitant with reduced NF-κB expression in pulmonary tissue. In the *in vitro* experiment, MTE markedly reduced NO and cytokine levels induced by LPS treatment, accompanied by decreased nuclear translocation of NF-κB.

Eosinophils are recognized as critical contributors to the pathogenesis of allergic asthma (Guthier and Zimmermann,

2022). In allergic asthma, eosinophils are recruited into lung tissue and activated by cytokines such as IL-4, IL-5 and IL-13, which exacerbate allergic responses, including AHR, airway inflammation, and mucus secretion through enhanced degranulation (Kwon *et al.*, 2020). Given these findings, eosinophils are considered an important parameter for evaluating the therapeutic efficacy of potential asthma treatments (Lombardi *et al.*, 2022).

In this study, MTE significantly reduced the number of eosinophils in the BALF of allergic asthmatic mice, alongside decreased cytokine levels and OVA-specific IgE. These effects ultimately suppressed AHR, inflammatory response, and mucus secretion in the asthma model. Based on these findings MTE effectively attenuates asthmatic responses induced by OVA inhalation.

NF-κB is a key transcription factor involved in various biological responses such as angiogenesis, cell adhesion, cell survival, invasion, inflammation, and metastasis (Barnabei *et al*., 2021). NF-κB is triggered by multiple stimuli, including cytokines, bacterial and viral infections, reactive oxygen species, and endotoxin, and it is implicated in the pathogenesis of various diseases (Prescott *et al.*, 2021). Under resting conditions, NF-kB is bound to inhibitory proteins (IκB) in the cytoplasm. During inflammation, receptors such as TNF, IL-1, or Toll-like receptor (TLR) are activated by various stimuli, activating the IκB kinase (IKK) complex. Activated IKK phosphorylates IκB, causing its degradation and subsequent release of NF-κB, which translocates to the nucleus and induces transcription of inflammation-related genes, such as cytokines, chemokines, adhesion molecules, and matrix metalloproteinases (MMPs) (Park *et al*., 2018; Alharbi *et al*., 2021).

In this study, MTE treatment significantly suppressed NF-κB expression, consistent with the *in vitro* findings, indicating that the protective effects of MTE were associated with inhibiting the NF-κB signaling pathway.

M. thunbergii possesses various pharmacological properties, including anti-inflammatory and antioxidant functions (Ma *et al.*, 2010; Kim *et al.*, 2013; Shin *et al.*, 2021). Previous studies have shown that *M. thunbergii* effectively inhibited NO production, a property attributed to its bioactive components such as quercetin, kaempferol, quercitrin, and afzelin (To *et al.*, 2023). These compounds have well-documented anti-inflammatory properties in multiple experimental models (Dong *et al.*, 2025; Hong et al., 2025; Wu *et al*., 2025; Xu *et al*., 2025).

Notably, quercetin has been reported to reduce allergic inflammation in OVA induced allergic asthma models and to effectively suppress the NF-κB signaling pathway (Sun *et al*., 2024; He *et al.*, 2025).

In conclusion, MTE effectively suppressed inflammatory responses in OVA induced allergic asthmatic mice and LPS stimulated RAW264.7 cells, an effect associated with the inhibition of NF-κB. Therefore, MTE is a promising therapeutic candidate for the treatment of asthma.

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