

Protective activity of mogroside V against ovalbumin-induced experimental allergic asthma in Kunming mice

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Abstract

We investigated the antiasthmatic effect of mogroside V (Mog V) in mice with ovalbumin (OVA)-induced asthma. Administration of Mog V effectively attenuated OVA-induced airway hyperresponsiveness and reduced the number of inflammatory cells in bronchoalveolar lavage fluid (BALF). Histological examination showed that Mog V reduced the inflammatory infiltration of the lungs in the asthmatic mice. ELISAs suggested that Mog V effectively decreased the levels of IL-4, IL-5, and IL-13 in BALF and serum levels of OVA-specific IgE and IgG1 in the asthmatic mice. A quantitative reverse-transcription PCR assay also indicated that Mog V decreased the mRNA levels of IL-17A, IL-23, and ROR γ t in the lungs of the asthmatic mice (the opposite effect on Foxp3 mRNA). Furthermore, Mog V significantly reduced the OVA-induced activation of NF- κ B in the lungs. This study indicates that Mog V alleviates OVA-induced inflammation in airways, and this effect is associated with a reduction in NF- κ B activation.

Practical applications

A traditional Chinese medicine herb has been reported to have a strong curative effect on asthma in clinical practice. *Siraitia grosvenorii* is known in China as a functional food product with the ability to improve lung function. Mogroside V is a triterpene glycoside isolated from *S. grosvenorii*. Nonetheless, the antiasthmatic effect of mogroside V has not been evaluated yet. The aim of this study was to investigate the antiasthmatic activity of mogroside V in mice with chemically induced asthma. The data from this study will provide some scientific evidence supporting wider use of *S. grosvenorii* in functional foods.

KEYWORDS

asthma, inflammation, Kunming mice, Mogroside V, OVA

1 | INTRODUCTION

Allergic asthma is a serious respiratory disease that is characterized by airway inflammation, reversible airway obstruction, airway remodeling, airway hyper-responsiveness (AHR), and mucus hypersecretion (Walsh, 2017). It is generally known that an imbalance of T helper type 1 (Th1) and T helper type 2 (Th2) cells plays an important role in the pathological processes of asthma (Zhu et al., 2016). The

typical Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 may induce the secretion of asthma-specific immunoglobulin E (IgE) and infiltration of inflammatory cells into lungs (Walsh, 2015, 2017b). Recently, an imbalance of Th17 and T regulatory cells (Tregs) was also found to be associated with asthma (Zou et al., 2018). Th17 cells, as the main factor, induce the inflammatory response and promote eosinophilic infiltration of the airways in patients with asthma (Guerra et al., 2017). Overproduced IL-17 also aggravates airway

inflammation and promotes bronchial asthma (Zou et al., 2018). In addition, IL-23 is an important factor enhancing the proliferation and maintaining the normal function of Th17 cells (McGeachy et al., 2009). Activated IL-23 can regulate the production of IL-17A and IL-17F by Th17 cells and aggravates airway inflammation (Halwani et al., 2017).

Forkhead/winged helix transcription factor p3 (Foxp3) is a specific transcription factor that is necessary and sufficient for promoting the development of Tregs and maintaining their normal function (Chen et al., 2018). Activation of Foxp3 can regulate the production of some anti-inflammatory cytokines, such as IL-10 and transforming growth factor (TGF) β and reduces the upregulation of Th2 cytokines; these effects modulate autoimmunity and immune tolerance (Zhang, 2018). Retinoid acid receptor-related orphan receptor (ROR γ t) has been reported as a necessary factor for differentiation of precursors into Th17 cells and maintains the secretion of IL-17A (Lazarevic et al., 2011; Park et al., 2014). Under normal physiological conditions, activated Foxp3 reduces the differentiation into Th17 cells by modulating the activation of ROR γ t (Chen et al., 2011).

Mogroside V is a cucurbitane-type triterpene glycoside that is isolated from the fruits of *Siraitia grosvenorii* and is used as a natural food sweetener in the functional-food industry (Zhou, Zhang, Li, Wang, & Li, 2018). Recently, many studies revealed that mogroside V has some health-promoting effects including antioxidant (Chen, Wang, Qi, & Xie, 2007), anti-inflammatory (Di, Huang, & Ho, 2011), and anti-pancreatic-cancer activities (Liu, Dai, Dou, Ma, & Sun, 2017). Mogroside V also protects mice from chemically induced damage to lungs (Shi, Zheng, Wang, Liu, & Chen, 2014; Tao, Cao, Xu, Xie, & Zhang, 2017; Tao, Yang, et al., 2017), attenuates high-fat-diet-induced obesity (Qi, Chen, Zhang, & Xie, 2008) and nonalcoholic fatty liver disease in mice (Zhang et al., 2018), and improves metabolism in mice with type 2 diabetes (Zhang et al., 2017). Nevertheless, the antiasthmatic effect of mogroside V has not been assessed yet. In this study, we employed a classic rodent model of

ovalbumin (OVA)-induced experimental asthma to investigate the anti-inflammatory activity and the potential mechanisms of action of mogroside V.

2 | MATERIALS AND METHODS

2.1 | Chemical reagents

OVA was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Mogroside V (Figure 1) was purchased from Layn Natural Ingredients Corp. (purity more than 98%; Guilin, China). The TRIzol Reagent, the oligo-dT18 primer, dNTPs, Moloney murine leukemia virus (MMLV) reverse transcriptase, and an RNase inhibitor were purchased from Invitrogen Life Technologies (Carlsbad, CA, USA). All the reagents were of analytical grade.

2.2 | Experimental animals

Male Kunming mice (6 weeks old, 16–18 g) were purchased from the Center of Experimental Animals of Guilin Medical University (Guilin, China). The mice were housed in a standard environment (12 hr light:dark cycle and room temperature) and had ad libitum access to food and water. The animal protocol used in this study was reviewed by the Institutional Animal Care and Use Committee of Guilin Medical University (IACUC-GMU, approval number: GLMC-201806003).

2.3 | Animal grouping and experiment design

Thirty-five mice were randomly subdivided into five groups (7 mice/group), which were designated as follows: a normal group, OVA group, and OVA + mogroside V groups (mogroside V at 2, 5, or 10 mg/[kg body weight]). Induction of experimental asthma in the mice was performed according to a method described by Zhang et al. (2017), with

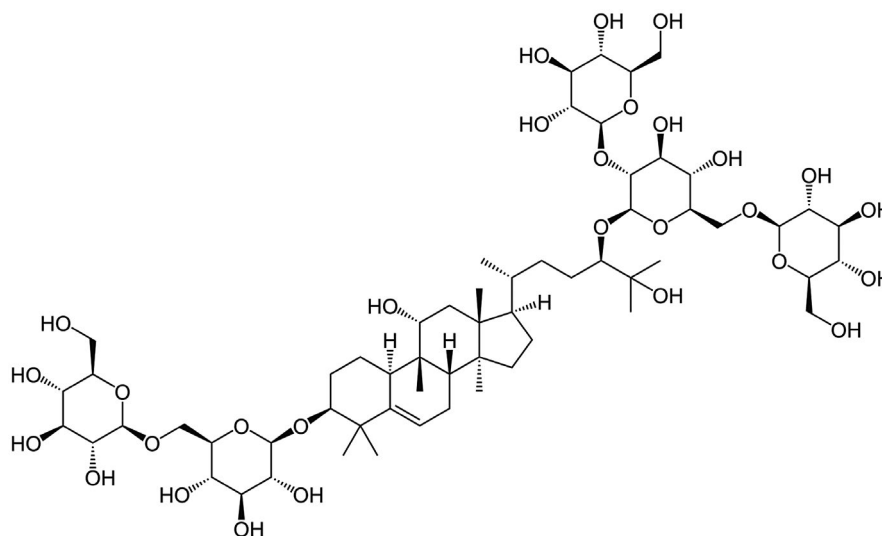


FIGURE 1 Chemical structure of mogroside V

a modification. On days 1 and 14, the mice were sensitized with the inducing reagent (100 μ l of a 0.05% aluminum hydroxide solution containing 20 μ g of OVA) by intraperitoneal injection (100 μ l). During the next treatment, the mice were given a 1% OVA solution via intranasal spray on days 21 to 23. Mogroside V was dissolved in phosphate-buffered saline (PBS, pH 7.4) for administration by oral gavage 1 hr before the OVA treatment on days 21 to 23. On day 24, all the mice were euthanized via CO₂ asphyxiation.

2.4 | Bronchoalveolar lavage fluid (BALF) collection, cell counting, and cytokine assays

A trachea in anesthetized mice was separated, cannulated, and lavaged with cold PBS (1 ml) five times. The collected BALF samples were immediately centrifuged (1,500 $\times$ g, 10 min) in an Eppendorf refrigerated centrifuge (5418R, Hamburg, Germany) at 4°C. Neutrophils, eosinophils, macrophages, and lymphocytes in BALF were stained with the Kwik-Diff Staining Kit (Solarbio, China) according to the manufacturer's instructions. The levels of IFN- γ , IL-4, IL-5, IL-12, IL-13, IL-17A, IL-23, and TGF- β in BALF were measured with commercial ELISA assay kits (Kete Biological Technology Co., Ltd., Jiangsu, China) according to the manufacturer's protocols.

2.5 | Measurement of AHR

The levels of AHR were measured by noninvasive whole-body plethysmography (Model PLY 3211; Buxco, Sharon, CT, USA) as described in another study (Wu, Chen, Lee, Ko, & Lue, 2016). All the animals were first kept in an individual ventilated chamber and received an initial baseline challenge of saline, followed administration of the increasing doses of methacholine (3.125, 6.25, 12.5, 25, and 50 mg/ml) for 3 min. The respiratory rate during the 3 min methacholine challenge and the enhanced pause (P_{enh}) were calculated.

2.6 | Histological analysis

Lung tissue was quickly collected from each animal, rinsed with normal saline, and fixed with a tissue fixative (10% neutral buffered formalin). Next, the well-fixed samples were dehydrated in ethanol and embedded in paraffin. Tissue sections (4 μ m thickness) were then prepared and stained with the Hematoxylin-Eosin Staining Kit (Solarbio). Histological images were acquired by means of a Leica

DM4B microscope equipped with a Leica DFC550 CCD digital camera (Leica Microsystems Inc., Buffalo Grove, USA).

2.7 | Measurement of serum levels of IgE, IgG1, and IgG2a

For the serum IgE, IgG1, and IgG2a assays, blood was collected from the inferior vena cava into vacuum blood collection tubes (Hanbailan Medical Devices Co., Ltd., Beijing, China) and centrifuged (3,000 $\times$ g for 10 min at 4°C) in the Eppendorf refrigerated centrifuge (5418R). The serum levels of IgE, IgG1, and IgG2a were determined with commercial ELISA kits (BOSTER Biological Technology Co., Ltd., Wuhan, China) according to the manufacturer's protocol.

2.8 | Measurement of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), myeloperoxidase (MPO), and malondialdehyde (MDA) levels in the lung tissue of mice

The collected lung tissue was washed with cold PBS and homogenized by ultrasonic pulverization to prepare a tissue homogenate. The levels of SOD, CAT, GSH-Px, MPO, and MDA in the lung tissue homogenate were determined using commercial kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

2.9 | Total-RNA extraction and quantitative reverse-transcription polymerase chain reaction (RT-PCR) assay

The collected lung samples were first rinsed with ice-cold normal saline. Then, the TRIzol Reagent (Invitrogen) was used to extract the total RNA according to the manufacturer's protocol. The extracted RNA (1 μ g) was mixed with a cocktail of reagents that contained oligo-dT18 (1 μ l), RNase inhibitor (1 μ l), dNTPs (1 μ l), MMLV enzymes (1 μ l), and 5 $\times$ buffer (10 μ l) to synthesize cDNA. The latter (2 μ l) was mixed with random primers (10 μ mol/l, 2 μ l), 2 $\times$ SYBR Premix Ex Taq II (10 μ l), 50 $\times$ ROX reference Dye (0.4 μ l), and double-distilled H₂O (5.6 μ l), and PCR was carried out on a QuantStudioTM 6 Flex Real-Time PCR System (Life Technologies) for 40 cycles at 94°C for 10 s, 60°C for 10 s, and 72°C for 10 s, followed by 10 min at 75°C. The relative levels of the mRNAs were calculated according to the 2^{- $\Delta\Delta$ Ct} formula ($\Delta\Delta$ Ct = average of Δ Ct control - Δ Ct treated). The sequences of the primers in this study are shown in Table 1.

TABLE 1 Sequences of primers used in this study

Primer name	Forward (5'→3')	Reverse (3'→5')
Mouse Foxp3	GGCCCTTCTCCAGGAGAGA	GGCATGGGCATCCACAGT
Mouse ROR γ t	TGGGACTGGAGGACCTTCTA	TCACCTCCTCCCGTGAAAAG
Mouse IL-17A	TCTCCACCGCAATGAAGACC	CACACCCACCAGCATCTTCT
Mouse IL-23	TTCTTCAGCAACAGCAAGGC	TCAGCAGCGACTCCTTTTCC
Mouse β -actin	GGCTGTATTCCCTCCATCG	CCAGTTGGTAACAATGCCAT

2.10 | Protein extraction and western blot analysis

The total lung tissue protein was extracted using cooled radioimmunoprecipitation assay (RIPA) buffer (Beyotime Biotechnology Co., Shanghai, China) from the lung samples rinsed with ice-cold normal saline, with centrifugation ($13,000\times g$, 30 min) in the Eppendorf refrigerated centrifuge 5418R at 4°C . The extracted protein was quantified using the Quartz Quick Start Bradford Protein Assay Kit (Bio-Rad Laboratories, Hercules, Calif., USA) and denatured by boiling (98°C) for the further experiments. An appropriate amount of total protein (20–30 μg) was separated by 10%–12% SDS-PAGE for 2 hr and transferred to nitrocellulose membranes. Membranes were sealed for 4 hr in a sealing fluid containing 5% of defatted milk, washed three times with PBS containing 0.05% Tween 20 (PBS-T), and incubated with primary antibodies against NF- κB p65 (sc-71675, Santa Cruz Biotechnology, Inc., Dallas, TX, USA), phospho-NF- κB p65 (p-NF- κB p65; sc-135768, Santa Cruz Biotechnology), and β -actin (AA128; Beyotime) for 2 hr at 4°C . After a wash with PBS-T, the blots were incubated with a horseradish peroxidase-conjugated goat anti-rabbit IgG antibody (Cell Signaling Technology Inc., USA) (secondary antibody) for 1 hr at room temperature. After three washes with PBS-T, the blots were incubated with enhanced chemiluminescence (ECL) HRP substrates (Millipore, Billerica, MA, USA) and visualized by means of FluorChem Systems (Protein Simple, San Jose, CA, USA). Densitometric analysis of the bands was conducted in the ImageJ software (NIH, Bethesda, MD, USA).

2.11 | Statistical analysis

All data are presented as the mean $\pm$ standard deviation (SD). Differences between the mean values of individual groups were assessed by one-way analysis of variance (ANOVA) and Duncan's multiple-range test. Differences were considered significant at $p < 0.05$. The SPSS 22.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used for the analysis.

3 | RESULTS

3.1 | Effects of mogroside V on AHR

The effect of mogroside V on AHR is displayed in Figure 2. P_{enh} in mice with OVA-induced asthma was significantly higher than that in normal mice ($p < 0.05$). After treatment with different doses of mogroside V, P_{enh} significantly diminished as compared with that in the OVA group ($p < 0.05$). The high dose of mogroside V (10 mg/kg) showed the best ability to reduce P_{enh} in the mice with OVA-induced asthma.

3.2 | Effects of mogroside V on histological features of lung tissue

The results of histological examination are presented in Figure 3. OVA treatment induced inflammatory-cell infiltration of the peribronchial and perivascular areas and caused airway epithelial

thickening and edema of the airway mucous membrane in the mice. By contrast, administration of different doses of mogroside V significantly reduced the OVA-induced infiltration by inflammatory cells, while the arrangement of airway epithelial cells was normalized in the lung tissue of the mice with OVA-induced asthma (Figure 3).

3.3 | Effects of mogroside V on SOD, CAT, GSH-Px, and MDA levels in the lung tissue of the asthmatic mice

As presented in Table 2, the OVA treatment significantly reduced the levels of endogenous antioxidant enzymes SOD, CAT, and GSH-Px in the lung tissue of mice. In contrast, after treatment with the different doses of mogroside V, the levels of SOD, CAT, and GSH-Px increased in the lung tissue of asthmatic mice. In the high-dose group (mogroside V at 10 mg/kg), the levels of SOD increased significantly (to $9.58 \pm 1.62 \text{ U}/[\text{mg protein}]$). In addition, 10 mg/kg mogroside V increased the levels of CAT (to $8.15 \pm 1.39 \text{ U}/[\text{mg protein}]$) and GSH-Px (to $11.80 \pm 1.72 \text{ U}/[\text{mg protein}]$). OVA treatment induced MDA production in the lung tissue of the mice. Administration of different doses of mogroside V attenuated the MDA formation in the lung tissue of the asthmatic mice. In particular, the high dose of mogroside V decreased the MDA level significantly (to $5.44 \pm 1.12 \text{ nmol}/[\text{mg protein}]$) relative to the OVA group.

3.4 | Effects of mogroside V on inflammatory-cell infiltration of BALF

These findings are depicted in Figure 4. OVA treatment induced the infiltration of BALF by inflammatory cells (such as neutrophils,

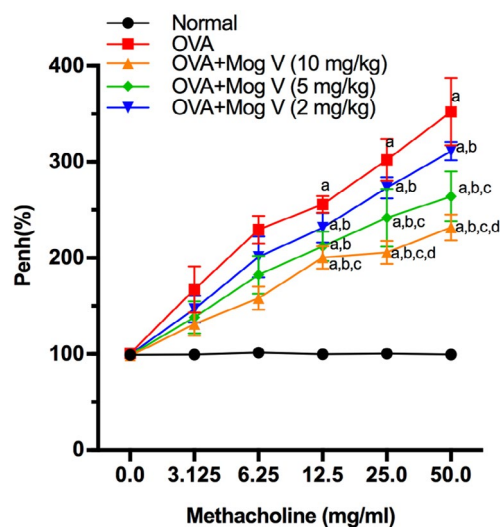


FIGURE 2 Effects of mogroside V (Mog V) on airway hyperresponsiveness (AHR) in Kunming mice ovalbumin (OVA)-induced allergic asthma. Data are expressed as the mean $\pm$ SD. (a) $p < 0.05$ as compared with the normal group; (b) $p < 0.05$ as compared with the OVA group; (c) $p < 0.05$ as compared with the mogroside V (2 mg/kg)-treated OVA group; (d) $p < 0.05$ as compared with the mogroside V (5 mg/kg)-treated OVA group

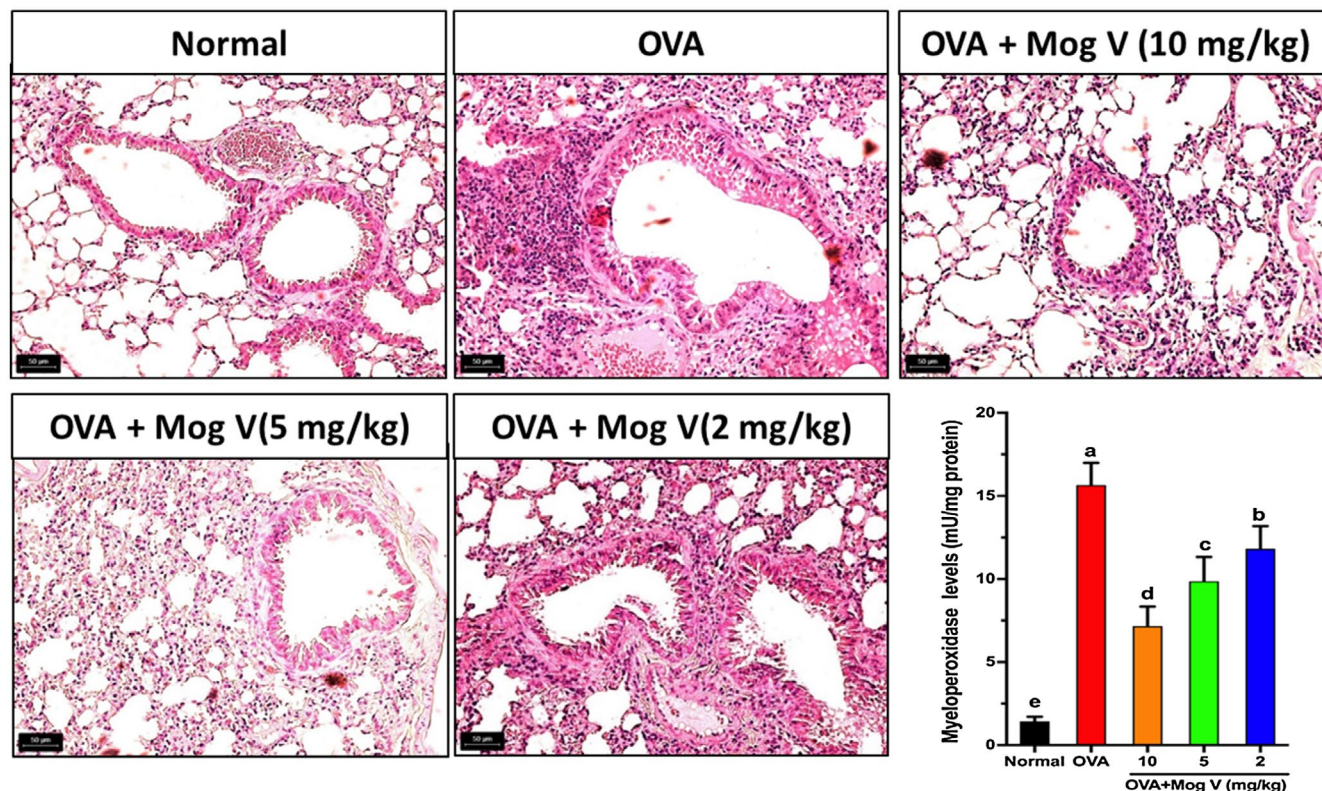


FIGURE 3 Histological observations and levels of myeloperoxidase (MPO) in the lung tissue from the mogroside V (Mog V)-treated Kunming mice with ovalbumin (OVA)-induced allergic asthma. The tissue sections were examined under the Leica DM4B microscope at $\times 200$ magnification. Data are expressed as the mean $\pm$ SD. ^{a-e}Bars with different letters are significantly different ($p < 0.05$) according to Duncan's multiple-range test

TABLE 2 SOD, CAT, GSH-Px, and MDA levels in the lung tissues of mogroside V-treated asthmatic mice

Group	SOD, U/(mg protein)	CAT, U/(mg protein)	GSH-Px, U/(mg protein)	MDA, nmol/(mg protein)
Normal	13.38 $\pm$ 1.20a	9.96 $\pm$ 1.12a	15.65 $\pm$ 2.10a	2.03 $\pm$ 0.68d
OVA	4.03 $\pm$ 0.69e	3.68 $\pm$ 0.87d	6.88 $\pm$ 1.05c	10.37 $\pm$ 1.59a
OVA + Mog V(10 mg/kg)	9.58 $\pm$ 1.62b	8.15 $\pm$ 1.39b	11.80 $\pm$ 1.72b	5.44 $\pm$ 1.12c
OVA + Mog V(5 mg/kg)	7.97 $\pm$ 1.19c	6.89 $\pm$ 1.01c	10.22 $\pm$ 0.53b	7.32 $\pm$ 1.39b
OVA + Mog V(2 mg/kg)	6.12 $\pm$ 1.08d	4.05 $\pm$ 0.50d	8.43 $\pm$ 0.97c	8.60 $\pm$ 0.71b

Note: Data are expressed as the mean $\pm$ SD.

^{a-e}Bars with different superscripted letters are significantly different ($p < 0.05$) according to Duncan's multiple-range test.

Abbreviations: SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

eosinophils, macrophages, and lymphocytes) in the mice. Mogroside V treatment reduced the OVA-induced infiltration of BALF by inflammatory cells in the mice. Among the mogroside V-treated groups, the high dose of mogroside V (10 mg/kg) showed remarkable inhibition of the infiltration of BALF by inflammatory cells (especially eosinophils, macrophages, and neutrophils) as compared with the other doses of mogroside V (2 and 5 mg/kg).

3.5 | The influence of mogroside V on inflammatory cytokines in BALF

Th2 cytokines, such as IL-4, IL-5, and IL-13, play an important part in the pathological processes of asthma (Walsh, 2015). As shown in Figure 5, OVA treatment significantly increased the levels of IL-4, IL-5, and IL-13 in the serum of the mice. Mogroside V attenuated the

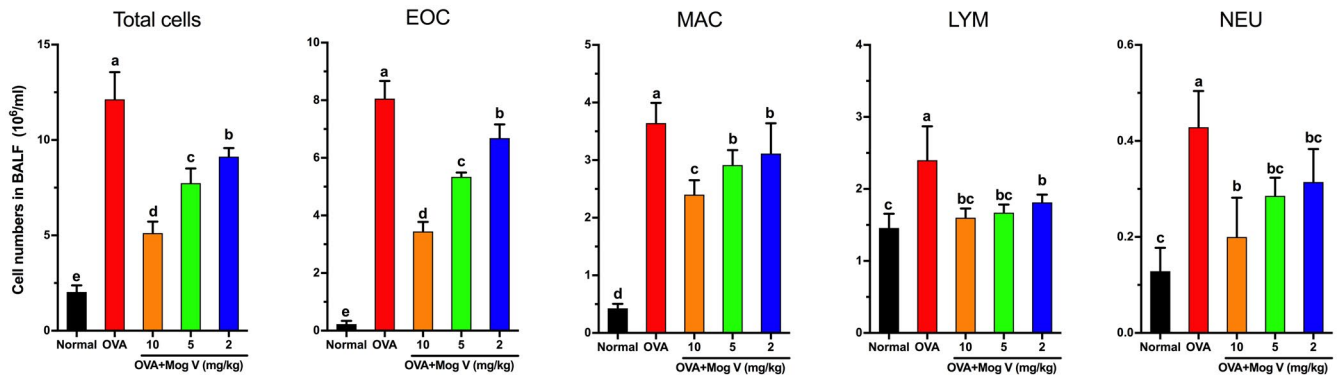


FIGURE 4 Actions of mogroside V (Mog V) on inflammatory cell counts in bronchoalveolar lavage fluid (BALF) of Kunming mice with ovalbumin (OVA)-induced allergic asthma. Data are indicated as the mean ± SD. ^{a-e}Bars with different letters are significantly different ($p < 0.05$) according to Duncan's multiple-range test. NEU, neutrophils; EOC, eosinophils; MAC, macrophages; LYM, lymphocytes

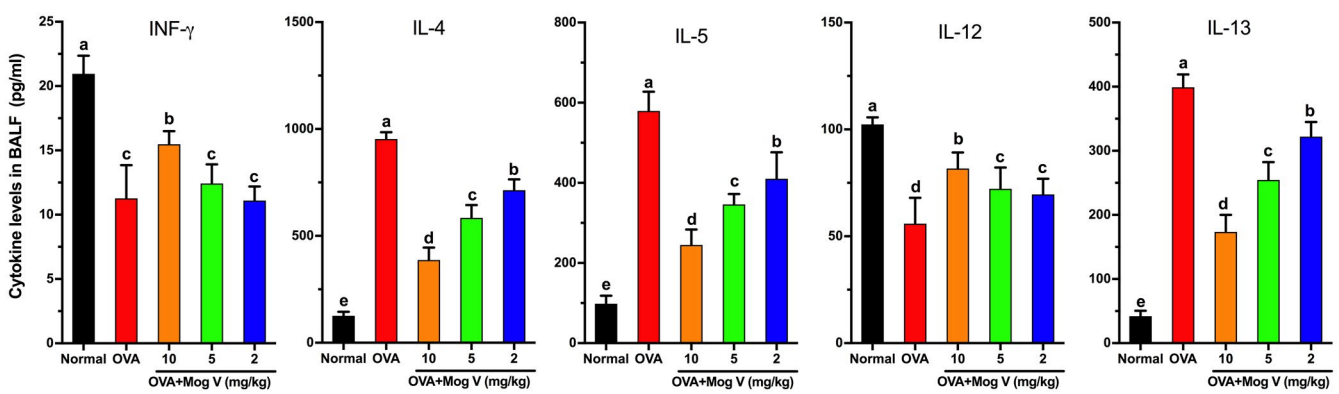


FIGURE 5 The influence of mogroside V (Mog V) on the levels of inflammatory cytokines in bronchoalveolar lavage fluid (BALF) of Kunming mice with ovalbumin (OVA)-induced allergic asthma. Data are expressed as the mean ± SD. ^{a-e}Bars with different letters are significantly different ($p < 0.05$) according to Duncan's multiple-range test

upregulation of these Th2 cytokines in serum. Mogroside V (10 mg/kg) caused the largest reduction in the concentrations of Th2 cytokines (IL-4, IL-5, and IL-13) as compared with the other mogroside V doses (2 and 5 mg/kg). In addition, when mogroside V was administered, levels of Th1 cytokines, IFN- γ and IL-12, increased in the serum of the asthmatic mice.

3.6 | Effects of mogroside V on IL-17A, IL-23, and TGF- β in BALF

As illustrated in Figure 6, increased levels of IL-17A and IL-23 were observed in mice with OVA-induced asthma. Mogroside V treatment significantly attenuated the OVA-induced upregulation of IL-17A and IL-23 in the BALF of the mice. In addition, we found that the mogroside V treatment increased the level of Treg-related TGF- β in the BALF of the asthmatic mice (Figure 6c).

3.7 | Effects of mogroside V on serum levels of IgE, IgG1, and IgG2a in the asthmatic mice

As shown in Figure 7, OVA treatment significantly upregulated of IgE and IgG1 in the serum of mice. When different doses of mogroside V

were administered, the serum levels of IgE and IgG1 decreased in the OVA-treated mice. The high dose of mogroside V (10 mg/kg) caused the largest decrease in the IgE and IgG1 levels in comparison with the other mogroside V doses (2 and 5 mg/kg) in the asthmatic mice. Nonetheless, there was no significant difference between 5 and 10 mg/kg mogroside V treatments in the asthmatic mice in terms of IgE and IgG1 levels ($p > 0.05$). In contrast, the high dose of mogroside V (10 mg/kg) significantly upregulated IgG2 when compared with the other doses of mogroside V in the asthmatic mice.

3.8 | Actions of mogroside V on mRNA levels of IL-17A, IL-23, Foxp3, and ROR γ t in the lung tissue of the asthmatic mice

As presented in Figure 8, OVA treatment significantly increased the mRNA expression levels of IL-17A and IL-23 in the lungs of the asthmatic mice. When different doses of mogroside V were administered, the OVA-induced upregulation of IL-17A and IL-23 mRNA diminished in the mice. Mogroside V (10 mg/kg) attenuated the OVA-induced decrease in the mRNA level of Foxp3 more strongly as compared to the other mogroside V-treated groups (2 and 5 mg/kg) of the asthmatic mice. Nonetheless, there was no

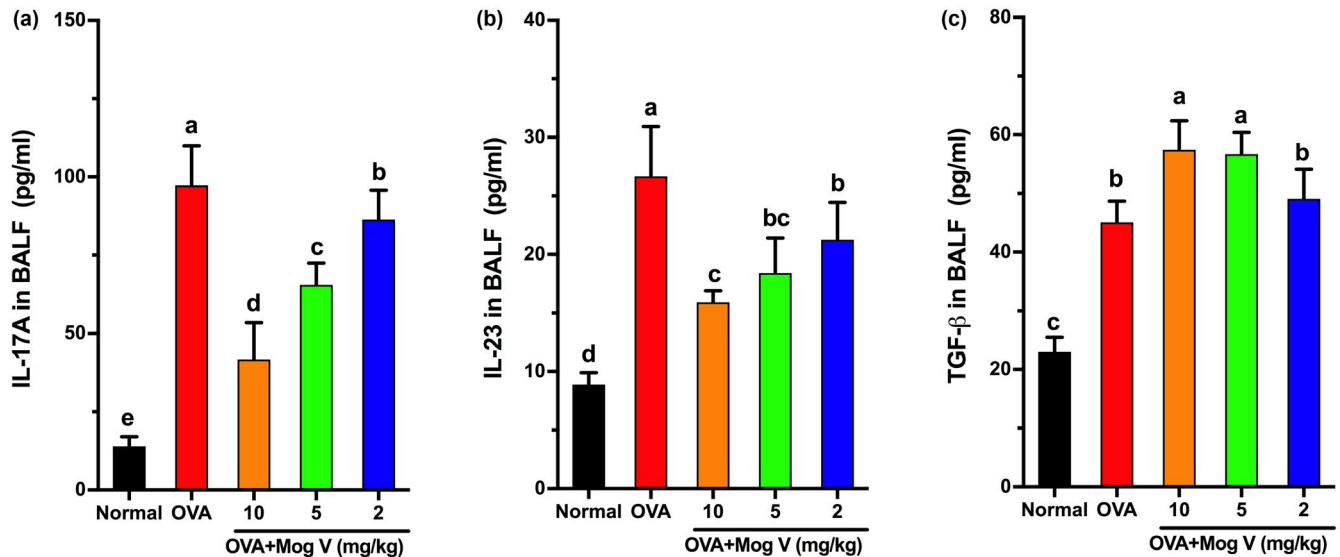


FIGURE 6 Effects of mogroside V (Mog V) on the levels of IL-17A (a), IL-23 (b), and TGF-β (c) in the bronchoalveolar lavage fluid (BALF) of Kunming mice with ovalbumin (OVA)-induced allergic asthma. Data are presented as the mean $\pm$ SD. ^{a-e}Bars with different letters are significantly different ($p < 0.05$) according to Duncan's multiple-range test

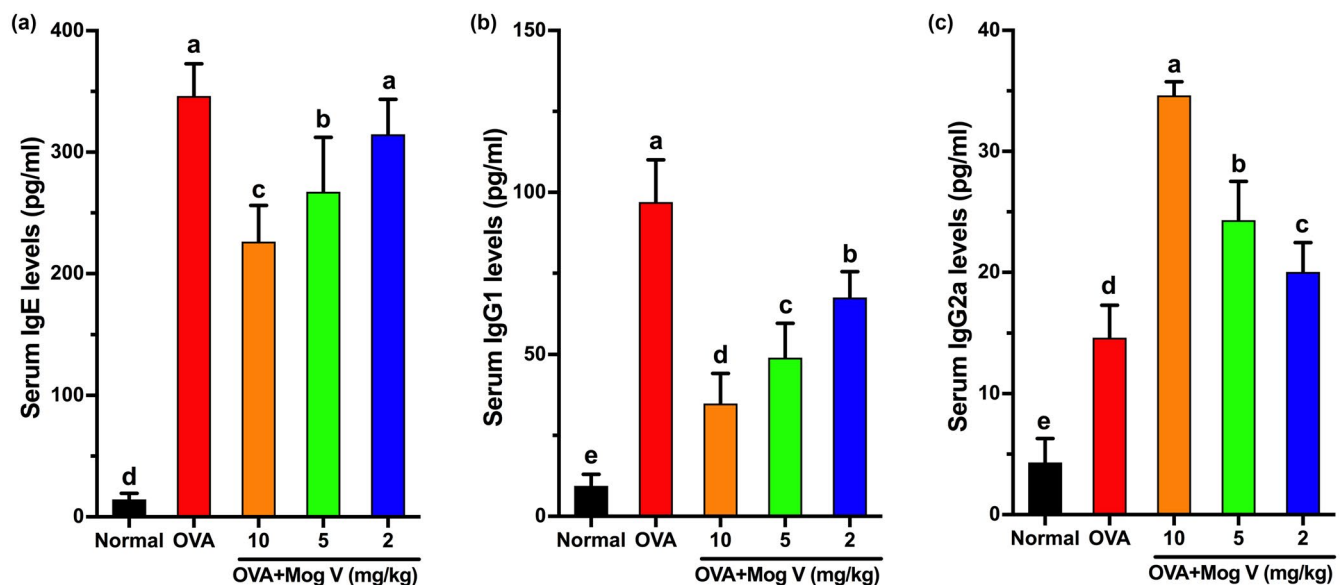


FIGURE 7 Effects of mogroside V (Mog V) on serum levels of IgE (a), IgG1 (b), and IgG2a (c) in Kunming mice with ovalbumin (OVA)-induced allergic asthma. Data are expressed as the mean $\pm$ SD. ^{a-e}Bars with different letters are significantly different ($p < 0.05$) according to Duncan's multiple-range test

significant difference between 2 and 5 mg/kg mogroside V-treated asthmatic mice in terms of Foxp3 expression levels ($p > 0.05$). In addition, OVA treatment increased the mRNA levels of RORγt in the lungs of asthmatic mice. Mogroside V (10 mg/kg) significantly attenuated the upregulation of RORγt mRNA as compared with other mogroside V-treated groups (2 and 5 mg/kg) of the asthmatic mice ($p < 0.05$).

3.9 | The influence of mogroside V on protein levels of NF-κB p65 and p-NF-κB p65 in the lung tissue of asthmatic mice

OVA treatment significantly increased the phosphorylation of NF-κB p65 in lungs as compared with that in normal mice ($p < 0.05$). As showed in Figure 9, the ratio p-NF-κB p65/NF-κB p65 in mice

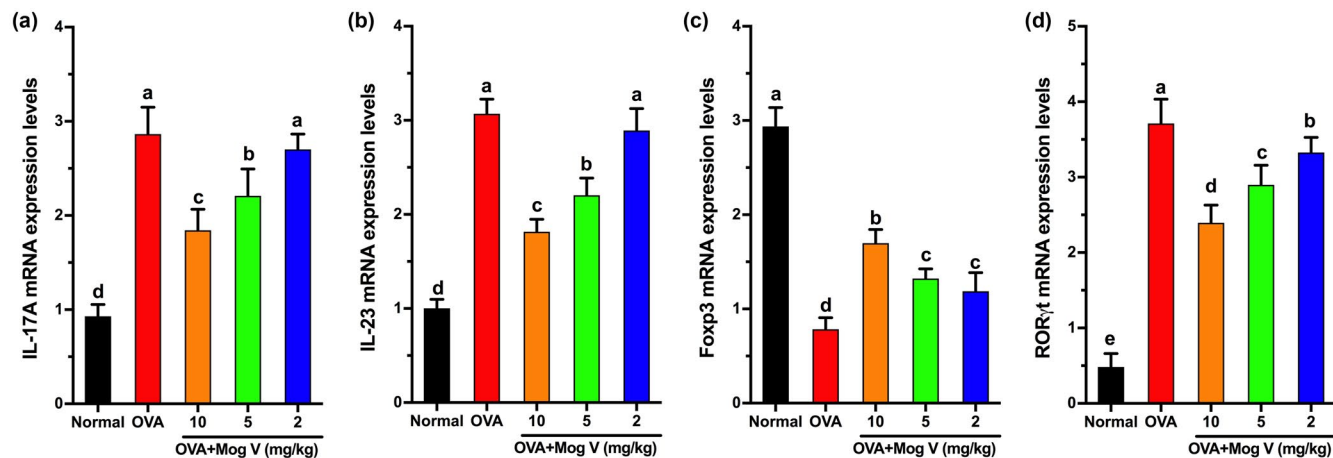


FIGURE 8 The actions of mogroside V (Mog V) on pulmonary mRNA levels of IL-17A (a), IL-23 (b), Foxp3 (c), and RORγt (d) in Kunming mice with ovalbumin (OVA)-induced allergic asthma. Data are expressed as the mean $\pm$ SD. ^{a-e}Bars with different letters are significantly different ($p < 0.05$) according to Duncan's multiple-range test

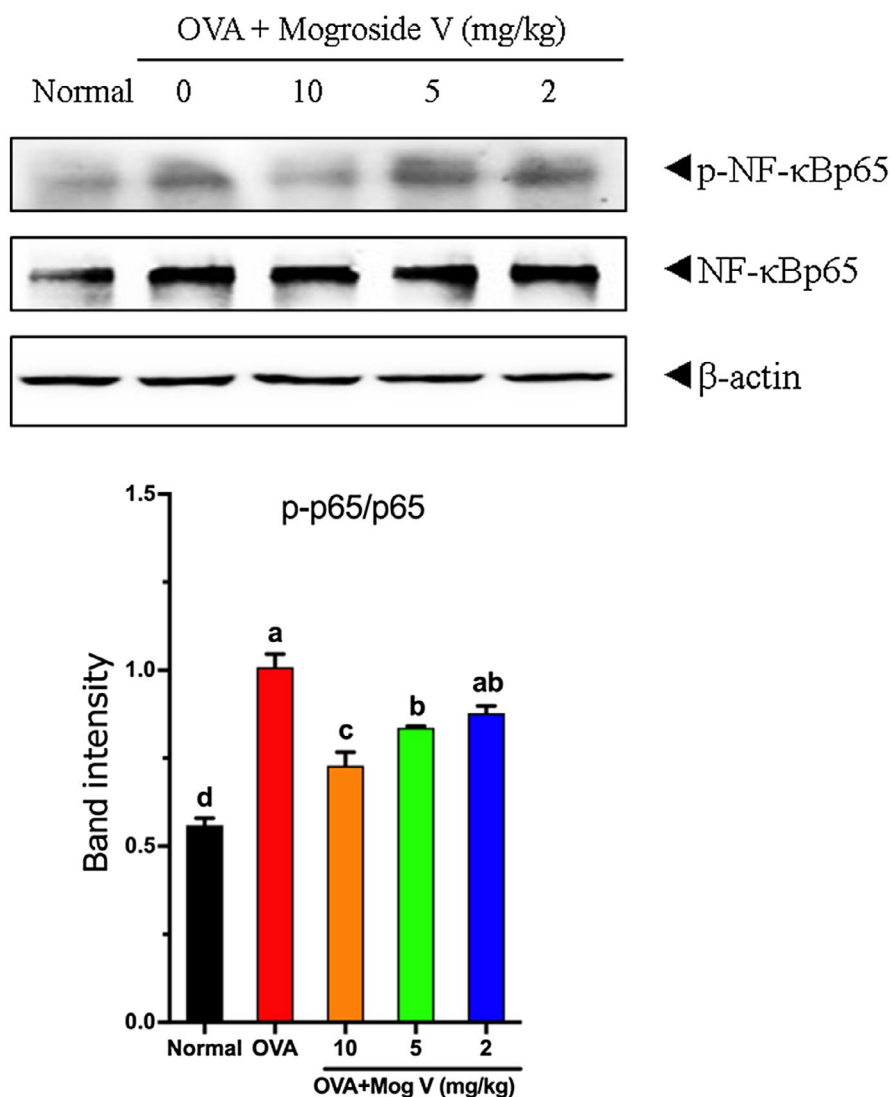


FIGURE 9 Effects of mogroside V (Mog V) on pulmonary protein levels of NF-κB p65 and p-NF-κB p65 in Kunming mice with ovalbumin (OVA)-induced allergic asthma. Data are expressed as the mean $\pm$ SD. ^{a-d}Bars with different letters are significantly different ($p < 0.05$) according to Duncan's multiple-range test

with OVA-induced asthma (~1.8) was higher than that in the normal group. By contrast, mogroside V attenuated the OVA-induced NF- κ B p65 phosphorylation in the lungs. As compared with the OVA group, the ratio p-NF- κ B p65/NF- κ B p65 was respectively decreased by 27.7%, 16.9%, and 12.8% after administration of 10, 5, or 2 mg/kg mogroside V. We also noticed that the high dose of mogroside V (10 mg/kg) caused the greatest reduction in the phosphorylation of NF- κ B p65 in the asthmatic mice.

4 | DISCUSSION

Allergic asthma is a disease of the respiratory system with an immune disorder and AHR. The chronicity of asthma imposes a heavy economic burden on the patients. Recently, a traditional Chinese medicine herb was reported to have a strong curative effect on asthma in a clinical study and in asthmatic animal models (Gandhi et al., 2018; Liu, Wang, He, & Ma, 2018). Some studies also reported the diterpene substance (such as phytol) with the antiradical, antimicrobial and cytotoxic activities in vitro (Pejin, Ciric, Glamoclija, Nikolic, & Sokovic, 2015; Pejin, Kojic, & Bogdanovic, 2014; Pejin, Savic, et al., 2014). Mogroside V is a triterpene substance, and many used in the traditional Chinese medicine. For these reasons, we tried to investigate the anti-asthmatic effect of mogroside V and evaluated its potential therapeutic utility in a classic model of asthma: OVA-induced allergic asthma in Kunming mice.

The pathogenesis of asthma is associated with many factors such as heredity, an immune disorder, and environmental problems. In particular, the severe immune disorder is the main feature of the pathophysiological process of asthma (Caminati, Pham, Bagnasco, & Canonica, 2018). We first found that mogroside V can attenuate OVA-induced AHR and decrease the number of inflammation-related cells (eosinophils and macrophages) in the BALF of asthmatic mice in this study. Next, in a histological assay, we observed that mogroside V treatment effectively reduced the infiltration of inflammatory cells into the lung tissue of the mice with OVA-induced asthma. In addition, mogroside V treatment remarkably decreased the OVA-induced upregulation of Th2 cytokines (such as IL-4, IL-5 and IL-13) in the BALF of the mice.

Recently, studies suggested that oxidative stress is closely related to the process of an inflammation reaction (Barreiro et al., 2013; Rahman & Adcock, 2006; René, Lieshout, & Folisi, 2015). Dietary antioxidants might improve asthma control and lung function in children or adults with asthma (Moreno-Macias & Romieu, 2014). Under normal physiological conditions, the endogenous antioxidant system exerts a protective action against oxidative stress induced by reactive oxygen species (ROS) and other free radicals, which is associated with an inflammatory reaction. ROS-induced oxidative stress also causes lipid peroxidation, DNA damage, and mutations in the proteins of a living organism. The endogenous antioxidant system is subdivided into enzymatic systems of SOD, CAT, and GSH-Px and the nonenzymatic system of glutathione (GSH). SOD is a metal-containing enzyme that is widespread in

the human body and catalyzes the dismutation reaction of superoxide (O_2^-) by producing oxygen (O_2) and peroxide (H_2O_2). H_2O_2 is removed by CAT and transformed to H_2O and O_2 . In addition, SOD can protect from O_2^- -induced inactivation of CAT. GSH-Px, another important endogenous antioxidant enzyme, reduces toxic peroxides to nontoxic hydroxyl compounds by oxidizing GSH to glutathione (GSSG); GSH-Px promotes the decomposition of H_2O_2 , thus protecting the structure and function of cell membranes from the effects of (and damage by) peroxides. In this study, we found that administration of different doses of mogroside V increased SOD, CAT, and GSH-Px activities in the lung tissue of asthmatic mice. MDA is a classic indicator of the level of oxidative damage in cells and tissues. OVA treatment significantly increased the MDA formation in our mice. Administration of mogroside V significantly attenuated MDA formation in the lungs of the asthmatic mice. Taken together, these results indicate that mogroside V is effective against oxidative stress in asthmatic mice.

It is well known that an imbalance of inflammatory factors, especially the imbalance of Th1 and Th2 cytokines, plays an important role in the pathological processes of allergic asthma (Caminati et al., 2018; Shi et al., 2011). Increased levels of such Th2 cytokines as IL-4, IL-5, and IL-13 are observed in human cases and in animal studies (Walsh, 2017b). Among these Th2 cytokines, IL-4 promotes the differentiation, proliferation, and activation of B cells; induces inflammatory cells eosinophils to infiltrate into the lung tissue; and increases the levels of IgE and IgG1 in serum (Barnes, 2008). IL-5 can control the formation and proliferation of eosinophils and enhances the IL-4-induced IgE secretion during asthma (Iftikhar, Schimmel, Bender, Swenson, & Amrol, 2018). In addition, IL-13 promotes the differentiation of B cells and directly induces an inflammatory reaction and AHR in the lungs of asthmatic mice (Karo-Atar, Bitton, Benhar, & Munitz, 2018; Lightwood et al., 2018). Inhibition of Th2 cytokine secretion is a widely approved therapeutic method for clinical asthma (Nguyen & Casale, 2011; Ntontsi, Papathanassiou, Loukides, Bakakos, & Hillas, 2018).

The imbalance of Th1 and Th2 cytokines may directly result in the production of asthma-specific IgE and IgG1. We observed that mogroside V treatment significantly increased the levels of Th1 cytokines IL-12 and IFN- γ in the BALF of the asthmatic mice. Both IL-12 and IFN- γ can reduce the formation of Th2 cytokines in asthma (Kubo, 2017). IL-12 is a key factor promoting the differentiation of T cells and helps to maintain a Th1-cell-mediated immune response while suppressing the activation of Th2 cells (Barreiro et al., 2013; Kubo, 2017). IFN- γ inhibits the aggregation of eosinophils in the airways and reduces the levels of IgE in serum (Elkord, 2006). These observations clearly indicate that mogroside V can decrease the production of Th2 cytokines by modulating the balance of Th1 and Th2 cytokines and by downregulating specific IgE and IgG1 to attenuate the inflammatory response in asthmatic Kunming mice.

In addition to the Th1 and Th2 cells, the Th17-Treg axis also performs an important function in the pathogenesis of asthma (Zou et al., 2018). In the present study, mogroside V treatment significantly attenuated the OVA-induced upregulation of IL-17A and IL-23 in the

BALF of mice. IL-17A, which is secreted by Th17 cells, may cause airway epithelial cells and inflammatory cells to release inflammatory mediators and is directly involved in airway inflammation of bronchial asthma (Halwani et al., 2017). IL-23 is an important factor for Th17 cell proliferation and maintains their normal function. IL-23 induces Th17 cells to secrete IL-17A and IL-17F, which will cause eosinophils to infiltrate airways and then aggravate asthma (Wakashin, Hirose, Iwamoto, & Nakajima, 2009). Reducing the up-regulation of IL-23 helps to decrease the serum levels of IL-17A and alleviate the symptoms of asthma (Li & Hua,). In contrast, mogroside V significantly increased the production of TGF- β in our asthmatic mice. TGF- β , as an anti-inflammatory cytokine generated by Tregs, has been reported to effectively modulate the differentiation and activation of Th17 cells and to reduce airway inflammation in a study on asthmatic animals (Zhang, 2018; Zhao & Wang, 2018). We also found that mogroside V effectively reduces the pulmonary levels of IL-17A and IL-23 mRNA expression in the asthmatic mice.

ROR γ t is a specific transcription factor promoting the differentiation of Th17 cells (Na et al., 2018). Many studies have suggested that elevated numbers of Th17 cells may directly enhance an inflammatory response in airways (Na et al., 2018; Zhao, Yang, & Gao, 2011). In our study, we observed that mogroside V treatment significantly decreased the mRNA levels of ROR γ t in the lung tissue of the asthmatic mice. In addition, mogroside V treatment attenuated the OVA-induced decrease in the mRNA levels of Foxp3 in these mice. As a transcription factor specific for Tregs, Foxp3 can reduce the proliferation of Th17 cells and maintain self-tolerance to alleviate autoimmune diseases and allergic diseases (Chen et al., 2018; Chen et al., 2011).

As a classic transcription factor, NF- κ B (and its signaling pathway) has been reported to perform multiple functions regulating the inflammatory response in many kinds of cells and has an important role in severe diseases such as allergic asthma (Miraghazadeh & Cook, 2018). Activated NF- κ B regulates the differentiation into Th2 cells and induces production of Th2 cytokines IL-4, IL-5, and IL-13 (Das et al., 2001; Zhu, Yamane, Cote-Sierra, Guo, & Paul, 2006). Reducing the activation of NF- κ B in lung tissue can relieve airway inflammation during asthma (Ma, Wei, & Zhang, 2018; Tang & Huang, 2018). In the present study, we found that mogroside V treatment was effective at reducing the OVA-induced activation of NF- κ B in the lungs of mice. In other studies, it was reported that both mogroside III and mogroside V attenuate lipopolysaccharide-induced lung inflammation and acute lung damage by reducing the activation of NF- κ B signaling pathways (Shi et al., 2014; Tao, Cao, et al., 2017; Tao, Yang, et al., 2017).

5 | CONCLUSIONS

The results of this study indicate that mogroside V can reduce an OVA-induced inflammatory response in airways, decrease the production of IgE and IgG1, and correct the balance of Th1 and Th2 cytokines in asthmatic mice. The potential protective mechanism of mogroside V's action in the mice with OVA-induced asthma may

be associated with a reduction in NF- κ B activation and reversal of the imbalance of Th1 and Th2 cytokines. Thus, mogroside V may serve as adjunctive medication for the treatment of allergic asthma.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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