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# Emodin Alleviates the Airway Inflammation of Cough Variant Asthma in Mice by Regulating the Notch Pathway

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Background:** This study investigated the effects and underlying mechanisms of emodin on cough variant asthma (CVA) in mice.

**Material/Methods:** The bronchial asthma mouse model was successfully established by use of ovalbumin (OVA) sensitization and challenge. The BALB/c mice were divided into 6 groups: a control group, an OVA model without or with emodin (15, 30, 60 mg/kg) group, and a dexamethasone (0.5 mg/g) group. The effect of the treatment was determined by measuring airway responsiveness. The levels of immunoglobulin molecules, as well as inflammatory cytokines in bronchoalveolar lavage fluid (BALF) and serum, were determined by ELISA. The lung tissues were stained by hematoxylin-eosin (HE). The expressions of Notch receptors (Notch 1–3) and Delta-like (DLL) 4 in the lung tissues were detected by RT-PCR and Western blot analysis.

**Results:** Compared with the model group, emodin treatment significantly increased the levels of immunoglobulin E (IgE) and IgG1/IgG2a in BALF and serum ($p<0.05$). HE results indicated that emodin inhibited the infiltration of inflammatory cells and that emodin reduced the levels of inflammatory cytokines, interleukin (IL)-5, IL-17, and interferon (IFN)-γ in BALF and serum ($p<0.05$). Furthermore, the expressions of Notch 1, 2, 3, and DLL4 in lung tissue were inhibited by emodin treatment.

**Conclusions:** The results demonstrated that emodin alleviated inflammation in CVA mice, which might be associated with suppression of the Notch pathway. Emodin might be a promising therapeutic agent for allergic asthma.

**MeSH Keywords:** **Cough • Emodin • Inflammation Mediators • Receptors, Notch**

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## Background

Cough variant asthma (CVA) usually presents with airway hyper-responsiveness, eosinophilic inflammation, and cough [1,2]. CVA has been regarded as the precursor of asthma because 50–80% of children and 10–33% of adults with CVA develop to typical asthma in a few years [2,3]. In CVA patients, there are no other "typical" asthma symptoms (such as wheezing or dyspnea), which makes diagnosis difficult [4].

Pulmonary function tests, bronchial hyper-responsiveness, and the degree of sputum eosinophils are often used to diagnose CVA. Existing guidelines on CVA therapy recommend that inhaled bronchodilators and corticosteroids be used as the initial treatment regimen [5,6]. Unfortunately, high-dose inhalation of bronchodilators and corticosteroids can cause a variety of pharmacologic vascular remodeling effects [7]. Furthermore, the long-term efficacy of these drugs, including the impact on lung function decline, remains unclear in the treatment of CVA. Therefore, it is necessary to find a new drug with low adverse effects for treatment of CVA.

Emodin, a Chinese herb, has been widely used in Chinese traditional medicine [8]. Emodin has become increasingly popular due to its health benefits, including anti-inflammatory and antioxidation action [9]. Emodin can inhibit the proliferation of multiple cancer cell types, such as human cervical cancer cells [10], breast cancer cells [11], and hepatocellular carcinoma cells [12]. Previous research also showed emodin helps in other diseases, including dementia [9] and liver injury [13]. However, little is known about the biological mechanism of emodinin in the treatment of CVA.

In this study, we tested the hypothesis that emodin protects against the inflammation in CVA mice through regulating the Notch pathway.

## Material and Methods

### Animals and care

Seventy-two male BALB/c mice, 8–12 weeks, weighing 18–22 g, were purchased from Suzhou Industrial Park Ai'erMaite Technology Co. (SCXK [Soochow] 2014-0007). The mice were maintained in a specific pathogen-free (SPF) environment with temperature 20~26°C, daily temperature fluctuation ≤4°C, humidity 40~70%, 12-h light/dark cycle, and free access to food and water. All animal procedures performed in this study were approved by the Animal Ethics Committee of Yantai Hospital of Traditional of Chinese Medicine (No. 2017009).

### Animal groups and model

Animals were randomly divided into 6 groups: a control group, an ovalbumin (OVA) model group, a low-dose emodin (15 mg/kg, L-emodin) group, a medium-dose emodin (30 mg/kg, M-emodin) group, a high-dose emodin (60 mg/kg, H-emodin) group, and a dexamethasone (DEX) group (0.5 mg/g).

The OVA model was established according to the method described in a previous study [14]. Animals were sensitized by intraperitoneal injection of 80 μg OVA (Grade V; Sigma-Aldrich, St. Louis, MO) in 0.1 mL and an equal volume of aluminum hydroxide (Sigma-Aldrich, St Louis, MO, USA) on day (D) 1 and D 14, respectively. Starting 10 days after the second sensitization, mice were challenge with atomized OVA (1.5% OVA dissolved into 0.9% physiological saline) for 45 min each day for 20 days. The control mice were treated with 0.9% physiological saline. The mice were intraperitoneally administrated emodin (15 mg/kg, 30 mg/kg, 60 mg/kg) and dexamethasone (0.5 mg/g, Sigma-Aldrich) 1 h before each challenge.

### Sample collection

At 24 h after the last drug administration, the mice were anesthetized by intraperitoneal injection of 10% chloral hydrate (0.3 mL/100 g). Bronchoalveolar lavage fluid (BALF) of the mice was collected immediately using warm (37°C) saline (2 mL/aliquot, 0.9% NaCl) lavaged to the right lung 3 times by gentle cannulation. Blood samples were collected into silicone-containing tubes (SST tube) (Becton Dickinson, Mountain View, CA), stored for 60±5 min at 25°C, and subsequently centrifuged at 1300×g at 4°C for 10 min. The serum was stored at –20°C until measurement for antibodies detection. The lung tissues were collected and frozen at –80°C.

### Airway responsiveness assessment

Airway responsiveness was measured by methacholine-induced airflow obstruction. The animals were anaesthetized through intraperitoneal injection of 7% hydrate chloral (0.5 mL/100 g), and then exposed to increasing concentrations of methacholine (0–50 mg/mL, Sigma-Aldrich). Lung airway resistance in the cannula of these mice was assessed using the Buxco Pulmonary Mechanics System (Buxco Electronics, NC, USA).

### Enzyme-linked immunosorbent assay (ELISA)

The levels of antigen-specific immunoglobulin (Ig) E, IgG1/IgG2a, interferon (IFN)-γ, interleukin (IL)-5, and IL-17 in the BALF supernatant and serum were determined using an enzyme-linked immunosorbent assay (ELISA) following the manufacturer's instructions (Thermo Fisher Scientific, Shanghai, P.R. China).

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### Histologic evaluation

The lungs were immersed in 4% paraformaldehyde for 12–14 h. The pulmonary tissues were then sectioned (5 μm), dewaxed, dehydrated in decreasing concentrations of ethanol, rinsed with distilled water, and stained using hematoxylin and eosin (HE) (Beijing Solarbio biotechnology Co., China). Microscopic images of stained sections were obtained using a microscope (Olympus, Japan) at ×100 magnification.

### Quantitative real-time PCR (RT-PCR) analysis

The levels of Notch receptors (Notch 1–3) and Delta-like (DLL)-4 in lung tissues were detected by RT-PCR. Total RNA of lung tissues was extracted using Trizol reagent (Takara, Dalian). We used 1 μL of cDNA with SYBR Green Master to configure the reaction system for PCR reaction. PCR amplifications were performed at 95°C for 5 min, followed by 30 cycles of thermal cycling at 95°C for 20 s, 60°C for 30 s, and 72°C for 30 s. The results were observed and photographed in an electrophoresis gel imaging system (Bio-Rad, USA). Each band value relative to the reference gene (β-actin) was calculated and analyzed using Image J software, and then normalized to compare the expression levels of Notch1, 2, and 3 and DLL4 mRNA in tissues. The primers used in this study were:
Notch1 forward, 5'-CCGTGGCTCCATTGTCTACCT-3';
Notch1 reverse, 5'-CATCGGTGGCACTCTGGAA-3';
Notch2 forward, 5'-CCAAGCGGAAGCAAGCAT-3';
Notch2 reverse, 5'-GGCGCTTGTGATTGCTAGAGT-3';
Notch3 forward, 5'- TACTGCATTTGTCCACCTGGAT-3';
Notch3 reverse, 5'-TCCAACCTCACCCCCATCT-3';
DLL4 forward, 5'-GACCTGCGGCCAGAGACTT-3';
DLL4 reverse, 5'-GCCAAATCTTACCCACAGCAA-3';
β-actin forward, 5'-TTGTTACCAACTGGGACG-3';
β-actin reverse, 5'-GGCATAGAGGTCTTTACGG-3'.

### Western blot analysis

The protein samples were analyzed using a BCA kit (Pierce Company). The samples were separated by 10–20% Ready Gels (Bio-Rad, USA) and transferred onto a polyvinylidene fluoride (PVDF) membrane for 30 min in a transfer electricity meter (Bio-Rad, USA). The PVDF nitrocellulose films were cleared and sealed with 5% milk. After washing, anti-Notch 1 (1: 500, Abcam, USA), anti-Notch 2 (1: 800, Abcam, USA), anti-Notch 3 (1: 1000, Abcam, USA), and anti-DLL4 (1: 1000, Abcam, USA) were added to incubate overnight at 4°C. Then, these films were washed 3 times with Tris-buffered saline tween (TBST) and incubated with HRP secondary antibodies (1: 5000, Sigma, USA) at room temperature for 1 h. Relative expression levels of each protein were normalized to endogenous control β-actin using Image J software.

### Statistical analysis

Statistical analysis was performed using SPSS 19.0 software. All data are shown as mean value ± standard deviation (SD). Statistical differences between groups were analyzed by one-way analysis of variance (ANOVA) with subsequent Dunnett's test. $p<0.05$ was considered as a statistically significant difference.

## Results

### Emodin alleviated airway resistance in OVA-challenged mice

We observed the effects of emodin on airway resistance (Figure 1A). Compared with the control group, airway resistance in other groups was significantly increased when the concentration of methacholine exceeded 10 mg/mL ($p<0.05$). Emodin treatment significantly decreased the airway resistance, especially at the dose of 60 mg/kg ($p<0.05$, Figure 1A). Similarly, the levels of antigen-specific IgE and IgG1/IgG2a in BALF and serum of mice were greatly increased by OVA when compared the control group ($p<0.05$, Figure 1B). Emodin treatment significantly reduced the levels of antigen-specific IgE and IgG1/IgG2a ($p<0.05$, Figure 1B).

### Emodin alleviated OVA-induced pulmonary tissues injury

We examined the pulmonary pathology by staining with HE (Figure 2). We found a marked infiltration of inflammatory cells into perivascular and peribronchial connective tissues in OVA-induced asthmatic lung tissues. Compared with the OVA group, inflammatory cells were inhibited in the emodin and DEX groups. The results revealed that emodin treatment repaired OVA-induced pulmonary tissue injury.

### Emodin decreased the expression of inflammatory cytokines

The expression of IL-5, IL-17, and IFN-γ in BALF and serum were analyzed (Figure 3). Compared with the control group, the expressions of IL-5 and IL-17 were increased and the expression of IFN-γ was decreased in the OVA model group ($p<0.05$). Compared with the OVA group, emodin treatment significantly decreased the secretion of IL-5 and IL-17 and enhanced the secretion of IFN-γ ($p<0.05$). The therapeutic effect was positively correlated with emodin dosage.

### Emodin attenuated airway remodeling associated with the Notch pathway

The expressions of Notch receptors (Notch 1, Notch 2, Notch 3, and DLL4) were measured by RT-PCR and Western

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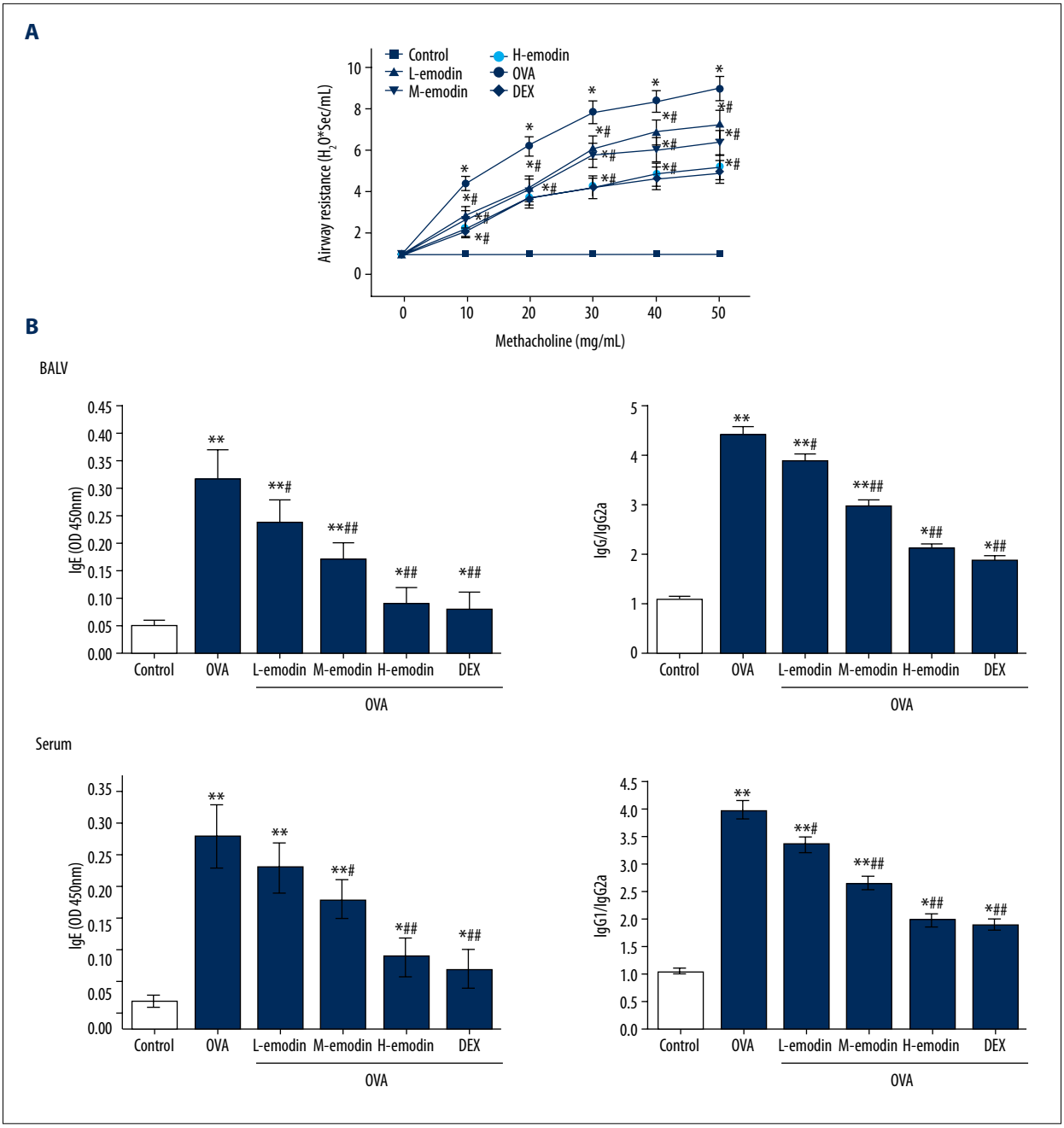


**Figure 1.** Airway hyper-responsiveness changes regulated by emodin. (**A**) Airway responsiveness of mice exposed to increasing concentrations of methacholine (0–50 mg/mL) under anesthesia. (**B**) Levels of antigen-specific IgE and IgG1/IgG2a in BALF and serum. OVA – ovalbumin; L-emodin – low-dose emodin; M-emodin – medium-dose emodin; H-emodin – high-dose emodin; DEX – dexamethasone. Data are presented as mean ±SD (n=5). Compared with control group, * $p<0.05$, ** $p<0.01$; Compared with OVA model group, # $p<0.05$, ## $p<0.01$.

blot analyses (Figures 4, 5). Compared with the control group, the expression of Notch receptors was prominently increased in OVA-induced lung tissues of mice ($p<0.05$). Compared with the OVA group, the levels of Notch 1–3 and DLL4 in the emodin groups were decreased with increasing dosage. The results were consistent between RT-PCR and Western blot analyses.

## Discussion

The currently used therapies for CVA are essentially as the same as those used for typical asthma: with bronchodilators, inhaled corticosteroids, and leukotriene modifiers [15,16]. Furthermore, the combination of a bronchodilator and an

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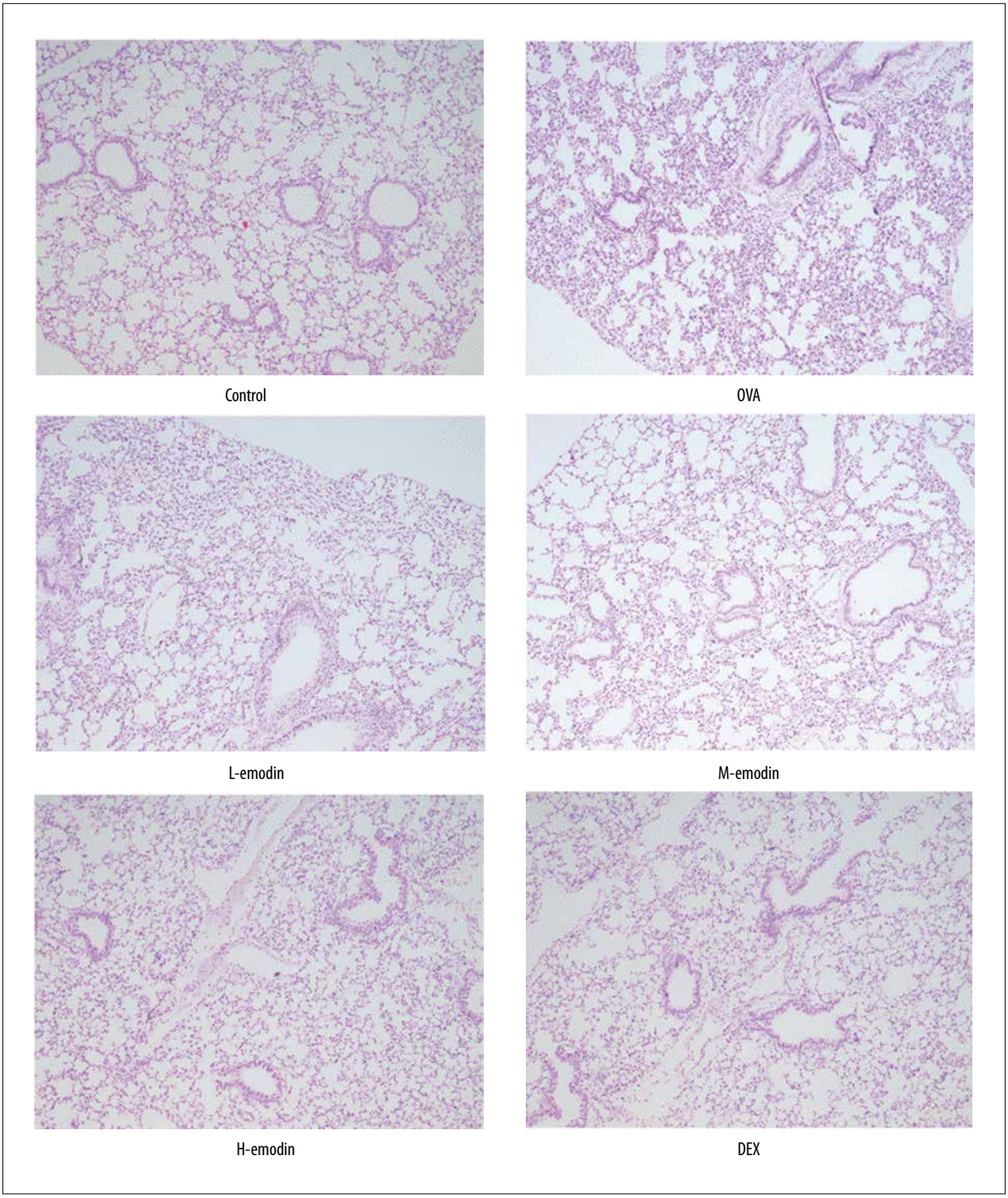


**Figure 2.** Pathological changes of lung tissues. HE staining slices from lung sections, magnification 100×. OVA – ovalbumin; L-emodin – low-dose emodin; M-emodin – medium-dose emodin; H-emodin – high-dose emodin; DEX – dexamethasone

inhaled corticosteroid appear to be useful [17–19]. However, the long-term efficacy and safety of these drugs need to be further investigated [18–20]. In contrast to Western medicine pharmacotherapies, traditional Chinese medicine aims to correct maladjustments and restore the self-regulatory ability of the body by influencing multiple bioprocesses. Chinese medicine has shown great efficacy in CVA treatment [21]. Emodin is an herbal medicine extracted from *Corchorus capsularis L.*,

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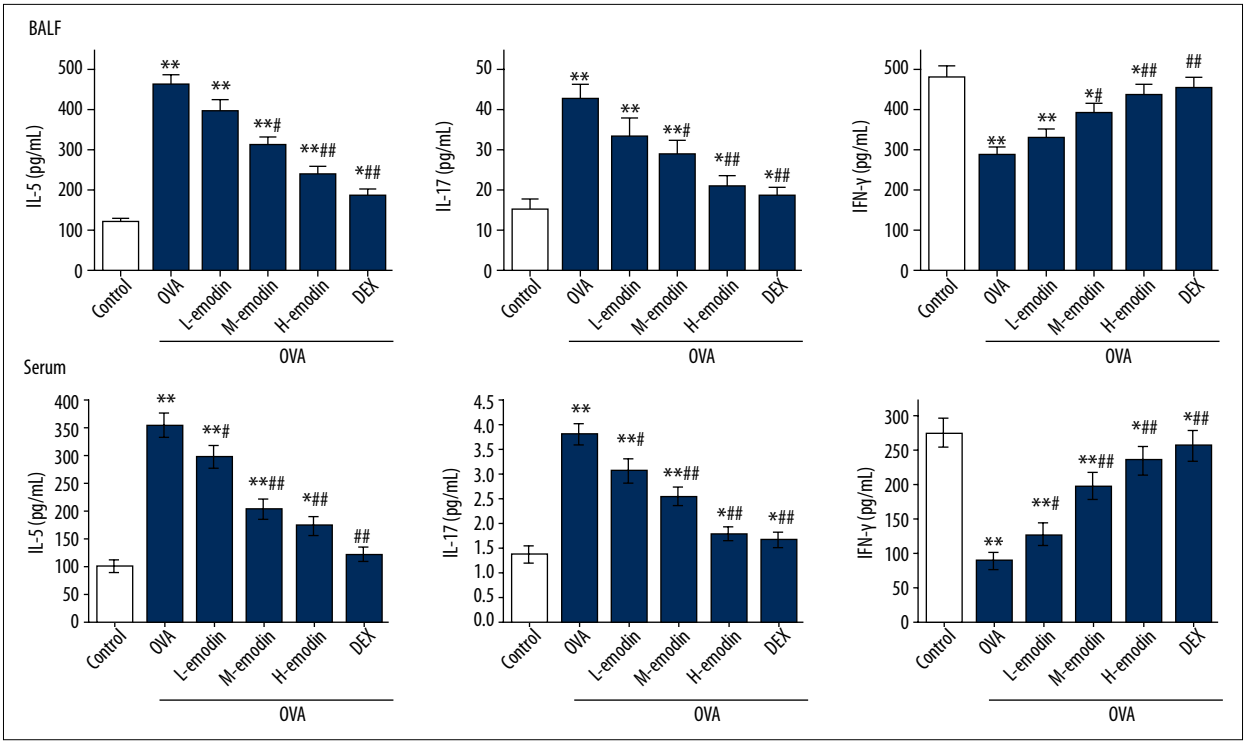


**Figure 3.** The levels of IL-5, IL-17, and IFN-γ in BALF and serum. OVA – ovalbumin; L-emodin – low-dose emodin; M-emodin – medium-dose emodin; H-emodin – high-dose emodin; DEX – dexamethasone. Data are presented as mean ±SD (n=5). Compared with control group, * $p<0.05$, ** $p<0.01$; Compared with OVA model group, # $p<0.05$, ## $p<0.01$.

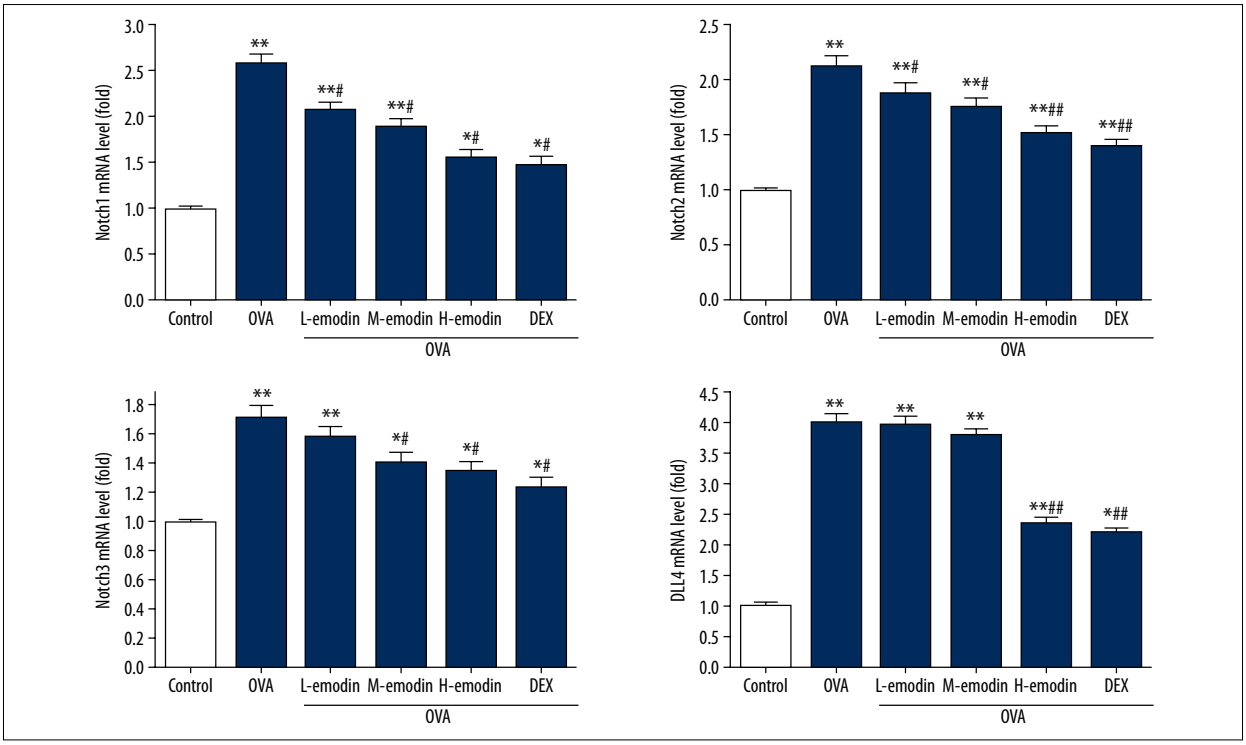


**Figure 4.** The levels of Notch 1, Notch2, Notch3, and DLL4 mRNA in lung tissues. OVA – ovalbumin; L-emodin – low-dose emodin; M-emodin – medium-dose emodin; H-emodin – high-dose emodin; DEX – dexamethasone. Data are presented as mean ±SD (n=5). Compared with control group, * $p<0.05$, ** $p<0.01$; Compared with OVA model group, # $p<0.05$, ## $p<0.01$.

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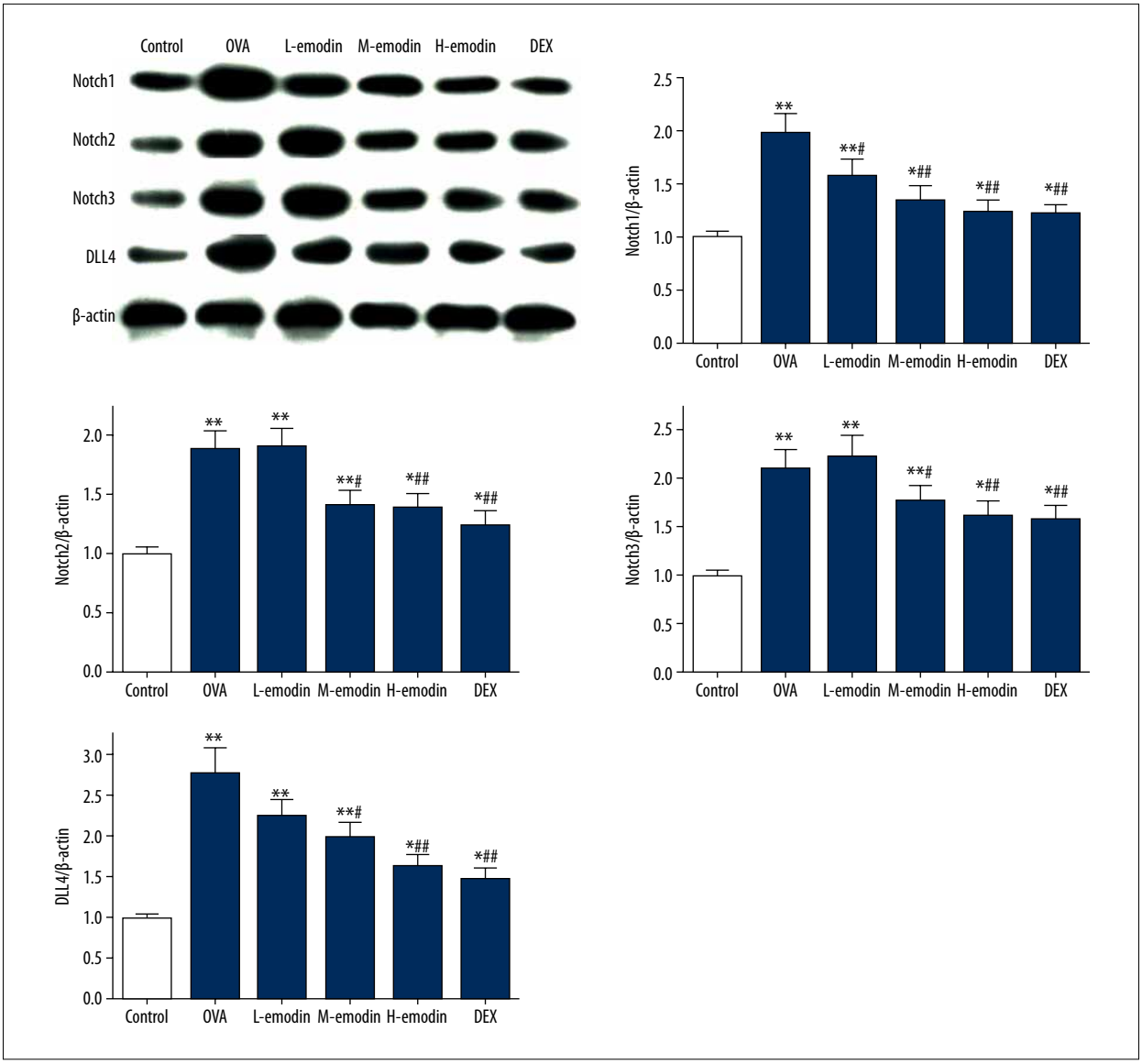


**Figure 5.** The levels of Notch, Notch2, Notch3, and DLL4 proteins in lung tissues. OVA – ovalbumin; L-emodin – low-dose emodin; M-emodin – medium-dose emodin; H-emodin – high-dose emodin; DEX – dexamethasone. Data are presented as mean ±SD (n=5). Compared with control group, * $p<0.05$, ** $p<0.01$; Compared with OVA model group, # $p<0.05$, ## $p<0.01$.

which is widely used to treat chronic cough in China. In this study, we investigated the therapeutic efficacy of emodin on CVA and found emodin had potential application in asthma.

In our study, OVA sensitization induced higher airway responsiveness and increased the levels of antigen-specific IgE and IgG1/IgG2a in mice. We found that emodin treatment mitigated airway hyper-responsiveness and that the efficacy of high-dose emodin (60 mg/kg) was similar to that of dexamethasone. Emodin treatment obviously ameliorated pulmonary histology and bronchial epithelial hyperplasia by suppressing inflammatory cells accumulation.

Four Notch receptors (Notch 1–4) and 5 Notch ligands (Jagged-1, -2, and Delta-like (DLL) -1, -3, and -4) exist in the mammalian Notch family, which have pleiotropic functions in regulating cell cycle and apoptosis [22]. Indeed, Notch has been shown to regulate the differentiation of T-helper (Th)1, Th2, Th9, Th17, and regulatory T cells (Tregs) in Th subsets [22,23]. Th1 cells are associated with a host of autoimmune conditions by governing immunity against intracellular bacteria and viruses. IFN-γ is produced when Th1 cells direct the expression of the T-bet transcription factors [24]. Th2 cells have been determined to have a central role in the pathogenesis of allergic asthma, which is dominated by the production of IL-4, IL-5, and IL-13 [25]. The predominant inflammatory cell type recruited into asthmatic lung

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tissues is the eosinophil, which is associated with the production of IL-5 [26]. Most IL-17 from Th17 cells has been thought to be directed toward indirect defense against extracellular bacteria and fungi in a broad spectrum of inflammatory conditions and autoimmune diseases [27]. Therefore, we assessed the expression of IL-5, IL-17, and IFN-γ in each group to determine the anti-inflammatory effectiveness of emodin in the treatment of CVA. In our research, emodin treatment reduced the levels of IL-5 and IL-17 and increased the expression of IFN-γ, which showed a dose-dependent effect, suggesting that the biological mechanism of emodin in CVA treatment is related to inflammation processes. Chen et al. also found that the mechanism of Chinese medicine in the treatment of CVA was highly related to the immune and inflammation processes by influencing the pathways of EGFR, VEGF, Gn-RH, and IL-17 [21].

Notch, as a regulatory signal, can enhance the competence of T effector cells and induces effector cell differentiation by paracrine cytokines [22,23]. Recent studies have made efforts to target Notch in T cells to relieve detrimental responses caused by excessive Th2 responses in allergic asthma [28]. Huang et al. demonstrated that Notch ligand DLL4 alleviates allergic airway inflammation via induction of a homeostatic regulatory pathway [29]. In the present study, we found that Notch receptors levels were significantly increased in OVA-induced lung tissues of mice ($p<0.05$), while the levels of the Notch 1–3 and DLL4 were decreased by treatment with increasing dosages of emodin. These results demonstrate that the mechanism of emodin therapy is highly related to the immune and inflammation processes by regulating the Notch pathways.

## Conclusions

Our study shows that emodin is effective in the treatment of CVA, which resulted from the alleviation of pulmonary immune response and healing of lung tissue injury. The mechanism appears to involve the Notch pathway. Our results may provide a new direction to explore the therapeutic mechanism of emodin in CVA therapy.

### Conflict of interests

None.

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