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Supplementation with Tetrahydrocurcumin Enhances the Therapeutic Effects of Dexamethasone in a Murine Model of Allergic Asthma

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Keywords
Tetrahydrocurcumin · Dexamethasone · Asthmatic mouse model · Airway inflammation · Therapy

Abstract
Background: Tetrahydrocurcumin (THC) is the major active metabolite of curcumin, which is a dietary factor derived from *Curcuma* species. Our previous study demonstrated a significant beneficial effect of THC in mice with allergic asthma. Glucocorticosteroids (GCs) are commonly used drugs in asthma. Whether THC supplementation could promote the beneficial effects of GC therapy on asthma has not yet been reported. The current study aimed to investigate the combined efficacy of GC and THC treatment in a mouse model of allergic asthma. ***Methods:*** BALB/c mice were randomly divided into 5 groups: the control group, ovalbumin (OVA)-induced group, and OVA-induced mice treated with dietary THC only, intraperitoneal injection of dexamethasone (DEX) only, or THC combined with DEX. The nasal symptoms, histopathological alterations of lung tissues, lung cytokine production, and Th cell subsets were assessed. ***Results:*** THC or DEX had beneficial effects on nasal symptoms and pathological lung changes, and the therapeutic effects between THC and DEX treatment were comparable. Importantly, compared to the monotherapy groups (THC or DEX only), the combination of THC and DEX showed a significantly reduced nasal rubbing frequency, lower mucus hyperproduction, lower Th2 and Th17 cell numbers as well as lower related cytokine levels (IL-4, IL-5, and IL-17A). ***Conclusions:*** Supplementation with THC can enhance the therapeutic effects of DEX to alleviate airway symptoms, lung inflammation, and the Th2 response. Our findings suggest that dietary administration of THC could act as an add-on therapy for asthma treated with GCs.

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Introduction

Allergic asthma is a chronic airway disease affecting more than 300 million people worldwide, and the prevalence has been estimated to reach 400 million cases by 2,025 [1, 2]. The increasingly urbanized incidence of allergic asthma suggests that a "Western lifestyle" might be one of the major driving factors, especially dietary habits. The critical role of diet in the development of asthma has been established [3, 4], and healthier diet behaviors are associated with fewer symptoms and better control of allergic asthma [5]. Therefore, the beneficial effects of certain nutrients on asthma outcomes are of growing interest, such as vitamin D [6, 7], resveratrol [8], and anthocyanin [9]. Additionally, our previous study demonstrated that tetrahydrocurcumin (THC), a major curcumin metabolite, exhibited anti-asthma properties in a murine model, and its inhibitory effects on airway inflammation were stronger than those of curcumin [10].

Inhaled glucocorticosteroid (GC) therapy has become a standard and first-line treatment for asthma; however, patients with severe asthma show little improvement after inhaled GC therapy. In addition, adverse effects are common in most patients due to long-term administration, such as glucose intolerance, dysphonia [11], and a reduction in bone mineral density [12]. Over the past decades, emerging combination therapies have offered further advantages compared to GCs alone [13]. For example, the dry powder of budesonide + formoterol fumarate dehydrate is one of the most widely used fixed combinations for asthma control. However, although this strategy reduces the intake of GCs and the risks of exacerbation, clinical evidence is limited, and side effects still exist [14].

Studies have illustrated that certain nutrients could act as add-on therapies with improved safety and fewer side effects. With regard to GCs, a combination treatment with dexamethasone (DEX) and vitamin D was reported in an animal model of allergic asthma, and the results showed that the combination therapy was more effective than monotherapy with either DEX or vitamin D [15]. In addition, attenuation of DEX-induced hyperglycemia, hyperlipidemia, and behavioral abnormalities was observed in rats that received this combination strategy [15]. Similar to the effects of vitamin D, curcumin and its metabolite THC could not only alleviate asthma symptoms but also improve GC-induced osteoporosis [16] and insulin resistance [17]. Considering that THC has stronger anti-asthma properties than curcumin, we wondered whether the efficacy and safety of THC and DEX combination treatment would be greater than monotherapy. Hence, we aimed to explore the effects of THC and DEX combination therapy on allergic airway symptoms and inflammation in an asthmatic murine model and compare the differences between combination therapy and monotherapy.

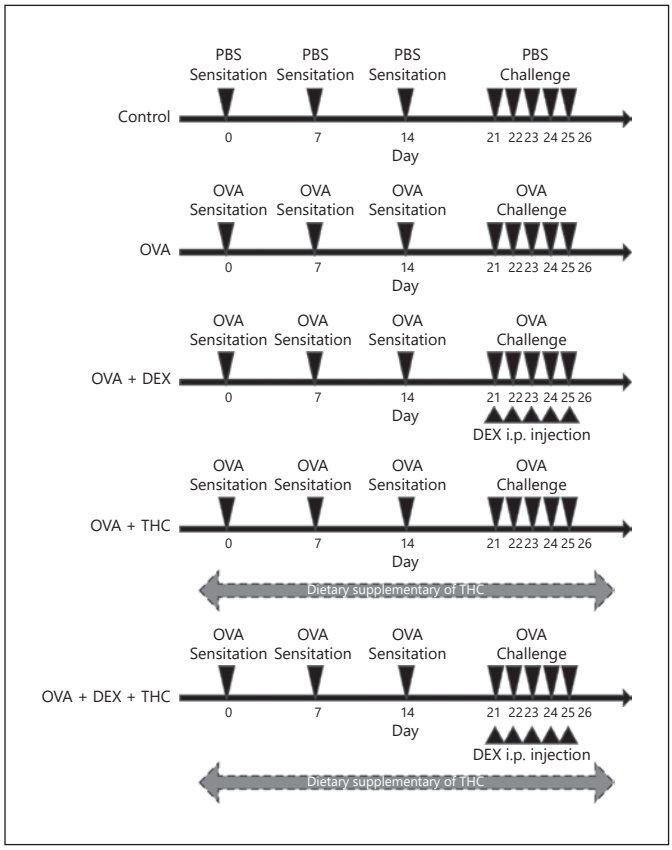

Fig. 1. Protocols of combination therapy (THC + DEX) or monotherapy (THC or DEX only) in a murine model of allergic asthma. Asthmatic mice were sensitized and challenged by OVA. From day 21–25, 20 mg/kg of DEX was injected into asthmatic mice. THC was mixed into the AIN-93G diet (800 mg of THC mixed with 1 kg of AIG 93G diet) and fed mice during the whole experiments. THC, tetrahydrocurcumin; OVA, ovalbumin; DEX, dexamethasone.

Materials and Methods

Animal Models

Four-week-old BALB/c mice (female) were purchased from Sun Yat-sen University Animal Center (Guangzhou, China) and were housed in a specific pathogen-free facility. The murine model of allergic asthma was established as previously reported [9, 10]. First step: mice were sensitized via i.p. injection of 200 μL of ovalbumin (OVA) solution containing 40 μg of OVA (Sigma-Aldrich, St. Louis, MO, USA), 2 mg of aluminum hydroxide (Thermo, Rockford, IL, USA), and 200 μL of PBS (pH = 7.3) on days 0, 7, and

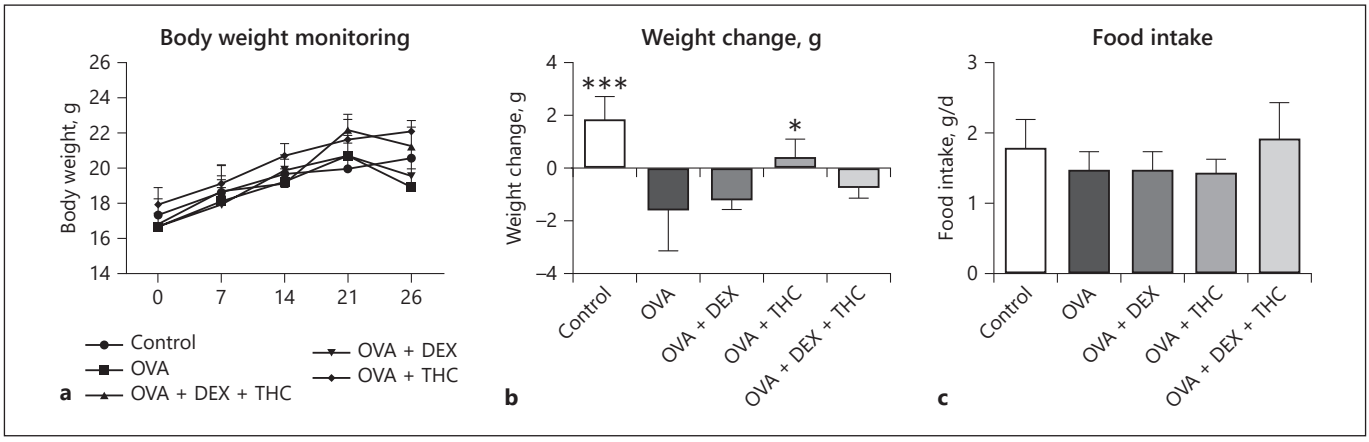

Fig. 2. Effects of the combination therapy (THC + DEX) on the body weight changes of asthmatic mice. **a** Body weight of each mouse was monitored on days 0, 7, 14, 21, and 26. **b** Body weight changes before and after OVA challenge. **c** Food intake of each group. Data are represented by mean ± SD, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with the OVA group. THC, tetrahydrocurcumin; OVA, ovalbumin; DEX, dexamethasone.

14. Second step: mice were challenged with 5% aerosolized OVA and 20 μL of intranasal OVA solution (40 mg/mL) from days 21–25. Experimental mice were fed an AIN-93G diet (Medicience Ltd., Jiangsu, China) and randomly divided into 5 groups (Fig. 1), including the control group (PBS only), OVA group (OVA-induced asthmatic mouse model), OVA + DEX (Sigma-Aldrich) group (2.5 mg/kg DEX), OVA + THC (Toronto Research Chemicals, Toronto, ON, Canada) group (0.08% THC mixed into the AIN-93G diet), and OVA + DEX + THC group (2.5 mg/kg DEX + 0.08% THC mixed into the AIN-93G diet). All experiments were approved by the Animal Ethics Committee of Sun Yat-sen University with license number SYXK Yue 2017-0080.

Body Weight Monitoring and Evaluation of the Nasal Symptom

The body weights and food intakes of each mouse were recorded every other day, and the body weight changes were evaluated before and after OVA challenge. After the final OVA challenge, rubbing frequencies of each mouse were counted within 10 min.

Histologic Analysis of Lungs

Fixed lung samples were embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin (H&E) or periodic acid-Schiff (PAS). The eosinophil infiltration was evaluated, and the goblet cell hyperplasia and mucus production were quantified as PAS-positive area ratio using ImageJ software (version 1.47, Media Cybernetics, Rockville, MD, USA).

T-Cell Subsets Analyzed by Flow Cytometry Assay

The single-cell suspension was prepared from fresh lung tissues and subsequently stimulated with Cell Stimulation Cocktail (including phorbol 12-myristate 13-acetate (PMA), ionomycin, brefeldin A, and monesin) for 5 h. Cell surface and nucleus staining were performed by monoclonal antibodies to determine the different T-cell subsets, including Th1 ($CD3^+$ $CD4^+$ IFN-γ^+), Th2 ($CD3^+$ $CD4^+$ IL-4^+), Th17 ($CD3^+$ $CD4^+$ IL-17^+), and Treg ($CD3^+$ $CD4^+$ $CD25^+$ $Foxp3^+$) cells. Monoclonal antibodies CD3e (PE-eFluor® 610), CD4 (APC-eFluor® 780), CD8a (FITC), IFN-gamma (APC), IL-17A (PE), IL-4 (PE-Cyanine7), CD25 (PE-Cyanine7), IL-10 (APC), and Foxp3 (PE) were purchased from eBioscience (San Diego, CA, USA). All data were acquired in FACSCalibur (BD, San Jose, CA, USA) and analyzed by FlowJo software (Treestar, San Carlos, CA, USA).

Cytokine Assay from Bronchoalveolar Lavage Fluid

Bronchoalveolar lavage fluid was collected immediately after euthanizing by cannulating the trachea, instilling with sterile saline, and the return lavage fluid should be more than 70%. The operations were repeated for 3 times. The concentrations of T-cell-related cytokines IL-4, IL-5, IL-13, IFN-γ, IL-17A, and IL-10 in bronchoalveolar lavage fluid were quantified by ELISA kits (eBioscience, San Diego, CA, USA) according to the manufacturers' protocols, and each cytokine was read at the absorbance of 450 nm using a multifunctional microplate detector (Tecan Spark 10M, Tecan, Männedorf, Zürich, Switzerland).

Statistical Analysis

Measurement data were represented by mean ± SD, and statistical analysis was carried out using SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). GraphPad Prism 7 software was used for statistical mapping. One-way ANOVA was performed followed by the Tukey-Kramer post hoc test for multiple comparisons. Data were considered to be significant when $p < 0.05$.

Results

THC but Not DEX or Combination Therapy Reversed Weight Loss in Mice Induced by OVA Challenge

Body weights of all mice were comparable at baseline and increased steadily from day 0–21. After OVA challenge, a marked decrease in mouse weight was observed compared to the controls. Dietary supplementation with

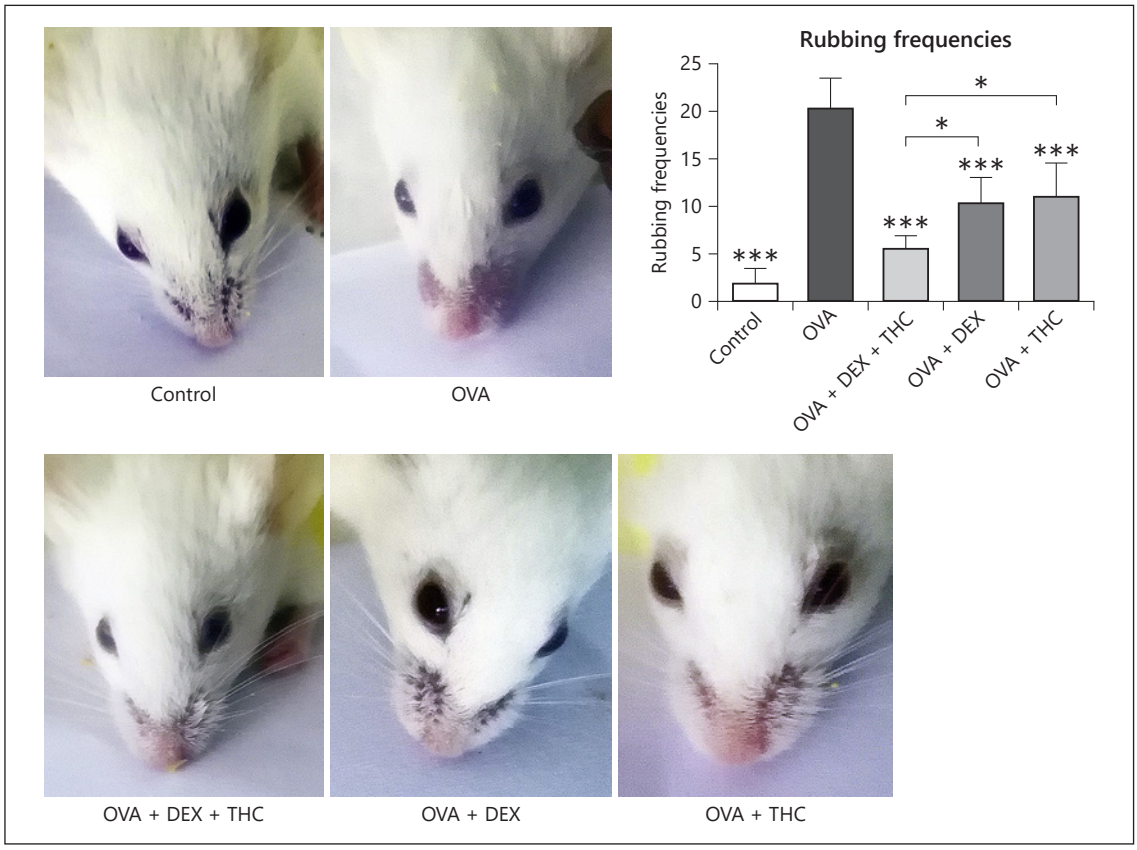

Fig. 3. Effects of the combination therapy (THC + DEX) on nasal symptoms. Representative pictures in each group are displayed, and the rubbing frequencies are evaluated after OVA challenge. Data are represented by mean ± SD, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with the OVA group. THC, tetrahydrocurcumin; OVA, ovalbumin; DEX, dexamethasone.

THC restored the weight loss induced by OVA challenge; however, weight loss was still observed in mice that received DEX or combination therapy (Fig. 2a, b). Food intake during the whole experiment showed no difference among groups (Fig. 2c).

THC plus DEX Treatment Showed a Lower Frequency of Nose Rubbing Than Monotherapy in Asthmatic Mice

Allergic rhinitis is a common event in asthmatic patients [18]; therefore, inflammatory responses in the upper airway should be noted as well. The rubbing frequencies of OVA group mice increased significantly after OVA challenge, and severe loss of bristles around the noses were observed. THC or DEX monotherapy alone significantly reduced the rubbing frequency compared to the OVA group, and the effects were comparable. Combination therapy showed a stronger inhibitory effect on the rubbing frequency than DEX or THC treatment alone (Fig. 3).

THC Plus DEX Treatment Showed Stronger Effects Than Monotherapy on Alleviation of Lung Inflammation

Lung tissues were stained by H&E and PAS for the evaluation of eosinophil levels and mucus production, respectively. Compared to the controls, higher eosinophil infiltration and mucus hyperproduction were observed in OVA-induced asthmatic mice. Monotherapy with either THC or DEX alone significantly reduced the number of eosinophils and the hyperproduction of goblet cells compared with the OVA group (Fig. 4a–d). The combination of THC and DEX treatment could not further reduce the eosinophil number but could decrease mucus production compared with mice treated with THC or DEX alone (Fig. 4a–d).

THC Plus DEX Treatment Was More Effective Than Monotherapy in Inhibiting Th2 and Th17 Cells

T-cell subsets in lung tissues were detected by flow cytometry, and the results showed that compared to the

controls, percentages of Th2 ($CD3^+CD4^+IL\text{-}4^+$) and Th17 ($CD3^+CD4^+IL\text{-}17A^+$) cells were elevated after OVA challenge. THC or DEX monotherapy showed comparable effects on reducing the percentages of Th2 and Th17 cells, and combination therapy showed stronger effects than DEX or THC treatment alone (Fig. 5a–c, f, g). No significant differences were noticed in the percentages of Th1 and Treg cells between the control, OVA-induced, and THC- or DEX-treated groups (Fig. 5d, e, h, i).

THC Plus DEX Treatment Showed Stronger Inhibitory Effects Than Monotherapy on Local Th2 and Th17 Cytokine Production

The Th2-related cytokines IL-4, IL-5, and IL-13 and the Th17 cytokine IL-17A were significantly increased after OVA challenge compared to the controls. THC or DEX monotherapy reduced the levels of IL-4, IL-5, IL-13, and IL-17A in BALB/c mice compared to the OVA group, and the inhibitory effects between THC and DEX treat-

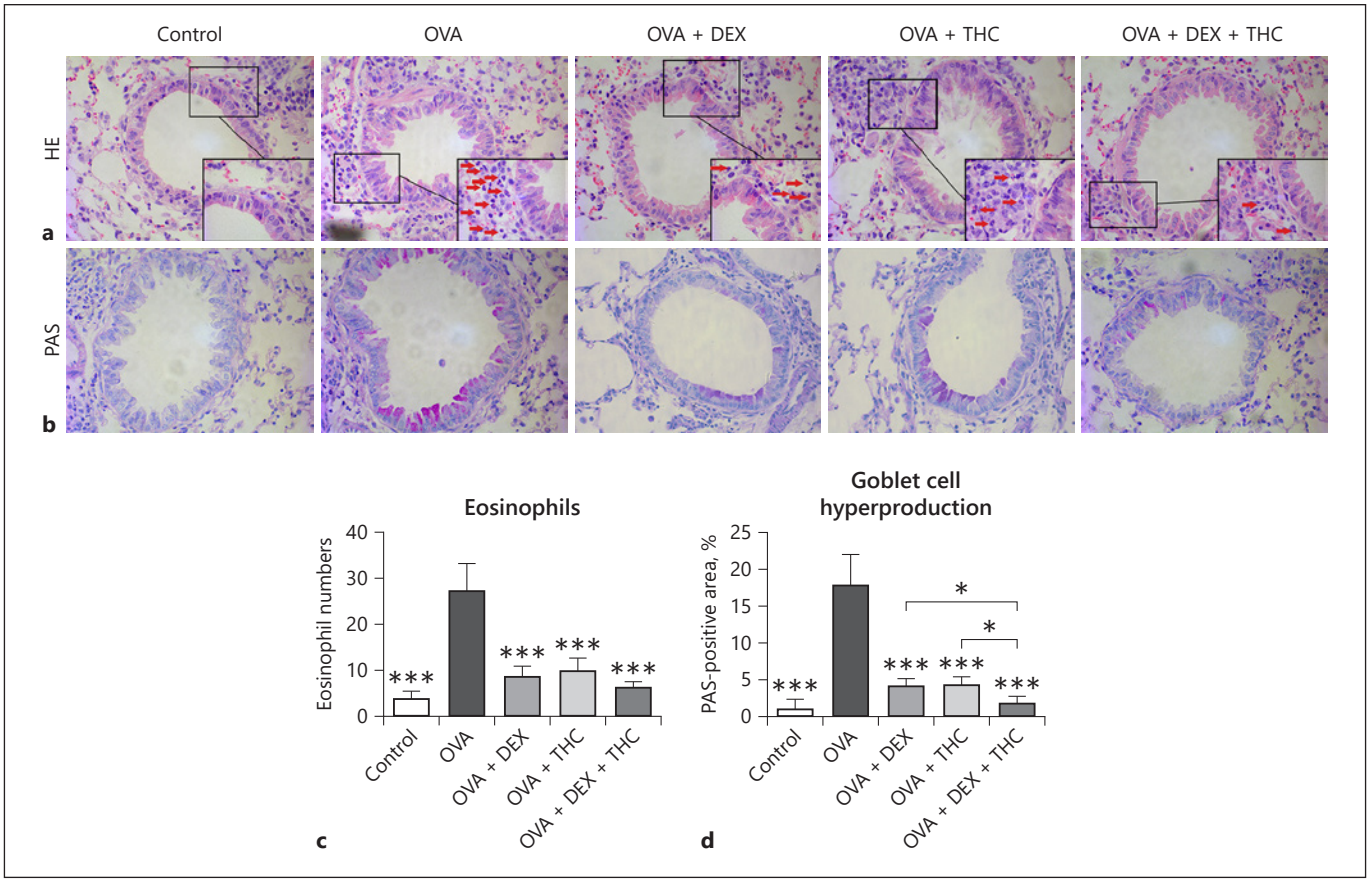

Fig. 4. Effects of the combination therapy (THC + DEX) on histopathology changes of lungs. Representative pictures of each group stained by H&E (**a**) and PAS (**b**) are shown; the red arrows point the eosinophils, original magnification ×400, scale bar, 50 μm. The bar charts demonstrated the infiltrations of eosinophils (**c**) and the percentages of PAS-positive area (**d**). Data are represented by mean ± SD, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ compared with OVA group. THC, tetrahydrocurcumin; OVA, ovalbumin; DEX, dexamethasone; H&E, hematoxylin and eosin; PAS, periodic acid-Schiff.

Fig. 5. Effects of the combination therapy (THC + DEX) on T-cell subsets in the lungs of asthmatic mice. **a** Cells were gated by a CD3+ CD4+ population. The representative pictures of Th1 (**b**), Th2 (**c**), Th17 (**d**), and Treg (**e**) cells are presented as scatter plots, and their bar charts are shown in (**f–i**) respectively. Data are represented by mean ± SD, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ compared with OVA group. THC, tetrahydrocurcumin; OVA, ovalbumin; DEX, dexamethasone.

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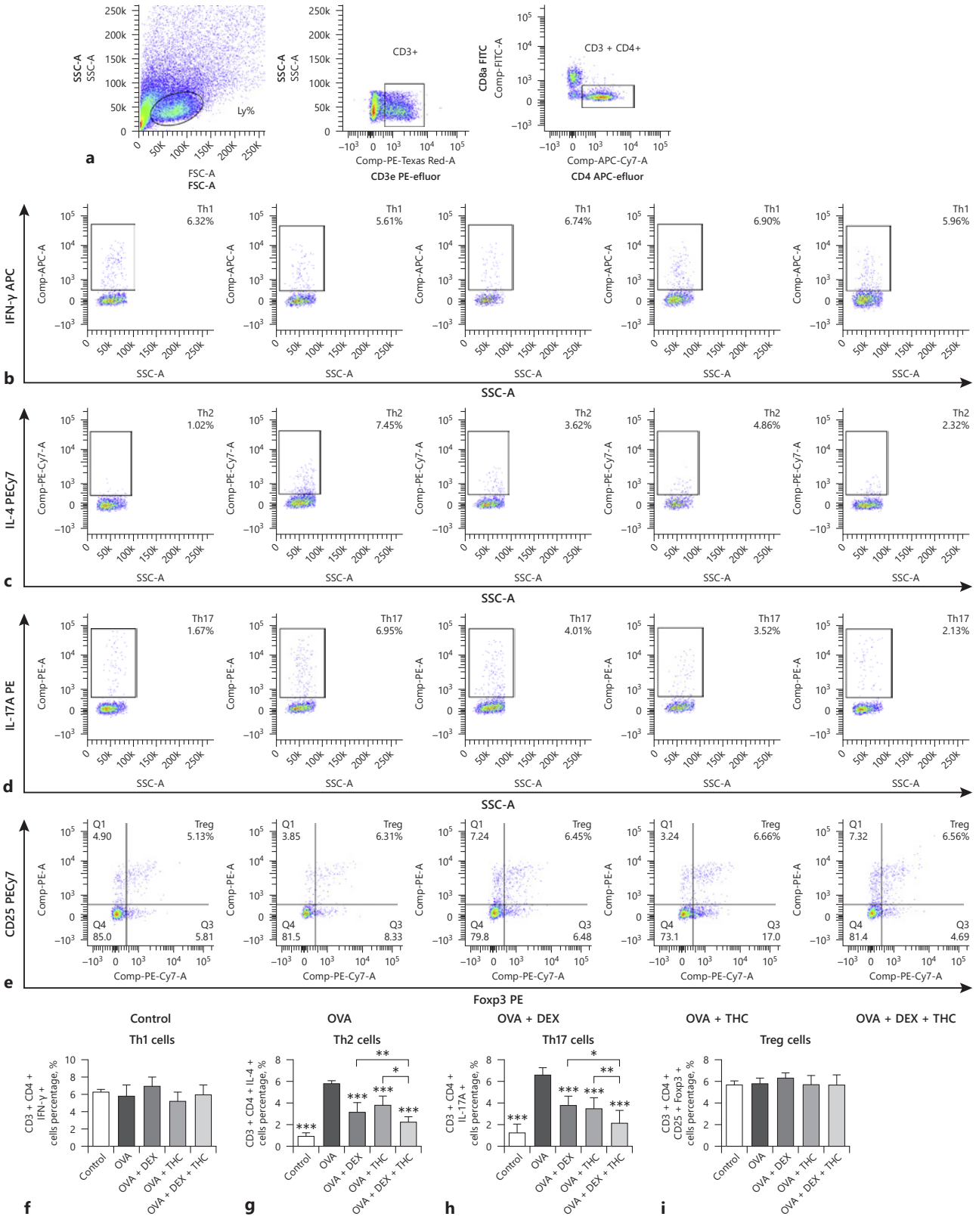

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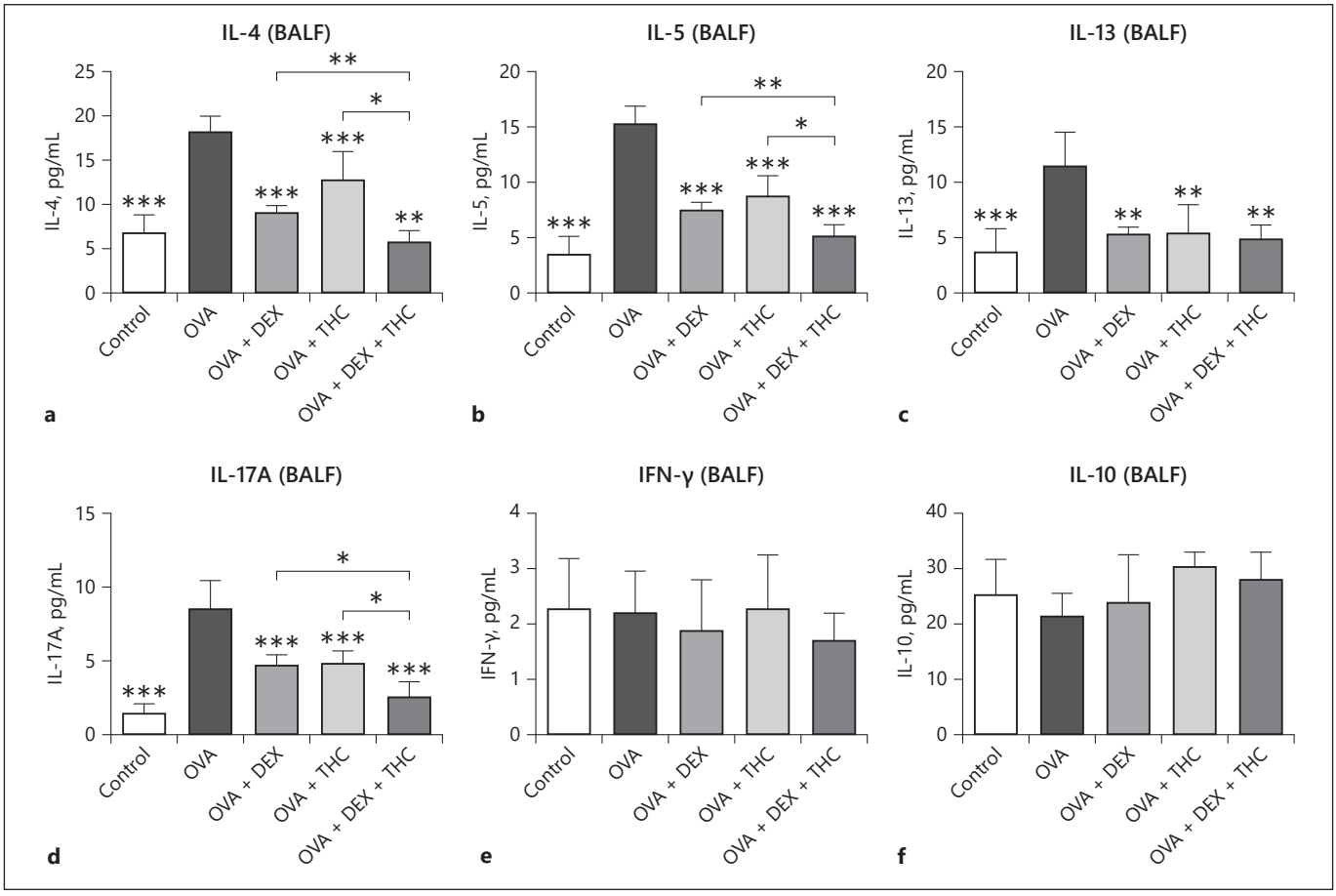

Fig. 6. Effects of the combination therapy (THC + DEX) on cytokine levels in BALF. Th2-related cytokines IL-4 (**a**), IL-5 (**b**), and IL-13 (**c**), and Th17 cytokines IL-17A (**d**), Th1 cytokines IFN-γ (**e**), and Treg cytokines IL-10 (**f**) were evaluated by ELISA. Data are represented by mean ± SD, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ compared with OVA group. THC, tetrahydrocurcumin; OVA, ovalbumin; DEX, dexamethasone; BALF, bronchoalveolar lavage fluid.

ment were comparable (Fig. 6a–d). IL-4, IL-5, and IL-17A but not IL-13 levels in mice that received combination therapy were lower than those in the monotherapy group (Fig. 6a–d). No differences in the levels of IFN-γ and IL-10 were observed among the control, OVA-induced, or THC- or DEX-treated groups (Fig. 6e, f).

Discussion

In the current study, our results from asthmatic mice showed that dietary supplementation with THC had effects similar to DEX treatment on alleviating nasal symptoms, lung pathological changes, and airway inflammation (Th2 and Th17 cells as well as related cytokines). Importantly, THC improved the therapeutic effects of DEX compared to monotherapy (THC or DEX only) manifested by fewer rubbing frequencies, lower mucus production, and a smaller Th2 and Th17 response. These results suggested that the therapeutic effects of combination therapy were superior to monotherapy, and dietary supplementation with THC has a potential application for clinical use as an alternative or add-on therapeutic strategy.

Although GC therapy is commonly applied in allergic airway inflammation, such as asthma and allergic rhinitis, some limitations of GCs still exist; for example, the current guidelines on dosing vary between countries, and side effects should not be ignored [19]. To maximize therapeutic effects while minimizing potential side effects, combination therapies with GCs have been explored, including other drugs [14], supplementary measures such as hypergravity [20] and nutrients [15]. Among these op-

tions, dietary nutrients might be the most convenient and safe. The superiority of combination therapy with nutrients and DEX compared to monotherapy could (1) improve the therapeutic effects of DEX, (2) decrease the dosage of DEX in the clinic, and (3) prevent or attenuate DEX-induced adverse effects.

The data presented in this study showed that the therapeutic effects between THC and DEX were comparable; both THC and DEX alleviated nasal symptoms and pathological lung changes and Th2 and Th17 responses. In addition, THC may have better safety prospects than DEX since its precursor, curcumin, is well tolerated in humans at even the high dose of 12 g per day [21], and toxicity studies in rats showed no harmful effects of THC at up to 400 mg/kg/day. Interestingly, THC but not DEX significantly reversed the weight loss induced by OVA challenge, probably due to the modulatory effects of THC on glucose and adipose metabolism [22]. Thus, THC might be considered an alternative therapy for allergic asthma.

Our previous study demonstrated that the immunemodulating properties of THC against asthma were at least partly targeted to the inhibitory effects of the Th2 response by suppressing the IL-4Rα-Jak1-STAT6 and Jagged1/Jagged2-Notch1/Notch2 pathways [10]. Similarly, DEX treatment significantly decreased the number of eosinophils, Th2 cells, and Th2 cytokines [23]. Therefore, a synergistic effect may exist between THC and DEX. GCs have been used via intramuscular or intravenous injection with the dose ranging widely from 2.5 to 80 mg/kg [24, 25]. We chose a relatively low dose of DEX for our experiments, and the therapeutic effects were enhanced when combined with THC. In addition, despite the lack of direct evidence, THC prevented symptoms that occur as side effects after GC treatment [15, 16], such as the deterioration of articular cartilage [26], the alleviation of vascular dysfunction and high blood pressure [27]. These findings suggested a potential protective role of THC against side effects caused by GCs, and the combination therapy of THC and DEX might be safer than DEX alone in the treatment of allergic asthma. Whether a higher dose of THC could further enhance the therapeutic effects of DEX and reduce side effects remains unknown, and more pharmacological experiments in the next stage should be performed.

In conclusion, our study demonstrated an enhancement of the therapeutic effects by combining THC and DEX to treat allergic asthma, and the effects between THC and DEX were comparable. Combination therapy with THC and DEX could have advantages in therapeutic implications as follows: (1) higher therapeutic effects than monotherapy; (2) reduced use of glucocorticoids; and (3) relief from side effects caused by GCs. Additional studies are still needed to evaluate the clinical effectiveness of this combination in humans.

Statement of Ethics

All experiments involving animals in the study were approved by the Animal Ethics Committee of Sun Yat-sen University with license number SYXK Yue 2017-0080.

Disclosure Statement

The authors declared that no conflict of interest exists.

Funding Sources

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Author Contributions

Y.Y. and C.W.L. designed the study. Y.F.W., Q.L., X.Y.Y,. and X.Z. performed sample processing and experiments. Y.L.S., X.Y.G., L.X., and L.S. analyzed the results. Y.F.W. and Y.Q.C. wrote the manuscript. Y.Y. and C.W.L. revised and edited the manuscript. All authors read and approved the final manuscript.

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