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ORIGINAL ARTICLE

Oral administration of *Lactobacillus plantarum* CQPC11 attenuated the airway inflammation in an ovalbumin (OVA)-induced Balb/c mouse model of asthma

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Abstract

This study investigated the antiasthmatic and anti-inflammatory effects of *Lactobacillus plantarum*-CQPC11 (LP-CQPC11) on ovalbumin (OVA)-induced asthmatic Balb/c mice. Administration of different doses of LP-CQPC11 (10^5, 10^7, and 10^9 colony-forming unit [CFU]/mouse) effectively reduced airway hyperresponsiveness (AHR) and the lung W/D ratio in asthmatic mice. LP-CQPC11 treatment reduced the accumulation of inflammatory cells in the BALF and attenuated histologic edema in asthmatic mice. Administration of LP-CQPC11 decreased the serum levels of OVA-specific IgE, IgE, and OVA-specific IgG1. LP-CQPC11 treatment decreased the levels of inflammatory cytokines (TNF-α, IL-4, IL-13, IL-5, and IL-6) in the BALF of asthmatic mice. In addition, LP-CQPC11 also elevated the mRNA levels of *Foxp3* and *T-bet* and decreased the mRNA levels of *Gata3* and *RORγt* in asthmatic mice lungs. Administration of LP-CQPC11 also reduced OVA-induced oxidative stress by improving the activities of GSH-Px, SOD, and catalase in the lungs. Finally, LP-CQPC11 treatment also significantly decreased the activation of the NF-κB pathway to modulate the inflammatory reaction in the lungs of asthmatic mice. The results from this study clearly demonstrated that oral administration of LP-CQPC11 exhibited outstanding activity in attenuating OVA-induced asthma in a mouse model. Furthermore, LP-CQPC11 may be an effective microecologic agent in preventing allergic asthma in the future.

Huan Lan and Zhongyu Gui contributed equally to this study.

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Practical applications

Allergic asthma is a common chronic inflammation-associated respiratory disease. Lactic acid bacteria (LAB) are known as a health product involved in modulating immune tolerance and play important roles in disease prevention and treatment. Many studies have reported that LAB, as probiotics, exhibits great antioxidation, anticancer, and anti-inflammatory activities and have health benefits in gastrointestinal disorders. In fact, human studies have confirmed that *Lactobacillus rhamnosus* strains have an effective activity to reduce the risk of allergic asthma. LP-CQPC11 was isolated from Sichuan pickled cabbages (a type of LAB-fermented vegetable product, also called Sichuan paocai) and was reported to reduce D-galactose-induced aging in mice in our previous study. However, the antiasthmatic and anti-inflammatory activities of LP-CQPC11 are unclear. The current study investigated the antiasthmatic and anti-inflammatory effects of LP-CQPC11 on OVA-induced asthmatic Balb/c mice.

KEYWORDS
asthma, inflammation, *Lactobacillus plantarum* CQPC11, NF-κB, OVA

1 | INTRODUCTION

As a common chronic inflammation-associated respiratory disease, allergic asthma is characterized by airway inflammation with abnormally increased asthma-specific immunoglobulin (Ig) E levels and typical T helper type (Th) 2 cytokine generation, eosinophilic infiltration, airway structural changes and remodeling, reversible airway obstruction, mucus hypersecretion, and airway hyperresponsiveness (AHR) (Walsh, 2017). In general, tobacco use, food allergies, environmental pollution, and genetic susceptibility are referred to as the main factors in asthma. Epidemiologic data suggest that approximately 273 million people suffer from total asthma (including asymptomatic and symptomatic asthma) worldwide, with about 1,000 people die every day (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Recently, the prevalence and incidence of allergic asthma have increased in many countries (Ellwood et al., 2017). In China, there are over 30 million children and adults with asthma (the overall prevalence of asthma is 4.2%) and approximately 200,000 patients die of asthma per year (Huang, K. et al., 2019; Huang, L. et al., 2019).

It is well known that many kinds of cells and their secreted cytokines are related to the pathogenesis of asthma. An imbalance in Th1/Th2/Th17 responses has been proven to play a vital part during the pathogenetic process of allergic asthma (Zhu et al., 2016). Actually, abnormal increases in the serum and bronchoalveolar lavage fluid (BALF) levels of Th2 cytokines, including interleukin (IL-5, IL-4, and IL-13), promote the development of asthma (Walsh, 2018). IL-13 and IL-4 can directly induce the secretion of IgE and reduce the generation of Th1 cells (Moran & Pavord, 2020). IL-13 and IL-5 induce eosinophils (EOCs) to differentiate and cause the accumulation of EOCs in the lungs (Wu, C. T. et al., 2019). IL-13 also induces the differentiation of T cells into Th2 cells, promotes the secretion of eotaxin and mucus, stimulates fibroblast proliferation, and participates in airway remodeling (Walsh, 2017). Recent studies have shown that Th17 cells play critical roles in allergic responses and some autoimmune inflammatory diseases. Activated Th17 cells secrete some inflammatory cytokines (such as IL-6, TNF-α, IL-22, IL-17A, and IL-17F) and promote the inflammatory reaction in asthma (Lambrecht & Hammad, 2015). IL-17 can recruit neutrophils (NEUs), induce bronchial eosinophilic infiltration, and aggravate the symptoms of asthma (Gurczynski & Moore, 2018). In addition, IL-23 is the central signaling mediator that promotes the generation of IL-17, IL-22, and IL-6 and maintains the function of Th17 cells in some inflammatory diseases, especially asthma (Cheng et al., 2016; Nakajima & Hirose, 2010).

On the other hand, T regulatory cells (Tregs), as the major immunosuppressive factor, modulate the inflammatory response in the course of asthma (Josefowicz et al., 2012). Activation of Tregs significantly decreases high AHR levels, reduces the generation of IL-13 and IL-5, and attenuates the accumulation of EOCs in the BALF of mice exposed to OVA (Joetham et al., 2017). Forkhead box P3 (Foxp3) is the main transcription factor that promotes the development of Tregs and maintains its normal functions. Activated Foxp3 helps Tregs generate IL-10 and transform growth factor-beta (TGF-β) to regulate immune tolerance (Zhang, 2018). In contrast, ROR-γt is an important factor that controls the activation of the Th17/IL-17 pathway, which promotes Th17 cells differentiation and maintains the generation of cytokines in the IL-17 family (Kim et al., 2017). Gata-binding protein 3 (GATA3), a specific transcription factor for maintaining the biologic activity of Th2 cells, promotes the production of Th2 cytokines (Zheng & Flavell, 1997). However, the differentiation of Th2 cells is blocked by activating the Th1-specific transcription factor T box transcription factor (T-bet) (Szabo et al., 2000).

Lactic acid bacteria (LAB) are known as a health product involved in modulating immune tolerance and play important roles in disease prevention and treatment (Kich et al., 2016; Liu et al., 2018). Many studies have reported that LAB, as probiotics, exhibits great antioxidation, anticancer, and anti-inflammatory activities and have health benefits in gastrointestinal disorders (Lee & Kim, 2020; Nowak et al., 2019; Suo et al., 2018; Wang et al., 2017; Zhao, Qian, et al., 2019; Zhao, Yi, et al., 2019). Inhaled glucocorticosteroids, long-acting bronchodilators (such as β receptor agonists, anticholinergics, and methylxanthine), and antihistamines are currently recognized as effective agents for asthma treatment in the clinic (Papadopoulos et al., 2022). However, long-term use of inhaled glucocorticosteroids or bronchodilators has some side effects such as osteoporosis and immunodeficiency (Barnes, 2011). Increasing evidence has indicated that modulating the gut microbiota may attenuate allergic asthma by affecting the "gut-lung axis" (Ver Heul et al., 2019; Zhang et al., 2018). Recently, oral administration of *Lactobacillus* strains (such as *L. rhamnosus* GG, *L. plantarum* K37, *L. salivarius* PM-A0006, and *L. bulgaricus* N45.10) was shown to exhibit beneficial health effects against allergic asthma in animal studies (Anatriello et al., 2019; Liu et al., 2014; Wu et al., 2016; Wu, C. T. et al., 2019; Zhang, 2018). In fact, human studies have confirmed that *L. rhamnosus* strains have effective activity to reduce the risk of allergic asthma (Cabana et al., 2017; Wickens et al., 2018).

LP-CQPC11 was isolated from Sichuan pickled cabbages (a type of LAB-fermented vegetable product, also called Sichuan paocai) and was reported to reduce D-galactose-induced aging in mice in our previous study (Qian et al., 2018). However, the antiasthmatic activities of LP-CQPC11 are unclear. Among many kinds of experimental animal models of asthma, the OVA-induced allergic asthma model is a classic model characterized by high levels of Th2 cytokines and IgE in the serum and BALF (Haspeslagh et al., 2017). To better understand the biologic activity of LP-CQPC11, we investigated the effect of LP-CQPC11 treatment on anti-inflammatory and antiasthmatic activities using the OVA-induced experimental asthmatic mouse model in the present study.

2 | MATERIALS AND METHODS

2.1 | Chemical agents

RT-qPCR kit (T2210-200T) was provided by Solarbio Life Science Co., Ltd (Beijing, China). OVA was provided by Tokyo Chemical Industry Co., Ltd. (Shanghai, China). Lactobacilli De Man, Rogosa, and Sharpe (MRS) broth medium was provided by Invitrogen Life Science Co., Ltd (Carlsbad, CA, USA). Commercial kits for evaluating superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), myeloperoxidase (MPO), and malondialdehyde (MDA) were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). The other chemical reagents were of analytical reagent.

2.2 | Preparation of a microbial strain

LP-CQPC11 was a kind gift from Dr. Zhao Xin (Chongqing Collaborative Innovation Center for Functional Food, Chongqing University of Education, Chongqing, China) and was preserved in the China General Microbiological Culture Collection Center (CGMCC, Beijing, China; preservation number: CGMCC 14960). For preparation of LP-CQPC11, the bacterial strain was first incubated with MRS growth medium at 30°C for 16–20 hr. After that, the culture medium was centrifuged (1,000 × *g* for 10 min at 4°C) and collected by a refrigerated centrifuge (X-22R, Indianapolis, IN, USA). All the cell pellet was harvested by washing (PBS, pH 7.4) for twice and then stored at −80°C for further study.

2.3 | Experimental animals

A total of 35 Balb/c mice (female, 5–6 weeks old, 20–22 g) were obtained from Hunan SJA Laboratory Animal Co., Ltd. Animals were housed under pathogen-free conditions (light/dark:12 hr/12 hr, 25 ± 1°C) and had free access to the water and standard mice chow. The animal protocol was examined and approved by the Institutional Animal Care and Use Committee, Guilin Medical University (GLMC-201905041) before being conducted.

2.4 | Experimental design and animal grouping

A total of 35 mice (n = 7 mice/group) were assigned to a group of normal mice, a group of model mice (OVA-induced asthmatic mice without treatment), and a group of treated mice (asthmatic mice administered different doses of LP-CQPC11). Experimental asthma mice were induced using the method previously described with a modification (Song et al., 2019). The mice were sensitized by intraperitoneal injection (100 μl/mouse) of inducer (0.05% aluminum hydroxide solution mixed with 20 μg OVA) on Day 1 and Day 14. After 1 week, the mice received an intranasal spray of a 1% OVA solution from 21 to 23 days. LP-CQPC11 was dissolved in a PBS solution (100 μl) and orally administered by gavage at different doses (10^5, 10^7, and 10^9 CFU/mouse) from Day 1 to Day 28. On Day 27, all mice were subjected to AHR evaluation. On the next day, all animals were euthanized with CO_2 asphyxiation. The right lung was quickly collected from all animals, the wet weight (W) and the dry weight (D) were recorded. The W/D ratio was then calculated.

2.5 | Determination of AHR levels

As the method described in previous study of our group (Song et al., 2019), the AHR levels were determined using noninvasive whole-body plethysmography (Buxco, Sharon, America; Model PLY 3211). In brief, all animals were housed in individual ventilated chambers and received an initial saline treatment to determine the

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baseline level of enhanced pause (Penh). Then, all mice were administered increasing concentrations of methacholine (3.125, 6.25, 12.5, 25, and 50 mg/ml) for 3 min, and the respiratory rate and Penh levels were computed.

2.6 | Tissue collection and histologic observation

Lung tissues were fixed in 10% buffered formalin (Servicebio), and subsequently, paraffin-embedded pulmonary samples were cut into cross-sections (4 μm). Paraffin slices were stained histochemical with hematoxylin & eosin (H&E) staining kit (Solarbio) and examined by a microscope (Leica DM4B).

2.7 | BALF collection and cell counting

The BALF was collected from the trachea by flushing of cold PBS (1 ml) and immediately centrifuged (1,000 × *g*, 10 min) at 4°C. Then, red blood cells (RBCs) were removed from the collected cells using RBC lysis buffer (Solarbio) and resuspended in normal PBS. The numbers of inflammatory cells (such as lymphocytes [LYMs], EOCs, NEUs, and macrophages [MACs]) in the BALF were determined by staining and counting using the Kwik-Diff Staining Kit (Thermo Fisher) according to the kit protocols.

2.8 | Measurement of the total anti-OVA IgE, IgE, anti-OVA IgG2a, and IgG1 levels in serum

To determine the serum levels of total IgE, anti-OVA IgE, anti-OVA IgG1, and anti-OVA IgG2a, blood was collected. Afterward, serum was obtained by centrifugation (3,000 × *g*, 10 min) with an X-22R refrigerated centrifuge (Beckman Coulter) at 4°C. The serum levels of total IgE (RXTY029), anti-OVA IgE (RXLQD12315), anti-OVA IgG1 (RXLQD12311), and anti-OVA IgG2a (RXLQD12312) were detected using the matched commercial enzyme-linked immunosorbent assay (ELISA) kits (Ruxin Biological Technology Co., Ltd., Quanzhou, Fujian, China).

2.9 | Measurement of cytokine concentrations in the BALF

The BALF levels of IL-4 (EK0405), IL-5 (EK0408), IL-6 (EK0411), IL-10 (EK0417), IL-13 (EK0425), and IL-23 (EK0466) were measured by the matched commercial ELISA kits (BOSTER). The BALF levels of C–C motif chemokine ligand (CCL)11 (MM-0195M2), CCL24 (MM-0880M2), and TGF-β (MM-0921M2) were measured by ELISA kits (MEIMIAN Biological Technology Co., Ltd., Jiangsu, China). The BALF levels of TNF-α (PT512), IFN-γ (P1508), and IL-17A (P1545) were measured by ELISA kits (Beyotime Biotechnology Co., Shanghai, China) based on industrial protocols.

2.10 | Measurement of p-NF-κBp65, NF-κBp65, IκBα, and p-IκBα in the BALF

The BALF levels of NF-κBp65 (ml058779) and p-NF-κBp65 (ml058778) were measured by ELISA kits (Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China) based on manufacturer's guidelines. The BALF levels of IκBα(ml058780) and p-IκBα (MM-45432M2) were measured by ELISA kits (Kete) based on industrial protocols.

2.11 | Quantitative reverse-transcription (qRT)-PCR assay

For qRT-PCR, extracted RNA (1 μg) from lung tissue was mixed with a reagent from a TaqMan One-Step RT-qPCR kit (Solarbio) according to the kit protocols and reacted using the QuantStudio™ 6 Flex Real-Time PCR System (Life Technologies) with conditions set to 50°C for reverse transcription, 95°C for 3 min for the initial denaturation, and followed by 35–50 cycles with denaturation at 95°C for 10 s, annealing at 56°C for 10 s, and extension at 72°C for 60 s. The relative expressions of the target gene were calculated with the $2^{-\Delta\Delta Ct}$ formula. Sequences of the primer were identical to those in our previous study (Song et al., 2019).

2.12 | Measurement of oxidative stress-related indices in mouse lung tissues

Lung tissue was shredded and lysed using precooling normal saline, and then homogeneously broken with a KZ-II high-speed homogenizer (Servicebio) at 4°C to determine the lung levels of oxidative stress-related indices. The levels of GSH-Px, catalase, SOD, MDA, and MPO in the lung tissue were detected by commercial kits.

2.13 | Western blot analysis

The protein of pulmonary tissue was extracted using precooled radioimmunoprecipitation assay (RIPA) reagent (P0013B, Beyotime) on ice. The extracted protein samples were subjected to centrifugation (13,000 × *g* for 20 min) with an X-22R refrigerated centrifuge at 4°C. After that, the protein concentrations of lung samples were measured by a BCA detection kit (P0012S, Beyotime), and then the samples were boiled at 98°C before further use. The total protein samples (20–50 μg) were separated by a BeyoGel™ 4%–20% SDS-PAGE precast gel (P0057B, Beyotime) for 90 min and then transferred to a polyvinylidene fluoride (PVDF) membrane. The membranes were then blocked with nonfat milk (5%) for 2 hr. Then, blocked membranes were washed three times using Tris-buffered saline containing 1% Tween-20 (TBS-T) (15 min/wash) and immediately incubated with the first antibodies (overnight at 4°C) NF-κBp65 (AF0246, Beyotime), phospho-NF-κBp65 (AF5875, Beyotime), IκBα (AF1282, Beyotime), phospho-IκBα (AF1870, Beyotime), heme

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oxygenase-1 (HO-1; AF1333, Beyotime), NF-E2-related factor 2 (Nrf2; AF7623, Beyotime), GAPDH (AF0006, Beyotime), and Lamin B1 (AF1408, Beyotime). After washed with three times of TBS-T solution, all membranes were further coincubated with an HRP-conjugated goat antirabbit IgG secondary antibody (Beyotime) for 45–60 min at 37°C. Following TBS-T washing three times, the blots were incubated with BeyoECL Plus (P0018S, Beyotime) and visualized with ChemiDoc XRS$^+$ Systems (Bio-Rad). Band densitometry was performed using ImageJ software (NIH, Bethesda, MD).

2.14 | Data collection and statistics

The results are presented as the mean ± *SD* and were statistically analyzed using SPSS 25.0 software (SPSS Inc., Chicago, IL). One-way ANOVA and Duncan's multiple range test were used to determine statistically significant differences between the treatments ($p < .05$).

3 | RESULTS

3.1 | Effect of LP-CQPC11 on AHR levels and the W/D ratio of the lungs

The Penh value is a well-known index to indicate levels of asthma in basic studies and clinical diagnoses (Nair et al., 2017). OVA-treated mice exhibited significantly elevated Penh values compared with normal mice ($p < .05$) (Figure 1). The different doses of LP-CQPC11 treatment significantly reduced the high AHR of asthmatic mice ($p < .05$). The A high dose of LP-CQPC11 (10^9 CFU/mouse) exhibited greater activity in reducing the Penh level than a moderate dose (10^7 CFU/mouse) or a low dose (10^5 CFU/mouse) in LP-CQPC11-treated asthmatic mice. As shown in Figure 1b, asthmatic mice had a higher W/D ratio than normal and LP-CQPC11-treated mice. Treatment with different doses of LP-CQPC11 significantly decreased the W/D ratio compared with no treatment ($p < .05$). The high dose of LP-CQPC11 (10^9 CFU/mouse) exhibited the strongest activity in reducing the W/D ratio among LP-CQPC11-treated mice ($p < .05$).

3.2 | Effect of LP-CQPC11 on histologic features of the lungs of asthmatic mice

OVA treatment significantly increases inflammatory cell infiltration into the perivascular and peribronchial areas and directly causes bronchial epithelium thickening and mucous membranes edema in mice. As shown in Figure 2, typical inflammatory cell infiltration and serious epithelial cell damage were seen in asthmatic mice lungs. However, all doses of LP-CQPC11 treatment decreased the infiltration of inflammatory cells into the bronchus of asthmatic mice. The high dose of LP-CQPC11 (10^9 CFU/mouse) also showed the best activity against inflammatory cell-induced epithelial cell damage in asthma mice lungs. In addition, administration of LP-CQPC11 also significantly decreased MPO activity in the inflamed lungs of asthma mice. The high dose of LP-CQPC11 (10^9 CFU/mouse) had better activity in reducing pulmonary MPO activity than the other doses (10^5 and 10^7 CFU/mouse) in asthma mice.

3.3 | Effect of LP-CQPC11 on the infiltration of inflammatory cells into the BALF of asthmatic mice

OVA treatment sharply elevated EOC, NEU, MAC, LYM, and total cell numbers in the BALF of asthmatic mice ($p < .05$) (Figure 3). The number of cells in the three groups of LP-CQPC11-treated mice was obviously lower than that in the only OVA-treated mice group ($p < .05$). In addition, administration of LP-CQPC11 significantly decreased the levels of EOCs, NEUs, MACs, and LYMs ($p < .05$). However, there were no significant differences between the moderate and low doses of LP-CQPC11 in the BALF levels of NEUs and LYMs ($p > .05$).

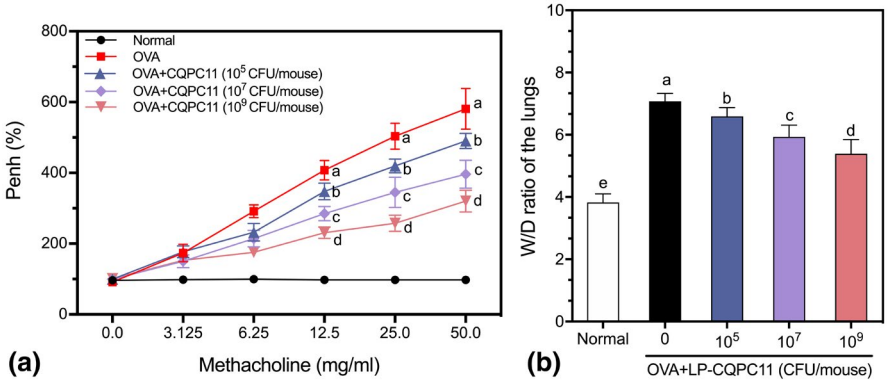


FIGURE 1 Effects of *Lactobacillus plantarum* CQPC11 on airway hyperresponsiveness (a) and the W/D ratio of the lungs (b) in OVA-induced allergic asthma Balb/c mice. Data are expressed as the mean ± *SD*. a–eBars with different letters differ significantly ($p < .05$), as determined by Duncan's multiple range test

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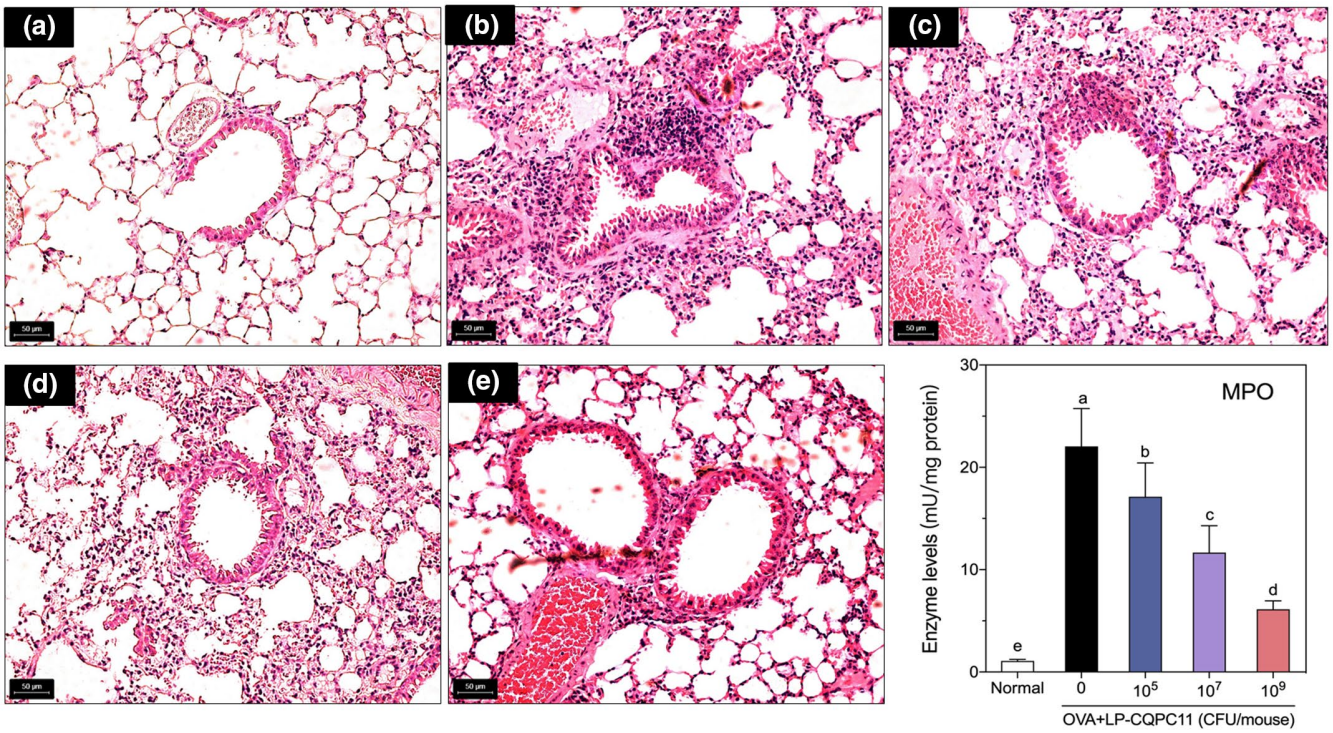


FIGURE 2 Histologic changes and MPO levels in the lung tissue of *Lactobacillus plantarum* CQPC11-treated OVA-induced allergic asthma Balb/c mice. The sections were observed using a Leica DM4B microscope at 200× magnification. Data are expressed as the mean ± *SD*. a–cBars with different superscript letters differ significantly ($p < .05$), as determined by Duncan's multiple range test. (a) Normal mice group, (b) OVA-treated asthma mice group, (c) OVA + LP-CQPC11 (10^5 CFU/mouse) treated mice group, (d) OVA + LP-CQPC11 (10^7 CFU/mouse) treated mice group, and (e) OVA + LP-CQPC11 (10^9 CFU/mouse) treated mice group

3.4 | Effects of LP-CQPC11 on the serum levels of total anti-OVA IgE, IgE, anti-OVA IgG1, and anti-OVA IgG2a in asthmatic mice

It is well known that elevated levels of IgE are a typical event during the course of asthma. The contents of total anti-OVA IgE, IgE, and anti-OVA IgG1 were significantly increased in the serum of asthmatic mice ($p < .05$) (Figure 4). Different doses of LP-CQPC11 treatment significantly decreased the generation of total anti-OVA IgE, IgE, and anti-OVA IgG1 compared with no treatment ($p < .05$). LP-CQPC11 treatment also induced the generation of anti-OVA IgG2a in asthmatic mice. The high dose of LP-CQPC11 (10^9 CFU/mouse) treatment showed the best activity than that in low and middle-dose LP-CQPC11-treated groups. However, there was no significant difference between the moderate (10^7 CFU/mouse) and low (10^5 CFU/mouse) doses of LP-CQPC11 in modulating the serum contents of anti-OVA IgG2a in mice with asthma.

3.5 | Effects of LP-CQPC11 on inflammation-related cytokines in the BALF of asthmatic mice

Asthma is an immunologic disease characterized by a misbalance in the Th1/Th2 immune reactions. Generally, Th2-type immune reactions mainly maintain and promote the pathogenesis of allergic asthma (Walsh, 2017, 2018). Elevated levels of Th2-like cytokines, including IL-5, IL-13, and, IL-4 promote inflammation in the lungs of asthma patients. Treatment with OVA significantly elevated the generation of Th2-like cytokines (IL-5, IL-13, and IL-4) in the BALF of asthma mice (Figure 5). However, oral administration of the high dose (10^9 CFU/mouse) of LP-CQPC11 significantly decreased the OVA-induced generation of IL-5, IL-13, and IL-4 in the BALF of asthmatic mice. In addition, LP-CQPC11 treatment also reduced the BALF levels of Th17-like cytokines (such as IL-17A and IL-23) and other inflammation-related cytokines (such as TNF-α, IL-6, and IL-23) in mice with asthma. In contrast, administration of LP-CQPC11 increased the BALF levels of the Th1-like cytokine IFN-γ and the Treg-like cytokines IL-10 and TGF-β. The infiltration of EOCs into the bronchi was associated with serious oxidative stress in the lungs of asthmatic mice. Administration of LP-CQPC11 was able to reduce the CCL11 and CCL24 (both typical markers of eosinophils) levels in the BALF of asthmatic mice.

3.6 | Effects of LP-CQPC11 on the mRNA levels of *Tbet*, *Foxp3*, *Gata3*, and *Rorγt* in the pulmonary tissue of asthmatic mice

The mRNA levels of *Tbet*, *Rorγt*, *Foxp3*, and *Gata3* in pulmonary tissue from asthmatic mice are shown in Figure 6. The mRNA levels

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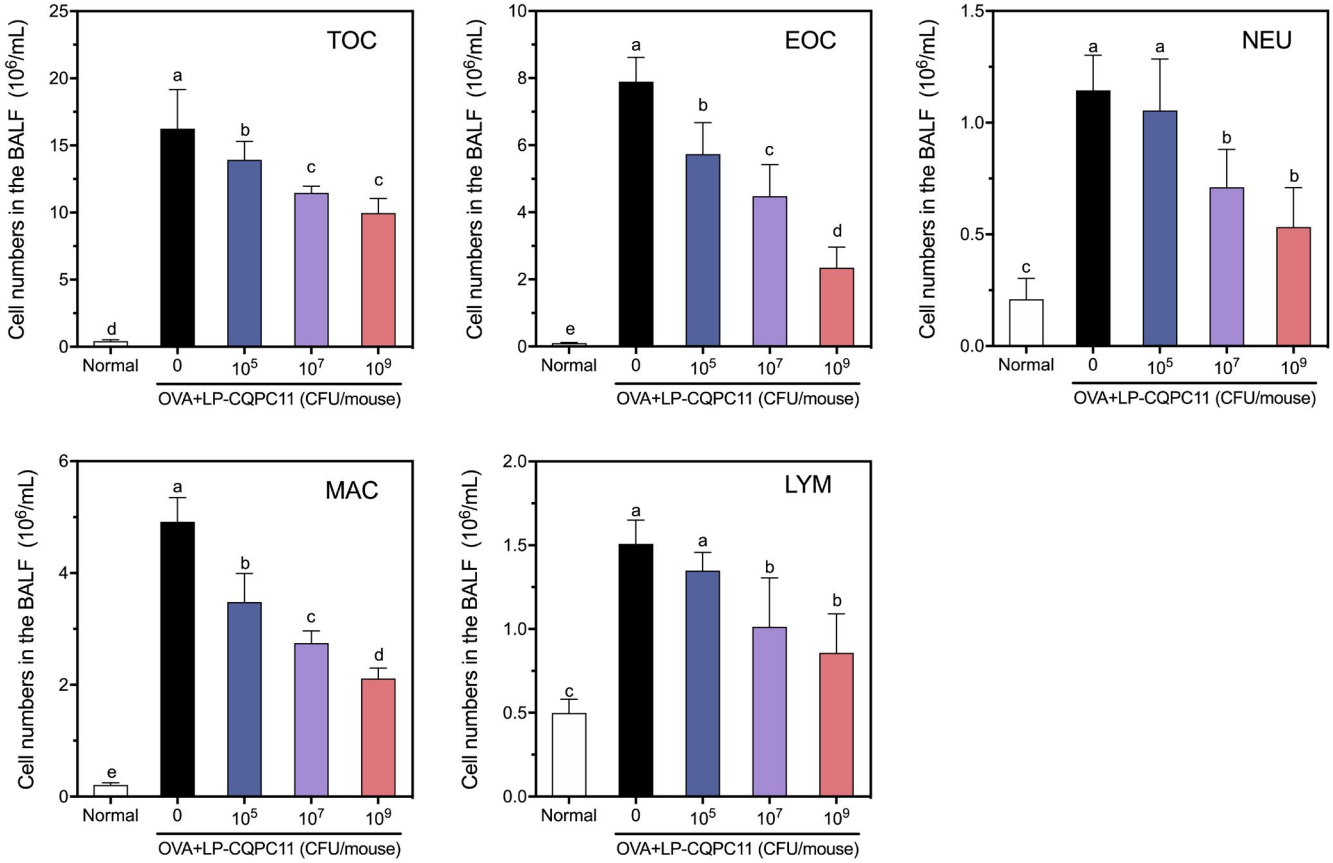


FIGURE 3 Effects of *Lactobacillus plantarum* CQPC11 on inflammatory cell counts in the BALF of OVA-induced allergic asthma Balb/c mice. Data are expressed as the mean ± *SD*. a–eBars with different superscript letters differ significantly ($p < .05$), as determined by Duncan's multiple range test. EOC, eosinophils; LYM, lymphocytes; MAC, macrophages; NEU, neutrophils

of *Tbet* and *Foxp3* were superiorly increased in the LP-CQPC11-treated asthmatic mouse group than that in control mice. The high dose of LP-CQPC11 (10^9 CFU/mouse) showed the strongest activity elevated in the mRNA levels of *Tbet* and *Foxp3* than other doses of LP-CQPC11 in asthmatic mice. OVA treatment also elevated the mRNA levels of *Rorγt* and *Gata3* in asthmatic mice lungs. The high dose of LP-CQPC11 (10^9 CFU/mouse) reduces the mRNA levels of *Rorγt* and *Gata3* better than the other doses of LP-CQPC11 (10^5 and 10^7 CFU/mouse).

3.7 | Effects of LP-CQPC11 on oxidative stress-related indices in the pulmonary tissue of asthmatic mice

Asthma is an oxidative stress-related disease associated with serious tissue damage (van der Vliet et al., 2018). OVA treatment induced significantly lessened in the activities of antioxidant enzymes, such as GSH-Px, SOD, and catalase, in asthmatic mice (Figure 7a). However, different doses of LP-CQPC11 treatment effectively elevated the activities of GSH-Px, SOD, and catalase in asthmatic mice. In LP-CQPC11-treated mice, the high dose (10^9 CFU/mouse) of LP-CQPC11 showed the strongest activity in promoting the activity of these antioxidant enzymes compared with the other doses. In addition, administration of LP-CQPC11 (especially the high dose of 10^9 CFU/mouse) also reduced oxidative stress-associated MDA generation in the lungs of asthmatic mice. The mRNA levels of SOD, catalase, and GSH-Px were also improved in asthma mice lungs (Figure 7b). The 10^9 CFU/mouse dose of LP-CQPC11 showed the best activity in increasing GSH-Px, SOD, and catalase activities compared with the doses of 10^5 and 10^7 CFU/mouse in asthmatic mice ($p < .05$). Both HO-1 and the transcription factor Nrf2 protein levels were decreased in asthmatic mice (Figure 7c). LP-CQPC11 treatment significantly enhanced the protein levels of HO-1 and Nrf2 in asthmatic mice lungs (Figure 7c).

3.8 | Effects of LP-CQPC11 on the protein levels of NF-κB p65 and p-NF-κBp65 in the pulmonary tissue of asthmatic mice

As shown in Figure 8a, the BALF levels of NF-κBp65, p-IκBα, and p-NF-κBp65 were increased sharply in asthmatic mice exposed to OVA. Following the different doses of LP-CQPC11 treatment, the BALF levels of p-NF-κBp65, NF-κBp65, and p-IκBα were significantly lower than those in untreated asthmatic mice. In addition,

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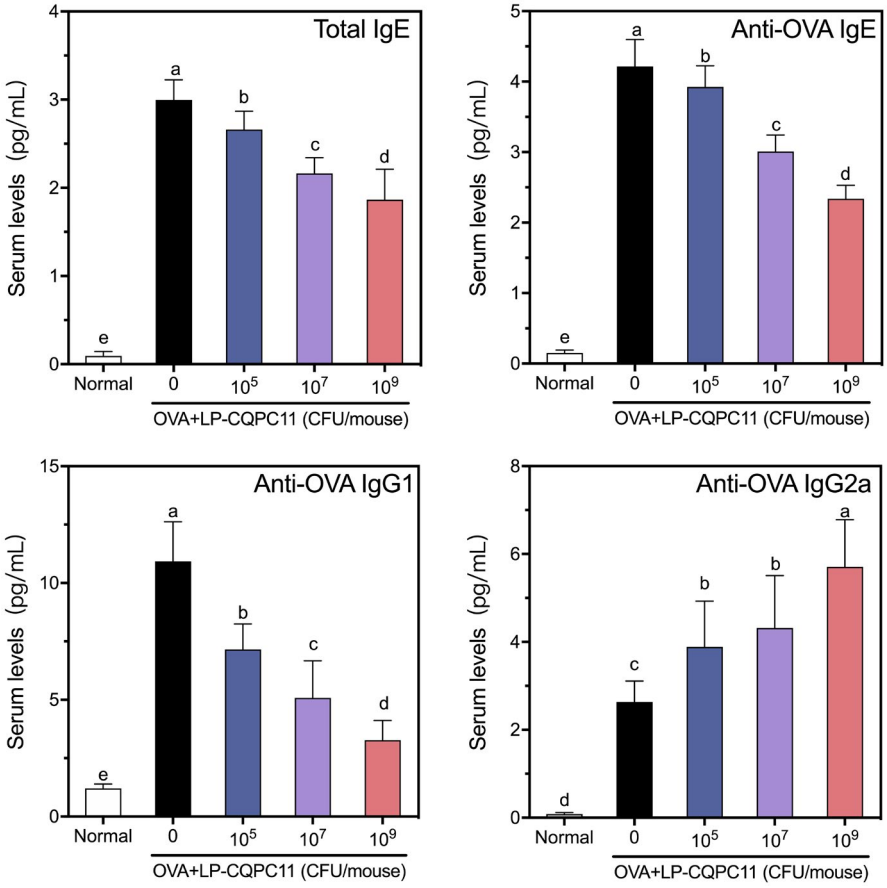


FIGURE 4 Effects of *Lactobacillus plantarum* CQPC11 on the serum levels of total IgE, anti-OVA IgE, anti-OVA IgG1, and anti-OVA IgG2a in OVA-induced allergic asthma Balb/c mice. Data are expressed as the mean ± *SD*. a–eBars with different superscript letters differ significantly ($p < .05$), as determined by Duncan's multiple range test

the protein levels of p-NF-κBp65 and p-IκBα were significantly increased in asthma mice lungs (Figure 8b). However, all doses of LP-CQPC11 treatment significantly decreased the p-NF-κBp65 and IκBα. The high dose (10^9 CFU/mouse) of LP-CQPC11 showed the strongest activity in decreasing the activation of the NF-κB pathway than the other doses of LP-CQPC11 in asthmatic mice.

4 | DISCUSSION

As a typical immunologic disease, the general treatment method for asthma is immunoregulatory therapy, which involves the use of corticosteroids. However, the use of corticosteroids only improves the symptoms of allergic asthma; it cannot completely cure asthma. On the other hand, corticosteroid therapy is also associated with some side effects and results in an increasing financial burden for patients. Recently, many studies have indicated that lactic acid bacteria may be effective immunoregulatory factor that can attenuate inflammation-related diseases, especially allergic asthma (Huang, K. et al., 2019; Huang, L. et al., 2019). In the current investigation, we attempted to appraise the potential antiasthmatic activities of LP-CQPC11 and investigate the potential mechanism using a model of experimental allergic asthma established in OVA-treated Balb/c mice.

We observed that oral administration of LP-CQPC11 improved the OVA-induced increase in the AHR levels. Our results were similar to those found in other LAB (such as *L. rhamnosus* GG and *L. plantarum* K37)-treated asthmatic mice (Liu et al., 2014; Wu et al., 2016; Wu, A. Y. et al., 2019). In addition, we also found that LP-CQPC11 treatment significantly decreased the W/D ratio in asthmatic mice.

The inflammatory reaction (such as the serious infiltration of inflammatory cells and edema) is generally known as the main event during the pathologic course of allergic asthma. The excessive accumulation of inflammatory cells, including NEUs, EOCs, MACs, and LYMs, is associated with promoting the generation of pro-inflammatory cytokines and chemokines and ultimately causes serious lung damage (McGregor et al., 2019). In this study, we observed the LP-CQPC11 treatment significantly attenuated the inflammation-induced edema and infiltration of inflammatory cells in the lungs of asthmatic mice. LP-CQPC11 treatment also significantly decreased the lung levels of MPO, which is a typical marker used to evaluate the activation of neutrophils and monocytes. In the observation of histologic changes, LP-CQPC11 treatment decreased the OVA-induced excessive accumulation of inflammatory cells, which causes serious inflammatory edema in asthmatic mice. We counted the number of total cells and classified cell types using Kwik-Diff staining of the BALF of asthmatic mice. Oral administration of

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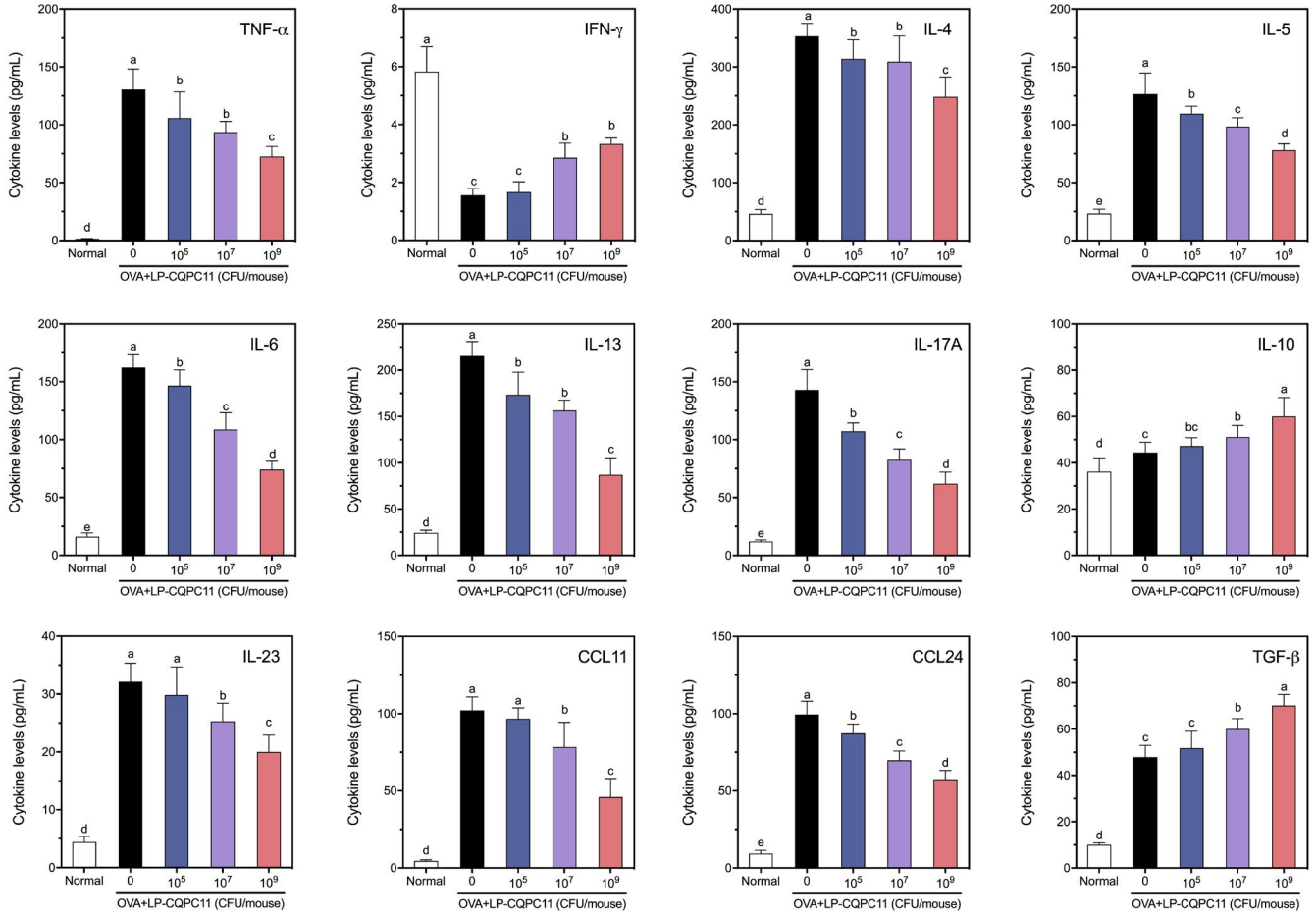


FIGURE 5 Effects of *Lactobacillus plantarum* CQPC11 on inflammation-related cytokine levels in the BALF OVA-induced allergic asthma Balb/c mice. Data are expressed as the mean ± *SD*. a–eBars with different superscript letters differ significantly ($p < .05$), as determined by Duncan's multiple range test

LP-CQPC11 significantly decreased the OVA-induced accumulation of EOCs, MACs, and LYMs, as well as total cells, in the BALF of mice with asthma. Our results were similar to those of other studies that reported that administration of *Lactobacillus* strains (such as *L. salivarius* PM-A0006, *L. bulgaricus* N45.10, *L. rhamnosus* GG, and *L. plantarum* K37) modulated the cell numbers in the BALF of asthmatic mice (Anatriello et al., 2019; Liu et al., 2014; Wu et al., 2016; Wu, C. T. et al., 2019; Zhang, 2018).

As we all know, EOCs act as a centrical role in the pathogenesis of asthma. Serious infiltration of EOCs into the bronchi and the associated induction of chronic airway inflammation are the main characteristics of asthma (Patel & Sur, 2017). The CC eotaxin chemokines, such as CCL26, CCL24, and CCL11, are potent chemoattractants in the recruitment of EOCs. CCL24 and CCL11 promote the migration of EOCs into the lungs, and CCL11 promotes the accumulation and degranulation of EOCs (Provost et al., 2013). Activation of EOCs can lead to the degranulation of mast cells, aggravate bronchial inflammation, and cause bronchial remodeling (McGregor et al., 2019). In this study, LP-CQPC11 treatment effectively decreased OVA-induced increases in CCL11 and CCL24 levels in the BALF of asthmatic mice. Liu et al. (2014) and Anatriello et al. (2019) reported that administration of *L. plantarum* K37 and *L. bulgaricus* N45.10, respectively, significantly decreased the total levels of eotaxin in asthmatic mice. Similar results were also observed in lung homogenates from *L. paracasei* NCC2461-treated OVA-induced asthmatic mice (Pellaton et al., 2012). Our results strongly suggest that LP-CQPC11, which has great activity against OVA-induced inflammation and asthma, is associated with a decrease in the infiltration of EOCs into the lungs of asthmatic mice.

The imbalance in Th1/Th2 cells is generally accepted as the direct cause of allergic asthma. Some typical Th2 cytokines, such as IL-13, IL-5, and IL-4, have been observed to be found at increased concentrations in the BALF and serum of human asthma patients and model animals (Walsh, 2017, 2018). These Th2 cytokines induce the overgeneration of asthmatic IgE and IgG1 in mice exposed to OVA (Patel & Sur, 2017). For example, activation of IL-4 maintains the biologic activity of B cells and enhances the generation of asthmatic IgG1 and IgE (McGregor et al., 2019; Patel & Sur, 2017). IL-5 also has activity in the recruitment and proliferation of EOCs and is involved in IL-4-induced IgE generation (Walsh, 2018). IL-6 enhances the activity of IL-4 and shifts the Th1/Th2 dynamic equilibrium toward Th2 responses, thus aggravating the Th2-specific immune response

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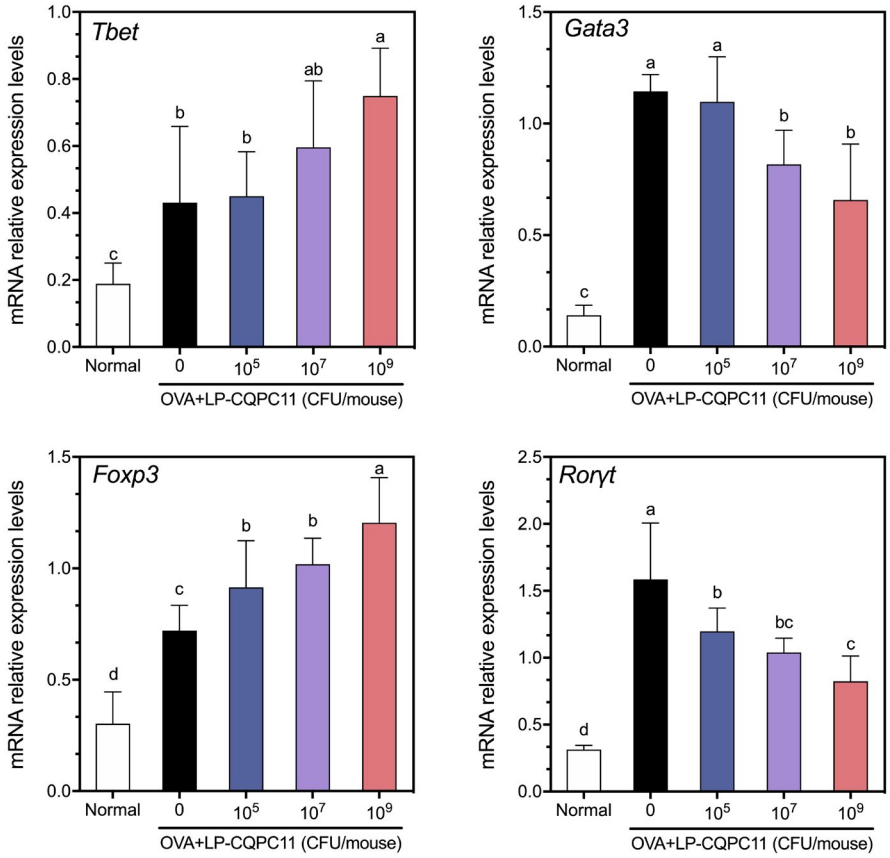


FIGURE 6 Effects of *Lactobacillus plantarum* CQPC11 on the mRNA levels of Tbet, Foxp3, Rorγt, and Gata3 in the lungs of OVA-induced allergic asthma Balb/c mice. Data are expressed as the mean ± *SD*. a–eBars with different superscript letters differ significantly ($p < .05$), as determined by Duncan's multiple range test

in asthma (Dienz & Rincon, 2009). In addition, Th2-like cytokine IL-13 also promotes B cells differentiation, directly induces pulmonary AHR, and aggravates inflammation in the airways (Maes et al., 2012; Moran & Pavord, 2020). Some studies have shown that reducing the activation of Th2 cytokines is an important medicinal approach for asthma treatment in the clinic (Klimek et al., 2019; Maes et al., 2012; Moran & Pavord, 2020). We observed that LP-CQPC11 treatment decreased the overgeneration of Th2 cytokines (IL-4, IL-5, IL-6, and IL-13) and elevated the content of IFN-γ in the BALF of asthmatic mice. Additionally, IFN-γ is a typical Th1 cytokine that exhibits anti-inflammatory and antiasthmatic activity to reduce the infiltration of EOCs into the airways and act against the Th2 cytokine-induced generation of IgE in clinical asthma therapy (Kubo, 2017). Our data were similar to those of other studies of *Lactobacillus* strain-treated asthmatic mice addressing the modulation of the Th1/Th2 imbalance (Anatriello et al., 2019; Liu et al., 2014; Wu et al., 2016; Wu, A. Y. et al., 2019; Zhang, 2018). Here, these results suggested that the antiasthmatic and anti-inflammatory capability of LP-CQPC11 were associated with modulating the imbalance in Th1/Th2 cells and reducing the generation of asthma-specific IgE and IgG1 in asthmatic mice.

Recently, the imbalance in Th17 cells/Tregs has also been found to act as a crucial role in exacerbating Th2 allergic diseases, such as allergic asthma (Zou et al., 2018). We observed that LP-CQPC11 treatment contributed to the apparent attenuation of BALF levels of IL-17A and IL-23 in asthmatic mice. As Th17 cells are a source of proinflammatory cytokines, IL-17A can cause the generation of IL-6 and IL-23 by activating the transcription factor RORγt and thereby promote bronchial inflammation in asthma (Kim et al., 2017; Na et al., 2018). The Th17 regulatory cytokines IL-23, IL-21, and IL-6 increase the levels of NEU and IL-17 cytokine generation in asthma (Halwani et al., 2017). IL-23 participates in the proliferation of Th17 cells and promotes the generation of IL-17A and IL-17F by Th17 cells, leading to infiltration of EOCs into the airways and aggravating asthmatic symptoms (Langrish et al., 2005). Inhibition of IL-23 activity helps to reduce serum IL-17A levels and relieve asthma (Li & Hua, 2014). Our results showed that LP-CQPC11 treatment reduced the BALF content of IL-17A and IL-23, which was similar to the effects observed in *L. bulgaricus* N45.10-treated asthmatic mice (Anatriello et al., 2019).

LP-CQPC11 also elevated the BALF levels of IL-10 and TGF-β in asthma mice. Both IL-10 and TGF-β are produced by Tregs and are known to maintain immune tolerance in many immune diseases (Palomares et al., 2014). The high levels of TGF-β mediated the activation of Foxp3 to promote the development of Tregs, inhibited the activation of RORγt, decreased the generation of IL-17, and finally

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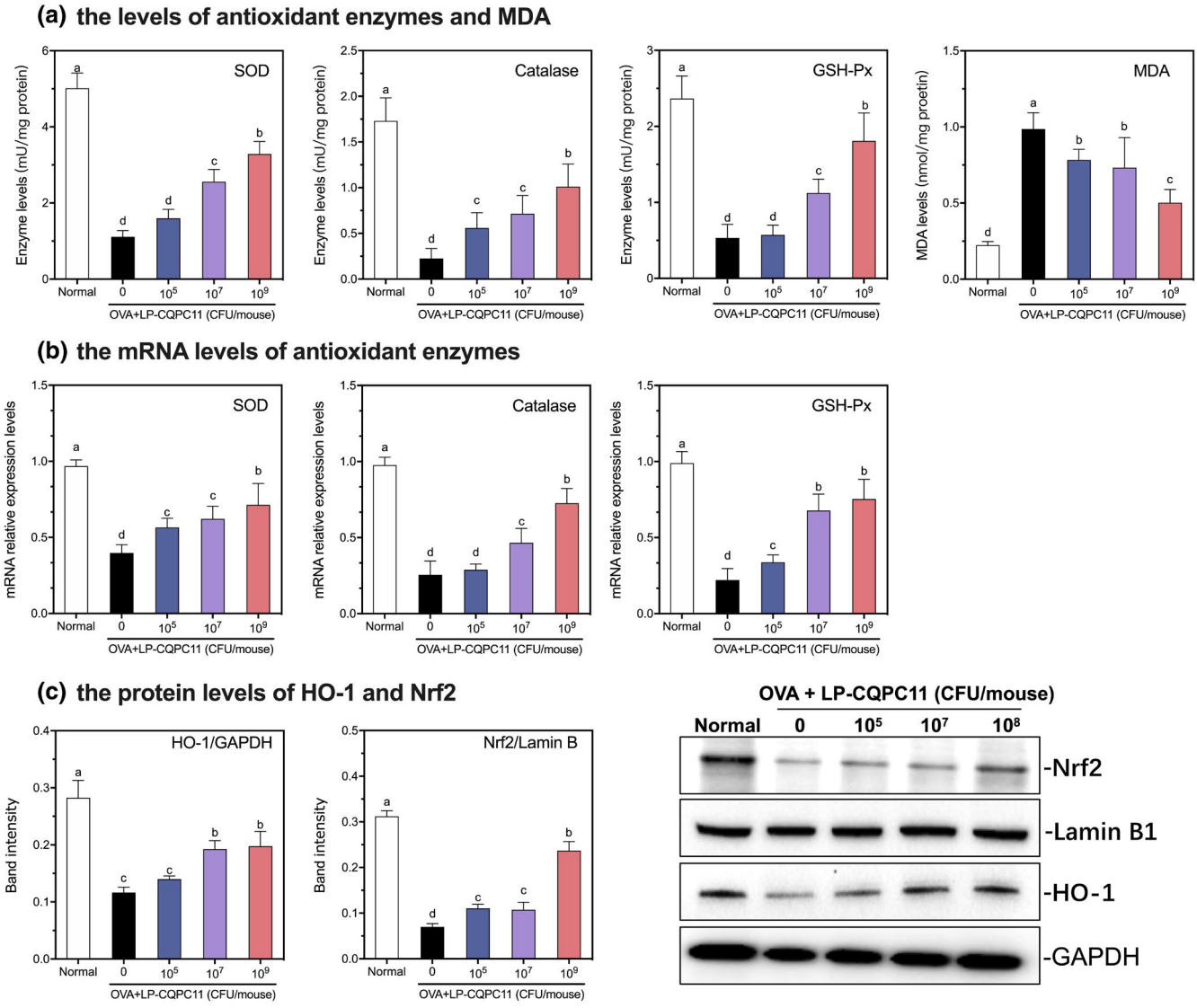


FIGURE 7 Effects of *Lactobacillus plantarum* CQPC11 on the levels of antioxidant factors (a, enzymatic activity; b, mRNA levels) and the protein levels of HO-1 and Nrf2 (c) in lung tissue samples from ovalbumin (OVA)-induced allergic asthma Balb/c mice. Data are expressed as the mean ± *SD*. a–dBars with different superscript letters differ significantly ($p < .05$), as determined by Duncan's multiple range test

attenuated airway inflammation in the asthmatic mouse model. TGF-β is an anti-inflammatory cytokine that is generated by Tregs, which is an activity to regulate the differentiation of Th17 cells and alleviates airway inflammation in asthma mice (Zhao & Wang, 2018; Zhao et al., 2011).

Some transcription factors, such as Th1-specific T-bet, Th2-specific GATA3, Th17-specific RORγt, and Treg-specific Foxp3, act as an important part during the proliferation and development of Th1/Th2/Th17 cells and Tregs. In the present study, our result suggested that LP-CQPC11 treatment effectively modulated the pulmonary levels of T-bet and GATA3 mRNA in the lungs of asthmatic mice. Both GATA3 and T-bet are key regulators that take part in Th1/Th2 differentiation in helper T cells. T-bet maintains the development of Th1 cells and inhibits the generation of Th2 cytokines. Activation of T-bet is able to decrease the generation of Th2 cytokines (IL-5 and IL-4) and promote the generation of Th1 cytokines in mice exposed to OVA (Kiwamoto et al., 2006). In contrast, GATA-3 promotes the Th2 cells differentiation and enhances the secretion of IL-5, IL-13, and IL-4 via the IL-4/STAT6 pathway (Zhu et al., 2016). Inhibition of GATA-3 activity can directly inhibit the increase of IL-13, IL-4, and IL-5 (Pai et al., 2004).

On the other hand, the imbalance between Foxp3 and RORγt also affects the course of asthma. Foxp3 is a Treg-specific transcription factor and surface marker and a positive regulatory protein in Tregs that is involved in regulating Tregs differentiation and proliferation (Chen et al., 2011). Foxp3 plays a role by regulating gene expression in Tregs, which can promote Treg development and participate in immune regulation. In contrast, RORγt, as a Th17-specific transcription factor, maintains the differentiation of Th17 cells, induces their generation of IL-17, and then participates in the Th17-mediated inflammatory response (Na et al., 2018). In this study, we found that orally administered LP-CQPC11, especially the high dose of

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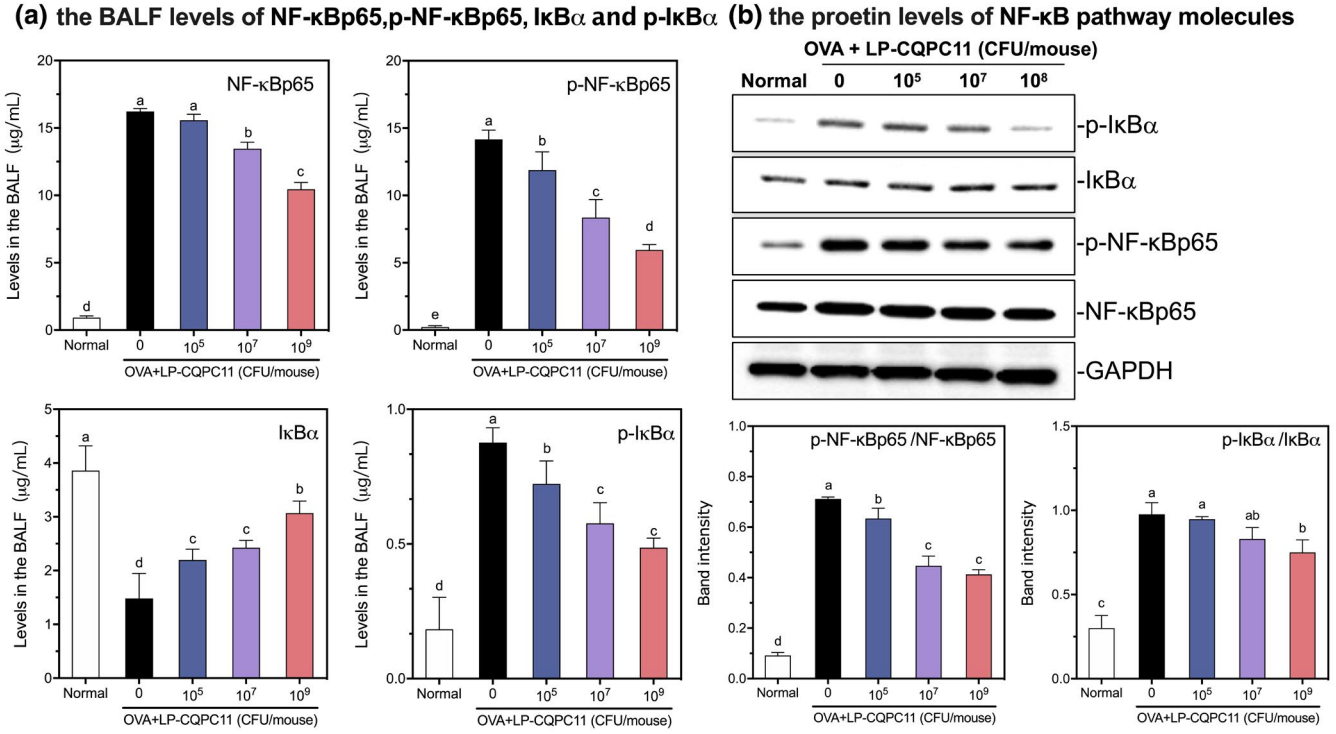


FIGURE 8 Effects of *Lactobacillus plantarum* CQPC11 on the BALF (a) and pulmonary protein levels (b) of molecules in the NF-κB pathway in OVA-induced allergic asthma Balb/c mice. Data are expressed as the mean ± *SD*. a–eBars with different superscript letters differ significantly ($p < .05$), as determined by Duncan's multiple range test

10^9 CFU/mouse, significantly elevated the levels of Foxp3 mRNA and reduced the levels of RORγt mRNA in asthma mice lungs. Foxp3 overexpression inhibits the activation of RORγt, promotes the differentiation of Tregs and maintains autotolerance by reducing the generation of Th17 cells, thereby alleviating allergic and autoimmune diseases (Chen et al., 2011; Josefowicz et al., 2012). In this study, LP-CQPC11 attenuates allergic asthma by regulating the mRNA levels of Foxp3/RORγt and T-bet/GATA3 and ultimately affects the dynamic equilibrium of Th1/Th2/Th17/Treg cells. In addition, Wu, C. T. et al. (2019) and Anatriello et al. (2019) also reported that *L. rhammosus* GG and *L. bulgaricus* N45.10 treatment, respectively, reduced OVA-induced airway inflammation and attenuated airway remodeling by modulating the mRNA levels of T-bet/GATA3 and Foxp3/RORγt in the lungs of mice with asthma.

Oxidative stress, such as endogenous/exogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS), induces tissue and organ damage in many kinds of diseases, especially allergic asthma (Lutter et al., 2015). During the pathogenesis of asthma, oxidative stress causes damage during bronchospasms and promotes inflammatory reactions in the lungs of asthmatic mice (Mishra et al., 2018). Improving the activity of the endogenous antioxidant system is the main method to protect against oxidative damage in the body. In general, the endogenous antioxidant system is classified into nonenzymatic factors (such as vitamins, glutathione, coenzyme Q10, uric acid, melatonin, and some natural phytochemicals) and enzymes (including SOD, catalase, GSH-Px, glutathione-S-transferase, and HO-1). In this study, we found that administration of LP-CQPC11 could improve the activity of antioxidant enzymes, such as SOD, catalase, and GHS-Px, and their mRNA levels in the lungs of asthmatic mice. Under physiologic conditions, SOD catalyzes superoxide (O_2^-), converting it into oxygen (O_2) and peroxide (H_2O_2) by a dismutation reaction. The generated H_2O_2 is continually decomposed into H_2O and O_2 by catalase. In addition, SOD also protects catalase against O_2^--induced dysfunction. As another important endogenous antioxidant enzyme, GHS-Px can transform toxic peroxides into nontoxic hydroxyl compounds via the oxidation of GSH into glutathione. GSH-Px also promotes the decomposition of H_2O_2 and protects the complete structure of the cell membrane as well as maintaining the physiologic function of a cell against interference and oxidative damage.

It is well known that the HO-1/Nrf2 system also acts as an important signaling pathway that shows powerful antioxidant activity against oxidative damage in tissues and organs (Ahmed et al., 2017). Our results strongly suggest that administration of LP-CQPC11 significantly promoted the protein expression levels of HO-1 and Nrf2 in the lungs of asthmatic mice. The activation of HO-1 is directly regulated by the transcription factor Nrf2. Activated Nrf2 is transferred into the nucleus, which is complex with antioxidant response elements and increases the activation of HO-1 (Li et al., 2019). The results from our study clearly indicate that LP-CQPC11 attenuates oxidative stress in the lungs of asthmatic mice by activating HO-1/Nrf2 signaling. Finally, our study also discovered a decrease in the level of oxidative damage-related MDA in LP-CQPC11-treated asthmatic mice exposed to OVA. The above results proved that LP-CQPC11 protected against oxidative damage in the lungs of

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asthmatic mice by improving the activity of the endogenous antioxidant system.

NF-κB is a classic transcription factor that refers to many inflammation-associated physiologic events, such as innate and adaptive immunity, autoimmune diseases, and cancer (Mitchell & Carmody, 2018). Under normal conditions, NF-κB binds with IκB to form an inactivation complex. Some stimulatory factors, such as proinflammatory cytokines, antigen receptors, growth factors, and LPS, may activate the IKK complex, which phosphorylates IκB. The phosphorylation of IκB causes its proteasomal degradation and ubiquitination, subsequently releasing NF-κB from the complex. Activated NF-κB translocates to the nucleus, either in conjunction with other transcription factors or alone, and initiates an inflammatory response (Mitchell & Carmody, 2018). In particular, activation of NF-κB induces T cells to transition into Th2 cells and promotes the generation of IL-13, IL-5, and IL-4 (Schwenger et al., 2005). Our study suggested that LP-CQPC11 treatment not only reduced the activation of the NF-κB pathway in the lung tissue but also decreased the BALF levels of pNF-κBp65 and pIκBα in asthmatic mice. Inhibiting the activation of the NF-κB pathway in lung tissue can alleviate airway inflammation during asthma (Mishra et al., 2018; Mitchell & Carmody, 2018; Schuliga, 2015). Our data proved that LP-CQPC11 attenuates OVA-induced airway inflammation by modulating NF-κB pathway activation.

5 | CONCLUSIONS

The present study clearly demonstrated that LP-CQPC11 significantly attenuated OVA-induced inflammation in asthmatic mice. The high dose of LP-CQPC11 (10^9 CFU/mouse) decreased the levels of IgG1 and IgE in serum and modulated the balance between Th1/Th2 cytokines and Th17 cells/Tregs in the BALF of asthmatic mice. This study showed the anti-inflammatory activity of LP-CQPC11 was related to the regulation of NF-κB pathway activation, the regulation of Th1/Th2 cells and Th17 cells/Tregs imbalance, and reduction of oxidative stress induced by inflammation in the asthmatic mice lungs. These data suggest that lactic acid bacteria LP-CQPC11 can be used as an immunoregulatory adjunctive reagent in the treatment of asthma in the future.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Huan Lan: Data curation; Investigation; Software; Writing – original draft. **Zhongyu Gui:** Funding acquisition; Supervision. **Zhen Zeng:** Formal analysis; Investigation. **Dayu Li:** Formal analysis; Project administration. **Bo Qian:** Project administration; Software. **Lin-yuan Qin:** Data curation; Formal analysis; Methodology; Software. **Ling Dai:** Data curation; Formal analysis; Software. **Jia-Le Song:** Funding acquisition; Writing – review & editing.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

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