



Bifidobacterium longum and *Lactobacillus plantarum* alleviate house dust mite allergen-induced allergic rhinitis by regulating IL-4, IL-5, and IL-10 expression

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ABSTRACT

We examined the effects of *Bifidobacterium longum* IM55, *Lactobacillus plantarum* IM76, and their (1:1 and 1:9) mixtures (PMs) on house dust mite allergen extract (HDMA)-induced allergic rhinitis (AR) in mice. Oral administration of IM55, IM76, or PM significantly suppressed HDMA-induced allergic nasal symptoms, IL-4 and IL-5 expression in the nasal mucosa, bronchoalveolar lavage fluid (BALF), and blood, and IgE level in blood. They suppressed HDMA-induced eosinophil, mast cell, and Th2 populations in BALF while the regulatory T cell population and IL-10 expression were increased. Treatment with IM55, IM76, or PM significantly reduced HDMA-induced IL-4, IL-5, IL-13, and eosinophil peroxidase expression and increased IL-10 expression in the colon. Furthermore, their treatments suppressed HDMA-induced Proteobacteria population and Proteobacteria to Bacteroidetes ratio in the gut microbiota. In conclusion, IM55 and IM76 may mitigate AR by suppressing IL-4, IL-5, and IL-13 expression and inducing IL-10 expression through the inhibition of gut Proteobacteria population.

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Introduction

Allergic rhinitis (AR) is an inflammatory disorder triggered by the interaction of allergens and IgE (Greiner, Hellings, Rotiroti, & Scadding, 2011; Skoner, 2001). The prevalence of AR ranges from 10% to 30% of the world's people (Shin, Jung, & Park, 2018; Skoner, 2001). Signs and symptoms include a runny or stuffy nose, sneezing, and red, itchy, and watery eyes. These symptoms are caused by allergic mediators released from innate-immunity-associated mast cells (MCs), eosinophils, dendritic cells, and macrophages and adaptive immunity-associated T helper type 2 (Th2) cells (Holgate, 2012; Wu & Zarrin, 2014). The activation of innate immunity-associated immune cells by allergens induces the expression of interleukin (IL)-4, IL-5, IL-10, and tumour necrosis factor (TNF)- α , which stimulate the differentiation of naïve CD4⁺ T cells into effector Th1, Th2, Th17, and regulatory T (Treg) cells (Holgate, 2012; Kaiko, Horvat, Beagley, & Hansbro,

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2008). MCs secrete histamine, IL-4, and IL-5 by the interaction of IgE-specific antigens complex (St. John & Abraham, 2013; Wu & Zarrin, 2014). These cytokines stimulate the differentiation of naïve T cells into Th2 cells, increase IgE production from B cells, and stimulate eosinophil activation, resulting in nasal and pulmonary inflammation. Moreover, IL-4 and IL-5 are highly expressed in AR patients (Baumann et al., 2013; Holgate, 2012). Patients with AR against house dust mites showed an increase in the eosinophil populations of the bronchoalveolar lavage fluid (BALF) and expression of IL-4, IL-5, and IgE for house dust mite allergens in the blood (Baumann et al., 2013; Thomas, 2012). To alleviate AR, H1 receptor antagonists, anti-leukotrienes, corticosteroids, and decongestants have been frequently used (Ricketti, Alandijani, Lin, & Casale, 2017). However, these drugs are not ideal because of their side effects.

Probiotics exhibit a variety of biological activities: they potentiate the immune response in humans and animals and suppress inflammatory and allergic responses (Lee, Song, Nam, & Lee, 2018; Tsiouris, Kelesi, Vasilopoulos, Kalemikerakis, & Papageorgiou, 2017). *Lactobacillus paracasei* 33 attenuated house dust mite-induced AR (Wang, Lin, Wang, & Hsu, 2004). *Bifidobacterium bifidum* G9-1 alleviated cedar pollen-induced allergic nasal symptoms (Tsunemine et al., 2015). *Bacillus coagulans* 09.712 mitigated shrimp tropomyosin-induced allergic symptoms (Fu et al., 2017). *Bifidobacterium longum* IM55 and *Lactobacillus plantarum* IM76, which were selected as acid- and bile acid-resistant probiotics, attenuated ovalbumin (OVA)-induced AR in mice (Kim, Kang, Kim, Han, & Kim, 2019). These findings suggest that probiotics may alleviate AR induced by a variety of antigens.

Therefore, to confirm whether IM55 and IM76 could alleviate house dust mite (*Dermaphagoides pteronyssinus*) allergen extract (HDMA)-induced AR, we examined their anti-allergic effects in mice with HDMA-induced AR.

Materials and methods

Materials

HDMA was purchased from Citegbiologics (Groningen, Netherlands). Dexamethasone was purchased from Sigma (St Louis, MO). The fixation buffer was purchased from BioGems International Inc. (Westlake Village, CA). FACS lysing solution was purchased from Becton Dickinson (San Jose, CA). PE-conjugated anti-FcεRIα, APC conjugated anti-CD117, PE-conjugated anti-Siglec-F, APC-conjugated anti-CD11b (M1/70), PE-conjugated anti-IL-4, PerCP-conjugated anti-CD4, PE-conjugated anti-FoxP3, and PerCP-conjugated anti-CD4 were purchased from Abcams (Cambridge, England).

Culture of *Bifidobacterium longum* IM55 and *Lactobacillus plantarum* IM76

Bifidobacterium longum IM55 (KCCM11961p, Korea Culture Center of Microorganisms, Seoul, Korea) and *L. plantarum* IM76 (KCCM11962p) were grown in general media for probiotics.

Animal

Female BALB/c mice (weight 19–21 g; 6 weeks old) were purchased from OrientBio (Seoul, Korea) and acclimatised for a week in wire cages (temperature, 20–22°C; humidity,

50 ± 10%; and light, 07:00–19:00). Mice were fed standard laboratory chow and water ad libitum. Animal experiments were approved by the Committee for the Care and Use of Laboratory Animals in the University (IRB No. KHUASP(SE)-18-098) and performed in accordance with the NIH and University Guidelines for Laboratory Animal Care and Usage.

Preparation of mice with HDMA-induced AR

Mice with HDMA-induced AR were prepared according to the method of Coomes et al. (2017). Briefly, mice were randomly separated into seven groups. Each group consisted of 8 mice. Six groups were intraperitoneally injected with HDMA (diluted 20 µg in aluminum potassium sulfate solution [2 mg/0.2 mL] on days 0 and 7 and intranasally challenged by daily dropping of 1% HDMA (20 µL/nostril) from day 14 to 20. Test agents (vehicle, IM55 [1×10^9 CFU/mouse/day], IM76 [1×10^9 CFU/mouse/day], PM [IM55:IM76 = 1:1 or 1:9, 1×10^9 CFU/mouse/day]), or dexamethasone [1 mg/kg/day]) were intragastrically administered once daily from day 15 to 20. The control group was treated with saline instead of test agents and HDMA. On day 21, mice were smeared with 1% HDMA (20 µL/nostril) in the nasal cavities and then nasal rubbing motions (nasal allergic symptoms) were counted for 10 min according to the method of Kim et al. (2019).

Flow cytometric analysis of MC, eosinophil, Th2, and cells in BALF

The populations of eosinophils, MCs, Th2, and Treg cells in the BALF were analyzed using a flow cytometer, as previously reported (Jang, Lee, Jang, Han, & Kim, 2019; Kim et al., 2019). Briefly, mice were killed and incised the skin over the larynx. BALF was flushed three times with the complete medium (1 mL), centrifuged at 5000 g for 5 min, and suspended in the medium. Cells (2×10^6 cells/mL) were incubated for 5 min with the Fc receptor blocking agent in 100 µL of FACS buffer (1 × PBS supplemented with 2% heat-inactivated fetal calf serum and 0.02% NaN₃). Monoclonal antibodies were then added to the samples, incubated for 45 min in the dark at 4°C, fixed with fixation buffer, lysed with FACS lysing solution (Becton Dickinson, San Jose, CA), washed, resuspended in FACS buffer, and analyzed using flow cytometer. Antibodies used were PE-conjugated anti-FcεRIα and APC conjugated anti-CD117 for MCs, PE-conjugated anti-Siglec-F and APC-conjugated anti-CD11b (M1/70) for eosinophils, PE-conjugated anti-IL-4 and PerCP-conjugated anti-CD4 for Th2 cells, and PE-conjugated anti-FoxP3 and PerCP-conjugated anti-CD4 for Treg cells.

Quantitative polymerase chain reaction (qPCR)

qPCR was performed with total DNA (100 ng) isolated from the mouse feces with SYBER premix in a Takara thermal cycler (Kim et al., 2019). The thermal cycling conditions were as follows: 95°C for 30 s, followed by 42 cycles of denaturation and amplification at 95°C for 5 s and 63°C for 30 s, respectively. Gene expression levels were calculated relative to bacterial 16S rRNA, using Microsoft Excel. Primers used is indicated in Table 1.

qPCR for IL-13 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was performed with total DNA(100 ng) purified from the colons in a Takara thermal cycler

Table 1. Primers used in the present study.

	Primer sequence	
	Forward	Reverse
Firmicutes	5'-GGA GYA TGT GGT TTA ATT CGA AGC A-3'	5'-AGC TGA CGA CAA CCA TGC AC-3'
Bacteroidetes	5'-AAC GCG AAA AAC CTT ACC TAC C-3'	5'-TGC CCT TTC GTA GCA ACT AGT G-3'
Proteobacteria	5'-GCTAACGCATTAAGTR YCCCG-3'	5'-GCC ATGCRGCACCTGT CT-3'
Bacterial 16S rRNA	5'-TCG TCG GCA GCG TCA GAT GTG TAT AAG AGA CAG GTG CCA GCM GCC GCG GTA A-3'	5'-GTC TCG TGG GCT CGG AGA TGT GTA TAA GAG ACA GGG ACT ACH VGG GTW TCT AAT-3'
IL-13	5'-GGAATCCAGGGCTACA CAGA-3'	5'-AGGAGCTGAGCAACATC ACA-3'
GAPDH	5'-TGCACTGGCAAAGTGG AGAT -3'	5'-TTTGCCGTGAGTGGAGT CATA -3'

using SYBER premix (Kim et al., 2018). Thermal cycling was performed at 95°C for 30 s by 50 cycles of denaturation at 95°C for 5 s and amplification 63°C for 30 s. Gene expression levels were computed relatively to GAPDH, using Microsoft Excel. Primers were prepared in MacroGen as shown in Table 1.

Enzyme-immunosorbent assay (ELISA)

BALF, nasal mucosa, and colon were homogenised on ice in 1 mL of RIPA lysis buffer containing 1% each of phosphatase and protease inhibitor cocktail and centrifuged at 15,000 *g* for 15 min at 4°C (Kim et al., 2018). To isolate plasma from blood, bloods were collected by retroorbital bleeding into ethylenediaminetetraacetic acid-coated BD Microtainer® tubes (Becton Dickinson, Franklin Lakes, NJ, USA) and centrifuged (13,200 *g*, 15 min). The supernatants of tissues and bloods were transferred to 96-well plates. IL-4, IL-5, IL-10, and IgE concentrations were determined, using commercial ELISA kits (Kim et al., 2019).

Statistics

All animal experimental data are described as the mean $\pm$ standard deviation. Significant differences were analyzed using one-way ANOVA followed by a Duncan multiple range test ($P < 0.05$).

Results

Effects of IM55 and/or IM76 on the nasal allergic symptom and blood IL-4, IL-5, and IgE expression in mice with HDMA-induced AR

In order to evaluate the effects of IM55 and IM76 on HDMA-induced AR in vivo, we orally administered IM55 and/or IM76 in mice with HDMA-induced AR and examined their anti-allergic effects. Exposure of mice to HDMA significantly increased allergic nasal symptoms, including nose itching, and IL-4 and IL-5 expression in the nasal epithelia (Figure 1). Oral administration of IM55, IM76, and their (1:1 and 1:9) mixtures significantly suppressed HDMA-induced allergic nasal symptoms and IL-4 and IL-5 expression while IL-10 expression was induced. Their treatments also alleviated HDMA-induced dilation of nasal epithelial cells, assessed by histological examination.

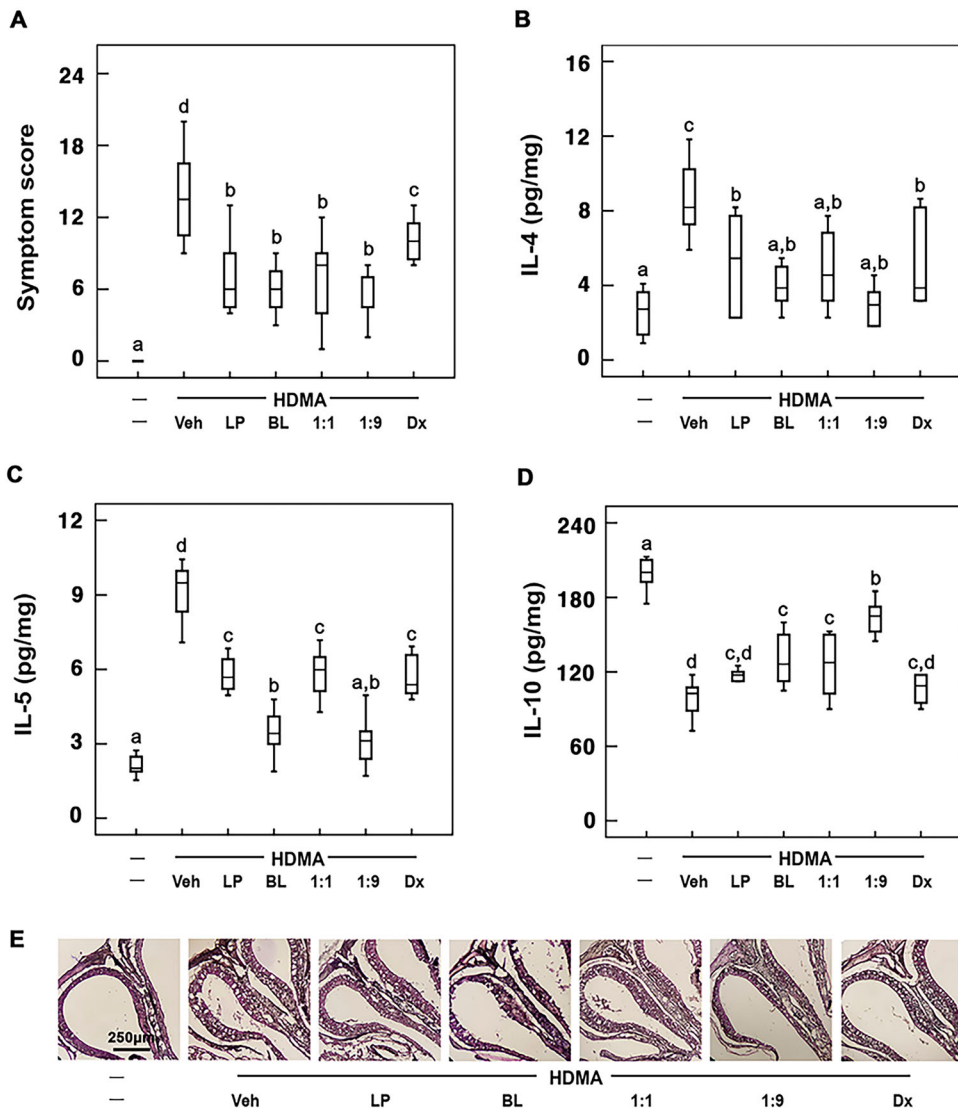


Figure 1. Effects of IM55, IM76, and PMs on the nasal allergic symptoms (A), nasal IL-4 (B), IL-5 (C), and IL-10 (D) in the nasal mucosa of mice with HDMA-induced AR (HAR). Cytokines were measured using ELISA kits. (E) Histological examination of nasal tissues, stained with H&E. Test agents (Veh, saline; Dx, dexamethasone [1 mg/kg/day , intraperitoneally]; LP, IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; BL, treated with IM55 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; 1:1, the [1:1] mixture of IM55 and IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; and 1:9, the [1:9] mixture of IM55 and IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]) were treated in HDMA-treated mice. Control mice (NC) were treated with saline instead of HDMA and test agents. Data are shown as box plots ($n = 8$). Means with same letters are not significantly different ($p < 0.05$).

Next, we examined the effects of IM55 and/or IM76 on IL-4, IL-5, and IgE levels in the blood of mice HDMA-induced AR (Figure 2). HDMA treatment significantly increased IL-4, IL-5, and IgE levels in the blood. However, treatment with IM55, IM76, or their mixtures reduced HDMA-induced IL-4, IL-5, and IgE levels in the blood.

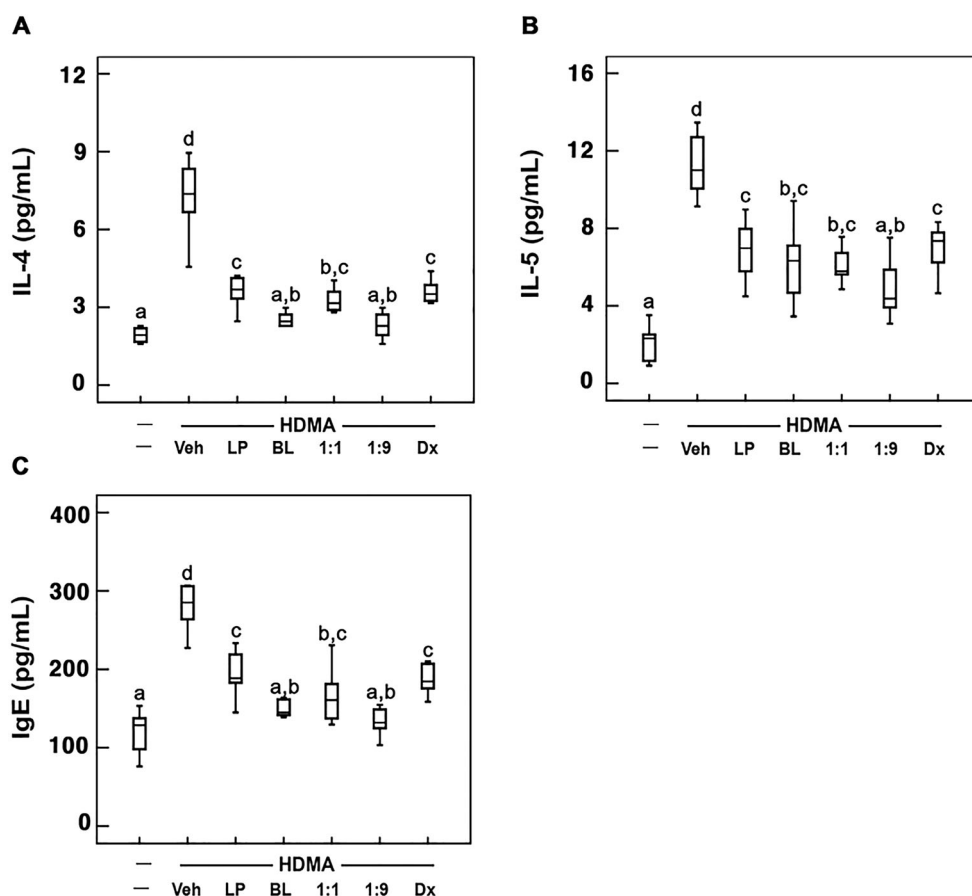


Figure 2. Effects of IM55, IM76, and PMs on IL-4 (A), IL-5 (B), and IgE levels (C) in the blood of mice with HDMA-induced AR. Test agents (Veh, saline; Dx, dexamethasone [1 mg/kg/day, intraperitoneally]; LP, IM76 [1×10^9 CFU/mouse/day, orally]; BL, treated with IM55 [1×10^9 CFU/mouse/day, orally]; 1:1, the [1:1] mixture of IM55 and IM76 [1×10^9 CFU/mouse/day, orally]; and 1:9, the [1:9] mixture of IM55 and IM76 [1×10^9 CFU/mouse/day, orally]) were treated in HDMA-treated mice. Control mice (NC) were treated with saline instead of HDMA and test agents. Data are shown as box plots ($n = 8$). Means with same letters are not significantly different ($p < 0.05$).

Effects of IM55 and/or IM76 on the MCs, eosinophils, Th2 cell, and Treg cell population and IL-4 and IL-5 expression in the BALF

To understand whether IM55 and/or IM76 could regulate the infiltration of immune cells into the BALF, we examined their effects on the MCs, eosinophils, Th2, and Treg cell population in the BALF of mice with HDMA-induced AR (Figure 3). HDMA treatment significantly increased the populations of allergic immune cells MCs, eosinophils, Th2, and Treg cells. However, their treatments reduced HDMA-induced populations of MCs, eosinophils, and Th2 cells in the BALF while the Treg cell population was increased. Furthermore, IM55 and IM76 suppressed HDMA-induced IL-4 and IL-5 expression in the BALF while IL-10 expression was increased (Figure 4).

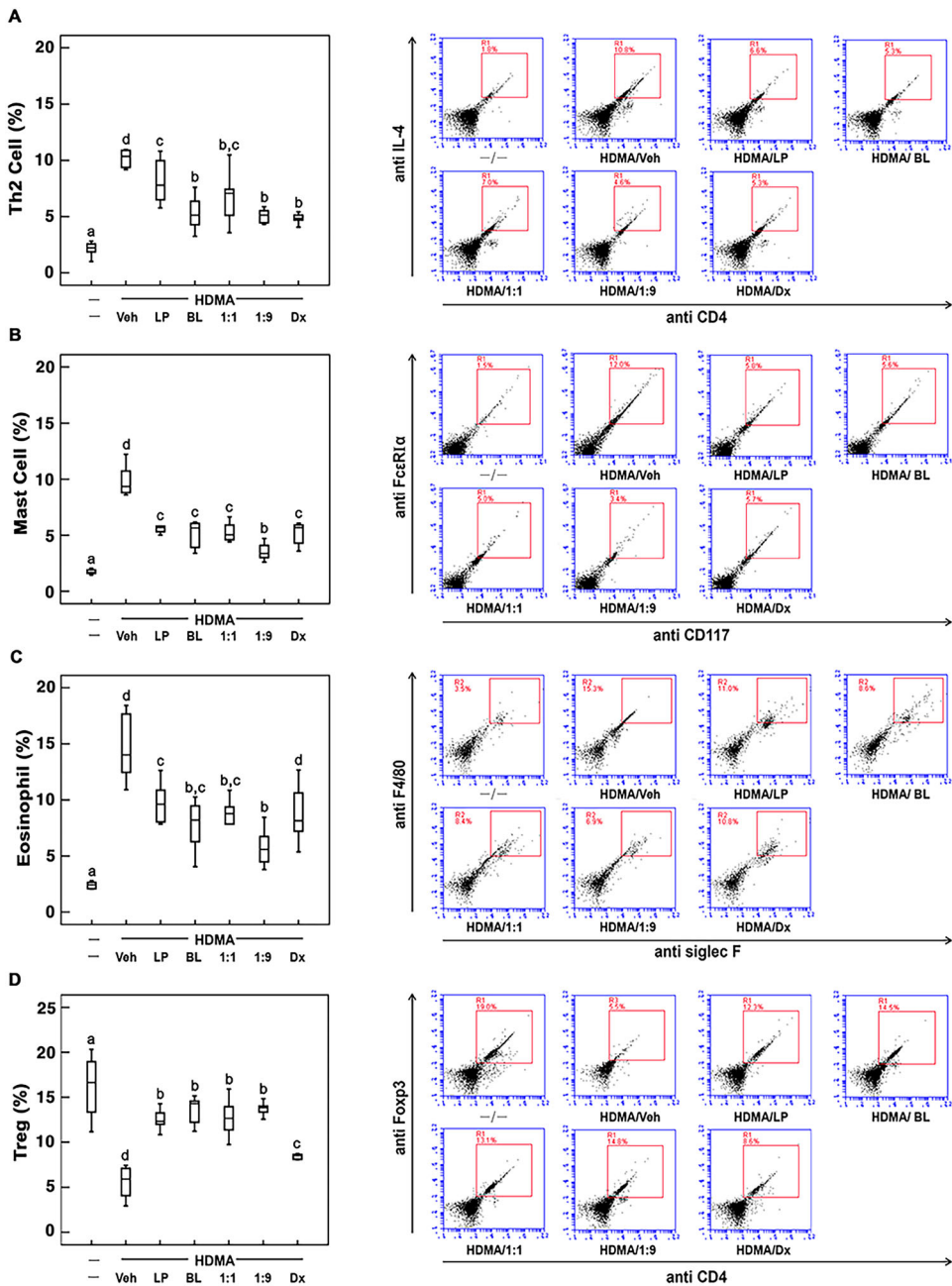


Figure 3. Effects of IM55, IM76, and PMs on Th2 cell (A), mast cell (B), eosinophil (C), and Treg cell (D) populations in the BALF of mice with HDMA-induced AR. Test agents (Veh, saline; Dx, dexamethasone [1 mg/kg/day , intraperitoneally]; LP, IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; BL, treated with IM55 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; 1:1, the [1:1] mixture of IM55 and IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; and 1:9, the [1:9] mixture of IM55 and IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]) were treated in HDMA-treated mice. Control mice (NC) were treated with saline instead of HDMA and test agents. Data are shown as box plots ($n=8$). Means with same letters are not significantly different ($p < 0.05$).

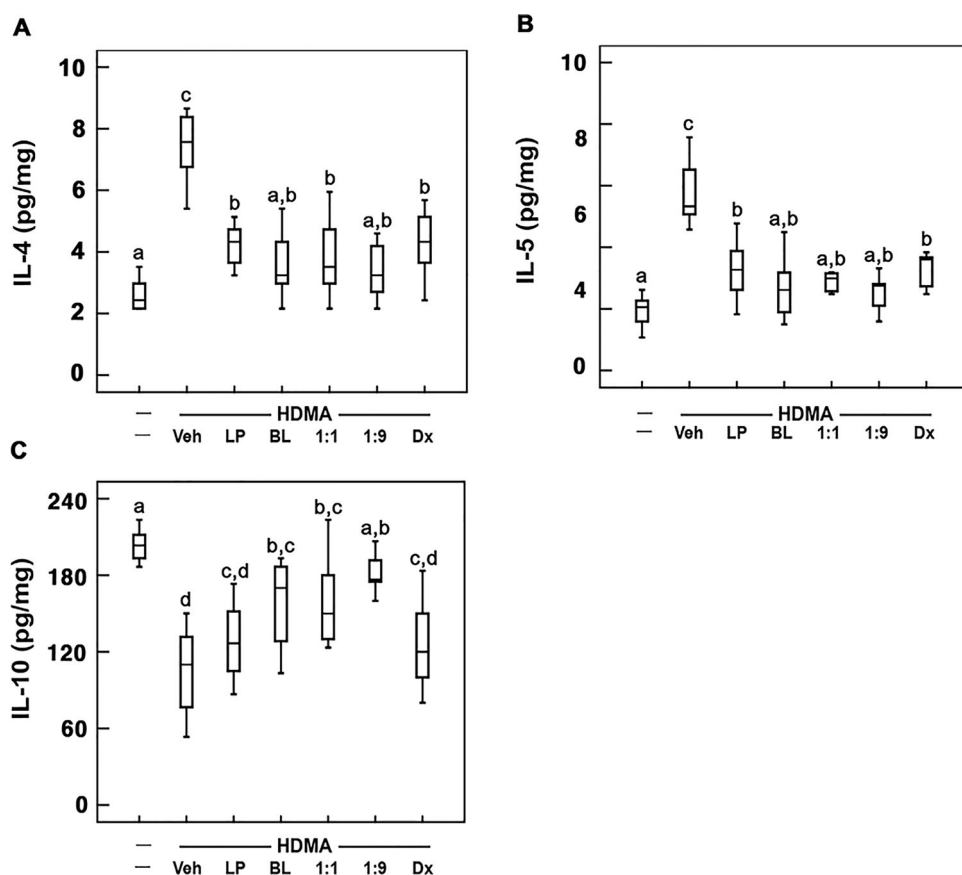


Figure 4. Effects of IM55, IM76, and PMs on IL-4 (A), IL-5 (B), and IL-10 (C) levels in the BALF of mice with HDMA-induced AR. Cytokines were measured using ELISA kits. Test agents (Veh, saline; Dx, dexamethasone [1 mg/kg/day , intraperitoneally]; LP, IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; BL, treated with IM55 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; 1:1, the [1:1] mixture of IM55 and IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; and 1:9, the [1:9] mixture of IM55 and IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]) were treated in HDMA-treated mice. Control mice (NC) were treated with saline instead of HDMA and test agents. Data are shown as box plots ($n=8$). Means with same letters are not significantly different ($p < 0.05$).

Effects of IM55 and/or IM76 on the colonic IL-4 and IL-5 expression and gut bacteria populations in mice with HDMA-induced AR

In order to understand the role of gut immunity and microbiota in the occurrence of AR, we examined whether IM55, IM76, or their mixtures could modify gut immunity and microbiota composition. HDMA treatment induced IL-4, IL-5, and IL-13 expression in the colon (Figure 5). However, IM55 and/or IM76 suppressed HDMA-induced IL-4 and IL-5 expression in the colon while IL-10 expression was increased. In particular, treatment with PM suppressed HDMA-induced IL-13 expression more potently than IM55 or IM76 treatment. HDMA treatment also shifted gut microbiota composition: in particular, they increased Proteobacteria and Firmicutes populations in gut microbiota composition and decreased Bacteroidetes (Figure 6). However, treatment with IM55 and/or IM76

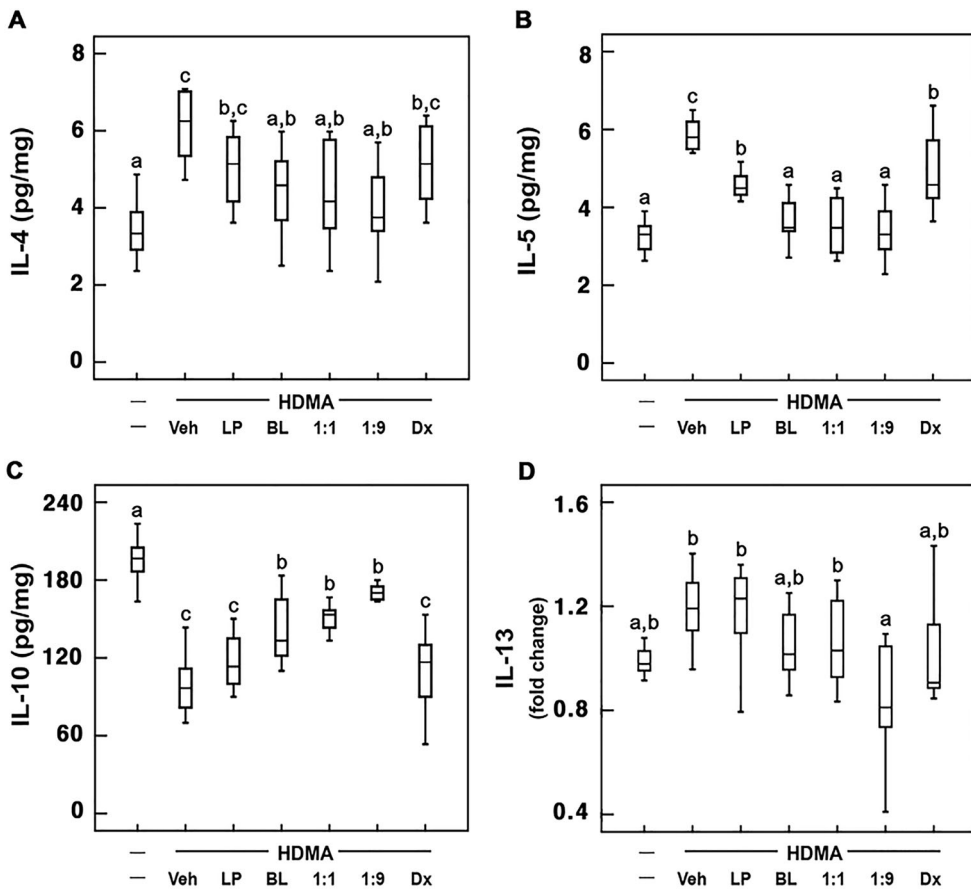


Figure 5. Effects of IM55, IM76, and PMs on the expression of IL-4 (A), IL-5 (B), IL-10 (C), and IL-13 (D) in the colon of mice with HDMA-induced AR (HAR). IL-4, IL-5, and IL-10 levels were measured using ELISA kits. IL-13 level was measured by qPCR. Test agents (Veh, saline; Dx, dexamethasone [1 mg/kg/day, intraperitoneally]; LP, IM76 [1×10^9 CFU/mouse/day, orally]; BL, treated with IM55 [1×10^9 CFU/mouse/day, orally]; 1:1, the [1:1] mixture of IM55 and IM76 [1×10^9 CFU/mouse/day, orally]; and 1:9, the [1:9] mixture of IM55 and IM76 [1×10^9 CFU/mouse/day, orally]) were treated in HDMA-treated mice. Control mice (NC) were treated with saline instead of HDMA and test agents. Data are shown as box plots ($n = 8$). Means with same letters are not significantly different ($p < 0.05$).

suppressed Proteobacteria and Firmicutes populations and the ratios of Firmicutes to Bacteroidetes and Proteobacteria to Bacteroidetes.

Discussion

Gut microbiota have a variety of physiological effects, including pathogen protection and immunomodulation (Prince, Mandel, Nadeau, & Singh, 2015). However, gut microbiota dysbiosis emasculates these physiological functions, leading to obesity, gastrointestinal inflammation, and allergic disorders (Goulet, 2015; Mukherjee, Joardar, Sengupta, & Sinha Babu, 2018). A recent study reports that microbial dysbiosis is closely associated with food allergy incidence (Pascal et al., 2018). Allergic markers such as blood IgE levels

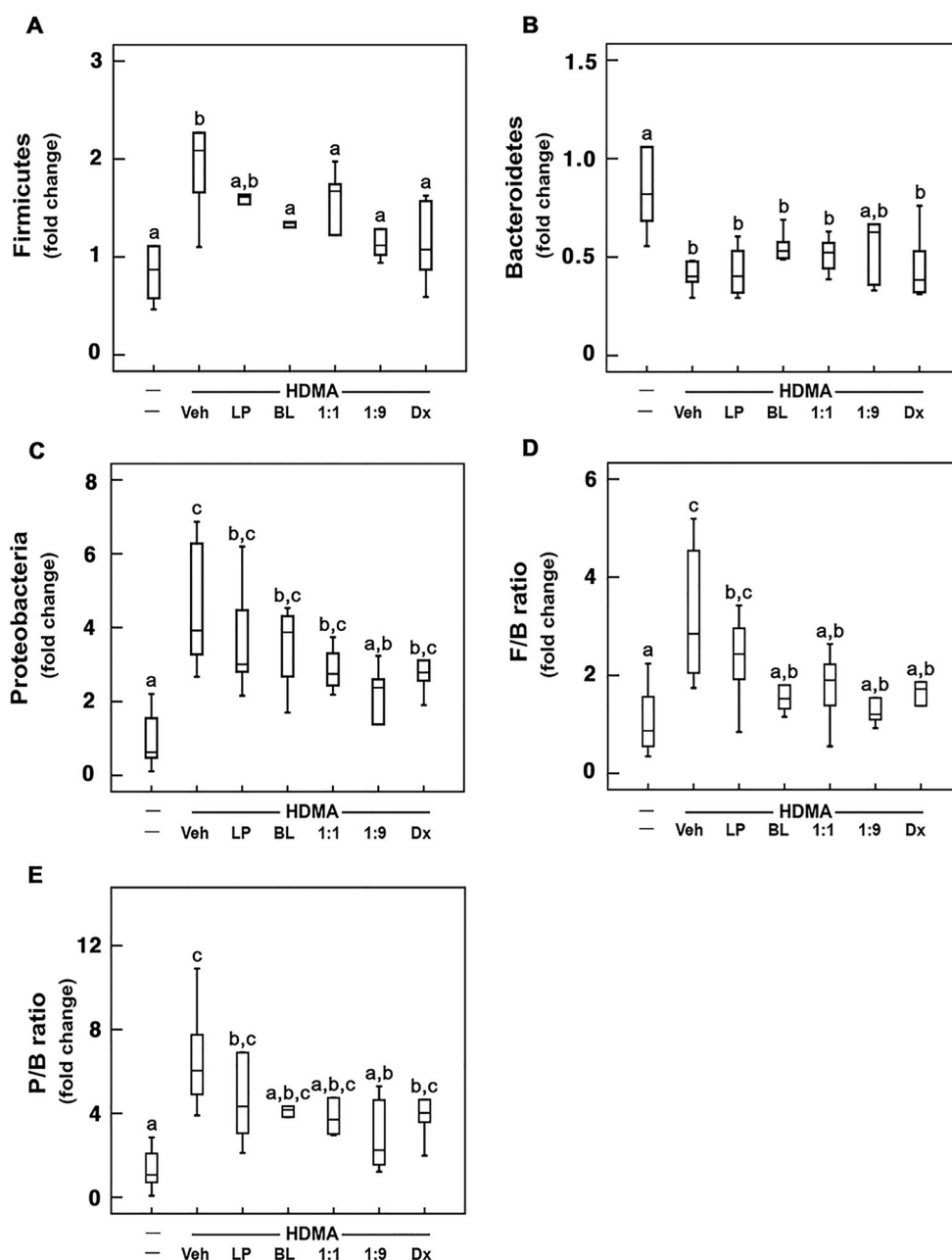


Figure 6. Effects of IM55, IM76, and PMs on the population of Firmicutes (A), Bacteroidetes (B), and Proteobacteria (C) and ratios of Firmicutes to Bacteroidetes (D) and Proteobacteria to Bacteroidetes (E) in the feces of mice with HDMA-induced AR (HAR). Gut microbiota composition was analyzed by qPCR. Test agents (Veh, saline; Dx, dexamethasone [1 mg/kg/day , intraperitoneally]; LP, IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; BL, treated with IM55 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; 1:1, the [1:1] mixture of IM55 and IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]; and 1:9, the [1:9] mixture of IM55 and IM76 [$1 \times 10^9 \text{ CFU/mouse/day}$, orally]) were treated in HDMA-treated mice. Control mice (NC) were treated with saline instead of HDMA and test agents. Data are shown as box plots ($n = 8$). Means with same letters are not significantly different ($p < 0.05$).

and basophil numbers are highly detected in antibiotics-treated and germ-free mice (Iwabuchi, Takahashi, Xiao, Miyaji, & Iwatsuki, 2007). These findings suggest that gut microbiota dysbiosis can induce IgE production and basophil-mediated immune responses.

In the present study, we also found that HDMA treatment caused allergic nasal symptoms and IgE, IL-4, and IL-5 expression in mice. Oral administration of IM55 and/or IM76 significantly reduced HDMA-induced allergic nasal symptoms, IgE, IL-4, IL-5, and IL-13 expression, and Th2 cell population in mice while the Treg cell population and IL-10 expression were increased. Kim et al. (2019) reported that IM55 and IM76 attenuated ovalbumin-induced AR in mice by regulating Th2/Treg balance. *Bifidobacterium longum* BB536 alleviated allergic symptoms in mice by suppressing Th2 activation (Iwabuchi et al., 2007). *Lactobacillus crispatus* KT-11 attenuated OVA-induced allergic nasal symptoms in mice by correcting Th1/Th2 balance and suppressing MCs population (Tobita, Yanaka, & Otani, 2010). *Lactobacillus rhamnosus* Lcr35 reduced OVA-induced AR in mice by inhibiting IL-4 expression. *Bacillus coagulans* 09.712 mitigated shrimp tropomyosin-induced allergic reactions by correcting Th1/Th2/Treg imbalance (Fu et al., 2017). These results suggest that some probiotics including IM55 and IM76 can alleviate AR by regulating IgE expression through the regulation of Th1/Treg balance, which regulates IL-4, IL-5, and IL-13 expression (Holgate, 2012; Kaiko et al., 2008). In the present study, IM55 and/or IM76 inhibited the infiltration of MCs and eosinophils into BALF and inhibited IL-4, IL-5, and IL-13 expression in the colon as well inhibited IL-4 and IL-5 in the nasal epithelia. *Bifidobacterium bifidum* G9-1 alleviated cedar pollen-induced AR by reducing eosinophil and neutrophil populations (Tsunemine et al., 2015). These results suggest that IM55 and IM76 can systemically suppress the activation of MCs and eosinophils by suppressing IL-4 and IL-5, and IL-13 expression in the colon.

Moreover, we found that IM55 and IM76 significantly modified HDMA-disrupted gut microbiota balance: they increased Bacteroidetes population and reduced the populations of Proteobacteria and Firmicutes. Enomoto et al. (2014) reported that oral administration of bifidobacteria to pregnant women reduced the occurrence of allergy in offspring via the regulation of gut microbiota composition. These findings suggest that probiotics IM55 and IM76 can regulate gut immunity by regulating gut microbiota composition, resulting in the attenuation of gut inflammation.

Conclusions

Intranasal challenge with HDMA caused AR in mice. Oral administration of IM55, IM76, and their (1:1 and 1:9) mixtures alleviated HDMA-induced AR by suppressing IL-4, IL-5, and IL-13 expression and inducing IL-10 expression with the restoration of disturbed gut microbiota.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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