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Antiallergic activity of *Lactobacillus plantarum* against peanut allergy in a Balb/c mouse model

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ABSTRACT

Antiallergic activities of *Lactobacillus plantarum* (*L. plantarum*) prepared from kimchi as orally administered probiotics were examined in type I peanut allergy mice models. Oral administration with *L. plantarum* restored the deteriorated profile of enteric flora in mice sensitized with peanut allergen and attenuated allergic symptoms, including diarrhea scores, clinical scores, serum specific immunoglobulin E (IgE) and histamine production. The mRNA expression of interleukin-10 and interferon- γ was suppressed and enhanced, respectively by *L. plantarum* administration. Thus, *L. plantarum* probably promoted anti-allergic activities via modulating enteric flora, intestinal cytokines mRNA expression in type I allergic mice, resulting in alleviation of allergic symptoms, including serum specific IgE and clinical hypersensitivity scores.

Abbreviations: LAB: lactic acid bacteria; ELISA: enzyme-linked immunosorbent assay; IFN: interferon; IL: interleukin; PBS: phosphate-buffered saline; PCR: polymerase chain reaction; PN: Ara h 2 in peanut; mRNA: messenger ribonucleic acid; IgE: immunoglobulin E; *L. plantarum*: *Lactobacillus plantarum*

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Peanut; allergy; Balb/c mouse model; *Lactobacillus plantarum*

1. Introduction

As an emerging health problem with increasing incidence and severity, food allergy affected approximately 3% to 8% of US children (Gupta et al., 2011; Keet et al., 2014; Sicherer, Munoz-Furlong, Godbold, & Sampson, 2010). Most of the allergy disorders are related to the ingestion of milk, egg, wheat, soy, fish, peanuts, tree nuts, and shellfish. Among the allergies, peanut is one of the most allergenic foods and reports of accidental ingestion of peanuts in unsuspected food are increasing (Dodo, Marsic, Callender, Cebert, & Viquez, 2002). In addition, peanut allergy has become a major health concern worldwide, in developed as well as the developing countries (Sun, Fu, & Wang, 2015). With reports from the United

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Kingdom, North America, and Australia that the prevalence of peanut allergy has doubled in 10 years and is approximately 1.8%, 1.4%, and 3.0% respectively (Du Toit et al., 2013). Seventeen allergen proteins identified in peanuts are Ara h 1 to Ara h 17 and the first two are the main allergens in peanuts (Cong, Lou, Xue, Li, & Chen, 2008; Koppelman, Wensing, Ertmann, Knulst, & Knol, 2003). Currently, strict dietary avoidance of peanut and peanut-containing foods is the only available approach to prevent peanut allergy (Fiocchi, Pecora, Valluzzi, Fierro, & Mennini, 2017). Recently, Abrahamsson et al. (2012) and Bisgaard et al. (2011) reported imbalances in intestinal microorganisms in patients with allergy disease. And a decrease in the microbial exposure in early childhood is closely associated with an increased morbidity in allergic diseases (Renz, Blumer, Virna, Sel, & Garn, 2006). The microbiota has been known to play an important role on the immune system, thus, there are extensive functional interactions between the gut microbiota and host metabolism or immunity (Donohoe et al., 2011). Intestinal mucous membranes can cause inflammatory reactions when food allergies occur. Studies have shown that probiotics can enhance the secretion of secretory immunoglobulin A and increase mucosal barrier to protect children from allergy (Gregoret, Perezlindo, Vinderola, Reinheimer, & Binetti, 2013). Huang, Shen, Liang, and Jan (2016) found that oral administration with *L.murinus* could attenuate food allergic responses, including allergen-induced diarrhoea, mast cell activation and serum immunoglobulin E (IgE) production. Allergy is generally associated with increased eosinophil counts and IgE-antibody concentrations. The supplementation of probiotic strains like *Lactobacillus* and *Bifidobacteria* or prebiotic like galacto-oligosaccharide reduced the concentration of allergen-specific IgE and Immunoglobulin G in the animal models (Ezendam & Loveren, 2008). Research shows that probiotics have alleviation of allergies to milk globulins, cow's milk, ovalbumin (OVA), etc. (Huang et al., 2016; Takeda et al., 2014), however, it is currently unclear if it possesses anti-allergic activity of peanut allergy. To circumvent this, we created a Balb/c mouse model of IgE-mediated anaphylaxis in response to peanuts, which will test the hypothesis that *Lactobacillus plantarum* (*L. plantarum*) may be a functional probiotic possessing anti-allergic and immunomodulatory activities.

2. Materials and methods

2.1. The preparations of probiotic bacteria and peanut allergen

Lactobacillus plantarum isolated from kimchi were suspended in de Man, Rogosa and Sharpe (MRS) liquid medium and incubated at 37°C for 48 h. The bacteria were collected by centrifugation and resuspended in PBS through adjusting at concentrations of 5×10^{10} colony forming units (CFU)/mL.

Unshelled raw peanuts used in this study was purchased from local market in Yangling, Shaanxi. Peanut allergen Ara h 2 (PN) was prepared as described previously (Hu et al., 2011; Long et al., 2016).

2.2. Animal model, challenge protocols and sample collection

Female Balb/c mice (22–24 g) were purchased from Laboratory Animal Center, School of Medicine of Xi'an Jiaotong University. The 7-week-old mice were housed in a

temperature-controlled room (20–22°C) with a relative humidity of $65 \pm 10\%$ and a 12-h dark-light cycle with free access to food and water. All animals were treated with humane care according to the guidelines established by the Northwest A & F University Animal Care and Use Committee throughout the experiment under the above conditions for one week acclimation period.

Mice were used in the experiment at 8 weeks of age and randomly assigned to three experimental groups, i.e. the negative control (CTL–), positive control (CTL+) and mice challenged with *L. plantarum*. Mice in CTL+ and *L. plantarum* groups were given subcutaneous injections of 100 µg of PN in PBS containing 1 mg $\text{Al}(\text{OH})_3$ on the 7, 14, 21 and 28 days respectively. Equal amounts of $\text{Al}(\text{OH})_3$ in PBS were received in negative control. On 21 days, mice in *L. plantarum* group were challenged with suspension of 5×10^{10} *L. plantarum* by intragastrical gavage once a week for 4 weeks. After that, blood samples were collected from the retro-orbital plexus and serum samples were pooled in equal volumes within each group to determine the histamine levels, IgE levels. Mice were also killed to collect gut segments from the ileums, which were snap frozen in liquid nitrogen and then stored at -80°C for later analysis of cytokine mRNA expression.

2.3. Culture of bacteria in faeces

Procedures for the culture of bacteria in faeces were performed as previously described (Huang, Cheng, Deng, Chou, & Jan, 2012). Briefly, the faecal samples were weight, suspended, serially diluted and cultured in triplicate on tryptic soy agar (TSA) plates and MRS agar plates under anaerobic conditions, which were a basic medium for non-specific bacteria and a selective medium for LAB. After incubation for 48 h, the density of microbes was expressed as CFU/g of faeces.

2.4. Clinical hypersensitivity signs of mice

The evaluation of diarrhea symptom was carried out as previous research (Hyung et al., 2017; Tanabe et al., 2015). The severity of diarrhea was assessed to a value of 0–3 using feces between 30 and 60 min after the challenge of PN. 0, no fecal matter or solid state; 1, funicular form; 2, slurry; 3, watery state.

Clinical scores were assessed as described previously (Yang & Mine, 2009). The scores were as follows: 0 indicated no signs; 1 indicated repeated scratching; 2 indicated puffiness around the eyes and snout, diarrhea, pilarerecti, and reduced activity with increased respiratory rate; 3 indicated wheezing, laboured respiration, and cyanosis; 4 indicated tremor and convulsions; and 5 indicated death.

2.5. The measurement of Ara h 2-specific antibodies in serum

The serum levels of Ara h 2-specific IgE was determined measured using ELISA according to the previously reported method (Wu, Chen, Lee, Ko, & Lue, 2016). In short, the 96-well microtitre plates were coated with 100 µL Ara h 2 (100 mg/mL) in 0.1 M carbonate buffer (pH 9.6) overnight at 4°C . The plates were washed with Tween 20 solution (0.05%) and then blocked with bovine serum albumin (3%) for 1 h at 37°C . After washing, 100 µL of sera diluted 20-fold in bovine serum albumin was added and incubated at 4°C

overnight. After washing, horseradish peroxidase-labeled anti-mouse IgE (Southern Biotechnologies Associates, Birmingham, AL, USA) diluted 10,000-fold was added to each well and the plates were incubated for 2 h at room temperature. The reaction was stopped by the addition of 100 μ L 2 M H₂SO₄. The antigen level was read at 450 nm on a microplate reader (Bio-Rad Pacific Ltd., Hong Kong, China).

2.6. Measurement of serum histamine levels

The histamine levels in the serum were measured according to the ELISA kit (Histamine EIA, LDN Labor Diagnostika Nord, Nordhon, Germany), as described by the manufacturer. Briefly, the histamine standards of known concentration were provided according to the manufacturer. Quantification of unknown samples was achieved by comparison of their absorbance with the reference curve. Serum samples (1:10 dilutions) were run in triplicate wells along with the histamine standards.

2.7. Real-time RT-PCR analysis of interleukin (IL) -10 and interferon (IFN)- γ

Real-time RT-PCR was used for relative quantification of cytokines gene mRNA expression. Briefly, Total RNA of ileums tissues was extracted using TRIzol reagent according to the manufacturer's instructions. The RevertAid First Strand cDNA Synthesis Kit (MBI Fermentas, Hanover, MD, USA) was used to synthesize complementary DNA (cDNA). The real-time fluorescence-monitored PCR reactions were performed using a 7900-HT fluorescence detection system (Applied Biosystems, Foster City, CA, USA) and a SYBR-Green qPCR kit (Applied Biosystems) according to optimized PCR protocols. To amplify IL-10, IFN- γ and β -actin cDNA fragments, the following sequences of PCR primers pairs and RT-PCR reaction conditions were used according to our previous study (Long, Yang, Wang, Hu, & Chen, 2015).

2.8. Statistical analysis

All analyses were performed with SPSS 16.0 software. Results were presented as means $\pm$ standard deviation (SD). The data were analyzed following one-way ANOVA analyses and differences considered to be statistically significant with a p -value threshold set at 0.05.

3. Results and discussion

3.1. Effects of *L. plantarum* on the density of enteric bacterial flora in mice sensitized with peanut allergen

The intestinal microbes are involved in the development of the host immune system and the maintenance of the immuno-balance in gastrointestinal tract (Hardy, Harris, Lyon, Beal, & Foey, 2013; Tanaka & Ishikawa, 2004; Umesaki & Setoyama, 2000). As a major risk factor, gut microbiota dysbiosis is regarded for food allergy (Cao, Feehley, & Nagler, 2014; Huang et al., 2016). In the present study, a significantly ($p < 0.05$) diminished density of faecal LAB was exhibited in the CTL+ group mice (Figure 1A). Meanwhile, an increased ($p < 0.05$) density of non-specific microbes was showed (Figure 1B).

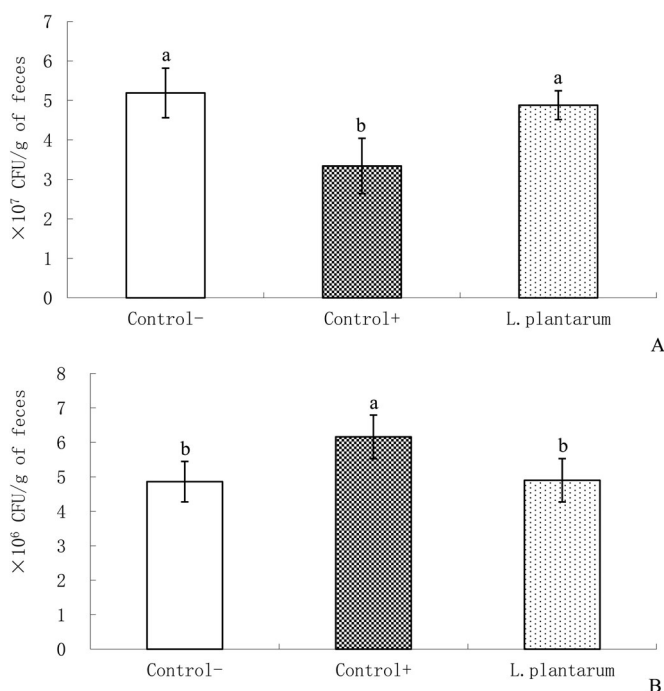


Figure 1. Effects of oral administration with *L. plantarum* on the density of LAB (A) and non-specific microbes (B) in faeces. The faecal samples were weight, suspended, serially diluted and cultured incubated in triplicate on MRS plates and TSA agar plates under anaerobic conditions. Data are expressed as mean $\pm$ standard deviations. Columns without the same letters indicate significant changes ($p < 0.05$) between groups of mice.

Recently, some research on food allergies has been focused on modulating the gut microbiota composition (Schiavi et al., 2011). Notably, administration with *L. plantarum* significantly enhanced the density of LAB and decreased the non-specific microbes in peanut-allergy mice ($p < 0.05$). These results are in line with the previous study (Huang et al., 2016) showing that oral administration with *L. murinus* increased density of LAB and restored the deteriorated profile of intestinal bacterial flora in allergic mice. Therefore, both LAB and non-specific microbes in the peanut-allergy mice group were restored to the levels similar to the CTL- group with the administration of *L. plantarum*.

3.2. Effects of *L. plantarum* on peanut-induced food allergy symptoms

The immunomodulatory role of *L. plantarum* in a food allergy mouse model was studied. Based on a previous publication, we modified our experimental regime by subcutaneous injections of PN. This model exhibited the characteristics of type 1 hypersensitivity reactions. Food allergies results in decreased intestinal absorption capacity and increased permeability (Marko & Pawliczak, 2017), then, diarrhea occurs. In the study, mice developed diarrhea 30–60 min after the repeated PN challenge. The signs of funicular form and slurry faeces were observed (Figure 2A), a typical symptom of food allergy. Compared to the CTL- group, mice in the CTL+ group show significantly ($p < 0.05$) increased

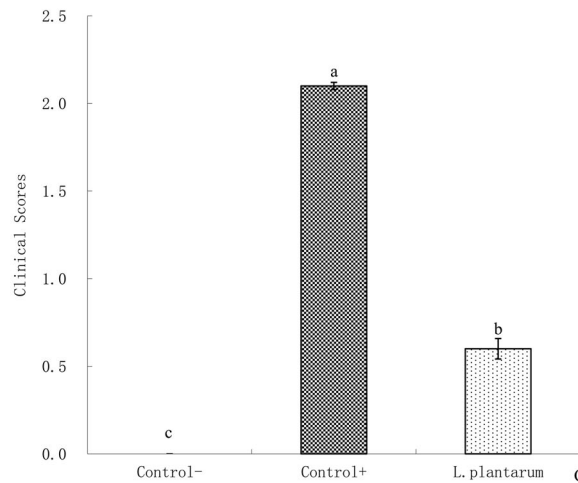
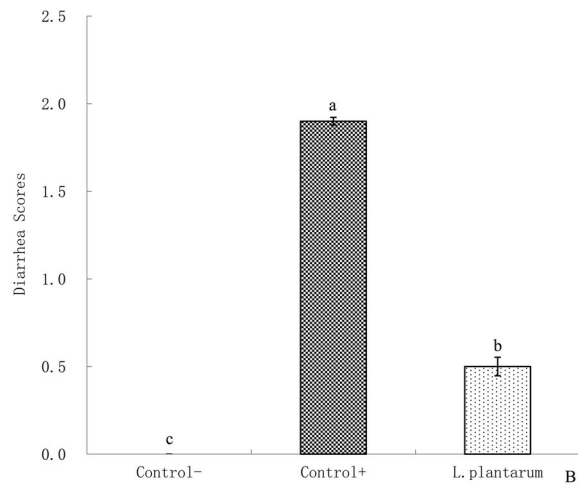
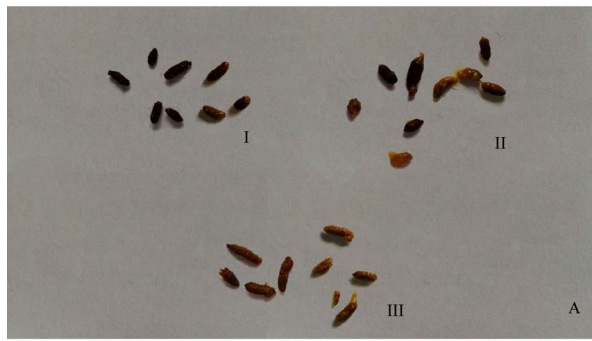


Figure 2. Clinical hypersensitivity signs including diarrhea symptom (A), diarrhea scores (B) and clinical scores (C) were represented to evaluate the severity of food allergy. I, II, III mean the negative control (CTL-), positive control (CTL+) and mice challenged with *L. plantarum*. The severity of diarrhea and clinical scores were assessed to a value of 0–3 using feces and 0–5 between 30 and 60 min after subcutaneous injections of PN and intragastric challenge, respectively. Data are expressed as mean $\pm$ standard deviations. Columns without the same letters indicate significant changes ($p < 0.05$) between groups of mice.

values of diarrhea (Figure 2B). With oral administrations of *L. plantarum*, mice showed attenuated diarrhea. The results were in line with Hyung et al. (2017) who reported that administration of lactic acid bacteria alleviates diarrhea challenged with ovalbumin.

In order to investigate whether alteration of *L. plantarum*-induced immune response caused relief of clinical symptoms, the clinical scores were further confirmed. In CTL+ group, repeated administration of PN led to higher clinical scores than the CTL− group ($p < 0.05$) with symptoms of allergy (Figure 2C), including diarrhea and reduced activity with increased respiratory rate and wheezing. Upon final oral challenge with *L. plantarum*, mice showed significant ($p < 0.05$) difference in clinical signs with the CTL+ group and little repeated scratching was observed in mice. The results showed that repeated oral administration of *L. plantarum* inhibited anaphylactic response induced by peanut allergen. It was initially demonstrated that a certain amount of *L. plantarum* had the antiallergic effects on peanut allergic mice.

3.3. *L. plantarum* decreased the levels of specific IgE in mouse models

Food allergy is today recognized as an immune-mediated state of hypersensitivity that results from an exposure to an allergen, usually a protein of food origin, sometimes also defined as type I allergy, an IgE-mediated immunologic reaction to specific foods (Hefle, Nordlee, & Taylor, 1996). The IgE binds to the high affinity IgE receptor and cross-links with allergens on mast cells, which trigger their degranulation. Then, histamine, leukotrienes and other mediators that induce symptoms of immediate hypersensitivity are released (Galli, Grimaldeston, & Tsai, 2008). Therefore, increased total serum IgE levels have been suggested as being predictive parameters of hypersensitivity (Ban & Hettich, 2001). As can be seen from Figure 3, the increased of serum IgE production in PN-induced food allergic model and the inhibitory effect by *L. plantarum* on IgE levels were presented ($p < 0.05$). These results demonstrate that *L. plantarum* attenuated food allergy symptoms through suppression of IgE systemic immune responses. Brandt et al. (2003) found that allergic diarrhea is mediated by a mechanism involving classic IgE-mediated mast cell activation. Furthermore, Huang et al. (2016) demonstrate that as an immunoactive probiotic, *L. murinus* administration attenuated allergic responses,

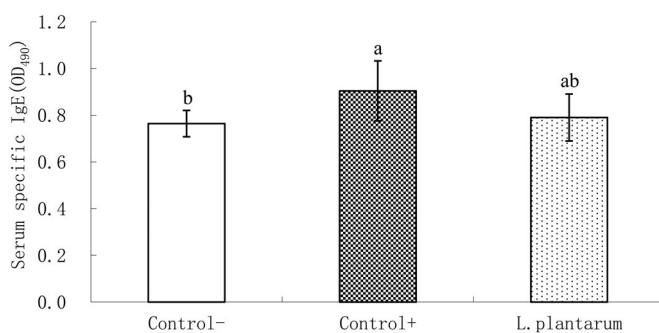


Figure 3. Effects of oral administration with *L. plantarum* on IgE binding in a mouse model of PN allergy. Serum specific IgE levels in PN-sensitized Balb/c mice was analysis by ELISA after repeated oral administration of *L. plantarum*. Data are presented as the means $\pm$ standard deviations. Columns without the same letters indicate significant differences ($p < 0.05$) between groups of mice.

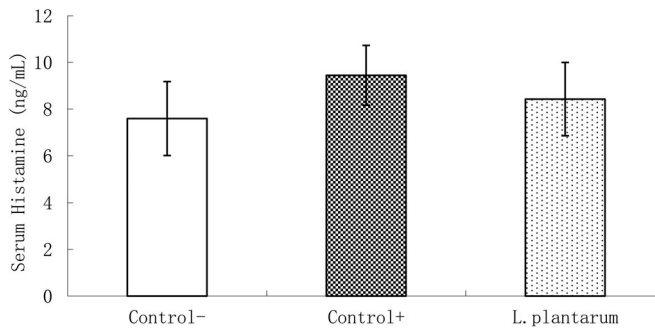


Figure 4. Effects of oral administration with *L. plantarum* on histamine levels in serum in a mouse model of PN allergy. Serum histamine concentrations was measured by ELISA in Balb/c mice after repeated intragastric administration sensitization with *L. plantarum*. Data are presented as means $\pm$ standard deviations.

including the occurrence of allergic diarrhea, mast cell activation and serum IgE production. In line with this notion, we showed that oral intake of *L. plantarum* effectively restored the admonished the diarrhea symptom and suppressed the IgE levels induce by peanut allergy.

3.4. *L. plantarum* inhibits the production of histamine in peanut allergy mice

Following mast cell activation, as a critical mediator, histamine increased at sites of allergic inflammation (Oksaharju et al., 2011), which caused type I allergic symptoms (Hata et al., 1998; Zhang, Yang, Rupa, Jiang, & Mine, 2012). In the present study, the CTL+ group mice demonstrated increased ($p = 0.076$) tendency levels of histamine compared to those in mice that were not sensitized to peanut allergen (Figure 4). Repeated administration of food allergy led to allergy with higher histamine levels, including shrimp, peanut and walnut (Long et al., 2015, 2016). Notably, Brandt et al. (2003) showed exposure of OVA-sensitized mice to repeated doses of intragastric OVA induced acute allergic diarrhea associated with increased intestinal permeability, which occurred by a largely histamine-independent process. With oral administration of *L. plantarum*, serum histamine level was diminished in the CTL+ group. Oksaharju et al. (2011) reported certain probiotic bacteria might diminish mast cell allergy-related activation by down regulation of the expression of high-affinity IgE and histamine receptor genes. In addition, it was previously reported that *L. plantarum* strain 06CC2 significantly alleviated allergic symptoms and reduced the ovalbumin specific IgE and histamine in the sera of ovalbumin-sensitized mice. Although *L. plantarum* may be able to control histamine levels, statistical significance did not be obtained due to the kind or dose of probiotic treatments. Therefore, further study is a need to be elucidated.

3.5. Cytokine mRNA expression in ileums tissues

To determine whether *L. plantarum* alter the inflammatory immune response, the cytokine mRNA expression profiles of IL-10 and IFN- γ that are associated with intestinal inflammation was assessed. Our results showed that the PN-sensitized mice expressed

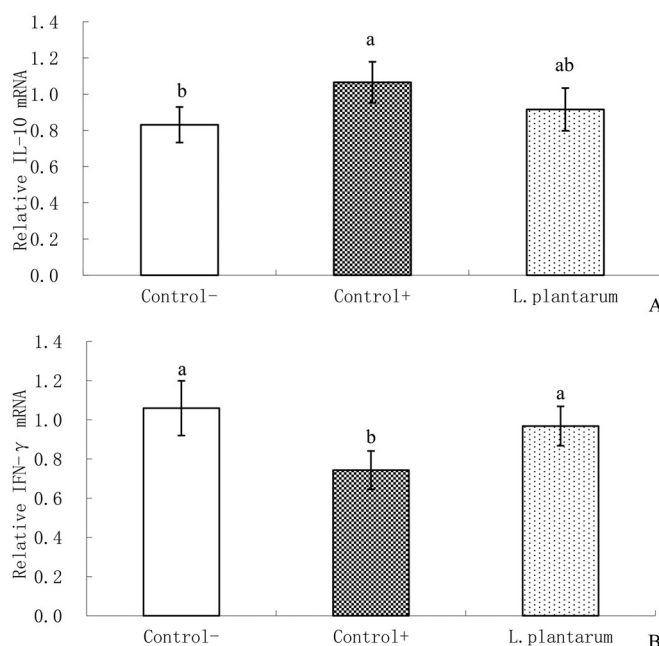


Figure 5. Effects of oral administration with *L. plantarum* on IL-10 (A) and IFN- γ (B) mRNA expression in a mouse model of PN allergy. After repeated intragastric administration sensitization with *L. plantarum*, the relative expression of IL-10 and IFN- γ mRNA in ileum tissues from Balb/c mice was analyzed by real-time RT-PCR. Data are presented as means $\pm$ standard deviations. Columns without the same letters indicate significant differences ($p < 0.05$) between groups of mice.

higher ($p < 0.05$) levels of IL-10 mRNA expression than the CTL- group, but the decreased tendency after treatment with *L. plantarum* (Figure 5A). Wu et al. (2016) also showed that after treatment with *Lactobacillus rhamnosus* GG (LGG), IL-10 levels in serum and Bronchoalveolar lavage fluid were significantly decreased compared to OVA-sensitized mice. Whereas Lammers et al. (2005) reported that cytokines IL-10 in mucosal gene expression was not altered through several probiotic therapies. Conversely, after oral probiotics, the levels of IL-10 and IFN- γ become significantly higher than those in non-treated mice (Kim, Choi, & Ji, 2008). *Lactobacillus* GG is thought to modulate the immune system by elevating anti-inflammatory IL-10 (Isolauri, Arvola, Sütas, Moilanen, & Salminen, 2000). These contradictory results might be caused by the kind or administration of allergen, or different probiotic treatments. So supplementary analyses aimed at verifying the mechanisms of probiotic therapy still remain to be resolved.

Herein, IFN- γ gene expression was significantly ($p < 0.05$) decreased in CTL+ group compared with the CTL- group (Figure 5B) and was effectively upregulated through oral administration of *L. plantarum*, which implies its possible application to allergic diseases. Furthermore, previous studies have shown that several probiotic therapies decreased IFN- γ mucosal gene expression (Lammers et al., 2005; Wu et al., 2016). In recent studies, IFN- γ increased significantly after treatment with oral administration of LGG (Wu et al., 2016) and strain 06CC2 (Takeda et al., 2014). These results support the theory that probiotic therapies including *L. plantarum* may be an effective anti-allergy therapy.

4. Conclusion

In conclusion, our results demonstrate that *L. plantarum* is a functional probiotic possessing anti-allergic activities in mice. Oral administration with *L. plantarum* may be beneficial for improving both microbial balance and cytokine mRNA expression, as well as associated with attenuated food allergy. Therefore, *L. plantarum* was suggested to be a useful functional food ingredient to alleviate type I allergies and was expected to develop the products. Meanwhile, the immunoregulatory mechanisms need further to elucidate.

Disclosure statement

No potential conflict of interest was reported by the authors.

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