

Antiallergic Effects of Probiotic Lactobacilli – Cellular and Molecular Mechanisms

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Abstract The continued increase in prevalence of allergic rhinitis particularly in developed countries is a matter of public health concern. Allergic rhinitis is characterized by an elevation in serum Immunoglobulin E (IgE) levels, which is caused by an imbalance in the expression of T helper cells (Th1-) and Th2-cytokines. Several studies have shown certain lactobacilli bacteria possess antiallergic properties; however the effect is strain and dose-dependent. The suggested mechanisms for the antiallergic effects include improvement of the T helper cells (Th) 1/Th2 immunobalance by inducing the Th1 cytokines and suppressing Th2-skewed immuno-response. Besides, lactobacilli can stimulate the regulatory T cells, which are vital in the maintenance of the immune balance through the production of immunosuppressive cytokines. Some lactobacilli have demonstrated the potential to modulate serum IgE, IgA and IgG production. However, the molecular mechanism for the immunoregulatory effect of probiotic lactobacilli is yet to be fully elucidated. This review highlights the novel opportunities for utilizing probiotics towards prevention or management of allergic diseases such as allergic rhinitis and mainly focuses on the potential cellular and molecular mechanism underlying the antiallergic effect of probiotic lactobacilli.

Keywords Probiotics, Lactobacilli, Th1/Th2 immunobalance, Allergic rhinitis

1. Introduction

The rapid rise in global prevalence of allergic rhinitis is a matter of public health concern especially in the developed world [1]. School children and young adolescents are the most affected compared with adults [2]. The increased trend has been partly attributed to the ‘hygiene hypothesis’, which suggests that modern methods of hygiene and sanitation have decreased children’s exposure to certain microbes, thereby leading to less bacteria-derived maturation signals during early immune development [3]. Allergic rhinitis is clinically mediated by elevated serum antigen-specific immunoglobulin (Ig) E that binds high affinity receptor (FcεRI) on the surface of mast cells [4]. This process sensitizes the mast cells to specific allergens. Subsequent exposures with the allergens result in the cross-linking of the antigen-specific IgE–FcεRI complex, inducing degranulation of inflammatory mediators such as histamine, prostaglandins, and cytokines (IL-4, IL-6, IL-8, IL-13, TNF-α) [5-7]. The stimulation of mast cells by allergens initiates intracellular signaling of two main pathways: (i) extracellular signal-regulated kinases (ERK)/

c-Jun N-terminal kinase (JNK), and (ii) phosphoinositide 3-kinase (PI3K)/Akt pathways. The downstream molecular events include elevated intracellular Ca²⁺ levels that signal degranulation; increased phospholipase A₂ activity in the plasma membrane releasing arachidonic acid-derived prostaglandins and leukotrienes; and enhanced expression of the mitogen-activated protein kinases (MAPK) family and nuclear factor-κB (NF-κB) signalling pathways leading to cytokines secretion [6, 8]. Besides, signaling of histidine decarboxylase (HDC), a rate-limiting enzyme, produces histamine from histidine [9]. Collectively, these mediators contribute to the inflammation of the nasal mucosa and allergic-response symptoms (sneezing, watery rhinorrhoea, itchy nose, nasal blockage), which ultimately have an impact on the loss in quality of life as well as socioeconomic implications [10]. Furthermore, allergic rhinitis has been identified as a risk factor for asthma development [11].

In recent years, more research has focused on appropriate dietary prevention methods in the management of allergic diseases. Probiotics are usually defined as viable microorganisms that when ingested in adequate amounts, can confer beneficial effects on human health [12]. However, a considerable number of recent studies have demonstrated that beneficial effects are not only achieved by live bacteria but also by heat-inactivated or isolated bacterial DNA or probiotic-cultured media [13].

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Lactobacilli are mainly consumed through fermented foods such as milk products. Epidemiological studies indicate an inverse correlation between the incidence of allergic diseases and intestinal microbiota populations, particularly lactic acid bacteria (LAB) belonging to the lactobacillus genus [14, 15]. Furthermore, randomized clinical studies have shown lactobacilli bacteria can improve nasal and ocular symptoms, and quality-of-life attributes in allergic subjects. These include *L. gasseri* A5 [16], *L. paracasei* 33 [17], *L. acidophilus* L-92 [18, 19], *L. casei* DN114001 [20], *L. plantarum*-14 [21], *L. paracasei* ST11 [22], *L. paracasei*-33 [23], *Lactobacillus* GG (LGG) and *L. gasseri* TMC0356 (TMC0356) [24]. However, in contrast, other studies have indicated *L. gasseri* OLL 2809 [25], *L. rhamnosus* GG [26], *L. paracasei* KW 3110 [27], *L. casei* Shirota [28], *L. rhamnosus* (ATCC 53103) [29], *L. gasseri* OLL2809 [25], and *L. acidophilus* [30] have no improvement effect on clinical parameters of allergic rhinitis when compared with the placebo groups. Nevertheless, these discrepancies on the beneficial effects have been largely attributed to the differences in the study design including consumption period, sample size, target population, lactobacilli strains and dosage [3, 31, 32].

2. Cellular and Molecular Mechanistic Antiallergic Effects of Lactobacilli

Although several clinical trials suggest probiotic lactobacilli may decrease and prevent allergic rhinitis symptoms and inflammatory markers, the mode by which they elicit these health effects are not fully understood [33]. The bacterial cell wall components (peptidoglycan) and the toll-like receptor (TLR-2) signalling pathway could be vital in the immunostimulatory effect of lactobacilli [34, 35]. The suggested mechanisms for the antiallergic effects include improvement of the T helper cells (Th) 1/Th2 immunobalance, stimulation of the regulatory T cells, and modulation of the IgE, IgA and IgG production as deliberated below.

2.1. Modulation of Th1/Th2 Immunobalance

Several *in vitro* and *in vivo* studies suggest that the probiotic antiallergic effects are strain-dependent and are mediated by improvement of the T helper cells (Th) 1/Th2 immunobalance by inducing the Th1 cytokines and suppressing Th2-skewed immuno-response [33, 36]. The Th2-cytokines (IL-4, IL-5, IL-6, IL-13, IL-9) increase the production of IgE, and stimulate mast cells and eosinophils, whereas Th1-cytokines (IL-12, IL-2, IFN- γ , IL-1 β) suppress IgE synthesis [34]. According to a study by Hong et al., *L. kefiranofaciens* M1 (LKM1), decreased Th2 cytokines (IL-5) and increased Th1 cytokines (IL-12, IL-2, IFN γ , and TNF- α , IL-1 β) in splenocyte and macrophage cells [35, 37]. Furthermore, *L. kefiranofaciens* M1 and respective supernatant showed strong potential to induce *in vitro* production of TNF- α , IL-1 β , IL-6 and IL-12 in RAW 264.7

cells and murine peritoneal macrophages [35, 37]. Sashihara et al., studied the effect of heat-killed lactic acid bacteria on cytokines of murine splenocytes and found *L. plantarum*, *L. gasseri* were strong inducers of IL-12 and there was a significant correlation between IL-12 stimulatory activity and amount of peptidoglycan (PGN) in the cells [38]. In addition, up regulation of IL-12, IFN- γ was significantly correlated with the down-regulation of IL-4. These effects were strain dependent and those lactobacilli with high IL-12p70 stimulatory effect showed marked modification of the IFN- γ and IL-4 balance. A previous study using sensitized mouse models showed LKM1 substantially inhibited Th2 cytokines (IL-6, IL-5, IL-1 β , IL-13, IL-4), and induced production of Th1 cytokines (IL-12, IFN- γ) as well as regulatory T cells [37, 39].

Clinical trials have shown the potential of probiotics to induce Th1 cytokines such as IL-12, IFN- γ [21, 40-42] and inhibit the Th2 cytokines such as IL-4, IL-5, IL-6, IL-13 in allergic subjects [16, 22, 24, 43]. However, other studies reported no difference in the Th1/Th2 cytokines ratio between the probiotic and the placebo groups [19, 44]. These inconsistent findings suggest that the effect of probiotics on the Th1/Th2 immunobalance is varied and strain-specific. Indeed, the strain-dependent differences in cytokine responses of human peripheral blood mononuclear cells (PBMC) to lactobacilli have been associated with the differences in microbe-associated molecular patterns such as lipoteichoic acid, peptidoglycan, and non-methylated CpG motifs [36, 38].

2.2. Modulation of Regulatory T Cells (Treg)

Lactobacilli probiotics can stimulate the regulatory T cells, which are vital in the maintenance of the immune balance through the production of immunosuppressive cytokines such as IL-10 and transforming growth factor (TGF- β) [4]. Dong *et al* demonstrated a positive correlation between IL-10 and IL-6 induction in human PBMC cultured with probiotic strains, and the authors suggested that the strain-specific IL-10 production by probiotic strains may be partly dependent on the induction of IL-6 [45].

2.3. Suppression of IgE Production

Decreased allergen-specific IgE in atopic individuals is generally associated with hypo-sensitization and resolution of allergic rhinitis [10]. Various mouse model studies have shown reduced production of IgE after administration of certain *lactobacilli* namely *L. pentosus* S-PT84 [46], *L. paracasei* KW 3110 [27], *L. gasseri* OLL 2809 [38], *L. acidophilus* L-92s [47], and *L. brevis* SBC 8803 [48]. According to Hong et al., oral feeding of *L. kefiranofaciens* M1 to mouse inhibited production of total-IgE and ovalbumin specific-IgE. Recent studies of LKM1 using sensitized mouse models showed diminished total and ovalbumin-specific IgE levels [37, 39], and reduced airway inflammation [39]. The authors observed that not only live

but also heat-killed *L. kefiranofaciens* M1 exhibited immunostimulatory activity. While evaluating the antiallergic effects of *kefir* lactobacilli in mouse model, Hong *et al.*, observed that the suppression of IgE production by heat-killed *L. kefiranofaciens* M1 probably occurs because of up-regulation of the expression of *Cd2*, *Cd3*, *Cd28*, *Stat4*, *Ifn γ* , (resulting in Th1 dominance); down-regulation of the complement system, elevation of CD4+CD25+ T regulator cells and reduction of CD19+B cells maturation [37].

Several allergic rhinitis-related clinical trials have indicated no effect on IgE levels upon consumption of *L. plantarum* HSK 201 [42], *L. casei* [20], *L. gasseri* PM A0005 [16], and *L. acidophilus* L-92 [18, 19]. However, other studies involving *B. longum* BB536 [40, 49], and *L. casei* Shirota [43] demonstrated reduced trends of allergen-specific IgE. Total IgE is often elevated in people with allergies, but it may be influenced by age, genetic predisposition, ethnicity, immune status, and some disease processes. Thus, measuring total IgE levels may have limited value as a screening test for allergic disease [50]. Indeed, some authors have indicated that the changes in clinical symptoms may not necessarily simultaneously correspond with the changes in the blood immunologic parameters including IgE levels [51], which may reflect the complexity in the mechanism of probiotic action. Thus, besides suppression of IgE or normalization of Th1/Th2, several mechanisms that could be involved in the antiallergic effect of probiotics in humans such as IL-17, T-regulators, natural killer cells, stabilized intestinal barrier, and restoration of normal gut micro-ecology [32, 36, 52, 53].

2.4. Modulation of IgA, IgG, IgM Antibodies

It has been reported that other allergen-specific antibodies such as IgG, IgG₄ and IgA are also involved during the development of allergic diseases. Miranda and colleagues found allergen-specific IgE and IgG₄ were higher in allergic children, but in contrast, allergen-specific IgA levels were higher in non-allergic children, implying that IgA may confer a protective effect by competitive exclusion of IgE production [54]. Several studies have demonstrated the potential of lactobacilli to modulate serum IgE, IgA and IgG production in subjects with allergic rhinitis. Giovannini *et al.* found insignificant effect of *L. casei* on total IgA, IgG and IgM levels [20]. In contrast, *L. casei* Shirota markedly induced grass pollen-specific IgG [43], whereas *L. paracasei* ST11 inhibited IgG₄ in subjects with pollen-allergy [22].

2.5. Promotion of Natural Killer Cells (NK) Activity

Although NK cells are largely associated with phagocytosis, growing evidence indicate they could, either directly or indirectly, play a significant role in the pathogenesis of allergy [55]. Probiotics influence dendritic cells to produce IL-12, which induces IFN- γ production by

the T and NK cells [56]. IFN- γ is a Th1 cytokine, thus confer antiallergic effects. Various *in vitro*, animal and human studies demonstrate probiotics can variably modulate the NK cell activity in a strain- and dose-dependent manner. Dong *et al.* studied selective effects of *L. casei* Shirota and reported enhanced NK activity in human PBMC [57]. Animal study using mouse model showed up regulation of genes involved in NK cell activation after administration of *L. brevis* KB290 [58]. Human studies showed *B. lactis* HN019 promoted NK cell activity in healthy subjects [59, 60, 61]. Other clinical studies showed enhanced NK activity after consumption of *L. rhamnosus* [62], *L. paracasei* [63] and *L. casei* Shirota [64].

3. Conclusions

In conclusion, the antiallergic effects of lactobacilli are mainly attributed to modulation of Th1/Th2 immunobalance, IgE production, and Treg production. This paper focuses on the cellular and molecular mechanisms underlying the antiallergic effect of probiotic lactobacilli in *in vitro*, *in vivo* and clinical trials, thus provides a detailed and better understanding of the antiallergic effects. It is anticipated that this could facilitate future studies on the potential of and utilization of novel lactobacilli for prevention or management of allergic diseases such as allergic rhinitis.

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