The Use of Probiotics in Respiratory Allergy

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Abstract: There is a high and steadily increasing prevalence of respiratory allergy throughout the world, especially in paediatric population and in industrialized and developing countries. A complex interplay between genetic and environmental factors has been implicated to explain this dramatic increase in prevalence of allergic diseases. It has been suggested that exposure to microbes plays a critical role in the development of the early immune system and may contribute to allergic diseases through their effect on mucosal immunity. Probiotics, microorganisms exerting beneficial effects on the host, are used in a great number of paediatric and adult diseases, mainly gastrointestinal disorders, but they have been proposed to be beneficial also in allergic diseases. Different trials have been published finding benefits in the use of probiotics in prevention and treatment of atopic dermatitis, but to date, studies have yielded inconsistent findings to support a protective association between their use on prevention of allergic rhinitis or asthma. However, probiotics may be beneficial in improving symptoms and quality of life in patients with allergic rhinitis although it remains limited due to study heterogeneity and variable outcome measures. As a result of these controversies, future investigations with a better standardization are needed. In this review, we summarize recent clinical research to elucidate the mechanisms of probiotics and their effect in respiratory allergy. According to published data, probiotics could emerge as a novel, complementary treatment option for allergic rhinitis but not for asthma.

Keywords: Probiotics, respiratory allergy, allergic rhinitis, asthma.

INTRODUCTION

Respiratory allergy affects an estimated 10 to 25% of the population and their prevalence is permanently increasing during the last three decades [1-3]. It seems to be more evident that allergy is the consequence of an interaction between genetic and environmental factors. Viruses, pollution, smoke and passive tobacco exposure, allergens or diet could play a key role in epigenetic changes, driving the immune system to an “allergic status”, specially if the exposure is early in life [4]. Microbiome includes mainly skin and mucosal bacterial flora, both aerobic and anaerobic bacteria, but also viruses and moulds, ordinary living in the same areas of the human body [5]. In later years, the focus has been placed has been placed on the intesinal microbiota which is the major source of microbial exposure, composed by 10 times the number of cells in the entire body [6]. It could interact with gut-associated lymphoid tissue and modulate immunologic and inflammatory responses [7]. After birth, the diversity of the gut microbiome increases with age [8]. A deprive microbial exposure or differences in patterns of microbial flora early in life, could change the balance of immune development contributing to explain this rapid increase in the prevalence of allergy. The disappearance of ancestral indigenous microbiota species or the loss of gut bacterial diversity has been observed in children at risk of asthma [9-11]. Prevalence of *Lactobacillus* in the first weeks of life [12] or the gram-negative/gram-positive ratio at 12 months of age, may affect the risk of developing allergic diseases [13, 14].

According to these findings, the role of beneficial bacteria in the form of probiotics to modify gut microbial composition has been explored. Probiotics have been used for the treatment of gastrointestinal disturbances, cardiovascular diseases, autoimmune diseases and obesity [15, 16]. For atopic diseases, there are numerous studies on the efficacy of probiotics for the prevention and treatment of atopic dermatitis [17-21]. Even the World Allergy Organization (WAO) has recently provided evidence-based recommendations suggesting the use of probiotics in pregnant woman with children at high risk of allergy, in women who breastfeed infants at high risk of allergy and, finally, in children at high risk of developing allergies, could be net beneficial for prevention of eczema [22].

Even though a large number of studies have evaluated the efficacy of probiotics for the prevention and treatment of IgE-mediated respiratory diseases, results have been at least controversial. The aim of this review was to evaluate the effect of probiotics in the setting of prevention and treatment of respiratory allergy, allergic rhinitis and asthma, according to current published evidence.

MECHANISM OF ACTION OF PROBIOTICS IN ALLERGIC DISEASES

According to the World Health Organization and the Food and Agriculture Organization of the United

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Nations, “probiotics are live microorganisms which, when administered in adequate amounts as part of food, confers a beneficial health effect by producing gut microflora on the host” [23]. They are usually anaerobic organisms that ferment ingested food products in the intestines to produce lactic acid. In medicine, probiotics are used as a supplementary therapeutic agent for several diseases. Probiotics may improve health by several mechanisms although its action mechanism has not been fully clarified. The mechanism of action of probiotics could be multi-faceted. The genre most commonly used in prevention and treatment of allergic diseases includes *Lactobacillus* and *Bifidobacterium*. Their biological features enable them to predominate and prevail over potential pathogenic microorganisms in the human digestive tract, by suppressing their growth or/and competing for binding sites on the intestinal mucosa. These bacteria affect T helper (TH) responses, eliciting TH_1 cytokine production or, indirectly, by stimulating T-regulation [24]. They have also been implicated in actively suppressing TH_2 responses. *Lactobacillus* bacteria affect T-regulatory cells by generating semi-mature dendritic cells and increasing the expression of CD40. Specifically, *L paracasei* NCC2461 inhibits Interleukin (IL)-4, IL-5 or interferon-γ while inducing specific regulatory cytokines such as transforming growth factor (TGF-β) and IL-10 [23]. Probiotics can also enhance local IgA production which affects directly the mucosal defenses [25] and they have been involved in the maturation of adaptive T-cell immunity by stimulating the production of IL-17 (which plays a role in the immune protection to extracellular bacteria) [26]. Moreover, it has been recently described that probiotics could also have a role in modifying genetic susceptibility to eczema in high risk children affecting specific Toll-like receptors genotypes [27].

ALLERGIC RHINITIS AND TREATMENT WITH PROBIOTICS

Studies have shown that probiotics may be useful in the treatment of AR (Table **1**). Different strains have been studied for AR. *Wassemberg et al*. investigated the effect of *L. paracasei* ST-11 strain in a group of 31 volunteer adult patients (18-35 years) with AR due to grass pollen confirmed by either positive skin prick test or specific IgE for grass pollen [28]. They were enrolled and randomized in a DBPC study in order to receive fermented milk containing ST11 or a placebo, administered out of the pollen season, in a cross-over setting, during a period of 4 weeks. A nasal provocation test was performed with a standardized grass pollen extract and clinical parameters were compared between the two treatment periods. Subjects who received ST11-fermented milk showed improvement of subjective nasal congestion and nasal pruritus, measured by a visual analogical scale (p=0.04), in comparison to those patients under placebo. However, no significant differences were observed in allergen dose that caused a reaction or obstruction measure by peak nasal inspiratory flow [28].

Perrin et al. also studied the same probiotic *L. paracasei* versus a blend of *L. acidophius* and *B. lactis* in a DBPC cross-over trial, enrolling grass pollen allergic patients (n=31) during 4 weeks, in two phases, out of the pollen season [29]. Although no effect was observed on nasal congestion, a significant reduction of nasal pruritus in the *L. paracasei* group was demonstrated. Moreover, leukocytes in nasal fluids and IL-5 secretion were also significantly decreased in patients under treatment with *L. paracasei*. *Costa et al*., studied, in a DBPC trial, the efficacy of the probiotic *L. paracasei LP-33* in 425 patients with AR to grass pollen treated with loratadine and presenting altered quality of life [30]. After a run-in period receiving loratadine alone for 7-10 days, patients with a Rhinitis Quality of Life Questionnaire (RQLQ) ≥ 2 were randomized to placebo or LP-33 in addition to loratadine for 5 weeks. Loratadine was then discontinued and, only LP-33 or placebo, were continued for two additional weeks. The study confirmed a significant improvement in the RQLQ which was the primary end-point, in the LP-33 group (p=0.0255) and in ocular symptoms (p=0.0029). On the contrary, no significant differences were observed in nasal symptoms. Previously, two randomized DBPC trials had demonstrated improvement in the quality of life in persistent AR with the use of probiotics. In one of them, 90 house-dust mites allergic children ingested LP-33 over a period of 30 days [31], and in other similar results were obtained in 80 children [32]. Finally, a significant improvement in the total symptom score was also found for the Japanese cedar pollen allergic patients after supplementation with *L. paracasei.* [33].

Other strains have been explored. *Lue et at* showed that the use of levocetirizine plus *L. johnsonii* was more effective than levocetirizine alone in 63 children with perennial AR of at least one year´s duration in a randomized, open-label cross-over designed trial [34]. Both groups had improved the total symptom score from diary cards, but improvement was significantly higher in the group under the combination of antihistamine and probiotic, while no significant differences were observed in quality of life and immunological parameters between both groups. The

Table 1: Representative Probiotics Studied in Treatment of Allergic Rhinitis and Rhino-Conjunctivitis

Probiotic	Population	n	Type of AR	Primary end-point	Significance	Source
L. acidophilus and B.lactis	Children	47	Birch pollen	Symptoms score	p=0.078	Ouwehand *et al*. (2009) [35]
E. coli strain Nissle 1917	Adults	34	Grass pollen	Symptoms score	p=0.257	Dölle *et al*. (2014) [36]
L. johnsonii EM	Children	63	Perennial Rhintis	Symptoms score	p=0.09	Lue *et al*. (2012) [34]
B. longum BB536	Adults	40	Japanese cedar pollen	Ocular Symptoms score	p=0.04	Xiao *et al* (2006) [37]
L. paracasei (LP-33)	Children	80	Perennial	Quality of life	p=0.037	Wang *et al* (2004) [32]
L. paracasei	Children	90	House dust mites	Quality of life	p< 0.0001	Peng *et al*. (2005) [31]
L. paracasei KW3110	Adults	126	Japanese cedar pollen	Symptoms score	p< 0.05	Yonekura *et al* (2009) [33]
L. paracasei ST-11	Adults	31	Grass pollen	Nasal Provocation Test	ns	Wassemberg *et al* (2008) [28]
L. paracasei NCC2461	Adults	28	Grass pollen	Nasal congestion	ns	Perrin *et al* (2014) [29]
L. paracasei 33	Adults	425	Grass pollen	Rhinitis quality of life (RQLQ score)	p=0.0255	Costa *et al* (2014) [30]

E. coli: Escherichia coli; L. acidophilus: Lactobacillus acidophilus; L. johnsonii: Lactobacillus johnsonii; L. paracasei: Lactobacillus paracasei; B. lactis: Bifidobacterium lactis; B. longum: Bifidobacterium longum.

differences persisted 3 months after the discontinuation of probiotics. The combination of *L. acidophilus and B. lactis* in children (n= 47) with birch pollen AR was studied over a period of 4 months [35]. Results showed prevention in the pollen-induced infiltration of eosinophils into the nasal mucosa and a tendency towards the reduction in nasal symptoms. The role of *Escherichia coli* Strain Nissle 1917 supplementation has been recently explored in grass pollen allergic subjects with AR, but no significant effect has been shown [36]. Finally, decreased eosinophils and diminished IFN-γ in peripheral blood were reported after the ingestion of *B. longum,* thus also reducing the need for medication in Japanese cedar pollinosis [37].

Vliagoftis et al. in a meta-analysis published in 2008, described the results of 12 randomized clinical trials with probiotics in AR. In 9 of them, there were some improvements in clinical outcomes [38]. However, the heterogeneity of studies advised caution in the interpretation of the results. In 2015, *Zajac et al*, have been published a systematic review and meta-analysis of probiotics for the treatment of AR [39]. A total of 23 studies with 1919 patients were identified, including 21 randomized double-blind placebo-controlled (DBPC) and 2 randomized cross-over studies. In 17 of the trials the results showed a significant clinical benefit from the use of probiotics, at least in one of the measured outcomes when compared to placebo, especially those in the field of quality of life. On the other hand, 6 showed no effect, specifically in the area of the rhinitis total symptom score. Despite including almost 2000 patients, the overall cohort remained fairly heterogeneous and there were also limitations for comparison between individual studies, specifically the variability in study designs, outcome measures and probiotic formulations tested. In spite of these shortcomings, the conclusion from this systematic review suggested that probiotics might have some beneficial effects in patients with AR according to current evidence.

THE USE OF PROBIOTICS IN PREVENTION OF ALLERGIC RHINITIS

Even though current data shows that probiotics have a therapeutic effect in AR, no effect has been observed in relation to the prevention of the development of AR [22]. Most studies exploring the role of probiotics in atopic disease have also focused on early manifestations of respiratory allergy. *Peng et al*. have systematically reviewed them to determine the role of probiotics in prevention of AR [40]. There were five trials from which information about AR prevention could be extracted. The outcome of the meta-analysis revealed no differences in the incidence of AR between the probiotic and placebo groups (odds ratio 1.07 [95% CI, 0.81-1.42]; p=0.64).

ASTHMA AND PROBIOTICS

Studies exploring the role of probiotics in AD have also focused on prevention of asthma development

Table 2: Representative Probiotics Used to Prevent Asthma Disease. No Effect on Prevention of Asthma was Found in any of the Trials

Probiotic	Source
L. casei	Giovannini *et al*. (2007) [44]
L. rhamnosus GG, L. acidophilus La-5 and *B. animalis subsp. lactis Bb-12*	Simpson *et al*. (2015) [45]
B longum (BL99.9) and *L. rhamnosus* (LPR)	Loo *et al*. (2014) [46]
L. acidophilus LA-5,	Bertelsen *et al*. (2014) [47]
Bifidobacteria and Propionibacteria	Kuitunen *et al* (2009) [41]
L. reuteri	Abrahamsson *et al.* (2013) [42]
L. rhamnosus	Rose *et al*. (2010) [48]

L. acidophilus: Lactobacillus acidophilus; L. reuteri: Lactobacillus reuteri; L. casei: Lactobacillus casei; L. rhamnosus: Lactobacillus rhamnosus; B. longum: Bifidobacterium longum; B. lactis: Bifidobacterium lactis.

(Table **2**). If probiotics are able to prevent atopic eczema, it would be expected that, treated-children in these trials would have less asthma later in life. However, results have been at the moment discouraging. In a Finnish DBPC trial, 1223 mothers with infants at high risk of allergy received a mixture of *Bifidobacterium* and *Propionibacteria* during the last months of pregnancy. Infants continued taking probiotics until the age of six months. A preventive effect on asthma was not found up to 5 years of age in the total cohort, but interestingly less IgE-allergic disease occurred in cesarean-delivered children receiving probiotics [41]. A large Swedish follow-up study (7 years) completing a DBPC trial evaluating the effect of *L. reuteri* on allergic disease and sensitization, showed that the administration of the probiotic during the last weeks of gestation and 1 year in infancy, did not lead to a lower prevalence of asthma at school age [42]. Another large study could not find a long-term effect of *Lactobacillus paracasei* F19 (LF19) on any diagnosed allergic disease. Researchers investigated the effect of LF19 during weaning, from 4-13 months of age, as a tool in primary prevention of allergic disease [43]. The intervention was completed by 171 children whereas 121 were finally assessed. However, there was no effect of LF19 on respiratory allergic disease, lung function measures or FENO at age 8-9. Moreover, *Giovannini et al*. showed that long-term consumption of fermented milk (12 months) containing *L. casei* (n=187, 2-5 year of age) might improve the health status of children with AR reducing the annual number of rhinitis episodes, but had no effect on asthma [44]. Furthermore, in a recent meta-analysis covering 17 randomized-controlled or quasi-controlled trials and reporting data from 4755 children, no effects were observed on wheezing or asthma [21]. No beneficial effects in prevention of asthma have been observed with other different strains and worldwide populations [45-48].

Nevertheless, it has been demonstrated that *L. salivarius* LS01 and *B. breve* BR03, alone and in combination, could slightly inhibit the growth of some clinical pathogens (*Escherichia coli* and *S. aureus*) and be able to decrease the secretion of pro-inflammatory TH_2 cytokines on peripheral blood mononuclear cells of allergic asthmatics [49]. Interestingly, the combination of both strains in the same formulation seemed to implement the immunomodulatory activity of each strain alone. This data shows promising probiotic features in allergic asthma but further research is needed.

CONCLUSIONS

Probiotics appear to have beneficial therapeutic effects in AR. They may improve the overall quality of life scores and nasal symptom scores of patients with AR, but the mechanism and the duration of this effect remains unclear. By contrast, in asthma and prevention of respiratory allergy diseases, the use of probiotics cannot be advised for general population at this point according to current data. Future research is required, including long-term follow-up studies and the use of standardized criteria, in order to address the role of probiotics in respiratory allergy.

REFERENCES

[1] Asher MI, Montefort S, Björkstén B, *et al*. ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006; 368: 733-43. http://dx.doi.org/10.1016/S0140-6736(06)69283-0

[2] Bjerg A, Hedman L, Perzanowski M, Wennergren G, Lundbäck B, Rönmark E. Decreased importance of environmental risk factors for childhood asthma from 1996 to 2006. Clin Exp Allergy 2014; 45: 146-53.
http://dx.doi.org/10.1111/cea.12439

[3] Hastan D, Fokkens WJ, Bachert C, *et al*. Chronic rhinosinusitis in Europe: an underestimated disease. A GA²LEN study. Allergy 2011; 66: 1216-23.
http://dx.doi.org/10.1111/j.1398-9995.2011.02646.x

[4] Holt PG, Sly PD. Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. Nat Med 2012; 18: 726-35.
http://dx.doi.org/10.1038/nm.2768

[5] Ursell LK, Haiser HJ, Van Treuren W, *et al*. The intestinal metabolome: an intersection between microbiota and host. Gastroenterology 2014; 146: 1470-6.
http://dx.doi.org/10.1053/j.gastro.2014.03.001

[6] Prescott SL, Bjorksten B. Probiotics for the prevention or treatment of allergic diseases. J Allergy Clin Immunol 2007; 120: 255-62.
http://dx.doi.org/10.1016/j.jaci.2007.04.027

[7] Hakansson A, Molin G. Gut microbiota and inflammation. Nutrients 2011; 3: 637-82.
http://dx.doi.org/10.3390/nu3060637

[8] Yatsunenko T, Rey FE, Manary MJ, *et al*. Human gut microbiome viewed across age and geography. Nature 2012; 486: 222-7.
http://dx.doi.org/10.1038/nature11053

[9] Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? Nat Rev Microbiol 2009; 7: 887-94.
http://dx.doi.org/10.1038/nrmicro2245

[10] Björkstén B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. Clin Exp Allergy 1999; 29: 342-6.
http://dx.doi.org/10.1046/j.1365-2222.1999.00560.x

[11] Arrieta MC, Stiemsma LT, Dimitriu PA, *et al*. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med 2015; 7: 307ra152.

[12] Sjogren YM, Jenmalm M, Böttcher MF, Bjorkstén B, Sverremark-Ekströn E. Altered early infant gut microbiota in children developing allergy up to 5 years of age. Clin Exp Allergy 2009; 39: 518-26.
http://dx.doi.org/10.1111/j.1365-2222.2008.03156.x

[13] Adlerberth I, Strachan DP, Matricardi PM, *et al*. Gut microbiota and development of atopic eczema in 3 European birth cohorts. J Allergy Clin Immunol 2007; 120: 343-50.
http://dx.doi.org/10.1016/j.jaci.2007.05.018

[14] Melli LCFL, Do Carmo-Rodrigues MS, Araujo-Filho HB, Solé D, De Morais MB. Intestinal microbiota and allergic diseases: A systematic review. Allergol Immunopathol (Madr) 2015.
http://dx.doi.org/10.1016/j.aller.2015.01.013

[15] Scott KP, Antoine JM, Midtvedt T, Van Hemert S. Manipulating the gut microbiota to maintain health and treat disease. Microb Ecol Health Dis 2015; 26: 25877.
http://dx.doi.org/10.3402/mehd.v26.25877

[16] Dutton RJ, Turnbaugh PJ. Taken a metagenomic view of human nutrition. Curr Opin Nutr Metab Care 2012; 15: 448-54.
http://dx.doi.org/10.1097/MCO.0b013e3283561133

[17] Kalliomäki M, Salminen S, Poussa T, Arvilomni H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomized placebo-controlled trial. Lancet 2003; 361: 1869-71.
http://dx.doi.org/10.1016/S0140-6736(03)13490-3

[18] Foolad N, Brezinski EA, Chase EP, Armstrong AW. Effect of nutrient supplementation on atopic dermatitis in children: a systematic review of probiotics, prebiotics, formula, and fatty acids. JAMA Dermatol 2013; 149: 350-5.
http://dx.doi.org/10.1001/jamadermatol.2013.1495

[19] Pelucci C, Chatenoud L, Turati F, *et al*. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. Epidemiology 2012; 23: 402-14.
http://dx.doi.org/10.1097/EDE.0b013e31824d5da2

[20] Dang D, Zhou W, Lun ZJ, Mu X, Wang DX, Wu H. Meta-analysis of probiotics and/or prebiotics for the prevention of eczema. J Int Med Res 2013; 41: 1426-36.
http://dx.doi.org/10.1177/0300060513493692

[21] Zuccotti G, Meneghin F, Aceti A, *et al*. Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. Allergy 2015.
http://dx.doi.org/10.1111/all.12700

[22] Fiocci A, Pawankar R, Cuello-García C, *et al*. World Allergy Organization-McMaster university guidelines for allergic disease prevention (GLAD-P): Probiotics. World Allergy Organ J 2015; 8: 4.
http://dx.doi.org/10.1186/s40413-015-0055-2

[23] Technological and commercial applications of lactic acid bacteria: health and nutritional benefits in dairy products. http://www.fao.org/docrep/fao/009/a0512e/a0512e00.pdf

[24] Smith-Norowitz TA, Bluth MH. Probiotics and diseases of altered IgE regulation: a short review. J Immunotoxicol 2015; May 15: 1-5.
http://dx.doi.org/10.3109/1547691X.2015.1044053

[25] Campeotto F, Suau A, Kapel N, *et al*. A fermented formula in pre-term infants: clinical tolerance, gut microbiota, down-regulation of faecal calprotectin and up-regulation of faecal secretory IgA. Br J Nutrit 2011; 105: 1843-51.
http://dx.doi.org/10.1017/S0007114510005702

[26] Isailovic N, Daigo K, Mantovani A, Selmi C. Interleukin 17 and innate immunity in infections and chronic inflammation. J Autoimmun 2015; 60: 1-11.
http://dx.doi.org/10.1016/j.jaut.2015.04.006

[27] Marlow G, Han DY, Wickens K, *et al*. Differential effects of two probiotics on the risks of eczema and atopy associated with single nucleotide polymorphisms to Toll-like receptors. Pediatr Allergy Immunol 2015; 26: 262-71.
http://dx.doi.org/10.1111/pai.12371

[28] Wassenberg J, Nutten S, Audran R, *et al*. Effect of *Lactobacillus paracasei* ST11 on a nasal provocation test with grass pollen in allergic rhinitis. Clin Exp Allergy 2011; 41: 565-73.
http://dx.doi.org/10.1111/j.1365-2222.2011.03695.x

[29] Perrin Y, Nutten S, Audran R, *et al*. Comparison of two oral probiotic preparations in a randomized crossover trial highlights a potentially beneficial effect of *Lactobacillus paracasei* NCC2461 in patients with allergic rhinitis. Clin Transl Allergy 2014; 4: 1.
http://dx.doi.org/10.1186/2045-7022-4-1

[30] Costa DJ, Marteau P, Amouyal M, *et al*. Efficacy and safety of the probiotic Lactobacillus paracasei LP-33 in allergic rhinitis: a double-blind placebo-controlled trial (GA²LEN Study). Eur J Clin Nut 2014; 68: 602-7.
http://dx.doi.org/10.1038/ejcn.2014.13

[31] Peng GC, Hsu CH. The efficacy and safety of heat-killed *Lactobacillus paracasei* for treatment of perennial allergic rhinitis induced by house-dust mite. Pediatr Allergy Immunol 2005; 16: 433-8.
http://dx.doi.org/10.1111/j.1399-3038.2005.00284.x

[32] Wang MF, Lin HC, Wang YY, Hsu CH. Treatment of perennial allergic rhinitis with lactic acid bacteria. Pediatr Allergy Immunol 2004; 14: 152-8.
http://dx.doi.org/10.1111/j.1399-3038.2004.00156.x

[33] Yonekura S, Okamoto Y, Okawa T, *et al*. Effects of daily intake of Lactobacillus paracasei strain KW3110 on Japanese cedar pollinosis. Allergy Asthma Proc 2009; 30: 397-405.
http://dx.doi.org/10.2500/aap.2009.30.3256

[34] Lue KH, Sun HL, Lu KH, *et al*. A trial adding Lactobacillus johnsonii EM1 to levocetirizine for treatment of perennial allergic rhinitis in children aged 7-12 years. In J Pediatr Otorhinolaryngol 2012; 76: 994-1001. http://dx.doi.org/10.1016/j.ijporl.2012.03.018

[35] Ouwehand AC, Nermes M, Collado MC, Rautonen N, Salminen S, Isolauri E. Specific probiotics alleviate allergic rhinitis during the birch pollen season. World J Gastroenterol 2009; 15: 3261-8. http://dx.doi.org/10.3748/wjg.15.3261

[36] Dölle S, Berg J, Rasche C, Worm M. Tolerability and clinical outcome of coseasonal treatment with *Escherichia coli* Strain Nissle 1917 in grass pollen-allergic subjects. Int Arch Allergy Immunol 2014; 163: 29-35. http://dx.doi.org/10.1159/000356328

[37] Xiao JZ, Kondo S, Yanagisawa N, *et al.* Effect of probiotic Bifidobacterium longum BB536 in relieving clinical symptoms and modulating plasma cytokine levels of Japanese cedar pollinosis during the pollen season. A randomized double-blind placebo-controlled trial. J Investig Allergol Clin Immunol 2006; 16: 86-93.

[38] Vliagoftis H, Kouranos VD, Betsi GI, Falagas ME. Probiotics for the treatment of allergic rhinitis and asthma: systematic of randomized controlled trials. Ann Allergy Asthma Immunol 2008; 101: 570-9. http://dx.doi.org/10.1016/S1081-1206(10)60219-0

[39] Zajac AE, Adams AS, Turner JH. A systematic review and meta-analysis of probiotics for the treatment of allergic rhinitis. Int Forum Allergy Rhinol 2015; 5: 524-32. http://dx.doi.org/10.1002/alr.21492

[40] Peng Y, Li A, Yu L, Qin G. The role of probiotics in prevention and treatment for patients with allergic rhinitis: A systematic review. Am J Rhinol Allergy 2015; 29: 292-5. http://dx.doi.org/10.2500/ajra.2015.29.4192

[41] Kuitunen M, Kukkonen K, Juntunen-Backman K, *et al*. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivery children but not in the total cohort. J Allergy Clin Immunol 2009; 123: 335-41. http://dx.doi.org/10.1016/j.jaci.2008.11.019

[42] Abrahamsson TR, Jacobsson T, Björkstén B, Oldaeus G, Jenmalm MC. No effect of probiotics on respiratory allergies: a seven-year follow-up of a randomized controlled trial in infancy. Pediatr Allergy Immunol 2013; 24: 556-61. http://dx.doi.org/10.1111/pai.12104

[43] West CE, Hammarström ML, Hernell O. Probiotics in primary prevention of allergic disease: follow-up at 8-9 years of age. Allergy 2013; 68: 1015-20. http://dx.doi.org/10.1111/all.12191

[44] Giovannini M, Agostoni C, Riva E, *et al*. A randomized prospective double-blind controlled trial on effects on long-term consumption of fermented milk containing Lactobacillus casei in pre-school children with allergic asthma and/or rhinitis. Pediatr Res 2007; 62: 215-20. http://dx.doi.org/10.1203/PDR.0b013e3180a76d94

[45] Simpson MR, Dotterud CK, Storrø O*, et al.* Perinatal probiotic supplementation in the prevention of allergy related disease: 6 year follow up of a randomized controlled trial. BMC Dermatol 2015; 15: 13. http://dx.doi.org/10.1186/s12895-015-0030-1

[46] Loo EX, Llanora GV, Lu Q, *et al.* Supplementation with probiotics in the first 6 months of life did not protect against eczema and allergy in at-risk Asian infants: a 5-year follow-up. Int Arch Allergy Immunol 2014; 163: 25-8. http://dx.doi.org/10.1159/000356338

[47] Bertelsen RJ, Brantsæter AL, Magnus MC, *et al.* Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases. J Allergy Clin Immunol 2014; 133: 165-71. http://dx.doi.org/10.1016/j.jaci.2013.07.032

[48] Rose MA, Stieglitz F, Köksal A, *et al.* Efficacy of probiotic *Lactobacillus GG* on allergic sensitization and asthma in infants at risk. Clin Exp Allergy 2010; 40: 1398-405. http://dx.doi.org/10.1111/j.1365-2222.2010.03560.x

[49] Drago L, De Vecchi E, Gabrieli A, De Grandi R, Toscano M. Immunomodulatory effects of *Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03 alone and in combination, on peripheral blood mononuclear cells of allergic asthmatics. Allergy Asthma Immunol Res 2015; 7: 409-13. http://dx.doi.org/10.4168/aair.2015.7.4.409

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