Probiotic Potential of *Lactobacillus* Species in Allergic Rhinitis

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Keywords

Allergic rhinitis · Allergy · *Lactobacillus* · *Lactobacillus casei* · *Lactobacillus paracasei* · Probiotics

Abstract

Since conventional allergy medication for asthma or allergic rhinitis (AR) can cause side effects which limit the patients' quality of life, it is of interest to find other forms of therapy. In particular, probiotic bacteria, such as *Lactobacillus* species, have shown anti-allergic effects in various mouse and human studies. For instance, administration of some *Lactobacillus* species resulted in nasal and ocular symptom relief and improvement of quality of life in children and adults suffering from rhinitis. Different changes in cytokine profiles, such as elevated Th1 and decreased Th2 cytokines, reduced allergy-related immunoglobulins and cell immigration have been found in both human and murine studies. Positive effects on patients like less activity limitations or fewer rhinitis episodes and longer periods free from asthma or rhinitis were also described following oral administration of *Lactobacillus* bacteria. However, it is still unclear how this type of lactic acid bacteria leads to changes in the immune system and thus inhibits the development of allergies or relieves their symptoms. This review gives an overview of current studies and draws conclusions concerning the usage of probiotic *Lactobacillus* strains in AR.

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Introduction

The “Allergic Rhinitis and its Impact on Asthma” (ARIA) guidelines classify allergic rhinitis (AR) as “intermittent” or “persistent” disorder, depending on the presence of symptoms within 4 weeks. Sometimes, the terms “seasonal” or “perennial” are connected with AR, instead of “intermittent” or “persistent” [1]. The severity of symptoms is defined as “mild” or “moderate/severe” depending on the impact on the quality of living [2]. The term hay fever is also often used as a synonym for AR [3]. Yet, not only outdoor allergens like grass or tree pollen cause AR but also indoor allergens such as animal hair or house dust mites (HDM) [2, 3]. Common symptoms of patients with this allergic disorder are rhinorrhea, nasal congestion or blockage, sneezing, watery or itchy or red eyes, and nasal itching [2, 4]. Additionally, the quality of life of patients with AR may be reduced as there are several comorbidities, for example, asthma or sinusitis [4]. One main goal of the AR management is to reduce the dosage and the frequency of medication. For instance, second-generation antihistamines or steroids are often prescribed as a long-term treatment for AR patients. Possible side effects of long-term treatment with allergy medication

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Table 1. Effects of *Lactobacillus* strains in animal and human studies [5, 6, 11, 14, 17, 18, 20–24, 26, 27, 32, 35–39, 41, 44–46, 50, 51, 53, 60, 66]

Outcome factor/area	Effect/reference		
<i>Immunological mediators</i>			
Th1 cytokines IFN γ and IL-12	↑ [35–39]	↔ [5, 11, 14, 17, 20, 44]	↓ [41]
Th2 cytokines IL-4, IL-5 and IL-13	↓ [5, 11, 14, 35–37, 39, 41, 44, 46, 50, 51, 53]	↔ [20, 38]	
Anti-inflammatory cytokine IL-10	↑ [5, 35, 37, 46, 50, 51]	↔ [14, 20]	↓ [53]
Anti-inflammatory cytokine TGF β	↑ [53]	↔ [20]	
Pro-inflammatory cytokines IL-6 and TNF α	↓ [23, 41]		
Foxp3	↑ [5, 53]		
<i>Immunoglobulins</i>			
IgE	↓ [22, 23, 32, 36, 38, 39, 41, 44–46]	↔ [5, 35, 53]	
IgG	↑ [41, 44]	↔ [53]	
Allergen-specific IgG1	↑ [37, 38, 44]		↓ [5, 36]
Allergen-specific IgG2a	↑ [36, 37, 44]	↔ [35]	↓ [38, 66]
IgG4	↓ [14]	↔ [46]	
IgA	↑ [22, 44, 66]		
<i>Cells</i>			
NK cells (CD16+CD56+)	↑ [22]		
T _{reg}	↑ [22, 50, 51]		
Ratio of T _{reg} /Th2 activity	↑ [46, 50, 51]		
CD103+ dendritic cells	↑ [51]		
Mast cells and/or eosinophils and basophils	↑ [11]	↔ [13, 22]	↓ [14, 23, 36, 38, 50, 51, 53]
Infiltration of neutrophils	↓ [36, 51]		
Amount/infiltration leukocytes	↓ [17, 36]		
Expression of CD86	↓ [51]		
<i>Microbiota</i>			
Bacteroidetes	↑ [50, 51]		
Proteobacteria and Firmicutes	↓ [50]		
<i>Symptoms/episodes/risk in AR</i>			
Risk in hay fever	↓ [26]		
Frequency of atopic eczema	↓ [27]		
AR symptoms: face-scratching	↓ [35]		
Nasal symptoms	↓ [6, 13, 14, 17, 20, 32, 35, 50]	↔ [16, 39]	
Ocular symptoms	↓ [6, 18, 20]	↔ [13, 16, 23]	
Rhinitis episodes	↓ [21]		
Longer episodes free from asthma or rhinitis	[21]		
Mucus hypersecretion	↓ [51]		
<i>Quality of life</i>			
Quality of life	↑ [6, 18, 24, 60]		
Emotional function	↑ [18]		
Activity limitations	↓ [60]	↔ [6]	
<i>Others</i>			
AHR	↓ [36, 51]		

↑ increase, ↓ reduction, ↔ no change. AHR, airway hyperresponsiveness; AR, allergic rhinitis; T_{reg}, regulatory T cells.

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can be drowsiness, gastrointestinal disorders, dry mouth, dizziness, headache, or infections [5]. Additionally, the window of effectiveness of these drugs is often limited by the time after the onset of an allergy. Besides, it is important to develop a safe, lifelong therapy for the prevention

of allergic reactions. In this regard, food with live and heat-killed probiotic strains would be a suitable option as both likewise alleviate symptoms of AR [5, 6]. Probiotics are described as “live microorganisms” with a “health benefit on the host,” when “administered in adequate

amounts” [7]. With their long track records for safety, strains of *Lactobacilli* and *Bifidobacteria* are widely used [8] and administered as drugs, medical or probiotic food [9]. *Lactobacillus* species belong to the so-called lactic acid bacteria (LAB), which produce bacteriocins and competitively exclude potential pathogens [9, 10]. In response to LAB administration, beneficial effects on the host were found such as modulation of immune responses with increased Th1 cytokines in mice fed with *L. casei* Shirota [10], lowered Th2/Th1 ratios following giving *L. delbrueckii* in yoghurt [11], or diminished Th2 cytokines after oral administration of *B. lactis* [12]. Further, *L. acidophilus* [13] and *B. lactis* [12] are described to reduce allergic nasal symptoms.

This review comprises 31 studies, 18 human trials and 13 mouse studies, which were selected from PubMed by a literature search using the key terms *Lactobacillus* AND Allergic Rhinitis, *Lactobacillus* AND Pollen Allergy, and *Lactobacillus* AND House dust mite. Research studies without clearly defined inclusion criteria, such as clinically diagnosed AR, were excluded. A general overview of the observed effects of probiotic *Lactobacillus* strains in the analyzed animal and human trials is presented in Table 1.

Administration of *Lactobacillus* Species Affects Allergic Symptoms in Patients with AR

Treatment with probiotic strains, such as *L. paracasei*, *L. acidophilus*, *L. casei* Shirota, *L. helveticus*, *L. rhamnosus* GG (LGG) showed alleviation of symptoms in AR or HDM patients. Generally, *Lactobacillus* bacteria studies were performed with adult or adolescent [6, 13–19] and numerous with young [20–26] AR patients. Table 2 presents human trials, which analyzed the effects of *Lactobacillus* strains on AR symptoms. 11 studies showed significant effects [6, 13, 14, 17, 18, 20, 21, 24–27], 3 did not [16, 19, 23]. In some studies, the effects of probiotics, taken alone or in combination with clinical medication, were evaluated [18, 20, 24]. In the study by Costa et al. [18], *L. paracasei* LP-33 was given as an add-on therapy to patients with AR symptoms during grass pollen season, who were currently treated with the antihistamine loratadine (10 mg/daily) [18]. The verum group had an additional improvement of 17.7% in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) global score compared to the placebo group ($p = 0.0255$). Although no significant differences were measured for nasal symptoms in RQLQ, but ocular symptoms changed positively for the *L. para-*

casei group ($p = 0.0029$; -1.75 ± 1.63 vs. placebo -1.36 ± 1.77). In another study, levocetirizine (5 mg) with or without *L. paracasei* (LP HF.A00232; 5×10^9 colony-forming units [CFU]/capsule) was used in children diagnosed with perennial AR [20]. Here, *L. paracasei* plus levocetirizine as a rescue medication showed a “synergistic effect” and led to lower individual symptoms for sneezing ($p = 0.005$), itchy nose ($p = 0.040$), or swollen puffy eyes ($p = 0.038$). Although there were no additional effects of *L. paracasei* when taken with levocetirizine, symptoms were relieved even after termination of medication intake. Additionally, the amount of taken antihistamines in the probiotic group decreased about 56% within the study period (100% week 1–8 vs. $43.35 \pm 38.53\%$ weeks 10.5–12) [20]. Ahmed et al. [24] demonstrated equal effects for cetirizine and LP-33 in children younger than 5 years suffering from perennial AR. Over 90% of these children showed symptoms, for example, rhinitis, sneezing, or nasal blocking. After 6 weeks of intervention, with either daily intake of probiotics (LP-33, 2×10^9 CFU) or cetirizine (2.5–5 mg), baseline symptoms of AR significantly improved in over 95% of all participants. Nasal blocking was reported to be fully improved in the probiotic group in 84.6% (88 of 104 patients) versus 85.5% (89 of 104 patients) in the cetirizine group. Other bothersome symptoms of perennial AR, such as rhinorrhea or sneezing, were equally alleviated, with no difference in treatment outcome [24]. Thus, *L. paracasei* seems to support the effect of clinical AR medication as an add-on therapy [18, 20] or could be even effective as AR medication [24].

Several studies with permitted use of asthma and allergy medication reported controversial results [13, 19, 21]. Giovannini et al. [21] found 33% less rhinitis episodes in the *Lactobacillus* group without any change in usage of medication during the study irrespective of the treatment protocol. A study on *L. acidophilus* L-92 [13] demonstrated significant alleviation of nasal symptoms medication score. It also demonstrated a beneficial trend for ocular symptom medication scores in the probiotic group compared with the control group. In contrast, Helin et al. [19] did not find alleviative effects of oral-administered bacteria. However, this study had a population of only 18 patients; therefore, the results should be viewed with caution.

Apart from nausea in some participants, no severe side effects were mentioned related to the intake of *L. paracasei* strains [24]. Therefore, this kind of probiotic treatment seems to be beneficial for patients suffering from perennial AR as it improves their quality of life by reduction of bothersome symptoms [24]. The study duration

Table 2. Effects of *Lactobacillus* strains on AR symptoms in humans

Type of allergy	Intervention/ probiotic strain	Placebo/ medication	Patients (number /age)	Duration	Outcome	Survey	Ref.
AR perennial	<i>L. p.</i> 33 tablet: 2×10^9 CFU	Cetirizine tablet 2.5–5 mg (depending on age)	212 children 26±16.64 m. Clinically presented AR symptoms	6 wks	Baseline symptoms ↓ (sneezing, rhinorrhea, nasal blocking, coughing, and feeding/sleeping difficulties; $p < 0.05$) Quality of life ↑	Simple AR questionnaire	Ahmed et al. [24]
Allergic disease (asthma, wheeze, hay fever, and rhinitis)	<i>L. rh.</i> HN001 capsule: 6×10^9 CFU or <i>B. lac.</i> HN019	Capsule: dextran, salt, and yeast extract	94 children (follow-up) 11 yrs	Start: wk 35 pregnancy; children: took capsules: birth till 2 yrs follow-up: 11 yrs	Risk in hay fever ↓ (12 m prevalence) ($p = 0.047$), at age of 11 yrs	ISAAC questions	Wickens et al. [26]
Pollen allergy grass pollen	<i>L. p.</i> NCC2461 sachets, single dose 5×10^9 CFU	Maltodex 5 g	131 adults 18–65 yrs	8 wks during pollen season	Nasal/ocular symptoms ($p > 0.05$) – quality of life ($p > 0.05$)	TNSS TOSS MiniRQLQ	Nembrini et al. [16]
AR grass pollen	<i>L. p.</i> NCC2461/ blend: <i>L. ac.</i> ATCC SD5221 + <i>B. lac.</i> ATCC SD5219 sachets: maltodex + <i>L. p.</i> /blend; 10^{10} CFU in 2 dL milk	<i>L. p.</i> vs. blend	31 adults 18–35 yrs	Cons.: 2 to 4 wks wash-out; cons.: 6–8 wks outside pollen season	Nasal pruritus with <i>L. p.</i> ↓ ($p = 0.05$)	VAS	Perrin et al. [17]
AR perennial HDM	<i>L. p.</i> HF, A00232 + levocetirizine capsule: 5×10^9 CFU	Placebo + levocetirizine	60 children 6–13 yrs	8-wk cons. and 4-wk follow-up	Individual symptoms sneezing ↓ ($p = 0.005$) itchy nose ↓ ($p =$ 0.040) swollen eyes ↓ ($p = 0.038$)	PRQLQ TSS NTSS	Lin et al. [20]
AR grass pollen	<i>L. p.</i> ST11 NCC2461 fermented milk (80 mL); combi. <i>L. h.</i> NCC1643 ($\geq 5 \times 10^9$ CFU), <i>L. p.</i> ST11 (as starter; $\geq 1 \times 10^7$ CFU)	Acidified milk	31 adults±18–35 yrs	Cons.: 8 wks + 6–8 wks wash-out outside pollen season	Nasal congestion score ($p = 0.04$) ↓	VAS	Wassenberg et al. [14]
Pollen allergy grass pollen	<i>L. p.</i> 33; 2×10^9 CFU; capsules + loratadine	Loratadine (10 mg) placebo: micro. cell and others	425 adults 18–60 yrs	5 wks during pollen season	Quality of life PRQLQ ↑ ($p = 0.0255$), emotional function ↑ ($p = 0.0095$), ocular symptoms ↓ ($p = 0.0029$)	RQLQ RTSS	Costa et al. [18]
Pollen allergy birch pollen	<i>L. ac.</i> + <i>B. lac.</i> capsules: 5×10^9 CFU probiotics combi.: 25% <i>L. ac.</i> + 75% <i>B. lac.</i> or placebo	Micro. cell	47 children 4.2–12.9 yrs	4 m starting prior to onset of birch pollen season, finished end of birch pollen season	Runny nose ↓ ($p = 0.078$) nasal blocking ↓ ($p = 0.101$) eye symptoms ($p > 0.05$) –	Diary	Ouwehand et al. [23]
AR, asthma birch pollen	<i>L. c.</i> 10^8 CFU/mL yoghurt: (200 mL) <i>L. bulg.</i> 10^7 CFU/mL, <i>S. therm.</i> 10^8 CFU/mL	Nonfermented milk (100 mL)	187 children 2–5 yrs	12 m	Longer episodes free from asthma or rhinitis ($p = 0.027$) rhinitis episodes per year ↓	Symptom diary	Giovannini et al. [21]
AR perennial HDM	<i>L. ac.</i> 92 3×10^{10} CFU/100 mL Heat-treated milk (100 mL)	Heat fermented milk without L-92	49 adults 34±3.4 yrs	Cons.: 8 wks observ. after cons.: 2 wks	Nasal symptoms ↓ ($p < 0.05$)	Ocular/nasal symptom medication score	Ishida et al. [13]
AR perennial HDM	<i>L. p.</i> 33 capsule: 5×10^9 CFU live and heat-killed strains	Milk powder capsules	90 children ± 14.5–16.6 yrs	30 d	Overall quality of life in frequency ↑ ($p < 0.0001$), level of bother ↓ ($p = 0.004$) in both probiotic groups (live/heat- killed) equally	PRQLQ (modified)	Peng and Hsu [6]

Table 2 (continued)

Type of allergy	Intervention/ probiotic strain	Placebo/ medication	Patients (number /age)	Duration	Outcome	Survey	Ref.
AR perennial HDM	<i>L. p.</i> 33 in fermented milk (containing <i>S. therm.</i> , <i>L. bul.</i>) 2×10 ⁹ CFU/ 200 mL	Yoghurt without <i>L. p.</i> 33	80 children Probiotic: 15.87±1.53 yrs	30 d	Overall quality of life in frequency ↑ (<i>p</i> = 0.037), level of bother ↓ (<i>p</i> = 0.048) nose symptoms ↓ (<i>p</i> = 0.041)	PRQLQ	Wang et al. [60]
Pollen allergy birch pollen	<i>L. rh.</i> GG 2 capsules (5×10 ⁹ CFU); 2×d	Micro. cell	36 children and adults 14–36 yrs	5.5 m: 2.5 m before pollen season, 1 m during and 2 m afterward	Allergic nose/eye/lung symptoms ↓ (<i>p</i> = 0.10–0.90)	Symptom diary (0–10 scale; 0 no symptoms, 10 most severe)	Helin et al. [19]
Atopic disease atopic eczema, AR, asthma	<i>L. rh.</i> GG capsules; 1×10 ¹⁰ CFU	Micro. cell	123 preg. women (18–35 yrs; history of eczema, AR, asthma) + newborns	2–4 wks (women) 6 m (infants) follow up: age of 2 yrs	Frequency of atopic eczema ↓ (<i>p</i> = 0.008)	SCORAD	Kalliomäki et al. [27]

AR, allergic rhinitis; *B. lac*, *B. lactis*; CFU, colony-forming units; combi, combination; cons., consumption; HDM, house dust mites; ISAAC, International Study of Asthma and Allergies in Childhood; *L. ac*, *L. acidophilus*; *L. bul.*, *L. bulgaricus*; *L. c.*, *L. casei*; *L. h.*, *L. helveticus*; *L. p.*, *L. paracasei*; *L. pl.*, *L. plantarum*; *L. rh.*, *L. rhamnosus*; m, month/months; maltodextrin, micro-cell, microcrystalline cellulose; NTSS, nasal total symptom score; observ., observation; PRQLQ, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RTSS, rhino conjunctivitis total symptom score; SCORAD, scoring atopic dermatitis; *S. therm.*, *Streptococcus thermophilus*; TNSS, total nasal symptom score; TOSS, total ocular symptoms; TSS, total symptom score; VAS, visual analog scale; wk/wks, week/weeks; yrs, years; ↑ improvement; ↓ reduction; –, no effect.

of 5–12 weeks was relatively short compared to another study with a duration of 1 year or longer. Thus, to support evidence, longer studies with a larger population are necessary. Only 1 study used AR medication without the combination with probiotics [24]. Another study suggested the probiotic effect in their study could have been influenced by the use of medication, and even a follow-up period of 4 weeks without medication intake was maintained to exclude this effect in an optimal way [20].

The administration period seems to be another important factor in the oral immunization against allergens and so for prevention of AR. For instance, *L. casei* showed most increased IgA + cell amounts versus control animals after 5 days of probiotic intake (*p* < 0.001), which could be due to the B-cell homing mechanism [28]. Allergen-specific immune response was also reduced when probiotics were taken after sensitization with birch and grass pollen, and less inflammation occurred [29]. Prevention of lung inflammation was also visible with *L. paracasei* NCC2461 and *B. longum* NCC3001 as they showed regulated systemic allergic responses after an application at the time of sensitization [29]. To evaluate preventive effects of *Lactobacillus* intake related to AR, some studies have gone further and focused on perinatal application [26, 27, 30]. LGG treatment was a good preventor of atopic diseases in infants of atopic parents with AR, asthma, or eczema [27]. Here, the form of administration, maternal intake of the probiotic capsule and breastfed children, or probiotic intake by infants themselves did not significantly influence the preventive effect of LGG (*p* = 0.74). Not only studies with children or pregnant women were conducted estimating protective effects but also with adults. *L. paracasei* ST11 had positive effects on patients suffering from grass pollen AR. For example, subjective nasal congestion (*p* = 0.04), IL-5 (*p* = 0.03), or IgG4 (*p* = 0.049) was reduced after the consumption of probiotic fermented milk compared with the placebo group [14]. Probiotics are even recommended by the WHO for pregnant women and their infants at high risk of having an allergic child or developing allergies, to prevent children from having eczema [31].

Immunological Effects of Probiotic Treatment with *Lactobacillus* Species

In few human studies, immunological and clinical parameters were assessed [13, 14, 16, 17, 20, 21, 23, 27]. Findings of significant changes of immunological outcome factors of these human trials are presented in Ta-

Table 3. Changes of immunological parameters in humans following treatment with *Lactobacillus* strains

Type of allergy/ disease	Intervention/probiotic strain	Outcome	Ref.
AR grass pollen	<i>L. p.</i> NCC2461 or blend: <i>L. ac.</i> ATCC SD5221 + <i>B. lac.</i> ATCC SD5219 powder sachets: maltodextrin + <i>L. p.</i> or blend; each 10 ¹⁰ CFU in 2 dL milk diluted before consumption	NCC2461: IL-5 ↑ (<i>p</i> = 0.005), IL-10 ↑ (<i>p</i> = 0.008), IL-13 ↑ (<i>p</i> = 0.001), IL-8 ↑ (<i>p</i> = 0.003) in vitro Leukocytes in nasal fluid ↓ (<i>p</i> = 0.009 NCC2461)	Perrin et al. [17]
Pollen allergy birch pollen	<i>L. c.</i> yoghurt drink (100 mL) <i>L. pl.</i> (4 strains: WCFS1/NIZ03400/NIZ02877/ CBS125632) 10 ¹⁰ CFU/mL	IL-10 ↑ (<i>p</i> = 0.04 CBS 125632) in vitro IgE ↓; Shiota (<i>p</i> = 0.011), <i>L. pl.</i> WCFS1 (<i>p</i> = 0.027), <i>L. pl.</i> NIZO3400 (<i>p</i> = 0.039), <i>L. pl.</i> CBS 125632 (<i>p</i> = 0.035) IL-5 ↓ (<i>p</i> = 0.03), IL-13 ↓ (<i>p</i> = 0.04) with <i>L. pl.</i> CBS 125632 in vitro	Snel et al. [46]
AR grass pollen	<i>L. p.</i> ST11 (NCC2461) fermented milk (80 mL) combi. of <i>L. h.</i> NCC1643 (≥5×10 ⁷ CFU) as a starter <i>L. p.</i> ST11 (≥ 1×10 ⁷ CFU)	Systemic immune markers: IL-5 ↓ (<i>p</i> = 0.03), IgG4 ↓ (<i>p</i> = 0.049), eosinophils ↓ (<i>p</i> = 0.037)	Wassenberg et al. [14]
Allergic disease (asthma, hay fever)	<i>L. g.</i> CECT5714 and <i>L. cor.</i> CECT5711 (each at least 10 ⁶ CFU/g) yoghurt (200 mL) with <i>L. bul.</i> (10 ⁷ CFU/g) and 2 probiotics (<i>L. g.</i> , <i>L. cor.</i>)	NK cells ↑ (<i>p</i> = 0.03), mucosal IgA ↑ (<i>p</i> = 0.01) suppressor T cells (CD4/CD25+) ↑ (<i>p</i> = 0.01), T _{reg} ↑ (<i>p</i> = 0.01), plasma IgE ↓ (<i>p</i> = 0.03)	Martínez- Cañavate et al. [22]
Pollen allergy birch pollen	Probiotics combi. of <i>L. ac.</i> , <i>B. lac.</i> (1:3) capsules: 5 × 10 ⁹ CFU	Stable fecal IgA concentration IL-6 ↓ (<i>p</i> = 0.0002), TNFα ↓ (<i>p</i> = 0.0005) during birch pollen season mucosal eosinophil infiltration ↓ (<i>p</i> = 0.013)	Ouwehand et al. [23]
AR grass pollen	<i>L. c.</i> Shiota daily dairy drink (65 mL) with alive <i>L. c.</i> 6.5×10 ⁹ CFU/ drink	IL-1β ↑ (<i>p</i> < 0.01) in vitro, IgG in treatment period ↑ (<i>p</i> < 0.01) IgE in treatment period ↓ (<i>p</i> < 0.05) and TNFα ↓ during pollen season (<i>p</i> < 0.01) cytokines for early and late pollen antigens: smaller increase of IL-5 (<i>p</i> = 0.01; 0.05), IL-6 (both <i>p</i> < 0.01) in vitro IFNγ ↓ (<i>p</i> = 0.02; 0.01) in vitro	Ivory et al. [41]

AR, allergic rhinitis; *B. lac.*, *B. lactis*; CFU, colony-forming units; *L. ac.*, *L. acidophilus*; *L. bul.*, *L. bulgaricus*; *L. c.*, *L. casei*; *L. cor.*, *L. coryniformis*; *L. g.*, *L. gasseri*; *L. h.*, *L. helveticus*; *L. p.*, *L. paracasei*; *L. pl.*, *L. plantarum*; combi, combination; spec., specific; T_{reg}, regulatory T cells; ↑ improvement/increase; ↓ reduction/decrease.

ble 3. One factor for the occurrence of allergic airway diseases, such as AR, is a disturbed balance between Th1 and Th2 cells, with a majority of Th2 cells [32, 33]. Th1 cytokines, IFNγ and IL-12, have been found to be downregulated in AR patients [34]. A significant decreased Th2 cytokine profile in response to probiotic treatment was found in 5 animal trials [35–39]. Moreover, significantly higher levels of IFNγ were found after the intake of *L. plantarum* [36], *L. helveticus*, and *L. gasseri* [35], and in vitro experiments with *L. plantarum* birch pollen allergy in a murine model showed similar augmenting effects on IL-12 and IFNγ [37]. In a human study with children, increased IFNγ levels were found after the intake of probiotics, in particular 2 *Bifidobacteria* strains and *L. acidophilus* AS031, and significantly improved TGFβ levels cor-

related with less atopic dermatitis occurrence [40]. But the role of probiotics in connection with IFNγ in allergic inflammation is still not clearly identified as the IFNγ production in the probiotic group in a human trial showed a significant decline [41].

In a dose-dependent manner, Gram-positive bacteria like *L. plantarum* NCIMB8826, *L. lactis* MG1363, *L. casei* ATCC393, and LGG hindered the production of Th2 cytokines IL-4 and IL-5 [42]. In vitro experiments showed strain-dependent effects of about 100 tested LAB strains [43]. IL-12 was used as a parameter for Th1 activity, while IL-4 was used for Th2 activity. As a whole, some strains were proved to be better IL-12 inducers or IL-4 repressors than others. For example, *L. paracasei* KW3110 was a good IL-12 inducer and IL-4 inhibitor. Therefore, LAB

seems to have the ability to intervene in the Th2 cytokine production pathway and to balance out the Th1/Th2 cytokine levels, which consequently could help prevent allergies [43]. Not only the latter animal model [43] showed effects of LABs on the cytokine profile but several others demonstrated a Th2 cytokine-diminishing effect due to *Lactobacillus* treatment (see Table 1).

The considerable reduction of IgE levels in animal studies [32, 36, 38, 39, 44, 45] and in human trials [22, 23, 41, 46] indicates a reduction of IgE-producing B cells by *Lactobacillus* bacteria. In vivo experiments with *L. paracasei* KW3110 revealed significant lower total IgE and reduced antigen-specific IgE levels ($p < 0.05$) than control animals without oral administration of this type of LAB [43]. The findings of Makino et al. [35] did not support this consideration because OVA-specific IgE levels were not significantly suppressed by the intake of probiotic *L. helveticus* H2171, although face-scratching and sneezing could be alleviated by almost one third compared to the control group. The same effect on allergic response was demonstrated in an OVA sensitization murine model with fermented yoghurt, containing bacterial starter cultures such as *L. bulgaricus*, *S. thermophilus*, and *L. paracasei* CNCMI-1518 (each 10^8 CFU/mL) [47]. In human trials, results are inconsistent. On the one hand, a small placebo-controlled study with *L. casei* Shirota demonstrated decreased IgE ($p = 0.05$) and enhanced early grass pollen-specific IgG ($p < 0.01$) in seasonal grass pollen-allergic rhinitis. On the other hand, only diminishing modification of birch pollen-specific IgE and none of birch pollen-specific IgG or IgG4 levels was found in response to probiotic treatment in other studies [22, 46]. In addition, Wassenberg et al. [14] found significant increased subjective nasal congestion by means of visual analog scale after treatment with *L. paracasei* ST11 ($p = 0.04$) without any measured change in grass pollen-specific IgE or IgG levels compared to placebo. Another mechanism, rather than just the IgE suppression, seems to be important for alleviation of allergic symptoms. A correlation between both immunoglobulins IgE and IgG could be seen. Symptoms were relieved due to blocked IgE binding and higher levels of IgG [48]. This could be one explanation for reduced allergy symptoms without lessened IgE levels as IgG was found to possibly block IgE binding activities [48].

Foxp3-positive regulatory T cells (T_{reg}) and their mediators IL-10 and TGF β play a major role in a balanced immune response with an inhibitory effect on eosinophils, mast cells, and basophils [49]. Significant effects of *Lactobacillus* strains on T_{reg} were demonstrated in both

animal and human studies [22, 50, 51]. For instance, *Lactobacillus* treatment was associated with expanded IL-10 levels [5, 46, 51], such as the increase in the IL-10 level about $24 \pm 13\%$ in response to intervention with *L. plantarum* [46]. In contrast, no associations of increased IL-10 levels and other species such as *L. reuteri*, *L. gasseri*, and *L. johnsonii* could be found [52]. Likewise, LGG showed contradictory results as the intake of this specific strain was related to an increase in IL-10 levels in 1 study [51] and decreased levels in another animal model [53]. A significant expansion of the $T_{reg}/Th2$ ratio was demonstrated in response to treatment with *L. plantarum* NIZ02877 (38%) and *L. plantarum* CBS125632 (68%) [46]. The expression of the transcription factor Foxp3 was upregulated in a preventive birch pollen allergy model in young mice with *L. paracasei*-treated mothers ($p < 0.001$) [53]. Also, Yamashita et al. [5] showed the same enhancing effect on Foxp3 ($p < 0.001$) and IL-10 levels ($p < 0.01$) in response to treatment with *L. helveticus* LH2171. The same strain was related to amplified IL-10 levels, reduced Th2 cytokines (IL-4, IL-13; $p < 0.05$), and positive effects on sneezing and face-scratching [35].

Additionally, allergic reactions could be influenced by regulating co-stimulatory molecules, such as CD40 or CD80. These are important for T-cell responses [43] and IgE production [33]. Inhibition of antigen-presenting cells by means of reduced CD80+ cells was found in an AR mouse model with *L. crispatus* KT-11 treatment [39]. In murine peribronchial lymph nodes, treated with OVA + LGG, less CD40 and significantly lowered CD86 molecules were detected [51]. Not only fewer active DC cells were found after *Lactobacillus* intervention in animal and human trials but also the infiltration of eosinophils and neutrophils and the amount of macrophages in the upper respiratory tract were influenced by probiotics [50].

It is widely known that a rebalanced gut microbiota can have positive effects on airway diseases and also alleviate gut inflammation [50]. The correlation of airway inflammation and gut microbiota disorder was investigated in 1 study [51]. LGG introduced a beneficial, significant increase in phylum Bacteroidetes ($p < 0.01$) and lowered Firmicutes [51]. In the same study, a decline in inflammatory eosinophils and neutrophils, less mucus hyperplasia, and decreased Th2 cytokines, IL-4 ($p < 0.05$) and IL-13 ($p < 0.01$), were found. Similarly, results were shown with the probiotics *B. longum* and *L. plantarum* in HDM-induced AR [50]. An important part of the mucosal barrier is IgA [22, 54]. Increased IgA levels were found in several studies [22, 23, 53]. Moreover, mice pretreated with recombinant LAB showed lowered IgE and in-

creased specific IgA levels [44]. As this effect is usually known for allergen-specific immunotherapy [49], probiotics with these kinds of immunoglobulin modulation characteristics can be helpful to prevent allergies. Probiotics such as *Lactobacillus* bacteria are known not to be stable gut microbiota inhabitants [55]. Hence, the modulative effect of LAB is possibly not only due to a balanced microbiota itself but combined with immunological changes.

Discussion

This overview supports the assumption that administration of *Lactobacillus* strains could positively affect AR patients by alleviating allergic symptoms. Negative effects were not reported; thus, the treatment with probiotic *Lactobacillus* strains appears to be suitable for AR patients. However, the comprised studies differ widely in used *Lactobacillus* strains, amount of administered *Lactobacillus* bacteria, form and duration of administration, accompanied therapy, and measured parameters.

In some study protocols, 1 *Lactobacillus* strain was used, while in others, different probiotics were combined or added to dairy products with several starter cultures. There is less information about a most suitable *Lactobacillus* candidate in connection with AR in human trials [46]. Consequently, studies evaluated the effect of different probiotic bacteria in vitro, followed by in vivo experiments with the most effective strains in animal [43] or human trials [46]. Snel et al. [46] used 5 different *Lactobacillus* strains in an out-of-season human trial with birch pollen to evaluate their effects. While the intervention groups had a small number of participants ($n = 9-11$), the results of this trial gave a hint on the possible beneficial effects of the used strains like the reduction of IgE or Th2 cytokines (IL-5 and IL-13) and an increase in anti-inflammatory cytokine IL-10. These results could be useful for enlarged study protocols. Another important factor for the evaluation of *Lactobacillus* effects in AR is the strain-specific limited survival in the human gastrointestinal system [56]. For example, orally administered *L. casei* in fermented milk could be found in feces of humans [56, 57], while viable *L. delbrueckii* subsp. *bulgaricus* could not be detected in all subjects after yoghurt ingestion at all times [58].

It is widely known that possible beneficial effects of any consumed probiotics such as *Lactobacillus* bacteria depend on their capability to survive different conditions during gastroduodenal transit like bile acids, pH, or en-

zymes. The probiotic effect is commonly accepted with a daily consumption of minimum 10^6 CFU/mL or gram of probiotics [59]. However, different effects on immunological and symptomatic parameters might be due to the used amount of *Lactobacillus* bacteria, which varied in the considered human trials from 10^8 CFU/mL [21] up to 3×10^{10} CFU/100 mL daily [13]. Moreover, the form of administration was not homogenous. *Lactobacillus* strains were given orally, but even here in different forms: capsules [6, 18–20, 23, 26, 27], yoghurt [21, 22], dairy drinks or milk [13–15, 46, 60], or tablet or sachet [17, 24] (see Table 2). Half of the considered human trials used capsules, revealed significant positive effects on nasal or ocular symptoms, and reduced the risk in hay fever or atopic eczema. But also, dairy products and yoghurt reduced allergy-related immune parameters such as IL-13, IgE, or improved AR symptoms. But yoghurt as a form for administration seems to be not ideal for investigating probiotic effects as it was ascertained to have beneficial effects on patients with allergic rhizopathy after daily intake for 4 months [61]. Numerous studies, such as Del Piano et al. [62], investigated the effect of different probiotic application forms. An improved resistance to gastroduodenal conditions with encapsulated bacteria in contrast to less effective nonencapsulated bacteria was found. Here, a good protective coating is proposed to support the beneficial effects even with a reduced amount of used cells [62]. Otherwise, 2 studies with *L. plantarum* 33, the same duration of 30 days, but different application forms (fermented milk [60] or capsules [6]) found similar positive effects on the quality of life or level of bother in their subjects. Normally, *Lactobacillus* bacteria are regarded as safe, and minor side effects were suffering from flatulence [63] or nausea [24]. But the form of administered bacteria should be chosen with mindful consideration because modulative effects in the immune system can be delicate for patients on immunosuppressive therapy [63]. Therefore, it is difficult to suggest which kind of application form is the most efficient one for all AR patients.

Moreover, the effect of probiotic *Lactobacillus* strains is difficult to access if in studies, the intake of antibiotics, of allergy or asthma medication was allowed [16, 19, 64]. Others did not even mention handling of medication before, during, and after treatment periods with *Lactobacillus* strains. Self-medication was permitted during symptoms, but this makes the significance of probiotic effects more complicated. It is a matter of common knowledge that especially antibiotics can unbalance the gut microbiota and therefore be one factor of developing allergic or

<i>Lactobacillus</i> strain	Administration	Duration	Season	Medication
<i>L. paracasei</i>	2 × 10 ⁹ CFU Tablet	6 weeks	In/out	Cetirizine Levocetirizine Loratadine
	5 × 10 ⁹ CFU Capsule	8 weeks	In	
	2 × 10 ⁹ CFU Capsule	5 weeks	In	
	5 × 10 ⁹ CFU Capsule	30 days	In	None
	5 × 10 ⁹ CFU Sachet	8 weeks	In	
	10 ¹⁰ CFU Sachet	8 weeks	Out	
	≥ 1 × 10 ⁷ CFU/mL Sachet	8 weeks	Out	
<i>L. casei</i>	2 × 10 ⁹ CFU Sachet	30 days	Out	
	10 ⁸ CFU/mL Dairy product	12 months	In/out	None
<i>L. casei</i>	6.5 × 10 ⁹ CFU/65 mL Dairy product	2 weeks	Out	
<i>L. casei</i>	10 ¹⁰ CFU/100 mL Dairy product	4 weeks	Out	
<i>L. plantarum</i>	10 ¹⁰ CFU/100 mL Dairy product	4 weeks	Out	
<i>L. acidophilus</i>	3 × 10 ¹⁰ CFU/100 mL Dairy product	8 weeks	Out	
<i>L. rhamnosus</i>	5 × 10 ⁹ CFU Capsule	4 months	in/out	None
<i>L. rhamnosus</i>	5 × 10 ⁹ CFU Capsule	5.5 months	In/out	

Fig. 1. Overview of study concepts for administration of *Lactobacillus* strains in AR. CFU, form and duration of administration, timing (in – or out of – allergen season), and additional medication are shown. CFU, colony-forming units.

inflammatory diseases [65]. The intake of dairy products containing probiotics within the study period was also handled in a completely different manner. However, the permitted use of medication or probiotic products can possibly mask effects of simultaneously taken *Lactobacillus* bacteria.

Another restraining factor for answering the question of possible effects of *Lactobacillus* bacteria on the organism is different outcome measures in studies related to

AR. Some studies [18, 19, 24, 26, 60] used only questionnaires and no immunological parameters for evaluation of changed allergic symptoms. The results of studies without immunological tests are less conclusive. Questionnaires as a measuring tool provide rather subjective results or actually have been modified by the authors [6]. Also, the assistance of parents in studies with children for filling out the surveys might have an impact on the results of clinical outcomes.

Factors related to the type of application, such as duration and timing of intake, seem to vary between the probiotics. The beginning of the probiotic intake varied from months before pollen season to the onset of pollen season. Moreover, the duration of LAB consumption in human trials differed from 2 weeks [27] to 12 months [21]. Figure 1 provides an overview of most of the intervention strategies and concepts used in the studies. For example, with *L. paracasei* NCC2461 and grass pollen-allergic rhinitis, different studies were conducted. Nembrini et al. [16] could not find significant changes of nasal symptoms with these *Lactobacillus* bacteria during the pollen season, whereas alleviative effects in nasal symptoms as well as enhanced cytokine secretion of IL-5, IL-8, IL-10, or IL-13 in pollen-stimulated peripheral blood mononuclear cells could be found in 2 out-of-pollen season studies [14, 17]. There was 1 placebo-controlled trial with an intake of LGG over 5.5 months [19]. Here, the intake started 2.5 months prior pollen season and participants were then asked to take the probiotics for 1 month during pollen season. The study ended 2 months afterward. Although it was a longer period over several months within and outside the season, which would suggest immunomodulatory effects, there was no significant alleviation of symptoms in response to treatment with LGG. The symptom scores increased in both groups, and thus, a positive effect of LGG could not be attributed. Still, in this study immunological parameters for the relation of symptomatic and immunological effects were not measured and the cohort was small ($n = 36$) [19]. Another trial, starting prior to pollen season and ending afterward, with *L. acidophilus* and *B. lactis* had no significant impact on total AR symptoms, but a reducing effect on inflammatory-related immune parameters, such as IL-6 or TNF α [23]. Therefore, an intake prior to the start of pollen season could be a good strategy for AR patients, but it is still unclear which probiotics are most effective and how long the probiotics should be taken. It is often desirable to have long-term investigations to investigate the effects of *Lactobacillus* bacteria on AR patients, and the LAB consumption period in the analyzed human studies was from just 2 weeks

[27] up to 1 year [21]. The intake of medication due to prevailing symptoms is understandable, but it is questionable if allergic patients would consume probiotic products without having any symptoms for a long time.

Conclusion

Lactobacillus species showed several effects on immunological parameters in allergic disease, but the exact mechanism is still unclear. Additionally, no specific *Lactobacillus* strain emerged as the most efficient one, and their modulatory effects seem to be strain-dependent. Since 11 of 14 human studies found significant effects of *Lactobacillus* strains on AR symptoms and no negative effects occurred, the treatment with probiotic bacteria seems to be suitable for AR patients. However, many parameters may influence the effect of probiotics, and therefore, a clear recommendation for a specific strain, and the dosage and timing of application is not yet possible. Further investigations and solid studies addressing mechanisms underlying the observed beneficial effects of probiotic treatments in rhinitis patients are required to make conclusive statements and to develop safe and less invasive or adjunctive therapies, respectively.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.C.S. and A.L. conceptualized the study and were involved in preparation and review of the manuscript.

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