allergies

Review

Efficacy and Safety of Oral Probiotics in Children with Allergic Rhinitis: A Review

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Abstract: The prevalence of allergic rhinitis is rising, and it is impacting children's growth and quality of life. To uncover unconventional treatment modalities, research was carried out to clarify the significance of novel components in the pathophysiology of allergic rhinitis. One of these elements was gut microbiota, which plays a crucial role in the development and evolution of allergic disorders. Specifically, dysbiosis, defined as impaired microbiota composition, characterizes allergic disorders. In light of this concept, probiotics (beneficial bacteria) may restore gut dysbiosis, rebalance the immune response, and indirectly influence the clinical course of allergic diseases. In this article, we discussed the role of the gut–lung axis in children and reported on new findings. We also reviewed the most relevant studies about probiotics in patients with allergic rhinitis.

Keywords: allergic rhinitis; oral probiotics; children; allergy; treatment; prevention; microbiota; gut–lung axis

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Citation: Klain, A.; Dinardo, G.; Indolfi, C.; Contieri, M.; Salvatori, A.; Vitale, S.; Decimo, F.; Ciprandi, G.; Miraglia del Giudice, M. Efficacy and Safety of Oral Probiotics in Children with Allergic Rhinitis: A Review. *Allergies* **2023**, *3*, 72–89. https://doi.org/10.3390/allergies3010006

Academic Editor: Ann-Marie Malby Schoos

Received: 14 December 2022
Revised: 11 February 2023
Accepted: 28 February 2023
Published: 7 March 2023

1. Introduction

Allergic rhinitis (AR) is a respiratory disease caused by an IgE-mediated inflammatory process mediated by one or more antigens (allergens) against which the subject is sensitized. The most common symptoms are rhinorrhea, sneezing, itching, nasal obstruction, and frequent conjunctivitis [1]. IgE antibodies are produced locally and in the lymphoid tissues in response to common environmental allergens. Mast cell degranulation occurs when allergens bind to specific IgE expressed over the cell surface. This results in the release of biochemical mediators including histamine, which represents the main factor in the acute allergic response [2]. A new AR classification considered the duration and severity of symptoms. According to it, AR can be subdivided into intermittent or persistent, based on the course of the symptoms, and into mild, moderate, or severe, according to the grade of clinical manifestations [3]. This classification evaluated the quality of life and the possible impact of rhinitis symptoms on the patient's life, such as school activities and free time [1]. The diagnosis is based on the consistency between clinical history of allergic symptoms and documented sensitization (such as production of allergen-specific IgE). In other words, the exposure to sensitizing allergen causes symptoms' occurrence. These symptoms can also negatively affect sleep quality, causing nocturnal awakenings. Diagnostic tests are aimed at demonstrating the in vivo and in vitro presence of allergen-specific IgE. The gold standard for IgE allergy testing is the skin prick test. A subsequent diagnostic step is the search for IgE antibodies directed toward specific allergenic molecules [4]. It is important to note that AR and asthma are due to type 2 inflammation of the airways, involving various cells, mainly eosinophils, mast cells, T lymphocytes, and their mediators [5]. Another important diagnostic tool can be the measurement of fractional exhaled nitric oxide, due to its ability to correlate with other parameters of airway inflammation, as demonstrated by the sharp and intense decrease in its levels when inhaled corticosteroids were administered [6,7]. The best

AR management approach would be altogether avoiding the offending allergens. However, this is rarely achievable, and limited data support the efficacy of environmental control interventions. In addition, there is limited evidence that any single environmental control measure results in improved AR symptoms or other AR-related outcomes. Therefore, although allergen avoidance would be the optimal treatment of AR, the evidence supporting this approach needs to be more extensive. Several classes of effective allergy medication treat different AR symptoms [8]. Central roles are played by oral and/or intranasal H1 antihistamines, intranasal corticosteroids (INCS), and the fixed combination of INCS and H1 antihistamines [9]. Regarding the treatment of intermittent mild or intermittent AR, oral non-sedating second-generation H1 receptor antihistamine (AH) drugs are preferred over a first generation H1-antagonist, which is associated with more adverse effects, such as sedation, excessive mucosal drying, and impaired motor coordination. Conversely, for persistent moderate or severe symptoms of seasonal rhino-conjunctivitis, daily use of an intranasal corticosteroid (INCS) or an intranasal antihistamine (INAH) is the treatment of choice [10]. If an INCS, as the first choice for the treatment of SAR or PAR, is not sufficient to control symptoms, the addition of an INAH would likely be the most appropriate next option [11]. However, intranasal corticosteroids are more effective than antihistamines in controlling inflammatory events, such as nasal obstruction [12]. A combination product of fluticasone propionate plus azelastine HCl was demonstrated to have greater efficacy in reducing nasal symptoms of AR when compared with either drug alone [13]. One of the most studied and used topical corticosteroids is mometasone furoate nasal spray (MFNS). Considerable evidence supports the efficacy of MFSN, which also demonstrates a remarkable safety profile. Namely, MFNS was found to significantly reduce allergic inflammation following exposure to the allergen [14]. Montelukast, an LTD4 (leukotriene D) antagonist, may be another therapeutic strategy for selected patients with AR, but it is less effective than nasal corticosteroids. Despite good safety and tolerability, montelukast has limited efficacy for treating moderate or severe AR compared to oral antihistamines [15]. Patients with moderate to severe AR, especially if they have cross-linked allergy disorders, who do not control their symptoms with medical treatment, can be good candidates for allergen immunotherapy (AIT), which is the only available disease-modifying treatment for AR [16–18]. AIT reduces medication use and symptoms in patients with AR, thus improving the quality of life of these patients [19]. It is more often administrated sublingually (sublingual immunotherapy, SLIT) or subcutaneously (subcutaneous delivery, SCIT). Several clinical trials demonstrated that SLIT and SCIT were both efficient, but with a safety profile that favored SLIT [20,21]. Adverse reactions are rare and they are more often represented by local reactions, such as itching and swelling. Uncontrolled asthma, history of severe systemic reaction to immunotherapy, and eosinophilic esophagitis are the principal contraindications to AIT [16].

However, drugs used to treat AR may accompany adverse side effects (e.g., dry mouth, drowsiness, dizziness related to anti-H1 drugs). The use of probiotics as an additional option is increasing globally. The consumption of probiotics is expected to modulate immune responses in AR patients, reduce the damage caused by inflammation, and restore a balanced gut microbiota [22,23]. Gut microbiota is known to function as immunomodulator, barrier, and protective tool against infections [24]. It is constituted of more than a trillion microorganisms reunited in a complex and dynamic ecosystem, regulating the immune system and systemic physiology [25].

2. Gut–Lung Axis

The gut microbiota is connected with the respiratory tract: alterations in the quantitative composition, qualitative content (biodiversity) or the activity and function of gut microbiota, known as dysbiosis, can affect the immunity and microbiota of the lung and vice versa. This crosstalk is called the gut–lung axis. The lung is, in turn, connected with upper airways, according to the concept of 'united airway disease' [26]. The upper-lower airways link occurs due to anatomical, physiological, pathological, and immunological

mechanisms, such as the common presence of ciliary epithelium, mucous glands, and the existence of the nose–pharyngeal–bronchial reflex [27]. This connection is essential to understand the link between the microbiota and bronchial and nasal hyperreactivity in healthy and diseased patients.

Probiotics are live microorganisms that, after oral administration, colonize the gastrointestinal tract with the goal of guaranteeing a health benefit to the host [28]. There are many probiotics, most of which can also be found naturally in the human body. They are classified into the following five species: the *Lactobacillus* group (e.g., *L. reuteri* RC-14), the *Bifidobacterium* group (e.g., *B. bifidum*), the *Streptococcus* group (e.g., *S. fecalis*), the *Bacillus* group (e.g., *B. subtilis*), and other organisms (e.g., non-pathogenic yeast *Saccharomyces boulardii*, *Escherichia coli*). They can help the respiratory, digestive, and immunological functions due to the ability to promote the maturation of the humoral responses, the IgA particularly, to improve the Th1 immune response and reduce Th2 cytokines, resulting in anti-inflammatory effects [29].

Oral probiotics can modulate the immune response of the respiratory system. They can contribute to treat, as add-on, and prevent respiratory diseases, such as asthma and AR by determining changes in gut microbiota and immune response [22]. Indeed, several studies indicated that probiotics could efficiently alleviate the symptoms of AR patients [30].

There have been promising developments in probiotics as adjuvant treatments for controlling nasal dysbiosis [31]. The use of probiotics was not only suggested to treat allergic diseases, but may be beneficial also for the immune response to viral respiratory infections, such as respiratory syncytial virus, rhinovirus [32], influenza virus [33,34], and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In particular, Coronavirus Disease 19 (COVID-19) is an infectious disease that affects mainly the respiratory system but also the gastrointestinal tract (GIT) [35]. The involvement of the GIT causes mild to severe symptoms, such as diarrhea, lack of appetite, abdominal pain, and vomiting [36]. During the infection, there is a reduction in biodiversity and richness of the gut microbiota, immune dysregulation, and prolonged infection may occur due to delayed SARS-CoV-2 clearance [37]. Due to the involvement of both respiratory and gastrointestinal systems and the relevant modifications that occur in local microbiota, therapies able to modulate the gut–lung axis and promote the eubiosis, such as probiotics, could be an important additional therapeutic strategy to fight COVID-19 infection [37,38].

To date, no relevant adverse events were observed for probiotic use; thus, probiotic use appears safe.

All these data demonstrate the importance and effectiveness of administering probiotics (as single strain or mixture) to modulate the gut and respiratory microbiota, thus improving prognosis and reducing symptoms in patients with allergic diseases and respiratory viral infections, such as COVID-19 (Figure 1).

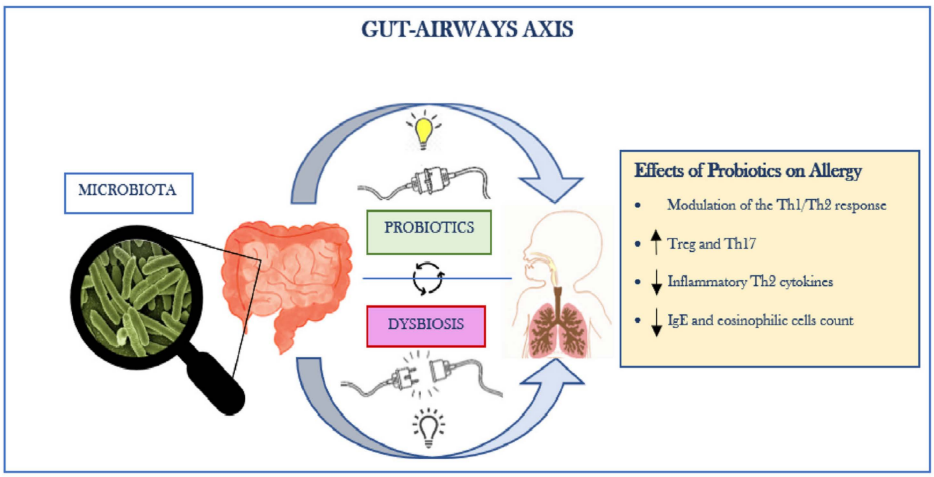

Figure 1. The Gut–Airways Axis.

3. Probiotic Food

It is important to remember that food can also be an important source of probiotics. Dairy products, in particular yogurt, yogurt products, and milk, are excellent probiotic carriers [39]. Yogurt can be subdivided into two different classes: the standard culture yogurt, which is made with *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, and bio- or probiotic yogurt, which is made by culturing additional microorganisms, generally *Bifidobacteria* and *Lactobacillus acidophilus* [40]. Many fermented food and beverages are another important source of probiotics, having several nutritional and therapeutic effects [41]. It is also possible to supplement many food products with probiotics, but their ability to deliver viable cells to the human gut may be different, because of the physical and chemical features of the food (e.g., pH, percentage of oxygen, presence of additives, titrable acidity), processing (e.g., fermentation conditions, cooling), storage (e.g., packaging materials), and microbiological parameters (e.g., strain probiotic chosen, inoculation) [42]. In the observational study conducted by Butler et al., the association between the intake of unpasteurised milk and dairy products for twelve weeks and the intestinal microbiota composition was evaluated. They enrolled twenty-four participants aged 18 to 65 years, with no chronic or current, mental or physical disease and collected their fecal samples at the beginning and end of the twelve weeks. They observed a significant increase in the presence of the genus Lactobacilli between the first and the twelfth weeks, thus demonstrating that dairy products can be a rich source of probiotic bacteria [43]. Ha-young Jeon et al. investigated the potential effects of the administration of a yogurt containing high-dose probiotics, such as *Lactobacillus acidophilus* and *Streptococcus thermophilus*, on viral respiratory infections such as influenza H1N1 and SARS-CoV-2 in an in vitro and in vivo experiment, using virus-infected animal models. They demonstrated that the administration of yogurt containing high-dose of probiotics could contribute to prevent and treat influenza H1N1 in a significant manner, reducing plaque formation in the virus-infected cells, and ameliorating the condition of influenza H1N1-infected mice. Unfortunately, the improvement effect for SARS-CoV-2 infection was less evident [44].

Commercial oral probiotic products are nowadays widely distributed, consumed and available, but there are still some concerns about their costs, efficacy, probiotic strain used, and treatment duration. It is important to remember that dietary intake has always played a major role in regulating intestinal microbiome composition and it can still represent a viable option to prevent or treat dysbiosis.

4. Probiotics and Allergic Rhinitis: Evidence and Challenges

In AR, drugs such as second-generation antihistamines or intranasal corticosteroids are prescribed for long-term control of symptoms [3]. Nevertheless, their long-term adverse effects could limit patients' daily lives, causing drowsiness, gastrointestinal disorders, dry mouth, dizziness, headache, or infections. Moreover, these drugs' effectiveness often depends on the time of the allergy's onset. Therefore, the regular administration of probiotics seems to be a suitable therapeutic option because of its safety in long-term treatment regimens and because it also leads to clinical improvement in AR patients [45–47]. Overall, probiotic use appears safe, although a risk of infectious complications (e.g., bacteremia, endocarditis, sepsis) has been described in the literature [48–50]. Virulence appears to differ by species, in particular, the *Lactobacillus* (e.g., *rhamnosus*, *acidophilus*) and *Bacillus* species seem to be the most dangerous. Sepsis following probiotic usage was mostly reported in immune-deficient/malnourished patients, with important comorbidities (e.g., HIV, diabetes) [48]. Some individuals had extensive ulcerations of the mucosa of the GIT, congenital heart diseases, or had undergone antitumor chemotherapies or ionizing radiation [49]. Most patients were also treated with broad spectrum antibiotics and covered with probiotics to prevent/treat the diarrhea which often follows [50]. Therefore, since such complications were just reported sporadically, and because of their proven utility, probiotics' use in AR seems reasonable.

5. *Lactobacilli*

Lactobacillus species belong to the so-called lactic acid bacteria (LAB), which also produce bacteriocins and competitively exclude potential pathogens [45]. Therefore, Lactobacilli have received considerable attention as potentially useful probiotics. Recent clinical and animal studies supported the idea that Lactobacilli, particularly some selected strains, can modify the host immune responses, leading to beneficial effects against allergic diseases [51–54]. Lactobacilli modulate the immune system by increasing Th1 cytokines [55], lowering Th2/Th1 ratios [56] or diminishing Th2 cytokines [45,57,58], and reducing IgE production and cell migration. Some strains reduce allergic nasal symptoms. For instance, some *Lactobacillus* species in particular (e.g., *L. acidophilus*) lead to nasal and ocular symptom relief, improvement of quality of life, and more extended periods of free-from-disease in children and adults suffering from AR [45]. A large variety of *Lactobacillus* strains exist. However, this review considered the strains that have demonstrated evidence of benefit.

L. casei (LC) is one of the most studied strains of the *Lactobacillus* species, not just in allergic diseases, but also in gastrointestinal disorders, as it survives the gastrointestinal tract and modulates its microbioma. Many researchers studied the application of LC. In a randomized control trial (RCT), the authors investigated the role of daily assumption of LC after one year of treatment on patients with AR. At the end of the study period, they found that children in the intervention group had fewer annual AR episodes and 33% lower occurrence of rhinitis symptoms (twice lower during the second quarter of intervention). They concluded that long-term LC consumption might improve children's AR [59].

Additionally, *L. paracasei* (LP) was reported to improve the quality of life of adolescents with perennial AR, and to represent a valuable add-on option [47,60,61]. In a RCT study by Peng et al., the effects of LP 33 on AR induced by house dust mites were tested on 90 patients randomized into three treatment groups: group A was treated with the live LP33; group B with the heat-killed LP33, and group C with placebo. After 30 days, compared with the placebo group, groups A and B significantly improved their overall quality of life. There was no significant difference in the efficacy of the heat-killed LP33 compared to the live variant, supporting the notion that allergic patients could be treated with heat-killed strains instead of live variants. Notably, no side effects were reported [47]. Even though LP 33 was shown to be equally effective as cetirizine in AR children [62–66], its use was recommended chiefly in association with antihistamine drugs. In support of this concept, in a double-blind RCT, *L. paracasei* (HF.A00232) was studied as a supplementary agent to levocetirizine in children with perennial AR. Sixty patients (6–13 years old) were randomized into two groups: one receiving levocetirizine plus placebo and the other receiving regular levocetirizine plus LP (HF.A00232) for the first eight weeks, with a shift to levocetirizine as rescue treatment during the following four weeks. Clinical parameters were recorded, and physical examination and Pediatric Rhinoconjunctivitis Quality of Life Questionnaires (PRQLQs) were administered at each visit. The probiotic-treated group experienced a significant improvement in symptoms (sneezing, itchy nose, and swollen eyes), and showed significantly lower PRQLQ scores even after discontinuing regular antihistaminic use. No significant differences in cytokine levels were found between the two groups. The researchers did not observe any add-on effect of LP (HF.A00232) as a supplement to levocetirizine in managing AR in the first eight weeks. By contrast, the subgroup of probiotic-treated who did not discontinue levocetirizine use and also used more rescue levocetirizine in the following period had progressively lower PRQLQ scores in the latter part of the study. Such improvement did not occur in the other subgroup. This result can be explained as the synergistic effect of LP (HF.A00232) and levocetirizine, which implied an approximately 56% reduction in levocetirizine use [61].

The supplementation of *Lactobacillus salivarius* (LS) strains induced a significant increase in IL-10, which acted as an immunomodulator with anti-inflammatory effects [67,68]. In a double-blind RCT conducted by a Taiwanese group, 199 children (6–12 years old) with AR and house dust mite sensitization were randomized into two groups: one treated with placebo and the other with LS PM-A0006. They were followed for three months. LS reduced

symptoms (nasal and eye symptoms) and medication scores compared with the control. Interestingly, no difference was found in specific immune and blood parameters between the probiotic and placebo group. This result was consistent with previous studies [69–72].

L. helveticus (LH) was examined in the study of Tamashita and co-workers. These authors demonstrated that LH2171 decreased the eosinophil counts in patients with symptomatic perennial AR. In addition, the LH2171-treated group experienced a significant clinical improvement, mainly concerning the stuffy nose, compared to the placebo group [73].

It was demonstrated that *L. reuteri* (LR) can also influence the immune system. LR CCFM1040, in particular, modulated type 2 inflammation and gut microbiota [74,75]. The mechanism through which it worked included modulating gut microbiota and metabolizing endogenous tryptophan to balance systemic and mucosal immune reactivity, thereby inhibiting airway inflammation [76–78]. In a recent RCT study, the supplementation with CCFM1040 decreased total symptom score (TSS), RQLQ, nasal congestion, watery eyes, rhinorrhoea, and sleep quality, and significantly improved eye symptoms in patients with AR. No difference in the blood and urine parameters and adverse effects were observed [79].

Most of the studies concerning *L. plantarum*, *gasseri*, and *rhamnosus* were carried out in animal models. Only a few studied the use of these strains in AR patients. Some were, in fact, conducted on mice, as in an experimental study carried out by Choi et al.; they demonstrated that the oral administration of *Lactobacillus plantarum* CJLP133 and CJLP243 in mice alleviated the symptoms of birch pollen (BP)-induced AR by reducing airway hyperresponsiveness, the histological scores, and the number of infiltrated cells in the nasal cavity and lungs. This probiotic mixture also restored the Th1/Th2 balance by enhancing the type 1 immune response [80]. Other studies were conducted on guinea pigs. A Japanese study investigated antigen-sensitized animals to demonstrate the improvement of nasal blockage measuring nasal airway resistance [81]. They proved that the oral administration of *L. rhamnosus* GG (LGG) and *L. gasseri* TMC0356 (LG TMC0356) significantly ameliorated the antigen-induced nasal blockage. Surprisingly, oral administration of LGG and TMC0356 did not substantially change the levels of serum antigen-specific IgG1, IgG2, and IgE or the numbers of inflammatory cells from nasal lavage fluid (NCLF) [54]. Other strains of LG were studied for their possible involvement in AR treatment. In a clinical trial conducted by Chen et al., 105 patients with asthma and AR were divided into two groups: one was treated with the LG strain A5 and the other was treated with placebo. After eight weeks, the airway function, clinical symptoms, and immunoregulatory cytokine production improved significantly in the probiotic group compared with the placebo group [82]. Some LG strains were also evaluated in association with other Lactobacilli. For example, it was proved that the daily assumption of *L. coryniformis* (LC) CECT5711 and LG CECT5714 in fermented products could modulate immunological parameters in healthy adults and children [83–86]. A Spanish randomized double-blinded trial conducted on children suffering from allergic rhinitis demonstrated that the consumption of products containing LG CECT5714 and LC CECT5711 reduced the plasma level of IgE and increased T-regulatory cells [58]. In addition, the administration of LP NCC 2461 resulted in beneficial effects in subjects with AR to grass pollen [87,88].

However, other studies did not show significant effects. Ouwenhand et al. observed that AR patients treated with *L. acidophilus* NCFMTM had a reduction in nasal eosinophil infiltration, but symptom severity did not significantly change [89]. Another study tested the effects of 8-week LA NCC 2461 supplementation in AR patients with grass allergy [90]. The probiotic administration did not significantly improve quality of life, IgE levels, total nasal symptom score (TNSS), total ocular symptom score (TOSS), and drug use. Finally, a Finnish RCT evaluated respiratory and eye symptoms and medication use in patients treated with *Lactobacillus rhamnosus* (LR) or placebo [91]. The 5.5-month treatment did not affect any clinical parameter (Table 1).

Table 1. RCTs on Lactobacilli in children with AR.

Reference	Objective	Population	Methods	Results
Giovannini et al., Pediatr Res. 2007 [59]	To investigate whether long-term consumption of fermented milk containing *Lactobacillus casei* (LC) may improve the health status of preschool children suffering from allergic asthma and/or rhinitis.	187 children 2–5 years of age with diagnosis of allergic asthma and/or AR proved by prick test.	Patients received 12 months of either fermented milk with LC (92 patients) or a placebo (95 patients). The number of fever or diarrhea episodes and the recurrence of asthma and rhinitis symptoms were recorded. The change in serum immunoglobulin (IgA, IgE, IgG, and IgM) were measured.	As compared to the control group, in the LC group: - The time free from episodes of asthma/rhinitis was longer; - There were fewer asthma and rhinitis episodes overall; - In children with AR, the mean duration of a single episode of diarrhea was lower. Any evaluated immunologic measure did not show a statistically significant difference between the two groups at baseline or after a 12-month intervention period. This held true even when children with asthma and AR were taken into account separately.
Lin et al., Indian Pediatr. 2013 [72]	To examine the effect of *Lactobacillus salivarius* (LS) on the symptoms and medication use among children AR.	199 children aged 6 to 12 years with a history of perennial allergic symptoms for at least three years with a positive skin prick test for *Dermatophagoides farinae* (DF) or *Dermatophagoides pteronyssinus* (DP).	All enrolled patients were randomly assigned either to the *L. salivarius* group or the placebo group (120 patients each). The 12-week course of treatment was followed by a 7-month surveillance period. At each visit, the severity of the child's AR was assessed using the specific symptoms scores (SSS) and symptom medication scores (SMS). In addition, parents were required to keep a weekly journal of their child's AR status. Blood samples were also collected.	In comparison to the untreated group (UT): - The symptoms scores (SS) of LS-treated group were significantly reduced at 8 and 12 weeks, specifically for eye and nose symptom scores, but not for the lung; - After four weeks, there was a statistically significant difference in the medication scores for rhinitis between the LS-treated group and the UT group; 1. There was no difference between the two groups in blood and immunologic profile level (blood cell and eosinophil counts and total IgE).

Table 1. *Cont.*

Reference	Objective	Population	Methods	Results
Lin et al., Pediatr Neonatol. 2014 [61]	To evaluate the effects of *Lactobacillus paracasei* (LP), strain HF.A00232, as a supplementary agent to levocetirizine in treating children with perennial AR.	60 patients aged 6–13 years with perennial AR longer than one year, with house dust mites allergy.	All patients were randomized into two groups: 28 were treated with levocetirizine plus placebo for 12 weeks and 32 with levocetirizine plus LP for the first 8 weeks, with a shift to usage of levocetirizine as rescue treatment during the last 4 weeks. At the initial screening visit, blood samples (to test for mite-specific IgE) and medical and allergy history were collected. Additionally, daily symptom diaries were given. At each visit, the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), Total symptom score (TSS), and nasal total symptom score (NTSS) were administered. Blood samples were taken to evaluate inflammatory cytokines at baseline and at week 8 and 12.	In comparison to the placebo group: - The mean change of individual parameters in PRQLQ scores in the LP group revealed lower scores for individual symptoms of sneezing, itchy nose, and swollen puffy eyes; - PRQLQ scores were lower in the LP group; - No difference in NTSS or TSS scores was noted; - There were no significant changes in cytokine levels between the two groups. Patients in the LP group had a significant decrease in symptom scores at the end of the study period (weeks 9 to 12) than at the beginning (weeks 1 to 8).
Ouwehand et al., World J Gastroenterol 2009 [89]	To investigate whether birch pollen allergy symptoms are linked with gut microbiota changes and whether probiotics (*Lactobacillus acidophilus* (LA) and *Bifidobacterium lactis* (BL)) affect these.	41 children (4–12 years old) with confirmed birch pollen-AR.	Children were randomly distributed in two groups to receive either a combination of LA NCFMTM and BL Bl-04 (20 patients) or a placebo (21 patients) for 4 months, starting before the birch pollen season. Symptoms were noted in a diary. Blood and fecal samples were collected.	In comparison to the UT group: - During the pollen season, fewer subjects in the probiotics group reported runny noses and nasal blocking ($p = 0.101$) and had infiltration of eosinophils in the nasal mucosa ($p = 0.013$); - Higher frequency of eye symptoms was reported in the probiotic group ($p = 0.066$); - Fecal IgA was lower in the probiotic group ($p = 0.028$). Concentrations of birch pollen-specific IgE and blood eosinophil counts increased in both groups. On the other hand, concentrations of IL-6 and TNF-a decreased in both groups, whereas concentrations of IL-10 were reduced in the placebo.

Table 1. *Cont.*

Reference	Objective	Population	Methods	Results
Ahmed et al., Pak J Med Sci. 2019 [66]	To evaluate the efficacy of *Lactobacillus paracasei* (LP-33), and compare it with cetirizine for the treatment of perennial AR in children.	212 children aged 6 to 60 months affected by AR.	Children were randomized into intervention group A (106 patients), which received probiotic LP-33, and control group B (106 patients), which received cetirizine for 6 weeks. Baseline AR symptoms were assessed after a two- and six-week follow-up.	At first and second follow-up visits, both groups A and group B majority participants showed at first a partial, then a complete, significant improvement in their baseline AR symptoms. Except for the symptoms of cough and feeding difficulties, which at the first visit appeared to be better treated by cetirizine ($p < 0.05$), there was no statistically significant difference between the two groups. Treatments with probiotics and cetirizine for persistent AR in children under the age of five were equally beneficial. ($p > 0.05$).
Chen et al., Pediatr Pulmonol. 2010 [82]	To determine whether daily supplementation with *Lactobacillus gasseri* (LG) *A5* for eight weeks may improve the symptoms and immunoregulatory changes in school children with asthma and AR.	105 asthmatic children (6–12 years old) with persistent AR.	Children were randomized into the probiotic-treated group (1 capsule of LG twice a day) or the control group (milk powder). The participants underwent clinical examinations every 2 weeks. A final evaluation was performed at week 10. Additionally, data regarding the need for drugs (such as beta2 agonists and oral prednisone), and blood samples were collected.	A significant decrease in clinical symptom scores for asthma and AR was shown in the LG-treated group compared to the placebo-treated one. The asthmatic symptoms and objective airway function measurements improved significantly in allergic asthmatic children who received probiotic supplementation. In addition, the cytokine IL-10 decreased in the probiotic group. There was no significant difference in the serum total IgE level, the degree of allergen sensitization, and no significant elevation in the Th1 cytokines before and after probiotic treatment.The medication scores decreased significantly in the probiotic-treated and control groups, with no significant difference.

6. Bifidobacteria

In the human gastrointestinal tract, Bifidobacteria are the dominant bacterial population. Bifidobacteria have an anti-bacterial function, protecting the organism from the proliferation of pathogenic bacteria, such as *Helicobacter pylori* [92]. Additionally, they are involved in the production of short-chain fatty acids and vitamins, and in the regulation of the immune response in allergic, autoimmune, and inflammatory bowel diseases [92]. *Bifidobacterium bifidum, B. longum, B. infantis,* and *B. breve* are the most prevalent species in breastfed infants. *B. adolescentis, B. animalis*, and *B. lactis* appear later [93].

It was shown that *Bifidobacterium longum*, alone and in association with *Lactobacillus plantarum*, alleviated AR symptoms and restored Th2/Treg balance in mice [94]. Similar results were observed with the supplementation of *B. breve* at 10^7 CFU or higher [95] and *B. bifidum* [96]. In humans, *B longum* supplementation significantly reduced nasal allergic symptoms and Th2-polarized immune response [71]. Bifidobacteria strains were frequently reduced in atopic children [78] and adults [79], and the BB12 strain, in particular, showed anti-Th2 properties by dampening allergic inflammation [80].

In a study performed by Di Pierro et al., pollen-allergic children aged 2–14 years were randomly assigned to three groups: untreated, preventive, and treated arm. The prophylactic and treated groups assumed a probiotic mixture, containing *Bifidobacterium animalis* subsp. lactis BB12, and *Enterococcus faecium* L3, for three months before the pollen season or during the pollen season, respectively [97]. The BB12 and L3 strains significantly decreased rhinitis symptoms, watery eyes, and cough/wheezing in the prophylactic group compared to the control arm. However, when the mixture was administered during the pollen season, there was lower efficacy. In addition, medication use was reduced. In another recent study, children with seasonal AR, aged between 4–17 years, were randomly assigned to two groups: placebo-treated and actively-treated with a supplementation containing a Bifidobacteria mixture (*B. longum* BB536, *B. infantis* M-63, and *B. breve* M-16 V) [98]. After two months, children who received the probiotic mixture showed a substantial improvement in symptoms and quality of life, while the use of rescue medications overlapped in the two groups.

7. Enterococci

Enterococci are among the first bacterial colonists after birth and can survive in large and small intestines. One of the strains with the highest relevance is *Enterococcus faecium* (EF), which is mainly used to contrast pathogenic intestinal bacteria and boost the effectiveness of other probiotic strains. *E. faecium* modulates the type 2 inflammation, as evidenced by ex vivo studies, and alleviated nasal symptoms and eosinophilia in mouse models [99,100]. In addition, *Enterococcus faecium* L3 (L3) promotes the preservation of endogenous colonic Bifidobacteria in children [101]. Regarding its potential use in AR, it was demonstrated that when administered as prophylactic treatment in AR patients, L3 strains significantly reduced the development of nasal, ocular, and bronchial symptoms [74]. A RCT study provided confirming results [102]. This trial included 250 patients (6 to 17 years old) affected by AR; they were randomly divided into an intervention group (treated with a daily oral administration of a probiotic mixture containing BB12 DSM 15,954 and EF L3 LMG P-27496 strain), and a placebo group. Treatment was administered during the three months preceding the typical onset of the symptoms. Only 203 children completed the study. At the end of the study, the nasal symptoms score (NSS) was significantly improved in the intervention group, and the intake of medications (oral antihistamines and local corticosteroids) was significantly reduced.

8. *Saccharomyces*

A Chinese RCT enrolled 90 children with AR to evaluate the efficacy of the combination of *Saccharomyces Boulardii* (SB) and cetirizine, compared to the use of levocetirizine only. Serum IFN-γ and interleukin-4 (IL-4) levels were measured. Thirty non-AR children were then enrolled as the healthy control group. The study was carried out for four weeks. Before

the treatment, serum IFN-γ levels were significantly lower in allergic subjects compared to the healthy group. In contrast, IL-4 was significantly higher in the two allergic groups than in the healthy group. At the end of the study period, the symptom scores of the two allergic groups were significantly reduced. The observational group showed indeed significantly lower nasal congestion, sneezing, nasal itching, and runny nose as compared to the control group. Additionally, INF-γ levels were considerably lower and IL-4 significantly higher in the observational group than in the control group [103].

9. Butyric Acid Producing Bacteria

Butyric acid producing bacteria (BAPD) belong to the Gram-positive Firmicute phylum. The most prevalent species are *Eubacterium rectale/Roseburia* spp. and *Faecalibacterium prausnitzii*. The functions of these bacteria in the gut and their impact on health are currently being uncovered [104]. Butyric acid's anti-inflammatory benefits are widely known. A plausible reason is the inhibition of deacetylase activity, which leads to hyperacetylation of histones and, as a result, suppression of nuclear factor-kappa B activation [105]. Decreases in members of BAPD have been reproducibly reported in the gut of intestinal bowel diseases (IBD) patients [106]. It was demonstrated that BAPD administration had a beneficial effect in IBD patients' inflamed intestinal mucosa [107]. Regarding allergic diseases, high levels of butyrate in early life were associated with protection against atopy [108]. The latest studies on the gut microbiota in children with allergic diseases supported the hypothesis that dysbiosis characterized by fewer BAPD leads to fewer regulatory T cells, resulting in cow milk protein allergy, food allergy, and asthma [109]. Therefore, BAPD supplementation alone or in combination with other probiotics could represent a new dietary option for infants and children with allergic diseases [110]. However, the majority of research was conducted on mice. The therapeutic and preventative role of BAPD may be uncovered by implementing additional research in humans in the near future.

10. The Role of Probiotics in the Prevention of Allergy during Pregnancy

The World Allergy Organization supports probiotic supplementation in pregnant women and infants at high risk of allergy [111]. In this regard, it is important to note that during pregnancy, there is an increase in the bacterial load and alterations in the maternal gut microbiota, such as the major representation of Actinobacteria and Proteobacteria and reduced the presence of *Faecalibacterium* and other short-chain fatty-acid producers [112,113]. These changes in maternal gut microbiota may have consequences in terms of immunity, health, and growth of the fetus [114]. It is known that maternal microbiota has a role in shaping the offspring's immune system in terms of immune gene expression and the number of innate immunity cells [115]. Furthermore, many studies showed the role of microbial exposure during pregnancy in preventing allergic disease in the offspring [116]. Creating an appropriate intestinal microbiota in neonates is crucial for guaranteeing them protection from enteric pathogens and local and systemic inflammation. This process is influenced by the infant's diet, maternal microbiome, and environment. Pregnancy and the period from birth to 24 months (B-24) are sensitive windows during which diet has a powerful influence on the life trajectory of health [117]. A recent analysis of four randomized, double-blind, placebo-controlled clinical trials found that administration of perinatal *L. rhamnosus* was associated with a decrease in allergic disease in infants with no safety concern [118]. In this regard, a meta-analysis performed by Zuccotti et al. suggested that the administration of probiotics during pregnancy prevented atopic dermatitis in children [64]. Accordingly, Bertelsen et al. showed that probiotic Lactobacilli and Bifidobacteria during pregnancy decreased the incidence of atopic dermatitis and rhinoconjunctivitis in children [119]. Another meta-analysis of seventeen randomized controlled trials performed by Du et al. demonstrated that supplementation with probiotics in pre- and postnatal periods successfully prevented asthma, but the effects depended on the type of probiotic mixture used [120]. It is important to note that probiotic supplementation may also have a protective role against preeclampsia, vaginal infections, gestational diabetes, later childhood disease, and maternal

and infant weight gain [121]. These data provide compelling evidence that the maternal microbiome influences the infant microbiome, which subsequently affects childhood health, and that the administration of probiotics during pregnancy, lactation, and postnatal life could be a safe and effective strategy to modify both the maternal and neonatal microbiota, thus improving pregnancy and neonatal outcomes [122]. On the other hand, some studies reported discordant results on the benefit of the use of probiotics in pregnancy, possibly due to the use of different strains of probiotics, study period, other methods of administration and follow-ups. In this regard, a randomized study by Boyle et al. recruited 250 pregnant women carrying infants at high risk of allergy disease. They administered to 125 women a probiotic supplementation with *Lactobacillus* GG each morning for thirty-six weeks of gestation until delivery, and to the other 125 women, they administered a maltodextrin placebo. They found no evidence that prenatal treatment with LGG prevented eczema [123]. A study by Simpson et al. recruited 415 pregnant women. They were randomized in a double-blind study to receive probiotic milk or placebo from thirty-six weeks of gestation until three months postpartum. The probiotic milk contained *Lactobacillus rhamnosos* GG, *L. acidophilus* La-5, and *Bifidobacterium animalis subsp. Lactis* Bb-12. Afterwards, they evaluated their children through clinical examinations and family questionnaires. The results suggested that there was no significant reduction in the prevalence of asthma, atopic sensitization, and allergic rhinoconjunctivitis, but only reduction in atopic dermatitis [124].

11. Conclusions

Most human studies showed that, compared to a placebo, probiotics alone or in combination with antihistamines can alleviate allergic symptoms and reduce the frequency and duration of AR episodes in the pediatric population [59,61,66,72,82,89]. In addition, there were no noticeable adverse reactions. However, most studies did not detect significant differences in immunological parameters and blood eosinophil count between the active and control groups.

It must be underlined that the duration of treatments, measure variables, strains employed, and clinical and functional characteristics of participants considerably differed across investigations. Most of the studies investigated *Lactobacillus* species and their modulatory effects on immunologic parameters in allergic disorders. By reviewing the literature, we found that no strain has emerged as the most effective as their effects seem to be strain-specific.

There has yet to be an agreement on the best *Lactobacillus* candidate to be used in AR human trials [45,79]. Although most of the studies proved the efficacy of probiotics in AR treatment, there are studies where their assumption did not show significant effects [58,89–91,125]. Therefore, their use is still controversial. Although it is currently exactly unknown how lactic acid bacteria affect the immune system, prevent the onset of allergies, or alleviate allergic symptoms. At present, the International Consensus Statement on Allergy and Rhinology reads: "Allergic Rhinitis: recommended to consider probiotics as adjuvant therapy, such as add-on, for patients with AR thanks to their ability to alleviate symptoms and enhance the quality of life without causing adverse effects" [126].

Author Contributions: A.K. drafted the sections on probiotics and allergy, conclusions, Figure 1, and Table 1. A.S. drafted the section on probiotics and allergy and Table 1. G.D. carried out the methodology and revision. C.I. and F.D. supervised the study. M.C. drafted the section on the Introduction, Gut-Lung Axis, Allergic Rhinitis, Probiotic Food, and Pregnancy. S.V. drafted the section on the Introduction, Allergic Rhinitis, and Pregnancy. G.C. was responsible for the revision. M.M.d.G. was responsible for the conceptualization, revision, and project administration. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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