REVIEW

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Probiotics, prebiotics and food allergy: a review

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Key words

Probiotics; prebiotics; food allergy; dysbiosis; microbiota.

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Impact statement

Probiotics and prebiotics are potential therapeutic interventions in managing cow's milk and peanut allergy. Oligosaccharides from breast milk show promising benefits in the prevention of atopic dermatitis, food allergy and asthma.

Summary

Background. *The prevalence of food allergy (FA) has increased, a possible consequence of intestinal dysbiosis, environmental or genetic factors. Currently, no formal indications exist for probiotic or prebiotic supplementation in FA. This review aims to analyze the role of probiotics and prebiotics in the prevention and treatment of FA.* ***Methods.*** *A PubMed/Medline search was carried out on articles published between 2011 and 2021 with the following query: ("Food Hypersensitivity"[Mesh]) AND (("Probiotics"[Mesh]) OR ("Prebiotics"[Mesh])). Subsequently, the titles and abstracts were analyzed and selected according to established criteria. After full reading of these articles, 54 were included and a narrative review was performed.* ***Results.*** *The review was structured in the following sections: 1) Cow's Milk Proteins Allergy (CMA), 2) Food Allergy to Peanuts and 3) Prevention of Food Allergy. In CMA, studies indicate that extensively hydrolyzed casein formula supplemented with Lactobacillus Rhamnosus GG aids in acquiring tolerance to cow's milk proteins, resolving gastrointestinal symptoms and preventing of other allergic manifestations. In peanut oral immunotherapy (OI), supplementation with Lactobacillus Rhamnosus CGMCC 1.3724 appears to promote sustained desensitization. However, the evidence supporting probiotics for preventing food allergies lacks robustness. Current evidence supports the use of oligosaccharides from breast milk in the first months of life for preventing atopic dermatitis, FA and asthma.* ***Conclusions.*** *The potential of probiotics to be used as therapeutic adjuvants in CMA and peanut OI is promising. However, there is inconsistency regarding the type of probiotic, the dose and duration of supplementation.*

Introduction

In last decades, food allergy (FA) prevalence has increased, particularly in industrialized countries, affecting up to 10% of children. Nonetheless, some figures are based on parent-reported data, potentially leading to overestimations (1, 2). Concurrently, clinical symptoms have also become more severe and FA prevalence is extending to older age groups (3). As in other chronic diseases, FA is the result of an interplay between genetic predisposition and environmental influences. Several factors have been identified as contributing to FA, encompassing both non-modifiable (male gender, Asian and African ethnicities, genetics and atopic dermatitis) and modifiable (microbial exposure/increased hygiene, use of antibiotics, diet, obesity, urban lifestyle and the timing/route of food exposure) elements (4-6). Cow's milk allergy (CMA) and peanuts are among the most common food allergens, exhibiting geographical and age-related variations (7, 8). Some of these have a high rate of recovery during childhood, such as CMA, egg allergy, wheat allergy and soy allergy; in contrast allergy to nuts and fish often persist over time (9). Typically, the immune system maintains a state of tolerance towards ingested food antigens (10). However, in individuals with FA there is an immunological deviation characterized by the impairment of Treg cell activation and their

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replacement by antigen-specific TH2 cells, leading to IgE-mediated, non-IgE-mediated or mixed (IgE and cell-mediated) allergic responses (5, 11). The management of FA involves allergen avoidance, desensitization therapies and acute drug treatments, in the event of accidental ingestion (5).

The human gastrointestinal tract is colonized by a complex ecosystem of microorganisms, called the intestinal microbiota (IM). Its composition undergoes continuous changes influenced by factors such as the intestinal mucosa, regular diet, peri-partum factors, medication use and interactions with the host immune system (12, 13). Dysbiosis refers to an unbalanced alteration of the IM, characterized by decreased microbial diversity and an overgrowth of proteobacteria, which has implications for shaping food tolerance (12, 14, 15). This implies that the IM plays a crucial role in programming the developing immune system in the early months of life, and the increased prevalence of allergies may be linked to intestinal dysbiosis during infancy (16, 17).

Probiotics are formed by strictly selected live microorganisms that, when administered in adequate amounts, confer a benefit in the health condition of the receiver (18). These microorganisms have a modulatory effect on IM, colonizing and suppressing the action of pathogens, as well as in metabolic control, with a regulatory effect on cholesterol absorption and glucose metabolism (19). Another impact is the immunomodulation of IM, with the induction and maintenance of immunological tolerance by 1) promoting Th1 cell production and Treg cell development; 2) supressing Th2 and IgE production (19-21).

Prebiotics are non-digestible food components that promote the growth and activity of a limited number of bacteria at the colonic level and modify the composition and activity of the IM to confer benefits to the host (22-24). The most commonly used prebiotics are non-digestible carbohydrates, such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS) (25). The rationale for the use of probiotics and prebiotics in food allergy is grounded in their potential to modulate the gut microbiota, regulate the immune system response, strengthen the gut barrier to reduce the translocation of allergenic proteins and other molecules into the bloodstream and reduce inflammation, all while maintaining a favorable safety profile.

In summary, FA is a complex disease caused by an immunological imbalance and therapeutic options are still limited. The increasing prevalence of FA highlights the need for further research to evaluate the potential role of probiotics and prebiotics in the prevention and treatment of this condition. Currently, there are no recommendations from scientific societies endorsing the use of a particular strain of probiotic or prebiotic for the prevention and treatment of FA (26, 27). Nevertheless, selected strains of *Lactobacillus* and *Bifidobacterium* have been investigated in this context. Notably, a recent systematic review as provided evidence supporting the potential benefits of probiotics, as they have been shown to promote immunomodulation, reduce clinical symptoms and may contribute to the management of children with FA (28). A recent review addressing probiotics supplementation in confirmed CMA, demonstrated that it could be beneficial for early acquisition of tolerance to cow's milk protein in affected individuals (29). Conversely, a distinct review focusing on the supplementation of probiotics and prebiotics in allergies concluded that they may serve as adjuncts in preventing atopic dermatitis but not other forms of allergic diseases. Furthermore, the effects of probiotics and prebiotics on the treatment of allergic diseases remain a topic of controversy (30).

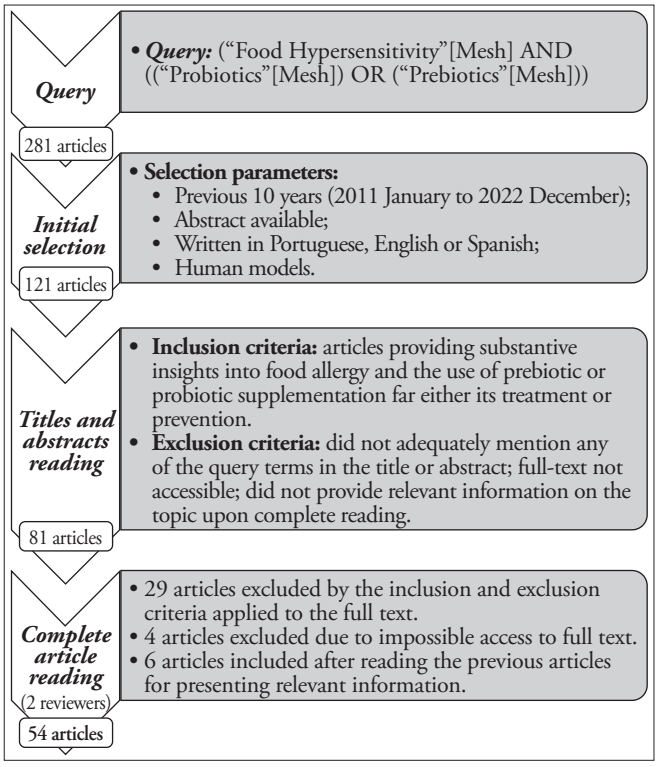
This article is a narrative review that aims to evaluate the existing literature on the use of probiotics and prebiotics in FA.

Methods

In this narrative review, the PubMed/Medline database was used and the search was conducted using the following query: ("Food Hypersensitivity"[Mesh]) AND (("Probiotics"[Mesh]) OR ("Prebiotics"[Mesh])).

To ensure the selection of current and relevant literature (31), articles published in the last 10 years (2011 January to 2022 December, inclusive), whose abstract was available for reading, written in Portuguese, English or Spanish and whose studies were in

***Figure 1** - Selection diagram of the articles used for the preparation of this narrative review.*



human models were included. The article typology did not constitute an exclusion factor. After this initial selection, articles were selected if they provided insights into FA and the use of prebiotic or probiotic supplementation for either its treatment or prevention. Exclusion criteria included articles that did not adequately mention any of the query terms in the title or abstract and those whose full text was not possible to access. Articles were also excluded after reading them completely, when they did not present relevant information on the topic. Six articles were included that were not in the initial selection, but were referenced in the articles read, as they presented relevant information related to the topic. In the end, 54 articles were included in this narrative review and an evaluation was carried out by two reviewers to ensure the relevance of the selected literature (**figure 1**).

Results

Immune tolerance is the most important therapeutic target in FA and is modulated by immune and non-immune mechanisms. Intestinal dysbiosis seems to contribute to the development of allergic diseases, as IM and its metabolites play an important role in immune tolerance (6, 26). However, it is still not clear that maintaining IM balance will induce food tolerance (16). Therefore, it is relevant to better understand the possible role of probiotics and prebiotics in the pathogenesis of FA.

The majority of studies carried out with prebiotics and probiotics are in CMA and peanut allergy. Other studies investigating fish and shellfish allergy, have not yielded clear beneficial results (32, 33). Therefore, the article is divided into tree topics for better clarification and comprehension: 1) Cow's Milk Proteins Allergy (**table I**); 2) Food Allergy to Peanuts (**table II**); 3) Prevention of Food Allergy (**table III**).

Cow's milk proteins allergy

CMA has an important economic and social impact. Elimination diets and extensively hydrolyzed milk formulas are the first line treatments. In severe cases, it may be necessary to use amino acids milk formulas (29, 34). **Table I** presents the results of 16 articles regarding probiotics in CMA.

The use of extensively hydrolyzed casein formula (EHCF) supplemented with *Lactobacillus rhamnosus* GG (LGG) in IgE-mediated and non-IgE mediated CMA has been proved to be more effective in preventing other allergic manifestations than the formula alone (35-38). In addition to this beneficial effect on the prevention of other atopic manifestations, there is also a modulation of tolerance to cow's milk proteins (CMP), which is earlier in children treated with EHCF and LGG when compared to children treated with EHCF alone within a period of 36 months (35, 37, 39, 40). Tolerance to CMP at

Table I *- Summary of probiotics and prebiotics and their impact in cow's milk allergy.*

Supplement	Article	Sample / Intervention / Duration / Dose	Outcomes	Main results
Probiotics				
Lactobacillus rhamnosus GG	Canani RB *et al.* 2013 (Prospective Cohort Study) (41)	n = 260 children with CMA / EHCF *vs* EHCF + LGG *vs* hydrolyzed rice formula *vs* SF *vs* amino acid-based formula / 12 months.	Rate of acquisition of milk tolerance.	EHCF accelerates tolerance acquisition in children with CMA when compared with other dietetic choices, this effect is augmented by LGG.
	Canani RB *et al.* 2016 (RCT) (35)	n = 220 patients with CMA / EHCF *vs* EHCF + LGG / 36 months.	Primary: occurrence of other allergic manifestations in CMA; Secondary outcome: acquisition of tolerance at 12, 24 and 36 months-old.	EHCF + LGG reduces the incidence of other allergic manifestations. EHCF + LGG accelerates the development of oral tolerance in children with IgE-mediated CMA.
	Canani RB, Sangwan N *et al.* 2016 (RCT) (42)	n = 39 (healthy children: 20; children with CMA: 19) / EHCF with *vs* without LGG.	Gut microbiota evaluation from fecal samples of 4 groups: (i) Healthy controls; (ii) CMA infants before treatment; (iii) CMA patients after EHCF alone; (iv) CMA patients after EHCF + LGG.	EHCF + LGG promotes tolerance in infants with CMA, in part, by influencing the strain-level bacterial community structure of the infant gut. *Blautia, Roseburia* and *Coprococcus* were significantly enriched following treatment with EHCF + LGG, but only Oscillospira was significantly different between infants that became tolerant and those that remained allergic. Most tolerant infants showed a significant increase in fecal butyrate levels.

Supplement	Article	Sample / Intervention / Duration / Dose	Outcomes	Main results
	Guest JF *et al.* 2018 (RCT) (45)	n = 220 children with CMA / EHCF + LGG *vs* EHCF alone *vs* AAF / 36 months.	Cost-effectiveness of EHCF + LGG *vs* EHCF alone or AAF in treating CMA in the US, from the perspective of third-party insurers and from parents.	The probability of developing tolerance to cow's milk was higher in EHCF + LGG *vs* EHCF alone or AAF. Infants fed with EHCF+LGG are expected to utilize fewer healthcare resources. Initial management of CMA with EHCF + LGG was a cost-effective strategy when compared to an eHCF alone or AAF.
	Guest JF *et al.* 2019 (Retrospective Cohort Study) (38)	n = 940 children with CMA / EHCF + LGG *vs* EHWF / 24 months.	Management of CMA and preventing other allergic manifestations.	First-line management of newly diagnosed CMA infants with EHCF + LGG appears to be more clinically effective than EHWF and may slow down the allergic march.
	Paparo L *et al.* 2019 (RCT) (39)	n = 20 children with CMA / EHCF + LGG *vs* SF / 12 months.	Evaluation of epigenetic mechanisms in CMA children (FoxP3 methylation rate; FoxP3 expression in $CD4^+$ T cells; IL-4, IL-5, IL-10, IFN-γ methylation rate, expression and serum concentration; miRNAs expression).	At 6 and 12 months, EHCF + LGG group showed a significant increase in FoxP3 demethylation *vs* SF group. EHCF+LGG group presented a higher increase in IL-4 and IL-5 and a higher reduction in IL-10 and IFN-γ DNA methylation rate *vs* SF group. A different modulation of miR-155, -146a, -128 and -193a expression was observed in EHCF + LGG group. Dietary intervention could exert a different epigenetic modulation on the immune system in CMA children.
	Guest JF Singh H 2019 (RCT) (40)	n = 220 children with CMA / EHCF + LGG *vs* EHCF / 36 months.	Cost-effectiveness of EHCF + LGG *vs* EHCF alone as first-line dietary management.	First-line management with EHCF+LGG instead of EHCF improves outcome, releases healthcare resources for alternative use, reduces the cost of patient management and thereby affords a cost-effective dietetic strategy.
	Nocerino R *et al.* 2019 (Prospective nonrandomized trial) (43)	n = 30 (healthy children: 110; children with CMA in the 1st year of life: 220) / EHCF alone *vs* EHCF + LGG *vs* healthy controls / 5 years and 4 months.	Occurrence of functional gastrointestinal disorders (FGIDs) later in life of children with CMA.	Increased risk for FGIDs in children with CMA, suggesting that EHCF + LGG could reduce this risk
	Basturk A *et al.*, 2020 (RCT) (53)	n = 106 children with CMA / Probiotic group: LGG (5 drops/day; LGG 1×10^9 CFU) + milk free diet (EHCF or breast milk of a mother on milk-free diet) *vs* placebo group: milk free diet / 4 weeks.	Symptoms (diarrhea, vomiting, mucousy or bloody stool, abdominal pain or distension, constipation, dermatitis and restiveness) recorded at the beginning and weekly during the study; Symptoms improvement between groups.	A significant improvement in symptoms (bloody stool, diarrhea, restiveness, abdominal distension, mucousy stool and vomiting) of infants receiving LGG + cow's milk-free diet was observed.
	Nocerino, *et al.* 2021 (Prospective Cohort Study) (37)	n = 365 patients with CMA / EHCF + LGG *vs* rice hydrolyzed formula *vs* soy formula *vs* EHWD *vs* amino acid-based formula / 36 months	Occurrence of other atopic manifestations and the time of immune tolerance acquisition.	EHCF + LGG for CMA treatment is associated with lower incidence of atopic manifestations. The 36-month immune tolerance acquisition rate was greater in the EHCF + LGG.

Supplement	Article	Sample / Intervention / Duration / Dose	Outcomes	Main results
***Lactobacillus rhamnosus* ŁOCK 0900, ŁOCK 0908 and *Lactobacillus casei* ŁOCK 0918**	Cukrowska B *et al.* 2021 (Multicenter randomized placebo-controlled trial) (46)	n = 151 children < 2 years of age with atopic dermatitis and CMA / Milk-free diet + mixture of three probiotic strains containing 1 × 10^9 CFU of selected bacteria (50% of *Lactobacillus casei* ŁOCK 0919, 25% of *Lactobacillus rhamnosus* ŁOCK 0908, 25% of *Lactobacillus rhamnosus* ŁOCK 0900) *vs* milk free diet alone / 12 months follow-up.	Primary: atopic dermatitis severity and changes in the proportion of children with clinical improvement *vs* no improvement *vs* deterioration. Secondary outcomes: levels of total serum IgE and the presence of allergen-specific IgE.	The probiotic strains are safe and induce beneficial effects in allergen sensitized patients. Supplementation of the children's diet with the probiotic preparation for 3 months resulted in a significant improvement in atopic dermatitis symptom severity.
***Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065**	Morisset M *et al.* 2011 (RCT) (47)	n = 129 infants with high risk of atopy / non-hydrolyzed fermented infant formula with HKBBST *vs* standard infant formula / 24 months.	Primary: Effect of HKBBST milk on the incidence of CMA and cow's milk sensitization; Secondary: effect of HKBBST milk on the incidence of sensitization and/or allergy to other allergens and the incidence of allergic symptoms during the study period.	HKBBST milk did not alter the proportion of CMA. HKBBST decreased the proportion of positive skin prick tests to cow's milk, and the incidence of digestive and respiratory potentially allergic adverse events at 12 months, and that of respiratory PAAEs at 24 months. Fermented milks may represent a new dietetic strategy to promote oral tolerance to cow's milk.
***L. casei* CRL431 and *B. lactis* Bb-12**	Dupont C *et al.* 2015 (RCT) (48)	n = 119 infants with CMA / EHCF *vs* EHCF + *L. casei* CRL431 and *B. lactis* Bb-12 / 7 months.	Assess the tolerance and hypo-allergenicity of the EHCF along with its safety for growth in infants fed with EHCF.	EHCF + *L. casei* CRL431 and *B. lactis* Bb-12 did not improve tolerance in children with CMA. EHCF is safe, hypo-allergenic and nutritionally suitable for infants with CMA.
Probiotics + Prebiotics				
***Bifidobacterium breve M16-V*, inulin and oligofructose**	Sorensen K *et al.* 2021 (Retrospective matched cohort study) (49)	n = 148 infants with CMA / AAF-S *vs* AAF.	Baseline characteristics, clinical symptoms, infections, healthcare usage.	AAF-S was associated with fewer symptoms, infections, medication prescriptions and healthcare contacts *vs* AAF. Infants prescribed AAF-S had a significantly higher probability of achieving asymptomatic management without HAF. AAF-S showed potential cost-savings of £452.18/infant.
	Chatchatee P *et al.* 2022 (RCT) (50)	n = 169 infants with CMA / AAF-S (n = 80) *vs* AAF (n = 89) / 12 months; age-appropriate diet advised by clinician.	CM tolerance by food challenge.	At 12 and 24 months, respectively, 49% and 62% of subjects were CM tolerant (AAF-S 45% and 64%; AAF 52% and 59%), and not differ significantly between groups. No difference in adverse events. Fewer hospitalization due to infections in the AAF-S group (9% *vs* 20%)
Prebiotics				
2' fucosyl-lactose and lacto-N-neotetraose	Nowak-Wegrzyn A *et al.* 2019 (Prospective Nonrandomized Trial) (52)	n = 67 children with CMA / whey-based EHF with 2'Fland LNnT ("Test") *vs* EHF without HMO ("Control") / 100% whey-based EHF with HMO 2'FL (1.0g/L) and LNnT (0.5 g/L).	Hypoallergenicity evaluation, symptoms and adverse events.	Test formula was tolerated on the modified intention to treat (98.4%) and on the per-protocol (98.4%) analysis, meeting the clinical hypoallergenicity criteria.

AAF: amino acid formula; AAF-S: amino acid formula with symbiotics; CMA: cow's milk allergy; EHCF: extensively hydrolyzed casein formula; EHWF: extensively hydrolyzed whey formula; HAF: hypoallergenic formula; HKBBST: heat-killed Bifidobacterium breve C50 and Streptococcus thermophilus 065; HMO: human milk oligosaccharides; LNnT: lacto-N-neotetraose; RCT: Randomized Control Trial; SF: soy formula; 2'FL: 2'fucosyl-lactose.

Table II *- Summary of probiotics and their impact, when combined with specific immunotherapy, in peanut allergy treatment.*

Supplement	Article	Sample / Intervention / Duration / Dose	Outcomes	Main results
Probiotics				
***Lactobacillus rhamnosus* CGMCC 1.3724 (LR CGMCC)**	Tang ML *et al.* 2015 (RCT) (57)	n = 62 children with peanut allergy / PPOIT *vs* placebo / 18 months / LR CGMCC at dose of 2×10^{10} CFU and POIT once daily according to protocol.	Primary: induction of sustained unresponsiveness 2 to 5 weeks after discontinuation of treatment Secondary: desensitization, peanut skin prick test, and specific IgE and specific IgG4 measurements.	Significant sustained unresponsiveness (PPOIT: 82.1% *vs* placebo: 3.6%), desensitization (PPOIT: 89.7% *vs* placebo: 7.1%), reduced responses in peanut skin prick test and peanut-specific IgE levels and increased IgG4 in PPOIT group. PPOIT group reported higher adverse events.
	Hsiao KC *et al.* 2017 (follow-up RCT) (58)	n = 48 / PPOIT *vs* placebo / 4 years after treatment cessation.	Assess long-term outcomes in peanut intake and adverse reactions to this ingestion.	Patient previously treated with PPOIT were significantly more likely to have continued eating peanut; PPOIT (n = 4) and placebo (n = 6) participants reported allergic reactions to peanut. PPOIT provides long-lasting clinical benefit and persistent suppression of the allergic immune response to peanut.
	Galvin AD *et al.* 2018 (follow-up RCT) (60)	n = 51 / PPOIT *vs* placebo / 12 months after treatment cessation.	FAQLQ-PF and FAIM scores.	Patient previously treated with PPOIT showed significant improvement in FAQLQ-PF and FAIM scales at 3 and 12 months post-treatment.
***Lactobacillus rhamnosus* ATCC 53103**	Loke P *et al.* 2022 (RCT) (61)	n = 201 children with peanut allergy / PPOIT *vs* placebo probiotic + POIT *vs* placebo / 18 months / POIT: titration until 2000 mg daily; LR ATCC: 2 × 1010 CFU daily dose of the LR ATCC.	Primary: sustained unresponsiveness to peanut protein for 8 weeks; Safety endpoints: adverse events during the treatment and the 12-month post-treatment period.	Sustained unresponsiveness was significantly higher in the PPOIT (46%) and POIT (51%) groups *vs* placebo (5%), with no difference between PPOIT and POIT. Addition of a probiotic did not improve efficacy of POIT but might offer safety benefits.

CFU: colony-forming units; FAIM: Food Allergy Independent Measure; FAQLQ-PF: Food Allergy Quality of Life Questionnaire; POIT: peanut oral immunotherapy; PPOIT: Probiotic (*Lactobacillus rhamnosus* CGMCC 1.3724) and peanut oral immunotherapy; RCT: Randomized Control Trial.

12 months in children with CMA was also found to be higher in those treated with EHCF supplemented with LGG compared to those supplemented with EHCF alone or with other formulas such as rice, soy or amino acid formula (41). The addition of LGG to EHCF leads to an enrichment of IM in certain strains of bacteria, associated with the production and increased levels of fecal butyrate. Butyrate has been identified as a regulator of the functional epithelial barrier and, as such, a facilitator of oral tolerance induction (42). Nocerino *et al.* also demonstrated that children with CMA have an increased risk of developing functional gastrointestinal diseases, likely due to intestinal dysbiosis. This study also suggested that the temporary use of EHCF supplemented with LGG might reduce this risk when used in 4-6-year-old children with a past history of CMA. Several mechanisms may be responsible for this effect, such as the modulation of the IM structure and function, with an increase in butyrate production, and its interaction with epigenetic mechanisms, the immune system and gastrointestinal tract (43). Thus, LGG associated with EHCF appears to contribute to a favorable intestinal homeostasis, adjusting the microbial, metabolic and immune profiles of the intestinal environment (44). LGG supplementation is associated with a complex intestinal mucosal response, positively modulating the immune system (41). Additionally, the use of EHCF with LGG seems to be a beneficial and cost-effective strategy compared to EHCF alone or with amino acid formulas (40, 45).

Different probiotics have also been investigated in the treatment of FA. In a study, including children with CMA, the administration of a probiotic preparation containing a mixture of *Lactobacillus rhamnosus* ŁOCK 0900, *Lactobacillus rhamnosus* ŁOCK 0908 and *Lactobacillus casei* ŁOCK 0918 has found to be safe and effective, inducing a significant decrease in the severity of symptoms in sensitized patients (46). Moriset *et al.* found that in children, with high risk of atopy, a non-hydrolyzed milk formula containing *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065, consumed from birth until one year old, did not result in a lower incidence of CMA, but did result in less sensitization in skin prick tests for milk.

Table III - *Summary of probiotics and prebiotics and their impact in preventing food allergy.*

Supplement	Article	Sample / Intervention / Duration / Dose	Aims and outcomes	Main results
		Probiotics		
Bifidobacterium breve **M-16V (Bb M-16V)**	Ezaki S *et al.* 2012 (Retrospective cohort study) (72)	n = 30 / Bb M-16V supplementation (n = 18) *vs* no supplementation (n = 12) / From small intestine surgery until full enteral feeding / 1 × 10^9 UFC of Bb M-16V in a package of 1 g suspended in 2mL of sterilized water, 0.5 mL was administered enterally 3 times/day.	Evaluate the preventive effects of probiotics on CMA in newborns that underwent small intestine surgery.	CMA was induced in newborns after small intestine surgery, and it is possible that the disruption of intestinal flora plays a role. Administration of Bb M-16V can reduce the incidence of CMA after small intestine surgery.
Bifidobacterium longum **(BL999) and** ***Lactobacillus rhamnosus*** **(LR)**	Loo EX *et al.* 2014 (RCT) (66)	n = 220 infants at risk for allergy / Cow´s milk supplemented with BL999 and LR *vs* cow´s milk not supplemented since birth until 6 months-old / 5 years.	Determine if early-life supplementation with probiotics has a long-term effect on allergic outcomes.	Supplementation of probiotics did not prevent allergic diseases, namely food allergy, asthma, allergic rhinitis, eczema and sensitization to inhalant allergens.
		Probiotics + Prebiotics		
Mixture of probiotics and prebiotics *(Lactobacillus Rhamnosus* GG (LGG) + *Lactobacillus rhamnosus (*LR) ATCC 53103 + LR LC705 + *Bifidobacterium breve* Bb99 + *Propionibacterium freudenreichii ssp. shermanii JS* + Galacto-oligosaccharides*)*	Peldan PS *et al.* 2020 (RCT double-blind) (69)	n = 1,223 pregnant women and fetuses with a high allergy risk / Probiotics *vs* placebo since 36 weeks pregnant until delivery and their offspring with the same mixture of probiotics and a prebiotic since birth until 6 months-old / 13 years / Mother's probiotic group: LGG and LR ATCC 53103 (5 × 10^9 CFU) + *LR LC705* (5 × 10^9 CFU) + *B. breve* Bb99 (2 × 10^8 CFU) + *Propionibacterium freudenreichii ssp. shermanii JS* (2 × 10^9 CFU); Children probiotic group: same probiotics + Galacto-oligosaccharide (0.8 g).	Evaluate the prevalence of IgE sensitization up to 13 years in high-risk atopy children.	No significant difference in the prevalence of IgE sensitization to any of the tested allergens was found at 2.5 and 13 years of follow-up. At 13 years, IgE sensitization to cat and/or dog dander was more common in the probiotic *vs* placebo group.
		Prebiotics		
6'-sialyllactose + 2'-fucosyllactose (2´FL)	Zehra S *et al.* 2018 (Experimental study) (74)	n = 24 of human colonic cell lines seeded per well and cultured for 72 h / Well plates with HMOs (n = 12) *vs* well plates without HMOs (n = 12) / Incubation for 24h at 37 °C then stored at -20 °C until analysis.	Understanding the mechanisms underlying the beneficial effects of HMO on intestinal epithelial cell responses associated with allergy and inflammation.	Modulation of Ag-IgE complex activation of human epithelial cells may have important implications for food-allergy. Structurally different oligosaccharides have distinct biological activities.

BL999: *Bifidobacterium longum*; CFU: colony-forming units; CMA: Cow´s milk allergy; HMOs: Human Milk Oligosaccharides; IgE: immunoglobulin E; LR: *Lactobacillus rhamnosus*; RCT: Randomized Control Trial; SCFAs: short-chain fatty acid; 2´FL: 2'-fucosyllactose; 6´SL: 6'-sialyllactose.

However, this combination of probiotics with a non-hydrolyzed milk formula decreased the incidence of respiratory and gastrointestinal allergic events during the first months of life, even after the formula was discontinued (47). In contrast, Dupont *et al.* found that supplementation of an EHCF with a combination of two probiotics, *Lactobacillus casei* CRL431 and *Bifidobacterium lactis* BB-12, did not improve the acquisition of tolerance in children with CMA (48).

Regarding the use of prebiotics and probiotics in combination, Sorensen *et al.* described that the use of amino acid formulas supplemented with the probiotic *Bifidobacterium breve* M16-V and prebiotics (inulin and oligofructose) in CMA was associated with fewer

symptoms, infections, pharmacological prescriptions and health services utilization compared to the use of amino acid formulas without supplementation. Furthermore, this strategy has also been shown to have a beneficial economic impact (49). Chatchatee *et al.* also evaluated the use of an amino acid-based formula including synbiotics (prebiotic oligosaccharides, oligofructose, inulin, and probiotic *Bifidobacterium breve* M-16V) in infants with confirmed IgE-mediated CMA. Their goal was to compare the development of tolerance to cow's milk and safety of this combination *vs* the administration of an amino acid-based formula alone. They found that at 12 and 24 months, the acquisition of tolerance was not different between groups. As Sorensen *et al*., they found that during this intervention the group receiving synbiotics required less hospitalizations due to infectious diseases (50).

Dairy formulas supplemented with GOS and FOS increase the number of bifidobacteria in the IM. In preclinical studies, breast milk oligosaccharides (HMO) have been shown to attenuate allergic responses, making the prevention and treatment of CMA a potential area of research and future studies (51). In addition to FOS and GOS, a hypoallergenic effect of EHCF supplementation with 2 HMOs (2-fucosyl, lactose and lacto-n-neotetraose) has also been described in infants with CMA, when compared to EHCF alone (52).

Non-IgE mediated cow's milk proteins allergy

The pathogenesis of non-IgE mediated food allergies, such as eosinophilic esophagitis, food protein-induced enterocolitis syndrome, or proctocolitis, differs from that of IgE mediated allergies. Therefore, the rationale for potential benefits cannot be directly compared.

Qamer *et al*. demonstrated that, in presumed CMA, probiotic supplementation was not associated with a faster resolution of hematochezia when compared with placebo. However, in confirmed CMA, probiotic supplementation revealed a higher rate of acquisition of cow's milk protein (CLP) tolerance at 3 years when compared with the use of formula without probiotic supplementation (29).

Studies have also shown that LGG supplementation of EHCF is more effective in treating gastrointestinal symptoms in children with CMA and in decreasing intestinal permeability, decreasing fecal calprotectin levels and reducing the presence of occult blood in children's feces (38, 41, 53). In a case series described by Martin *et al.* infants aged 1-3 months who were clinically diagnosed with allergic proctocolitis saw complete symptom resolution with the administration of LGG probiotic alone, without requiring any dietary restrictions. These cases underscore the potential role of IM in the development of food allergies, and further research is warranted to elucidate the pathogenesis of allergic proctocolitis (54).

Food allergy to peanuts

Peanut allergy ranges from mild exacerbations to severe anaphylactic episodes, persisting throughout an individual's lifetime. Currently, no effective long-term treatment is available (55, 56). This section focuses on the use of pro/prebiotics in association with immunotherapy.

Recent studies have demonstrated the promise of specific oral immunotherapy (OI) as a treatment for peanut allergy (55, 57). Additionally, the combination of recombinant allergens with certain strains of probiotics has been shown to be a safe and immunologically effective strategy, given the modulating properties of probiotics in the immune system. Probiotic supplementation is carried with the goal of improving peanut desensitization and oral tolerance (55). The four main studies concerning supplementation of probiotics in association to OI are described in **table II**. Tang *et al.* performed the first randomized clinical trial of a combination therapy of OI for peanut and the probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 (LR CGMCC) (57). This was also the first placebo-controlled trial to perform a double-blind oral challenge after a period of peanut food avoidance in allergy patients. They concluded that the use of OI plus LR CGMCC was highly effective, with 7 out of 9 treated children achieving possible sustained desensitization over time (57). Additionally, the use of OI plus LR CGMCC was also associated with a lower sensitization in skin prick tests, a decrease in the value of specific IgE and an increase in specific IgG4, suggesting a modulation of the allergic response to peanut (57). Subsequently, the same working group confirmed the efficacy of the combination therapy (OI plus LR CGMCC) and maintenance of peanut desensitization 4 years after discontinuation of treatment in most cases (58). In order to clarify the advantage and contribution of the probiotic in relation to OI, a study is being developed which compares the following intervention groups: 1) placebo; 2) combined therapy (OI plus LR CGMCC); and 3) OI alone (56). The group is also developing a similar study, but with OI for egg with the same probiotic (LR CGMCC), in order to induce desensitization in patients with egg allergy (59). Regarding quality of life, Galvin *et al.* proved that the use of OI and LR CGMCC was well tolerated and did not have a negative impact on the quality of life reported by parents, or on psychological well-being. In contrast, there appears to be an improvement in the quality of life reported by parents in cases of sustained response to treatment (60).

Another *Lactobacillus* – *Lactobacillus rhamnosus* ATCC 53103 (LR ATCC) – have been studied by Loke *et al.* and they found that both OI plus LR ATCC and OI alone were effective at inducing sustained unresponsiveness, with no significant differences between groups. Besides this, they found that addition of LR ATCC might offer a safety benefit compared with OI alone, with less adverse reactions, particularly gastrointestinal symptoms and in preschool children (61).

Prevention of food allergy

Studies reveal a lack of robust scientific evidence for the effectiveness in preventing FA with supplementation of specific strains of

probiotics in pregnant or breastfeeding women or in children with a high-risk atopy (18, 62-66). **Table III** comprises the four main articles found in the literature concerning prevention in food allergy.
Regarding supplementation during pregnancy, Ogrodowczyk *et al*. evaluated the associations between offspring's immunological markers (specific IgE profile and cytokine content) and maternal intake of special diets. They found that gestational probiotic supplementation yielded ambiguous results, likely due to variations in probiotic strains, doses, reasons, duration of use, and the route of administration. Gestational probiotic supplementation did not alleviate the severity of allergies in offspring, as indicated by high levels of total IgE and cytokines (67). Instead, when considering supplementation of pregnant/ breastfeeding women and newborns, a systematic review and meta-analysis conducted by Zhang *et al.* in 2016, reported that prenatal and postnatal administration of probiotics to mothers and newborns, could reduce the risk of atopy and food hypersensitivity, particularly in families at high risk of atopy. Despite this, the authors acknowledged the need for further studies to determine the optimal probiotic strain, dose and duration of therapy, as well as studies with longer follow-up periods (68). In this regard, a double-blind randomized clinical trial by Peldan *et al.* involving 1,233 pregnant women (whose fetuses were at high atopic risk) and their offspring, found that supplementation with a mixture of probiotics from 36 weeks of gestational age to birth and infants supplemented with the same mixture of probiotics and a prebiotic from 0 to 6 months did not affect the prevalence of sensitization to allergens up to age 13. Nevertheless, there was a tendency towards sensitization to aeroallergens in the probiotic-supplemented group at age 13 (69).

Discussion and conclusions

No studies have reported the effect of supplementation with specific strains of probiotics during pregnancy or lactation as a primary prevention of CMA (70, 71). However, the effect of mixtures of probiotics and prebiotics to increase IM diversity has been shown to reduce the risk of necrotizing enterocolitis in preterm neonates and may have similar benefits for the prevention of FA (51). Additionally, probiotic supplementation in newborns with short bowel syndrome, after intestinal resection surgery, seems to reduce the incidence of CMA in this population (72).
The prebiotic role of dietary oligosaccharides can be compared to that of HMOs. Clinical trials have demonstrated that dietary intervention with oligosaccharides in the first months of life can prevent atopic dermatitis, FA and asthma (73). Breast milk is considered the ideal diet for the first 6 months of life. However, in the absence of breastfeeding, milk formulas with the addition of certain HMOs have been shown to have a health benefit. Different oligosaccharides have different biological activities. Zehra *et al.* found that 6`SL and 2`FL HMOs modulate the Ag-IgE activation complex of human epithelial cells, which may have implications for FA (74).
Several studies advocated the need for further research to clarify the presence or absence of intestinal dysbiosis in patients with FA and to evaluate the role of different probiotics in modulating IM, its function and composition (6, 75, 76). Goldberg *et al*. in 2020, demonstrated that gut microbiota composition of allergic patients was significantly different compared to age-matched controls. In individuals with FA, IM was less diverse and less abundant in bacterium producing short chain fatty acids (SCFA). Consequently, the feces of these patients had decreased concentrations of SCFA, which may play a role in the allergic cascade. Furthermore, he demonstrated that each FA is associated with a different IM composition (77).
Also, Nowak-Węgrzyn *et al.* reported that interventions focused on correcting the alterations present in the IM of children with allergies, through supplementation with probiotics, may have potential application in the prevention and treatment of FA (36).
The safety and tolerability of probiotic and prebiotic supplementation has been well established in previous studies, with no reported adverse effects (78). However, further research is needed to fully understand the role of these interventions in the prevention of FA (62).
Concluding, in recent years, numerous studies have been conducted to investigate the potential influence of microbiota, probiotics and prebiotics supplementation on the prevention and treatment of FA. However, the results of these studies have been contradictory and inconsistent. This lack of consistency arises from the wide range of probiotics and prebiotics used in different studies, as well as the varying age groups that have been studied. To date, scientific societies have not issued formal recommendations for the use of probiotics or prebiotics in the treatment or prevention of FA.
Despite this, some studies have yielded promising results suggesting that probiotics may serve as therapeutic adjuvants in the management of CMA and peanut-induced allergies. The differences in the composition and diversity of IM in children with FA may also support the role of intestinal dysbiosis as a potentiator of allergies and the need to balance and promote intestinal homeostasis, through the supplementation with probiotics and prebiotics.
In the future, studies under strict methodological protocols are needed, in order to clarify the specific types of probiotics and prebiotics, their optimal dosage, therapeutic regimens and routes of administration.

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JFR: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, validation visualization, writing – original draft, writing – review &

editing. CP: conceptualization, data curation, project administration, resources, software, supervision, validation, visualization, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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