

REVIEW

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Potential beneficial effects of kefir and its postbiotic, kefiran, on child food allergy

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Food allergies are known as the public health problem, affecting people of all age groups, but more commonly in babies and children, with consequences for nutritional status and quality of life. The increase in the consumption of healthy foods has consequently led to an increased demand for functional foods with specific health benefits. Thus, the pharmaceutical industry's interest in natural products has grown every time and is therefore considered as an alternative to synthetic drugs. Kefir has been outstanding for several years as promising in the manufacture of various pharmaceutical products, due to its nutritional and therapeutic properties for the treatment of many diseases. Currently, a wide variety of new functional foods are appearing on the market, representing an important segment. Postbiotics, for example, has stood out for being a product with action similar to probiotics, without offering side effects. The kefiran is the postbiotic from kefir that promotes potential beneficial effects on food allergy from the intestinal microbiome to the immune system. In this context, it is necessary to know the main promoting component of this functional effect. This review compiles the benefits that kefir, and especially its postbiotic, kefiran, can bring to food allergy. In addition, it serve as a subsidy for studies on the development of innovative nutraceutical products, including the use of kefiran as an alternative therapy in food allergy.

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1. Introduction

The prevalence of food-borne allergic diseases has increased alarmingly in the last two decades, becoming a global health problem because it involves manifestations that harm the all-ages population's quality of life, such as asthma, rhinitis, anaphylaxis, eczema, urticaria, and angioedema. This problem has mainly affected babies and children in the last two decades, which makes this condition even more worrisome due to the indiscriminate use of synthetic drugs that can lead to the emergence of several side effects.^{1,2}

The pharmaceutical industry's interest in natural products has been growing due to their chemical and biological diversity, which makes it possible to use them in the treatment of several diseases. Therefore, it is considered as an alternative to synthetic drugs.³ In this scenario of natural products, kefir has been highlighting for some years as promising in the manufacture of various pharmaceutical products.⁴

Kefir, fermented milk produced from kefir grains, has shown great interest for researchers in recent years due to its nutritional and therapeutic properties for the treatment of many diseases, with action in the control of glucose⁵ besides having antibacterial effects,⁶ hypocholesterolemic,⁷ antihypertensive,⁸ anti-inflammatory,^{6,9} antioxidant,¹⁰ anticancer,¹¹ antithrombotic¹² and antiallergenic,⁹ and more recently anti-osteoporotic effects.¹³ Studies have shown that kefir has beneficial effects on lactose intolerance, a common food adverse reaction in allergic patients. This is because kefir is made from grains, not from typical probiotics derived from dairy products. Bacteria and cultures active in the beverage feed on much of the lactose, making it easier for the body to break down and digest the remaining lactose.^{14–16}

Postbiotics, on the other hand, have been gaining prominence for being a product with action similar to probiotics, with a promising role in improving immunological tolerance and treatment of food allergy, but without offering side effects associated with its ingestion.¹⁷ The kefiran, exopolysaccharide (EPS) present in kefir grains, is an example of postbiotics. EPS also has properties that improve the technological or sensorial characteristics of the food, functioning as a thickener, stabilizer, emulsifier, and gelling agent, in addition to being a great alternative for individuals with cow's milk allergy, since kefir

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is not obtained directly from cultivation with milk, such as kefir. Thus, kefir demonstrating great potential for the development of products by the food in the industry.¹⁸

Kefiran has potential beneficial effects on food allergy (FA) from the intestinal microbiome to the immune system. The composition of the intestinal microbiota is a key factor in modulating allergic responses to food.¹⁹ Thus, probiotics and postbiotics act in the maintenance of intestinal homeostasis. Thus, kefir can contribute to the modulation of the innate immune system, but it also interacts with adaptive immunity, contributing to the balance of Th1/Th2 cells with dominant Th1 antigen-specific T cells.

In this context, although kefir has been shown to have anti-inflammatory and antiasthmatic effects in the previous studies,²⁰ it is still necessary to know its main component promoting its functional effect. This review, therefore, discusses the problem of FA and the characteristics and health benefits already identified of kefir and its postbiotic component: the kefiran. As well as offering subsidies to the theory that postbiotics can be used as a new therapeutic support strategy to improve immunological tolerance and the treatment of food allergy in a specific way, without undesirable effects or opportunistic infections, especially in babies and children.²¹

2. Methodology

This review article is the product of analysis and bibliographic research carried out in the databases: MEDLINE (PubMed), Science Direct and Web of Science, by consulting articles published in specialized journals in the last two decades, regarding the role of kefir in health and more specifically in food allergy. The search was carried out using, alone and in combination, the following descriptors: food allergy; child allergies; kefir; kefiran, microbiome. The selection of articles involved the following criteria: clarity of the subject addressed, objectivity, relevance and pertinence to the theme, published in the last 20 years in English. 126 articles were selected that presented content with best contributed to the fulfillment of the work's objective.

3. Food allergy

3.1 Concept, classification and pathophysiology

Food allergy (FA) has been emerging as an epidemic that can affect all age groups and appears at any point in life. The foods most commonly involved in these reactions are cow's milk, chicken eggs, peanuts and nuts, and less frequently the allergens from soybeans, wheat, fish and seafood.²² Allergy can be divided into three types: IgE mediated, mixed (IgE mediated/cell-mediated) and non-IgE mediated.²³

IgE-mediated reactions are characterized by increased production of immunoglobulin E (IgE) and mast cell degranulation, which results in the release of histamine, in addition to

other chemicals that mediate this condition.²⁴ These reactions occur immediately up to two hours after ingesting the allergenic protein, and skin manifestations (atopic dermatitis, urticaria, angioedema), gastrointestinal (edema and itching of the lips, tongue or palate, vomiting and diarrhea), respiratory (asthma and rhinitis) and systemic reactions (anaphylaxis with hypotension and shock).²³

The mixed reactions are IgE-mediated with the participation of T lymphocytes and pro-inflammatory cytokines. In this group, clinical manifestations include IgE-mediated and non-IgE-mediated reactions, that is, both are involved in the reaction.²⁵

Non-IgE-mediated reactions occur in the absence of specific IgE antibodies, involving cells of the immune system, mainly T lymphocytes and usually causing gastrointestinal manifestations. The most common forms are Eosinophilic Esophagitis and Food Protein-Induced Allergic Proctocolitis (FPIAP), or in its most acute form: food protein-induced enterocolitis (FPIES).²⁵

The development of the allergic response is the result of a series of molecular and cellular interactions involving CD4+ T cells, which are categorized into two subgroups according to the production of cytokines: T helper 1 (Th1) and T helper 2 (Th2).²⁶ In this context, when dietary antigens cross the gastrointestinal mucosal barrier and the immunological barrier consisting of immunoglobulin A (IgA) secretion, they can enter the intestinal mucosa through the M cells located on the Peyer's plate. This interaction leads to the proliferation of T lymphocytes and the synthesis of cytokines by promoting the Th2 response, which secretes interleukins (IL): IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, these cause the activation and differentiation of B lymphocytes into plasma cells, which are responsible for the synthesis of the antigen-specific IgE antibody, thus being related to the immune reactions mediated by eosinophils and mast cells against allergens. In contrast, Th1 cells produce cytokines mainly related to phagocytosis-mediated defense against intracellular infectious agents, inhibiting the production of IgE by interferon-gamma (INF- γ) secretion. These two types of cells are important for the preservation of the immune response since the imbalance between the defense mechanisms makes the individual susceptible to immunological diseases, such as allergies.^{1,26}

However, these mechanisms may still be immature or deficient in infants and children, for example, the IgA secretory system does not reach maturity until four years of age.²⁷ Also, intestinal proteolytic activity is not fully developed until approximately two years of age and intestinal microvilli are immature, leading to a change in antigen binding and transport by mucosal epithelial cells. Thus, all these condition can compromise the integrity of the intestinal barrier, increasing the permeability to proteins by altering one or more factors, which leads to the passage of macromolecules, triggering systemic immunization. This fact explains this increased susceptibility for gastrointestinal infections and FA in the first years of life.¹

Studies show a coexistent relationship between asthma and FA, so that allergies may develop in the first year of life preceded-

ing the development of asthma since 4–8% of children with asthma have FA and approximately 50% of people with FA present allergic reactions involving acute respiratory symptoms.²⁸ Allergic asthma is characterized by chronic inflammation of the lungs induced by allergens along with airway hyperreactivity, being associated with the increase of eosinophilia induced by these allergens, calciform cell hyperplasia, allergen-specific IgE production, and dominant cytokines of the Th2 response, such as IL-4, IL-5, and IL-13.²⁹

Food allergies may also cause several health damages, especially in children, such as lower growth rates in children with allergy to cow's milk protein (ACMP) in the first year of life.³⁰ As in the study by Mehta *et al.*,³¹ where children with ACMP who avoided all forms of milk had significantly lower height and weight ($P = 0.047$, $P = 0.0006$, respectively) compared to controls. This cohort study was divided into 4 age groups (<2 years, 2–5 years, 6–11 years and >12 years), their results demonstrated that despite the nutritional importance for the age group <2 years, allergy seems to influence children's weight and height mainly after 2 years of age, indicating that the 2–5-year-old children were significantly smaller, with similar behavior in the age group of 6 to 11 years, where growth occurs more rapidly.

3.2 Epidemiology

It is known that the prevalence of food allergies is increasing, however, epidemiological data remain scarce due to lack of records, diagnostic difficulties and different methodologies used. In the United States, prevalence estimates range from 1 to 10%, most of which are self-reported.²⁷ The National Health and Nutrition Examination Survey (NHANES) found the prevalence of 6.53% of self-reported FA in children between 2007 and 2010, with infant food allergies being the most common: milk (1.94%), peanuts (1.16%) and shellfish (0.87%).³² Research shows that allergies to cow's milk, eggs, wheat and soy usually disappear during childhood. On the other hand, allergies to peanuts, nuts, fish, shellfish and sesame tend to persist throughout life.³³

Lyons *et al.*,³⁴ in a multicentre cross-sectional study, investigated the prevalence of food allergy in European school-aged children (7 to 10 years), through self-reported FA, food sensitization, probable FA (symptoms plus IgE sensitization) and FA confirmed by a food challenge. The study was divided into 3 phases: phase I, data on self-reported FA were collected through a screening questionnaire sent to a general sample. In phase II, data on FS and probable FA were obtained through a questionnaire on reactions to 24 foods and serological tests. In phase III, the food challenge was carried out for children selected from the previous phases. The prevalence of self-reported FA ranged from 6.5% to 24.6%; the prevalence of FS ranged from 11.0% to 28.7% and the prevalence of probable FA ranged from 1.9% to 5.6%. The foods that appeared most frequently due to probable FA were: milk, egg, fish and shrimp. Peaches, kiwis, peanuts, hazelnuts, apples, carrots, celery, lentils and walnuts were the most common plant foods in most countries, along with hazelnuts, apples, carrots and celery.

The review of Warren *et al.*,³⁵ brings some studies with interesting epidemiological data. For example, the cohort study HealthNuts (Australian population-based cohort, which has utilized gold standard oral food challenges to confirm diagnoses), provides relevant information on the prevalence of IgE-mediated food allergies proven by an oral food challenge, skin prick testing and convincing clinical history; where a higher prevalence of allergy to eggs (8.8%), peanuts (3%), milk (2.7%) and sesame (0.8%) was found, to be over 10% in a population-based cohort of 12-month-old infants.³⁶ When evaluating 4-year-old children, they observed a prevalence confirmed by an allergic challenge of egg, peanut and sesame at 1.2%, 1.9% and 0.4%, respectively; suggesting that almost two-thirds of cases of allergy to these foods are resolved between 1 and 4 years of age.³⁷ In the United States, a cross-sectional survey of more than 50 000 families estimated that IgE-mediated FA affects approximately 1 in 12 children.³⁸

On the prevalence in Brazil, in the study by Dias *et al.*,³⁹ 3897 children aged 4 to 59 months were investigated, where parents initially filled out questionnaires about food reactions. Subsequently, a selection of children with dietary reactions reported by their parents was made and they were subjected to additional tests such as clinical interview, physical examination, allergic tests and, if necessary, food challenge to complete the diagnosis of FA. Thus, an estimated allergy prevalence of 1.9% in babies and 0.4% in preschoolers was observed with emphasis on cow's milk, eggs and wheat as the main allergens. Another relevant piece of data from this study is that among the 604 patients with FA reported by their parents, only 4% (24) had a confirmed diagnosis of FA after additional tests while the prevalence of parent-reported FA was 23.5% in infants and 17.6% in preschoolers. Therefore, 96%, that is, 580 children who claimed to have food according to their parents, were excluded in subsequent diagnostic tests, of which approximately half already excluded suspect food from the diet for a period. In summary, the prevalence of FA with a confirmed diagnosis was much lower than that reported by parents, which serves as a warning to health professionals about the risk of overestimation of cases of FA and food exclusion or overdose of unnecessary medications, which can result in impaired children's growth and development, especially in their early years.

3.3 Risk factors

The risk factors for FA are family history, where having parents or brothers and sisters with allergies increases by seven times the chance of the child developing the same allergy; exposure to environmental factors, nutritional status of the individual and presence of chronic infection or acute viral diseases. In addition, patients with coexisting atopy (atopic dermatitis, asthma) have an increased risk of more severe development of food allergic reactions.^{1,40}

The hypothesis of excessive hygiene that consists of low exposure to microorganisms and the reduction of infections in early childhood has been pointed out as a determining risk factor for the development of allergies through the imbalance

of the immune system, favoring the profile of Th2 lymphocytes instead from Th1.⁴¹

The indiscriminate use of some medications can also contribute to the individual's susceptibility to FA. For example, antacids reduce the digestion of allergens, resulting in increased exposure to intact protein.³³ As well, the use of antibiotics could facilitate the appearance of allergies, as they cause harm to the diversity of the microbiota.⁴¹

The insufficiency of vitamin D and/or vitamin A has been considered among the possible risk factors for the development of FA, due to their well-recognized immunoregulatory and tolerogenic functions. Other factors related to eating habits such as reduced consumption of omega-3-polyunsaturated fatty acids; the low intake of fruits and vegetables, reflected in the reduced consumption of antioxidants; or even, the presence of obesity, being considered an inflammation, would favor allergic sensitization.^{33,42}

However, there is no scientific evidence that a specific nutrient is more important in terms of preventing food allergies. But it is known that dietary factors during pregnancy (where the maternal diet acts as a possible sensitization route, through the amniotic fluid or umbilical cord blood); even during lactation (where proteins can pass through human milk to the baby); and/or early childhood are associated with increased allergenic propensity. Tolerance to food allergens usually occurs in the first 1000 days, a crucial period for the development and health of the child, which comprises from pregnancy to the second year of the baby's life. Thus it is believed that the delay in the introduction of potentially allergenic foods in babies is responsible for the absence of the tolerogenic signals emitted from the intestine after food ingestion, which contributes to the breakdown of the integrity of the skin barrier, allowing the exposure of food and environmental allergens through the skin that can increase sensitization, favoring allergic responses rather than tolerogenic.^{33,41}

3.4 Diagnosis

For the diagnosis of a FA, observational control by the person responsible for the child is necessary to provide much crucial information for the construction of the clinical history of this disease. For example, knowing when the first contact with the possible allergen was made, how the food was prepared, how much was ingested that triggered the symptoms, the time between ingestion and the appearance of the symptoms, the nature of the symptoms, the time interval since the last reaction, *etc.* Thus, the diagnosis of FA can be based on the clinical history and oral tolerance, where an elimination diet and an oral provocation test (TPO) are usually performed in a doctor's office, which consists of the absence of symptoms after elimination of the possible allergen in the diet of the child or a breastfeeding mother if this reaction was *via* breast milk.⁴³

TPO is an essential diagnostic test and can be considered the diagnostic gold standard of FA, in the case of the double-blind placebo-controlled food challenge. However, it is a complex test, as it can put the patient at risk of severe anaphylactic reactions if the desired food tolerance is not achieved.

Some tests can predict the risk of serious anaphylactic reactions, such as molecular or component-resolved diagnostics and the basophil activation test, which can assist in personalized treatment based on the patient's molecular and clinical profile.⁴¹

Some tests or exams can assist in the diagnosis if properly interpreted as an addition to the epidemiological context and clinical history of the patient, for example, the determination of serum-specific IgE for food and the skin prick test of immediate hypersensitivity.⁴² These isolated tests without a supporting clinical history cannot be used for the definitive diagnosis of FA, as the positive result means only sensitization and not an allergy.³³

In addition, the delay in diagnosis often observed in clinical practice exposes children to a state of bad nutrition, making unnecessary food restrictions or erroneous food exchanges, not to mention the frequent consumption of processed foods by children in those age groups who may be poor substitutes for the food allergens.^{31,44}

3.5 Treatment

Among the current recommendations in the treatment of FA, there is the strict avoidance of the allergen with the care that includes reading ingredients on the labels and cross-contamination. In addition, it is also necessary to immediately control allergic reactions in case of accidental exposures, which can be related not only to meals, such as, for example, babies who frequently bring their hands or objects to their mouths, which can lead to exposure to allergens even if indirectly. For this, epinephrine autoinjectors have been prescribed as an emergency medication administered early to the first clinical signs of anaphylaxis, reverting hypotension, shock, or other allergic symptoms in a few minutes, such as urticaria, bronchospasm, edema, *etc.* Other drugs such as antihistamines have been used in the case of itching and hives, or H2 receptor blockers that can be useful to treat gastrointestinal symptoms.^{41,45}

Glucocorticoids are also commonly used to treat many inflammatory and immunological diseases, such as allergy. However, continued exposure or in high doses of steroids, show a negative correlation of the duration and dose of glucocorticoid use with bone mineral density, resulting from low bone resorption with disproportionate reduction in bone formation.^{46,47} In this context, a systematic review and meta-analysis study found that the bone mineral density of children using glucocorticoids was significantly lower compared to healthy controls.⁴⁸ However, the effect of glucocorticoids in children is not limited only to the decrease in bone mineral density and the development of pediatric osteoporosis but also causes growth retardation, through inhibitory effects on the secretion of the growth hormone (GH) function, causing thus a consequent loss of nutritional status.^{49,50}

Regarding the new therapeutic perspectives, although currently there are no treatments approved by the Food and Drug Administration (FDA) for FA. Antigen-specific immunotherapy is a treatment option that has been used in a more promising way. The technique consists of providing an increasing

amount of allergen over an extended period to suppress food-allergy symptoms, that is, it is the induction of desensitization and, subsequently, of specific immune tolerance to allergens, performed only in large centers with staff specialized equipment. The success and side effects of these techniques will depend on the route (oral, subcutaneous, sublingual and epicutaneous), accumulation protocol, maintenance dose, or used food.^{51,52}

Oral immunotherapy (OIT) is the most studied immunotherapy route. Administration starts with a very low dose of allergen that gradually increases over months until a maintenance dose is reached. Successful OIT treatment contributes to desensitization (ability to tolerate a food challenge during active treatment) and a lack of sustained response (ability to tolerate a food challenge after treatment discontinuation, around one to three months after an interruption).⁵³ This route appears to be more effective for FA than other routes because larger doses can be administered, but it is not clear how safe it is. Thus, to improve or maintain its effectiveness, adjuvant therapy with IgE monoclonal antibody omalizumab has been used in severe allergies to peanuts, milk, eggs, or multiple allergies, with significant clinical improvement in adults and children.⁵²

Omalizumab works by preventing the degranulation of mast cells and basophils and the consequent clinical manifestations triggered by the released mediators. Thus, before starting the OIT, to obtain a reduction in the levels of free IgE, patients are treated every two weeks with an injection of omalizumab for eight weeks. Thereafter, both therapies are administered in combination for a period of overlap, until the biological suspension of the drug.⁴¹

Subcutaneous immunotherapy was discontinued a few years ago due to the serious adverse reactions seen during therapy. In turn, in Sublingual Allergen Immunotherapy (SLIT), food protein is administered in liquid form, maintained for two minutes *via* sublingual and then ingested, this treatment lasts an average of one year. SLIT is less effective than OIT, due to the maintenance doses, which, as already mentioned, can be higher in the OIT, varying from milligrams to grams, while in SLIT, micrograms usually range from a maximum of seven milligrams. But it can be a good option for patients with severe allergies who cannot tolerate OIT for safety reasons, as this approach has a favorable safety profile, with minimal side effects, or it can be used as an evolution therapy for OIT.^{45,52}

Epicutaneous immunotherapy (EPIT), performed by repeated application of an allergen to intact skin, has been studied mainly in patients with allergies to cow's milk and peanuts. This approach can lead to desensitization more effectively in children aged six to eleven than in older children and adults. On this route, the starting dose is the maintenance dose, which is lower than that used for other investigative therapies. It does not present any serious adverse effect, being limited to localized erythema, eczema, itching and/or hives at the application site.⁵⁴

Other strategies aim to help develop tolerance to allergenic foods such as the early introduction of baked forms containing

milk and eggs, in children with allergies to these foods. Currently, there is evidence in the literature that 70% to 75% of children with allergies to cow's milk and eggs can tolerate them when extensively heated. The use of probiotics in babies with allergies also appears as a strategy due to manipulation of the microbiome that may be considered for both preventive and therapeutic interventions.^{33,51}

Despite the conventional treatment for food allergy, studies indicate a greater demand for the use of alternative treatments, such as Traditional Chinese Medicine, it is believed that one of the reasons for this demand is the adverse effects caused, because although the general health risk appears to be low, some groups of traditional medicines have been associated with serious side effects. In addition, the access or cost of medicines already used conventionally also appears as reasons for seeking alternatives treatments.⁵⁵ Complementary medicine encompasses treatments beyond the scope of conventional allopathic medicine. Complementary medicines include products that contain medicinal herbs, vitamins, nutritional supplements, aromatherapy preparations, acupuncture, homeopathy, herbal medicines, ayurveda, probiotics and non-pharmaceuticals supplements.^{56,57}

In herbal medicine, plant extracts are generally used in the form of teas, capsules and tinctures. One of the most cited treatments within this class is herbal formula-2 for food allergy (FAHF-2) investigated by Li *et al.*^{58,59} This formula contains nine different medicinal herbs and is quite effective against anaphylaxis in an animal model and a human clinical trial, showing to be a promising therapeutic alternative of long duration in food allergy.

4. Kefir

4.1 Definition and main characteristics

According to Żółkiewicz *et al.*,⁶⁰ there are currently four main ways of modulating the intestinal microbiota: the use of prebiotics, probiotics, symbiotics or postbiotics. Prebiotics are non-digestible substances that benefit the host by stimulating the growth and activity of bacterial strains present in the intestine. Eg human milk oligosaccharides (HMO), lactulose and inulin derivatives. Probiotics are live microorganisms, which are administered in adequate amounts and confer health benefits to the host; the best known are bacteria of the genera *Lactobacillus*, *Bifidobacterium* and *Streptococcus*, as well as yeast *Saccharomyces*. Symbiotics are the combination of prebiotics and probiotics in one product. Postbiotic, on the other hand, is a substance released by or produced through the metabolic activity of the microorganism, which has a beneficial effect on the host, directly or indirectly, that is, without necessarily the presence of the microbial population.⁶¹

Kefir appears as a probiotic resulting from the symbiotic fermentation of milk by lactic acid bacteria (LAB) and yeasts contained in an exopolysaccharide and protein complex, the kefir grains. About lactic acid bacteria, they are Gram-positive and catalase-negative microorganisms that produce lactic acid

as the main product of lactose fermentation, can produce specific flavors and aromas in foods, and benefit human health. *Lactobacilli* and *Bifidobacteria* are the most commonly known strains.⁶² Yeasts are essential to promote an ideal environment for the growth of kefir bacteria, three yeast genera are commonly isolated from kefir grains: *Saccharomyces*, *Kluyveromyces* and *Candida*.⁶³ Therefore, kefir is a fermented drink manufactured through the incubation of kefir grains (starter culture), usually in milk or a mixture of water and sugar.¹⁵

Kefir originates in the Caucasus Mountains, its name derives from the Slavic Keif, which means “well-being” or “living well”, due to the sense of health and well-being promoted in those who consume it. Kefir differs from other fermented products because it is produced from kefir grains which comprise a specific and complex mixture of lactic acid and acetic acid-producing bacteria and lactose fermenting and non-fermenting yeasts living in a symbiotic association.¹⁵

Kefir grains are gelatinous granules of irregular shape, with white or slightly yellow coloration, respectively they present a cauliflower appearance and the size varies of 2–3 cm of diameters.⁶⁴ The production of kefir grain is based on the continuous culture medium. They can come from fermentation in milk (milk kefir) or fermentation in water and sugar (water kefir) and they are acidified and fermented increasing biomass, which grows only from pre-existing grains.⁶⁵ This increase in the mass of kefir grains is due to the increase in the biomass of microorganisms together with the increase in the amount of the matrix composed of proteins and polysaccharides. The grains are generally removed from the milk after the fermentation process and used in a new fermentation.¹⁴

In general, the grains present soft texture, an acidic taste and slightly effervescent, moisture between 89–90%, 0.8% (w/w) lactic acid, 0.25 (w/w%) alcohol, pH between 4.2 and 4.6, carbon dioxide content of 1.05 g L⁻¹, forming other products such as pyruvic acid, hippuric acid, propionic acid and butyric acid diacetyl and acetaldehyde, the latter two are the main flavoring components.^{14,66}

4.2 The microbial composition of kefir

In addition to the physical-chemical composition, some variants that influence as characteristics of kefir, such as, the age of the grains, the raw materials, the technology used in the processing and the microbiota. The microbial composition may vary according to the origin, the substrate and the culture maintenance methods. The LAB predominates in kefir grains with values around (10⁸–10⁹ UFC mL⁻¹), while yeast and acid-acetic bacteria (AAB) have equal values of (10⁵–10⁶ UFC mL⁻¹) following closely the lactic bacteria.¹⁴

In this respect, the species that make up milk kefir are *Lactobacillus paracasei* ssp., *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* ssp. *bulgaricus*, *Lactobacillus plantarum*, and *Lactobacillus kefirianofaciens*, *Lactobacillus kefir*, *Lactococcus lactis* subsp. *lactis*, *Streptococcus thermophilus*, *Lactobacillus helveticus*, etc. As for yeasts, many species have already been isolated in the Kefir grains, the most prevalent

being *Saccharomyces cerevisiae*, *S. unisporus*, *Candida kefir*, and *Kluyveromyces marxianus* ssp.⁶⁷ These yeasts have a relevant role in the manufacture of fermented milk products, since they provide essential growth nutrients and are responsible for altering pH, secrete ethanol and produce CO₂.⁶⁸ They are responsible for providing an environment for bacterial proliferation, besides producing metabolites that cooperate for the aroma and taste of kefir.⁶⁹

Already the composition of the microbiota of water kefir is consisting of *Kluyveromyces*, *Candida Pichia* and *Saccharomyces* genera from yeasts (*Saccharomyces florentinus*, *Candida valdiviana*, *Pichia fermentans*, *Zygosaccharomyces fermentati* e.g.) and *Lactobacillus*, *Lactococcus*, *Leuconostoc* and *Streptococcus* genera from LAB (*Lactobacillus hilgardii*, *Lactobacillus nagelii*, *Lactobacillus hordei* *Lactobacillus kefir* e.g.), and more rarely some *Acetobacter* species (*Acetobacter orientalis*, *A. tropicalis* e.g.) were found.⁷⁰

4.3 Nutritional composition of kefir

The kefir grains are composed, for the most part, of proteins and polysaccharides in which a diverse microbiota exists.^{71,72} Kefir has excellent protein content, which can be presented in two ways: intact and partially digested, which facilitate its use by the organism.⁷³ During fermentation of kefir the amino acids leucine, lysine, valine and serine are generated, also occurring increase of aspartic acid and alanine when compared to milk.⁷⁴ The level of free amino acids in fermented kind of milk varies according to the milk used, the composition of the starter culture and the preparation method.⁷⁵

The vitamin content of kefir is influenced by the type of milk and microbiota grains.⁷¹ During fermentation, the concentrations of pyridoxine, vitamin B12, folic acid, biotin, thiamine and riboflavin increase. And during cooling (used to preserve for later consumption), alcoholic fermentation leads to the accumulation of CO₂, ethanol and B-complex vitamins. In addition, kefir is a good source of B vitamins, especially B1, B2, B5, B6 and B12, which among its benefits involve performance in the nervous system and liver, aid in the treatment of skin, increase of energy, among others. Kefir is also rich in K vitamin, which has an essential function in blood clotting, and in C, A and D vitamins, important immunomodulators.^{14,76}

It also contains minerals Mg, Ca and P, directly related to bone metabolism, even when it is not produced in milk.¹⁴ The study by Tu *et al.*⁷⁷ revealed better efficacy in the use of kefir compared to the use of calcium carbonate (CaCO₃), a fact that can be justified by the high availability of calcium, the optimal Ca : P ratio of 1 : 3, and the presence of other minerals important for bones such as magnesium and zinc. Other microminerals are recorded, such as copper, iron, manganese, cobalt and molybdenum in kefir.

In this sense, due to its rich nutritional content, it is believed that kefir can also have a beneficial effect on health, as well as a potentiating effect on the growth of allergic children and adolescents, since despite the existence in the market of some foods already fortified with calcium, are rarely enriched with D vitamin, which is not the case with kefir,

which, in addition to several nutrients, has a good D vitamin content.⁵⁰

In addition, the medium used for the growth of kefir grains is also of great importance. These kefir grains may stop growing if the medium used does not contain all the growth factors for the bacteria. In addition, the amount of glucose is essential for the synthesis of important polysaccharides.¹⁴ Polysaccharides appear as the main component of kefir grains. While kefir is present in milk kefir grains, LAB isolated from water kefir grains can produce dextrans.⁷⁸

4.4 Functional foods of kefir

Functional foods act on promoting health and preventing diseases. Medicinal plants in the form of extracts or essential oils have been increasingly studied to be incorporated into foods to improve their functional properties, including dairy products, such as kefir, due to their GRAS (generally recognized as safe) character. The combination of these bioactive components from plants with lactic acid bacteria from kefir, improves the viability of probiotic organisms as well, giving a longer shelf life to functional drinks.⁷⁹ In addition, the addition of food-based ingredients, such as fruits and plants, can better accept kefir, since it is known that its consumption *in natura* is generally not well accepted by the consumer due to its acid flavor and strong smell. In this way, the development of a functional product based on kefir from the addition of bioactive components can provide better flavor, smell, visual aspect in addition to offering health benefits.

Studies show benefits already identified on the consumption of functional products developed with the kefir matrix. For example, in the study of Perna *et al.*,⁸⁰ the kefir fortified with honey (30% w/v) showed the highest ferric-reducing antioxidant power and *Rosmarinum officinalis* essential oil (0.15% w/v) presented a great antioxidant activity. The addition of lyophilized wild garlic powder (1% p/v) to kefir, decelerated the fermentation stage, exhibiting a significantly higher pH value and a lower lactic acid content.⁸¹ In the study of Setiyoningrum *et al.*,⁸² an increase of 12.4% in the antioxidant activity of kefir was also observed when added with cinnamon extract at a concentration of 8% v/v.

4.5 Kefiran: a postbiotic

Despite the studies showing the efficacy of probiotics in several diseases, Kothari *et al.*,⁸³ in their review, show that the commercialized extrapolation of the same probiotic product to a large number of partially characterized microbial formulations puts into question its efficacy and safety. Especially, in neonatal or high-risk patients, some probiotic strains can take advantage of the weak immunity of these groups and turn into opportunistic pathogens. Therefore, despite the promising therapeutic role of probiotics, further studies are needed to clarify the efficacy, safety and regulatory use of strains. Given this, there is a growing interest in postbiotics. These do not contain live microorganisms but have health benefits through mechanisms similar to probiotics, but with lower risks associated with their ingestion.

One of the classes of postbiotics is biopolymers, which are naturally occurring polymers formed from plants, animals or microorganisms. During their growth, microorganisms produce biopolymers that can be released outside the bacterial cell wall, forming a heterogeneous group of substances called EPS. This group includes polymers from the kefir microflora: kefiran and dextran.⁶⁰

These postbiotics can interact with eukaryotic cells, modulate immune function and activate the relevant signaling pathways to induce gastrointestinal homeostasis, strengthen the endogenous probiotics of each host instead of adding unknown strains. Therefore, the use of postbiotic has been gaining prominence for its promising role in improving immune tolerance and treating FA without causing effects. These postbiotics can interact with eukaryotic cells, modulate immune function and activate the relevant signaling pathways to induce gastrointestinal homeostasis, strengthen the endogenous probiotics of each host instead of adding unknown strains. Therefore, the use of postbiotic has been gaining prominence for its promising role in improving immune tolerance and treating food allergy without causing side effects.¹⁷ In addition, the use of postbiotics also seems promising for the treatment of cow's milk allergy, due to the possibility of obtaining the formulation of products similar to kefir made with non-dairy raw materials, since kefir is obtained from its isolation of kefir grains. Kefiran, the main exopolysaccharide of kefir grains, together with yeasts and acid-lactic bacteria make up kefir. On the chemical structure, this polysaccharide is a repetitive branched unit of hexa or hepta-saccharide, which is composed of a regular unit of pentasaccharides, in which one or two residues are randomly attached, it is composed of equal parts of galactose and glucose, is responsible for the binding of the microorganisms in the kefir grains and is therefore responsible for keeping the microbiota attached to the matrix that will be multiplied. Due to its chemical conformation, kefiran is not hydrolyzed by digestive enzymes from the human gastrointestinal tract, in turn, it cannot be absorbed, but it can be fermented by bacteria from the colon. Its production is related to the presence of *Lactobacillus kefirifaciens* and *Lactobacillus kefir* in the grains, especially the first one, which acts after 48h of cultivation.^{84,85}

More than half of the dry kefir grain weight consists of kefiran. The production of kefiran by LAB is optimized through the control of fermentation conditions and modification of milk composition. Studies have shown that fermentation temperature (25 °C), stirring speed (80 rpm), and choices of sources of carbohydrates (lactose), protein sources, vitamins (thiamine) and minerals (FeCl₃) are factors that increase the production of kefiran. In addition to the combination of LAB with non-fermenting yeasts of lactose, for example, *Saccharomyces cerevisiae*, due to the assimilation of lactic acid, which in turn contributes by stimulating LAB growth and kefiran production.^{85–87}

The kefiran has been used at the industrial level due to its ability to serve as a moisture, oxygen and carbon dioxide con-

troller, besides being used as an emulsifying agent, adhering texture to food.^{10,64} The study by Radhouani *et al.*,⁸⁸ revealed that kefir is a promising candidate in the field of biomaterials, the formation of biofilms and tissues, and can also act in regenerative medicine, replicating the mechanical and viscoelastic characteristics of the tissues, with possible beneficial effects in the prevention or treatment of diseases or defects bony and cartilaginous or also in the healing of wounds.

On the current market situation involving these products, in recent years, research with materials obtained from microbial EPS for commercial use has been demanding that it be produced on a large scale and at low cost, in addition to that, the isolation procedure must be easy and with high yields.⁸⁹ Taking this into account, the EPS of kefir grains, kefir, can be an affordable alternative for industrial application. Because granular biomass kefir fermentation offers the possibility of eliminating the use of centrifugal separators that have high energy demand and require high industrial investments.⁹⁰ In addition, EPS from kefir can be used for the development of innovative nutraceutical products on the market, as an alternative in the treatment of pathologies.

5. Benefits of kefir/kefiran on FA: from the intestinal microbiome to the immune system

The composition of the intestinal microbiota plays an important role in the immune system, being recognized as a key factor in modulating allergic responses to food, due to its potential to promote epithelial barrier function and to stimulate an appropriate immune response.¹⁷ Therefore, Fig. 1 illustrates the mechanisms that kefir/kefiran exert to promote beneficial effects on the intestinal microbiome and, consequently, on the immune system.

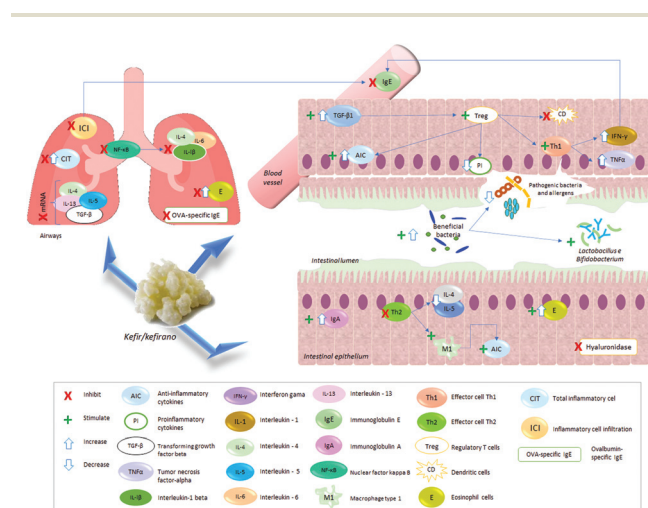


Fig. 1 The benefits of kefir/kefiran on food allergy: from the intestinal microbiome to the immune system.

The kefir/kefiran modulates the intestinal microbiota by stimulating the growth of beneficial bacteria, *Lactobacillus* and *Bifidobacterium*, and inhibiting the proliferation of pathogenic bacteria in the intestinal lumen, maintaining the integrity of the intestinal barrier, reducing exposure to the allergen and sensitization to the antigen; promotes the proliferation of regulatory T cells (Treg) that act in suppressing the expression of antigen-presenting dendritic cells (CD) in the mucosa of the gastrointestinal tract (TGI) and inducing the maturation of leukocytes by antigen-specific T cells type Th1 (IFN- γ , TNF- α).

In turn, IFN- γ secretion inhibits the production of serum IgE; it stimulates the secretion of TGF- β from intestinal epithelial cells, resulting in increased expression of Treg cells in the colon, and consequently in increased synthesis of anti-inflammatory cytokines (AIC) and reduced pro-inflammatory cytokines (PI); it also promotes the exchange of M1/M2 macrophages, increasing the amount of M1 and stimulating the intestinal IgA response; it has also been shown to act by inhibiting hyaluronidase, an enzyme with pro-inflammatory activity; in the lung (bronchoalveolar lavage) it inhibits the increase in the total inflammatory cell count (CIT) and eosinophils (E); reduces serum concentrations of ovalbumin-specific IgE (OVA-specific IgE) due to suppression of inflammatory cell infiltration (ICI) and mRNA expression of cytokines IL-4, IL-5, IL-13 and TGF- β in pathways aerial; inhibits the NF- κ B signaling pathway, reducing the synthesis of cytokines IL-1 β , IL-4 and IL-6 in lung tissue.

5.1 Effects of kefir/kefiran on the intestinal microbiome

Modulation of the intestinal microbiota of an individual using probiotics has emerged as a possible treatment of allergic symptoms and prevention of the allergy's development. The human microbiome is the set of all microorganisms that reside in the human body, that is, it is the sum of microorganisms and genomic characteristics in a specific environment. This intestinal microbiota can be altered by introducing new bacterial species into the gastrointestinal tract or by promoting the growth of beneficial bacteria that already exist through the ingestion of probiotic food products. Studies point to the microbiome as an integral component of human physiology, being considered an important mediator between health and disease. Thus, the imbalance between commensal bacteria and pathogens, known as intestinal dysbiosis, can potentiate FA through immune dysregulation.^{91–93}

According to Liu *et al.*,²⁶ the consumption of kefir and kefiran in an animal model was able to increase the number of microorganisms considered beneficial, such as *Lactobacillus* while decreasing harmful microbial species, such as *Clostridium perfringens*.

In the cross-sectional observational study by Fazlollahi *et al.*,⁹⁴ when evaluating the intestinal microbiome, by sequencing 16S ribosomal RNA from fecal samples from 141 children aged 3–16 months with egg allergy and controls, it was possible to identify that the microbiome is affected by a FA, indicating new goals prevention or therapeutic intervention. Thus, it is believed that intestinal dysbiosis during early life can sig-

Table 1 Studies related to the benefits that kefir or kefiran can promote in the microbiome

References	Substrate administered	Beneficial effects
Bolla <i>et al.</i> ¹⁰⁰	A mixture (MM) constituted by kefir-isolated microorganisms administered <i>ad libitum</i> in drinking water	- Prevent diarrhea and enterocolitis triggered by <i>C. difficile</i> .
Franco <i>et al.</i> ¹⁰¹	Kefir 1 : 100 dilution in drinking water	- A significantly reduce the intensity of <i>Giardia</i> infection and increase in the percentage of CD4(+) T cells
Bolla <i>et al.</i> ¹⁰²	The kefir-isolated microbial mixture containing three bacterial and two yeast strains (MM)	- Protect intestinal epithelial cells against <i>Shigella flexneri</i> invasion - Inhibition of the signaling <i>via</i> NF- κ B that in turn led to the attenuation of the inflammatory response
Hamet <i>et al.</i> ¹⁰³	Kefiran 300 mg L ⁻¹ administered <i>ad libitum</i> in the drinking water	- Alteration of the fecal and intestinal microbiota increasing the number of populations of <i>Bifidobacteria</i> , with no change in the <i>Lactobacillus</i> population.
Erdogan <i>et al.</i> ¹⁰⁴	BALB-c mice were divided into three groups: the control group (CK, n:10), the kefir grain group (GK, n:10), and the starter culture group (SK, n:10). The mice were fed a dose of 0.3 mL day ⁻¹ of kefir for 15 days by oral gavage.	- It was reported that probiotic microorganisms (<i>L. acidophilus</i> and <i>Bifidobacterium</i> spp.) were highest in the GK group and increased the content of indicated probiotics in the intestinal microbiota. - Kefir grains show antifungal activity against <i>Trichoderma koningii</i>

nificantly affect inflammatory responses and the development of allergic diseases.⁹⁵

In this context, the epidemiological response to the increase in the prevalence of FA in recent years occurs from the binomial microbiome-immune response of the individual, suggesting early childhood as a crucial factor in the moment of microbial intervention.⁹⁶ The interaction between food and commensal microbes can quickly and reproducibly alter the human microbiome,^{97,98} and the use of probiotics can be an efficient approach to immunological tolerance to food antigens, as they contribute to the restoration of intestinal permeability, making the intestinal epithelial barrier more selective, in addition to acting in the modulation of the inflammatory condition response.⁹⁹

Among the probiotics, kefir stands out due to its participation in the regulation of the composition and activity of the intestinal microbiome. Associated with this aspect, this probiotic, when compared to *Lactobacillus* yogurt, has several beneficial bacterial species and yeasts, not found in yogurt, that act in the control and elimination of destructive pathogenic bacteria or yeasts such as *Lactobacillus* *Caucasus*, *Leuconostoc*, *Acetobacter* and species of *Streptococcus*. These yeasts also strengthen the intestine, being more resistant to pathogens like *E. coli*. Moreover, another advantage is the lower cost and practicality, since it is possible to produce it in a domestic environment.⁵ Table 1 presents some studies in which the consumption of kefir or kefiran has changed the microbiome.

5.2 Effects of kefir/kefiran on the immune system

The preventive and therapeutic effect of probiotics on allergic symptoms has been gaining scientific and public health repercussions, mainly due to the association between the intestinal microbiota and food sensitization in early life, thus suggesting that the microbiome may play a role in the development of FA.¹⁰⁵

Probiotics have been gaining ground in the literature not only for their role in the development and maintenance of homeostasis in the gut but also emerges as a potential agent of the immune system. Probiotics modulate the innate immune system through some actions, such as strengthening the intestinal barrier, producing antimicrobial metabolites, the competition of pathogenic microorganisms for nutrients and act to acidify the intestinal environment to prevent the growth of pathogenic bacteria.¹⁷ Dendritic cells, as well as macrophages and monocytes, identify when the organism comes into contact with the allergen and presents it to T cells, and can also produce pro-inflammatory cytokines, thus triggering the acquired immune response.¹⁰⁶

The homeostasis of the intestinal microbiota when interacting with acquired immunity contributes to the proliferation of Tregs cells promoting the suppression of cells presenting antigens of the intestinal mucosa and stimulates the expression of the toll-like 4 receptor (TLR-4) responsible for the recognition of lipopolysaccharide (Gram-negative bacteria). In addition, it induces the maturation of this leukocyte by antigen-specific T cells of the type Th1 (IFN- γ , TNF- α). The microbiota is also capable of limiting bone marrow basophil precursors, thereby reducing basophil-mediated allergic inflammation; stimulate the secretion of TGF- β from intestinal epithelial cells, leading to the expansion of colon Treg cells and inducing key anti-inflammatory molecules (IL-10 and ICOS) in cells; improved gut IgA responses; regulating gut microbiota population and function in the production of postbiotics, because the effectiveness of probiotics is highly dependent on microbial strains, the number of probiotic cells and type of probiotic carrier.^{96,107–109}

On the other hand, intestinal dysbiosis disrupts this homeostasis, leading to a reduction in the synthesis of short-chain fatty acids, which can delay the maturity of intestinal epithelial cells, making it a non-selective organ and, alter the differentiation of Treg cells.⁹³ However, according to Shu

Table 2 Antiallergic effect of bacterial strains present in kefir

Bacterial strains present in kefir	Antiallergic effect	Ref.
<i>L. acidophilus</i> <i>L. reuteri</i>	Stimulation differentiation of Th1 cells	Torii <i>et al.</i> , ¹¹³ Smits <i>et al.</i> ¹¹⁴ Flinterman <i>et al.</i> ¹¹⁵
<i>L. acidophilus</i> <i>L. reuteri</i> <i>L. rhamnosus</i> <i>L. plantarum</i>	Suppressed differentiation of Th2 cells	Torii <i>et al.</i> , ¹¹³ Aitoro <i>et al.</i> ¹¹⁶
<i>L. casei</i>	Maintaining the integrity of the intestinal barrier	Zhai ¹¹²
<i>L. paracasei</i>	Inhibition of serum IgE levels	Fujiwara <i>et al.</i> ²⁴
<i>L. reuteri</i>	Tolerogenic DCs development	Smits <i>et al.</i> ¹¹⁴
<i>L. casei</i>	Increased IL-12 level suppresses serum OVA-specific IgE and IgG responses and systemic anaphylaxis	Shida <i>et al.</i> ¹¹⁷
<i>L. casei</i> <i>L. rhamnosus</i> <i>L. fermentum</i>	Activation of the Th1 immune response by production of cytokines IL-12 and IFN- γ	Shida <i>et al.</i> ¹¹¹
<i>L. fermentum</i>	Suppressed inflammatory cell infiltration in airways and BALF; Reduced OVA-specific IgE Abrogated mRNA expression of IL-4, IL-5, IL-13, and TGF- β .	Nawaz <i>et al.</i> ¹¹⁸
<i>L. rhamnosus</i>	Reduced acute skin allergic reaction, anaphylactic symptoms, body temperature, increased intestinal permeability, IL-4, IL-5, IL-13 production, and specific IgE	Aitoro <i>et al.</i> ¹¹⁶
<i>L. kefirianociensis</i> M1	Inhibition of OVA-specific IgE production Increased levels of cytokines produced by Th1 cells Reduction of cytokines produced by Th2 cells.	Hong <i>et al.</i> ¹¹⁹

et al.,¹¹⁰ postbiotics, partially allow restoring the intestinal microbiota even after dysbiosis, conferring aim beneficial microorganisms to the host. This shows an advantage of isolated kefir concerning kefir fermented drink.

Thus, studies show that the bacterial strains of kefir can modulate the Th1/Th2 equilibrium towards a dominant state of the Th1 response, suppressing the immune response of the Th2 phenotype, among other effects on allergic disease, as shown in Table 2. For example, Shida *et al.*¹¹¹ demonstrated the activation of the Th1 immune response by probiotic lactobacilli, through the production of cytokines such as IL-12 and IFN- γ . In the study by Fujiwara *et al.*,²⁴ oral administration of *Lactobacillus paracasei* in rat models with induced allergy stimulate Th1 response, by the maturation of antigen-presenting cells and still showing inhibition of serum IgE levels. In addition, the intake of fermented milk with *Lactobacillus casei* can maintain the integrity of the intestinal barrier during exposure to pro-inflammatory cytokines, leading to the restoration of the physiological gastric condition after inflammatory stimuli.¹¹²

In this same context, Lee *et al.*⁹ demonstrated, by histological study, an antiasthmatic effect for kefir by inhibiting eosinophilia in lung tissue and mucosal hypersecretion by goblet cells (mucus-secreting) in the airway, kefir was also able to reduce cytokines such as interleukin-4 and interleukin-13 to normal levels, and IgE levels.

Chen *et al.*,¹⁰ observed the anti-inflammatory and anti-oxidant activity of kefir, since peptides from this probiotic were able to inhibit the NF- κ B signaling pathway and thus

reduce the synthesis of pro-inflammatory cytokines: IL-1 β , IL-4, IL-6 and TNF- α in the lung tissue, in addition to reducing the concentrations of reactive oxygen species, by increasing the activity of the total superoxide dismutase enzyme in the lung.

These results are also supported by other authors^{5,120} who evaluated the anti-inflammatory action of kefir in other situations such as, for example, healing, where kefir was able to potentially reduce pro-inflammatory cytokines: IL-1 and TNF α , improve TGF- β 1 levels and improve the exchange of M1/M2 macrophages. It has also been shown that the kefir polysaccharide extract can inhibit the hyaluronidase enzyme, which has pro-inflammatory activity. When compared with ethanolic propolis extract, the kefir polysaccharide extract demonstrated greater anti-inflammatory activity.⁶⁷ In addition, Umeda *et al.*¹²¹ suggest that kefir reduces the permeation of antigen in the intestine when plasma concentrations of ovalbumin decrease after intragastric administration in BALB-c mice fed with lyophilized kefir, contributing to suppression and desensitization to the antigen. Thus, this and some studies presented in Table 3 already show possible benefits that kefir can promote in FA.

The active inflammatory state may also impair bone growth independently of dietary intake by the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), IL-1 and IL-6, commonly altered in allergies, it can alter the differentiation and function of osteoclasts, resulting in alterations in bone remodeling and modeling. In addition to these effects on osteoclasts, these cytokines may also impair osteo-

Table 3 Study characteristics, parameters and secondary outcomes related to the benefits that kefir can promote in food allergy

Author	Experimental design	Beneficial effects
Umeda <i>et al.</i> ¹²¹	After 1 week of acclimatization, the mice were deprived of food for 12 h and then intragastrically administered either 0.3 ml of PBS containing 20 mg of ovalbumin (OVA, Grade V, Sigma, MO, USA.) or the same solution supplemented with 5 mg of freeze-dried kefir	- Reduced penetration of antigen in the gastrointestinal tract - Contribute to suppression of sensitization to the antigen
Vinderola <i>et al.</i> ¹²²	Groups of BALB-c mice received 200 ml day ⁻¹ by gavage of lyophilized fractions: F1 (kefir solid part) or F2 (kefir supernatant) suspended in phosphate-buffered saline (PBS, pH 7.4) at a concentration of 0.5 mg ml ⁻¹ protein) for 2, 5 or 7 consecutive days.	- F1 and F2 can stimulate immune cells of the innate immune system, to down-regulate the Th2 immune phenotype or to promote cell-mediated immune responses against tumors and intracellular pathogenic infections.
Lee <i>et al.</i> ²⁰	BALB/c mice sensitized and challenged to ovalbumin and treated with kefir (50 mg kg ⁻¹ administered by intra-gastric mode) 1 h before the ovalbumin challenge	- It inhibited the increase in total inflammatory cell count and eosinophil count in Broncho alveolar lavage. - It reduced the concentration of IL-4 and IL-13 cytokines and total immunoglobulin E (IgE)
Kwon <i>et al.</i> ¹²³	3 groups of BALB-c mice sensitized with ovalbumin (1) simulated awareness plus challenge with PBS; (2) sensitization plus challenge with ovalbumin; (3) sensitization plus challenge with ovalbumin and treated with kefir 1 h before the challenge with ovalbumin. (4) sensitization plus challenge with ovalbumin and treated with 1 h before the challenge with ovalbumin.	- Kefiran decreased the number of eosinophil cells - Kefiran decreased the release of cytokines IL-4 and IL-5
Hong <i>et al.</i> ¹¹⁹	Injected BALB-c mice intraperitoneally with ovalbumin treated with <i>Lactobacillus kefirifaciens</i> M1 (M1) and <i>Lactobacillus kefirifaciens</i> M2 (M2), which were isolated from kefir grains.	- Suppression of IgE production by <i>Lactobacillus kefirifaciens</i> M1 leading to a shift in the Th1/Th2 balance toward Th1; - Elevation of CD4+ CD25+ Tregs and reduction of activated CD19+ B cells.
Nakamura and Mitsunaga ¹²⁴	4 groups of BalB-C mice (7 weeks): G1 (10) = control – not sensitized G2 (10) = sensitized without treatment G3 (10) = sensitized with low dose treatment (100 mg kg ⁻¹ for 49 days) G4 (10) = sensitized with high dose treatment (500 mg kg ⁻¹ for 49 days)	- Increased anti-inflammatory cytokine: IL-17 - Decreased pro-inflammatory cytokines: IFN- γ and IL-4, - Decreased plasma IgE.
Davras <i>et al.</i> ¹²⁵	3 groups: BalB-C mice G1 = control: 300 μ l of PBS for 2 weeks G2 = 300 μ l of kefir produced from kefir grains for 2 weeks G3 = 300 μ l produced from the kefir starter culture for 2 weeks	- Increased: IgA, IgG, IL-10 - Decreased: IL-4, IL-12, TLR-4
Qosimah <i>et al.</i> ¹²⁶	5 groups of ovalbumin-sensitized BALB-c mice received 5 different treatments: G1 = positive control (ovalbumin), G2 = negative control received NaCl G3 = T1 (kefir dose of 300 mg kg ⁻¹ for 14 days + ovalbumin), G4 = T2 (dose of kefir 600 mg kg ⁻¹ for 14 days + ovalbumin), G5 = T3 (dose of kefir 900 mg kg ⁻¹ for 14 days + ovalbumin).	- Groups that received kefir showed increased B cell activation and proliferation compared to the positive control group. -The T3 group proved to be the best for B cell activation. - IgE decrease in all groups that received kefir
Vinderola <i>et al.</i> ¹²⁷	BALB/c mice were fed with commercial kefir ad libitum (diluted 1/10, 1/50, 1/100 or 1/200) or pasteurized kefir (diluted 1/6, 1/10, 1/50, 1/100) for 2, 5 or 7 consecutive days.	- Increasing the number of IgA+ intestinal and bronchial cells phagocytic potential for peritoneal and pulmonary macrophages - An increasing expression of the cytokines IL-4, IL-6 and IL-10 of the small intestine

blast function, inhibition of differentiation and increase apoptosis.^{30,50}

In a study with humans, Adiloğlu *et al.*¹²⁸ evaluated the response of kefir ingestion in the innate immune system of 18 healthy people for 6 weeks and observed an increase in the

Th1-type immune profile, a reduction in the Th2-type response and, consequently, in the allergic response. These authors also state that kefir promotes a reduction in the expression of the IL-8 cytokine, which can lead to neutrophil chemotaxis, in addition to being responsible for increasing the expression of

IL-5, increasing the secretion of IgA in the gastric and intestinal mucosa.

Based on these findings, it is understood that kefir and mainly biopolymers originating from kefir, as kefir has beneficial effects for the treatment of allergic disorders. Therefore, the development of a kefir-based product to inhibit IgE production or reduce clinical signs is a useful approach to preventing or treating allergic diseases.

6. Conclusions

Based on the foregoing, we can see the probiotic and nutritional importance of kefir and its components, mainly kefir, thus suggesting that kefir can be considered one of the most promising foods in terms of prevention of allergies and increased mucosal resistance to gastrointestinal infections, mainly due to its antiallergic, antioxidant and anti-inflammatory properties.

Scientific evidence points to a fundamental protection function of postbiotics in food allergy. Thus, kefir can be used as a new strategy to improve immune tolerance and the treatment of FA without undesirable side effects or opportunistic infections, especially in babies and children.²¹ In addition, this biopolymer, which is produced from kefir's live microorganisms, is obtained by isolating the kefir grains, thus being free of any allergic trace originating from its cultivation. Thus, it is understood that it may be useful as supportive therapy in food allergies and also act in the adequacy the nutritional status of allergic children, contributing to the avoidance of nutrient-depleting syndromes, intestinal modulation and the fight against the growing deficit, which are common inadequacies in children with food allergies.

Finally, this review serves as a basis for studies using kefir as a promising matrix in the development of innovative nutraceutical products for alternative therapy in food allergy.

7. Limitations

Despite being a product of natural origin and the absence of possible serious side effects, a limiting factor in the acceptance of kefir is the consumer's resistance to obtain a product that does not have an effect as fast as medicines, as consumption of these foods must be regular so that their benefits are achieved.

In addition, sensory changes must also be taken into account, as consumer acceptance is an essential factor to be considered. Knowing the kefir's acid flavor, its consumption *in natura* is generally not well accepted, it was found that the addition of bioactive compounds from fruits and ingredients such as honey, for example, improves the sensory characteristics of this functional drink. In addition, the efficacy of probiotics is highly dependent on the microbial species or strains and the type of the probiotic carrier. An alternative also to

these limitations of kefir is the use of its isolated polymer: kefir as already discussed above.

8. Future directions

Functional dairy products, such as kefir, are a promising segment of the dairy industry, especially when they are enriched with their isolated bioactive compounds, such as postbiotics: the kefir, for example; or antioxidant compounds present in essential oils and plant extracts, which provide the body with a better immune defense and intestinal microbiota, enabling its use as supportive therapy in FA.

In addition, they seem appropriate for daily and continuous use and can be part of a healthy diet and offer essential nutrients to the human body without the presence of side effects. For better efficiency of these nutraceutical products from kefir or its polymers, an appropriate approach would be to investigate its enrichment with components capable of giving the drink better sensory and specific properties that please the consumer.

Therefore, as previously discussed, postbiotics maintain an efficacy similar to probiotics, but without serious side effects. However, further studies are needed to directly compare substances belonging to both groups. Likewise, studies that characterize novel postbiotics and investigate their beneficial potential in food allergy. Also necessary for clinical trials to determine the adequate dose and optimum administration frequency of postbiotic supplements. These researches are important for a better understanding of how postbiotics can be used as an adjunct therapy to either prevent or treat food allergy in humans, especially in children.

Conflicts of interest

There are no conflicts to declare.

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