Revista Brasileira de Ciências Biomédicas
RBCBM

THE USE OF ORAL PROBIOTICS IN THE TREATMENT OF ATOPIC DERMATITIS

Gabriella da Silva Tenori[1], Giovanna de Oliveira Bonatti[1], Jessica Domingues da Conceição[1], Milka Gomes de Souza[1], Ricardo Yuji Santos Yoshinaka[1], Paulo Urbano[2A]

[1]Student of the pharmacy course at Universidade Anhembi Morumbi - São Paulo - Brazil
[2]Teacher of the pharmacy course at Universidade Anhembi Morumbi - São Paulo - Brazil

ABSTRACT

Atopic Dermatitis (AD) is a chronic disease that generates scaly lesions on the skin, generates itching, erythema and affects 20% of children and about 5% of adults. Currently AD is considered a systemic disorder associated with the development of other comorbidities, whose pathophysiology is not completely understood, but there is a strong correlation with the dysfunction of the skin physical barrier and immunobiological dysregulation. The present study aims to analyze the effectiveness of the use of probiotics administered orally for the adjuvant treatment of patients with AD, evaluating their effectiveness, which are the most used, the correlation with the intestinal microbiota and the immune system, if there is greater effectiveness according to the age group and which strains and dosages are most indicated. The study used a prospective literature review, academic material in Portuguese and English, in the PubMed, Scielo and LILACS databases from 2017-2022 for works on the topic of probiotic use in AD. The literature review showed that although the first-choice treatment for AD is corticosteroids, probiotics as an adjuvant can reduce the need for corticosteroids. The most used strains are *Lactobacillus plantarum* and *Lactobacillus fermentum*, but the doses vary greatly between authors and commercial presentations, ranging from $5\text{-}10\times10^9$CFU for the first microorganism and $1\text{-}2\times10^9$CFU for the second. The higher incidence of efficacy of its in children and controversial conclusions on dosage was due to several factors, such as environmental, diet, which is indicative of the need for future studies to establish dose and identify proven clinical efficacy.

Keywords: Probiotics. Atopic dermatitis. Microbiota.

Abbreviations

AD – Atopic Dermatitis
AMP – antimicrobial peptide suppression
CLA – Conjugated linoleic acid
EO – ω-hydroxy ceramides
FFA – fatty acids
FLG – Filagrin
GI – gastrointestinal
IL – interleukin

LC – Langerhans cells
PMAP – pathogen-associated molecular pattern
SCFA – short chain fatty acids
SCORAD - Scoring Atopic Dermatitis
STAT - signal transducer and transcription activator
Th – T-helper
TLR – Toll-like receptors
TSLP – thymic stromal lymphopoietin
TSLPR – thymic stromal lymphopoietin receptor

^Corresponding author: Paulo Urbano - E-mail paulo.urbano@anhembi.br - https://orcid.org/0000-0001-7621-1208

INTRODUCTION

AD, also known as atopic dermatitis, is a chronic disease characterized by scaly, pruritic, and erythematous lesions on the flexural surfaces[1]. The disease affects up to 20% of children and 2% to 5% of adults worldwide, resulting in high utilization of health care services. AD usually begins in childhood, with 60% of patients developing AD before the age of one year and 90% by the age of five [2, 3].

Compared with children who do not have AD, children with this condition are more likely to develop food and environmental allergies (15% vs 4%), asthma (25% vs 12%), and allergic rhinitis (34% vs 14%). AD Patients are also more likely to develop ear infections (27% vs. 22%), strep throat (8% vs. 3%), and urinary tract infections (8% vs. 3%) [2]. The immune system (IS) is a complex system of tissues, cells and molecules distributed throughout the body with the task of protecting against possible harmful microorganisms and malignant cellular transformations[4].

AD has been considered more recently as a systemic disorder associated with an increased risk of several comorbidities: allergic and non-allergic so-called food allergies, respiratory disorders, cutaneous and extracutaneous infections, neuropsychiatric conditions, other inflammatory and autoimmune diseases, lymphoma, and diseases cardiovascular diseases, all with important implications for diagnosis and treatment[2]. Even if the pathophysiology of AD is not fully understood, many studies have shown that skin barrier dysfunction and IS dysregulation contribute to the pathobiology of AD. The epidermis plays the role of a physical and functional barrier, and skin barrier defects are the most important pathological findings in skin with AD. Filagrin, keratins, intercellular proteins, and transglutaminases are key proteins responsible for epidermal function. Deficiencies in these proteins accelerate the penetration of allergens and microbes into the skin. [5].

The pathogenesis of the disease is complex and includes impaired skin barrier function and an imbalanced SI with enhanced T-helper signaling: Th2, Th17 and Th22, resulting in overproduction of pro-inflammatory cytokines against common environmental allergens. In addition, AD patients have an increased burden of Staphylococcus aureus cutaneous colonization, which is associated with disease severity and exacerbation. Intestinal permeability is increased in AD patients. In addition, infants born by cesarean section have lower colonization with Bacteroides and higher with Clostridium. In addition, early colonization with Escherichia coli has a protective role for AD[6].

A point that has gained the attention of researchers in the area is the correlation of the intestinal microbiota in the origin and development of AD, the advance in sequencing technology has allowed the survey of this correlation[4]. Environmental, genetic and immunological markers are some of the elements responsible for the development of AD. There is also agreement on the relationship between allergens in the digestive tract and food diversity in the development of AD in children up to 5 years of age, while respiratory allergies predominate in children over 5

years of age[7, 8]. The gastrointestinal tract of a newborn (GI) is sterile at birth; the microflora that develops in the early postnatal period is involved in the activation of both innate and adaptive immunity. The development of atopy occurs when inadequate microbial stimulation leads to an imbalance in the gut microflora that favors the persistence of a dominant Th2 immune response in the newborn[8].

Probiotics are live microorganisms that, when administered in sufficient quantity, have benefits for the health of the host. They have the property of modulating the intestinal microbiome and immunological state and improving the intestinal barrier; these effects are responsible for reducing the allergic phenomenon and the severity of AD[7].

Bearing in mind the findings in the literature that infer an improvement in AD with the use of probiotics, the present study aims to develop the main concepts about the use of probiotics for AD curative purposes.

DISCUSSION

We can consider that AD occurs due to the recurrent chronic inflammatory condition of the skin. In addition to its increase in industrialized countries and affecting children, it generates a significant impact on the quality of life of patients, through the direct and indirect costs that the patient and his family cost[6].

It is the most common skin disease in children that is usually tied to other atopic manifestations such as rhinitis, asthma, and food allergy. Its onset is more frequent in children from 5 years of age, and this is the best time for diagnosis and treatment. The term "eczema" is no longer used to refer to AD, because it is also associated with various conditions of skin inflammation[9].

There is a direct relationship between the increase in AD in industrialized countries since 1970. In the United States of America, it was possible to identify that there is a prevalence of 10.7% of children with AD in relation to 7.2% of adults. Although it is better characterized at 5 years of age of the patient, there is a higher incidence between 3 and 6 months of life, but it is still feasible to occur at any age. Naturally, AD resolves when the child reaches adulthood, and about 30% of patients will continue to present symptoms of the disease also in adulthood [10].

Although the pathophysiology is not clear up to the time of the development of this study, there are two main theories proposed to explain the cause of AD, the inside-out and outside-in hypotheses. The inside-out hypothesis assumes that the triggering of an allergy results in a weakened skin barrier that favors the introduction and presentation of the allergen. This would suggest that inflammation is responsible for a disrupted skin barrier, leading to increased penetration of allergens and microbes that trigger a reaction. The out-to-in hypothesis states that the disrupted skin barrier precedes AD and is necessary for immunologic dysregulation to occur. For example, negative FLG regulation, which is necessary for proper skin barrier function, may make the skin more susceptible to immune dysregulation and lead to AD. It is unlikely that the two theories are unique, and both likely play a role in the pathogenesis

of AD[3].

In addition to the financial impact, AD presents symptoms of pruritus, which can be associated with emotional impacts, and it is also possible to generate suicidal ideation in patients. Therefore, one of the main objectives of treatment is the reduction of itching. Emotional stress also increases itching, and this increase can generate sleep disturbance, which affects two-thirds of patients with AD. The main complaint is the difficulty of performing morning activities, which generates daytime fatigue. In children, the frequency of poorly slept nights may be associated with higher rates of development of attention deficit disorder, short stature, and headaches. All these consequences can generate social embarrassment, due to pruritus and decreased self-esteem. This impact extends to the patient's parents and caregivers[10].

There are 2 main risk factors for the development of AD:

1) genetic abnormality in the FLG gene to change this expression,

2) family history of atopic disease.

A family history of atopic disease is strongly correlated with AD, as approximately 70% of patients with AD are positive for this risk factor. The risk for AD increases two- to threefold with the number of atopy-positive parents or three- to fivefold (1 or 2 parents, respectively). In addition, maternal history may be more informative for AD[4].

Concordance rate studies for AD are higher for identical twins than for fraternal twins (about 80% and about 20%, respectively)[11]. Thus, there is a genetic predisposition to the development of AD. Genome scans indicated multiple chromosomes involved, with the strongest binding region on chromosome 1q21. Other risk factors cited include an urban environment, higher socioeconomic level, higher educational level in the family, female gender (after 6 years), and smaller family size[12].

The FLG gene is responsible for the development of the prophylactic protein found in the granular layer of the epidermis, which collects structural proteins to create a strong barrier matrix. FLG mutations are most common in Caucasians. Approximately 10% of individuals descended from Europeans are heterozygous carriers of a loss-of-function mutation in FLG, resulting in a 50% reduction in protein expression. In the presence of FLG mutations, the disease is more severe and persistent, occurring primarily in the early stages AD and showing a predisposition to asthma. Genetic abnormalities of the FLG gene have also been associated with peanut allergy, contact dermatitis, and infections such as herpes virus. Since FLG mutations are found in only about 30% of European patients with atopic disease, other genetic variants of the epithelium should also be considered[9, 11, 12].

The epidermis of the skin consists of several layers that act as a barrier to prevent water loss and protect the body from foreign substances such as microorganisms and allergens. The FLG gene on chromosome 1q21.3 encodes a key protein for epidermal differentiation. This gene was originally identified as the gene involved in ichthyosis vulgaris, and several loss-of-function mutations have been reported in European and Japanese patients with AD[5, 9].

Since then, several studies have shown that the FLG gene plays a key role in skin barrier function and FLG gene mutations are an important risk factor for AD. Other skin barrier factors may include deficiency of skin barrier proteins, increased peptidase activity, deficiency of certain protease inhibitors, and lipid abnormalities. High molecular weight allergens in pollen, mite particles, microorganisms, and foods can penetrate the skin barrier only if there is a disruption of the epidermal barrier. The strong barrier matrix formed by the FLG gene, together with the proteins and lipids attached to it, forms the stratum corneum, the outermost layer of the epidermis, which normally provides a barrier against microorganisms and allergens and minimizes transepidermal water loss. Alterations or deficiencies of the FLG lead to an abnormality in the permeability of the barrier function[5, 13].

Patients with AD have a genetic dominance of Th2 cells that can decrease the expression of FLG and other skin barrier molecules. Genetically altered mice in which overexpression of Th2 cytokines was produced spontaneously developed skin barrier defects and AD. Clearly, many of these cytokines are targets for novel therapies to treat AD[3, 12].

The filagrina gene on chromosome 1q2 encodes FLG, an important structural protein of the stratum corneum (EC). The formation of the degradation products of urocanic acid and carboxylpyrrolidic acid contributes to the hydration of EC and the acidic pH of the skin[6, 9].

FLG mutations are known to impair skin barrier function, increasing the risk for AD. Th-2 alterations are directly associated with a higher incidence of AD. It is also known that positive regulation of interleukin (IL) 4 and IL -3 reduces FLG expression and leads to skin barrier defects.

Polymorphisms of various immune pathway genes are associated with an increased risk of AD by alternating t-helper (Th) signaling pathway type 2. Positive regulation of interleukin (IL) 4 and IL-13 reduces FLG expression, which leads to skin barrier defects. A gain of functional polymorphisms of type 2 cytokine receptors (IL-4R and IL-13R) are also implicated in the pathogenesis of AD. Other genes related to the immune system that contribute to the development of AD include IL-31, IL-33, signal transducer and transcription activator (STAT) 6, thymic stromal lymphopoietin (TSLP) and its receptors (IL-7R and TSLPR), interferon regulatory factor 2, Toll-like 2 receptor, and high affinity IgE receptor α gene (FcεRI) in specific populations. In addition, recent studies have shown that vitamin D receptor polymorphisms and cytochrome P450 variant family 27 subfamily A member 1 (CYP27A1) are associated with AD. *It is known that CYP27A1* participates in the metabolism of vitamin D3, which plays an essential role in immune modulation – Fang *et al.*, 2021.

Figure 1 – Cellular and molecular mechanisms in the injured skin of patients with AD. A skin barrier defect caused by genetic factors and inflammatory influences facilitates the penetration of irritants, microbiological products, and allergens. The Th2 pattern of lymphocytes is predominant in the acute phase and is also present in the chronic phase of AD. Other lymphocyte subpopulations (Th1, Th17 and Th22) are also detectable on the skin, as are other cell

types, such as inflammatory and eosinophile cell populations, are also found in increased numbers on injured skin. Selected inflammatory mediators are also shown, some of them serving as target molecules for new treatment attempts.
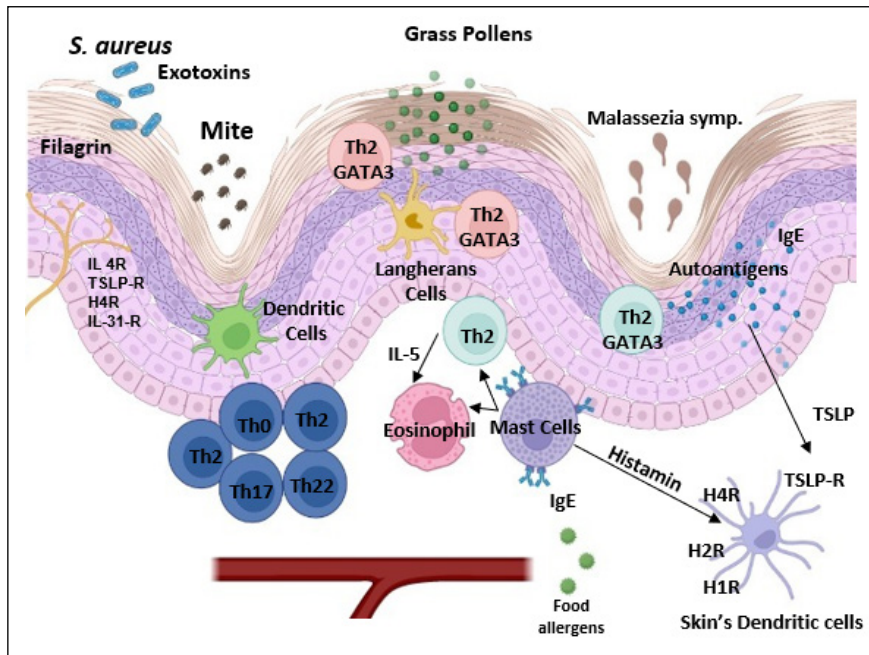
Source: Adapted from Kings and Aarestrup, 2019.

Immune cytokines type 2 as well as IL -4 and IL -13 play an important role in the production of chemokines, skin barrier dysfunction, suppression of antimicrobial peptides (AMP) and allergic inflammation. Interestingly, IL -31 has been reported to increase the release and production of brain-derived natriuretic peptide and coordinate the release of cytokines and chemokines from skin cells, causing itch in patients with AD [13].

Moreover, TSLP is highly expressed in the epidermis of patients with AD, and its production is triggered by exposure to environmental factors such as allergens, microorganisms, diesel exhaust, cigarette smoke, and chemical irritants. In a Korean birth cohort study, high expression of TSLP was detected on infant skin 2 months before the development of clinical AD at 24 months of age using skin tape samples [7].

Although blockade of inflammation caused by type 2 improves the symptoms of AD, the pathogenesis of AD is not exclusively explained by Th2 immunity. In this context, IL -17 was reported to reduce the expression of FLG and involucrin. The strongest Th17 activation was observed in blood and acute skin lesions of AD in Asian patients compared with European-American patients. Furthermore, AD is divided into extrinsic and intrinsic, and Th17 cytokine production is higher in intrinsic AD with normal immunoglobulin E levels than in extrinsic AD. ILAlso -22 is highly regulated on the skin of patients with AD and is associated with skin barrier dysfunction and abnormal epidermal markers such as keratin 6 and keratin 16 [7, 14].

Notably, the transition to the chronic phase is evidenced by the onset of Th1 cell activation and the sustained activation of th2 and th22 cells (Figure 2). Interestingly, tumor necrosis factor α in combination with Th2 cytokines altered the expression of early and terminal differentiation products and decreased the levels of free long-chain fatty acids (FFA) and ω-hydroxyceramides (EO) attached to ester [7].

Several studies link the development of AD to changes in gut microbial diversity and composition. More than 1,000 different microbial species live in the TGI, and the number of bacterial cells is about ten times higher than that of eukaryotic cells in the human body [4].

Prepartum microbial assemblages were found in the placenta and meconium, indicating early microbial colonization in life. After birth, the intestinal microbiota and mucosa begin to establish themselves and are influenced by birth, such as natural delivery or cesarean section [9, 15].

Lactobacillus, Prevotella, and Sneathia spp. are the predominant bacterial communities in the gut of naturally born infants and resemble the vaginal microbiota of their own mothers, whereas the microbial communities in cesarean section infants resemble the skin microbiota and are dominated by *Staphylococcus, Corynebacterium*, and *Propionibacterium spp*. suggesting the role of mode of delivery on the diversity and structure of the original microbiota. Thereafter, the diversity of the gut microbiome increases rapidly, and nutritional factors, including breast milk feeding and infant formula feeding, become the major confounding factors affecting the diversity and composition of the gut microbiome. *Lactobacillus* and *Bifidobacterium* are the dominant gut microbiota in infants who are breastfed at 12 months of age, but *Roseburia*, *Clostrium*, and *Anaerostipes*, which

belong to *Clostirdia*, are enriched in the gut microbiota of children who are no longer breastfed. Lactobacillus, Bifidobacterium and Bacteroides can break down oligosaccharides from breast milk into small sugars and use them as a growth advantage. Therefore, these are the most abundant bacterial communities in the intestines of breastfed infants[4, 8].

Figure 2 - Effects of cytokines on the epidermis on AD.
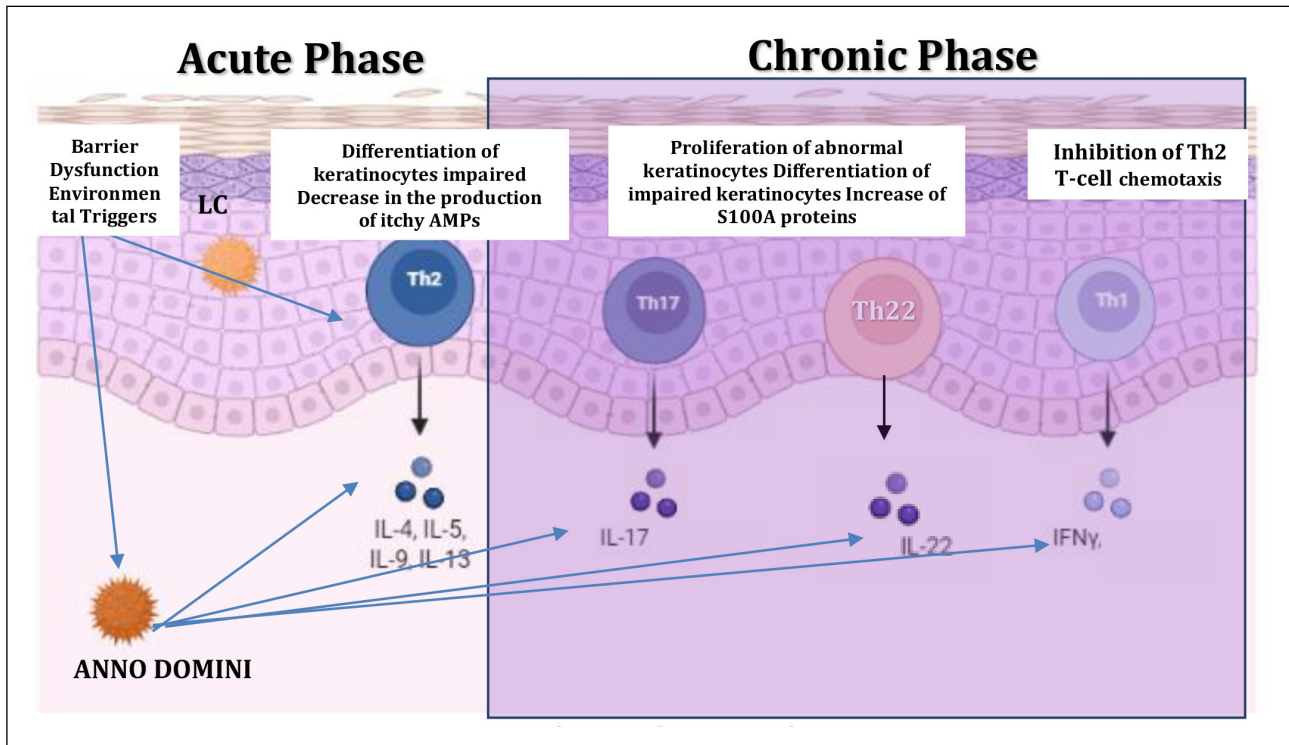
Source: Adaptation by Rusu *et al.* , 2019.

Enterococci and Clostridia are the predominant bacteria in formula-fed infants, and GI contains fewer bacterial cells and more species than in breast-fed infants. By age 3, the microbial composition of the gut changes to resemble that of the adult[9]. Diversity and bacterial composition are closely related to the occurrence and development of various diseases such as acute infectious diarrhea, constipation, obesity, and depression, underscoring the importance of bacterial diversity and colonization in early life for future health (see Table 1) [16].

Table 1 – Changes in the intestinal microbiota of patients with atopic dermatitis.

Type of study	Nation/Year	Changes in the intestinal microbiota
Healthy babies (n=66), babies with AD (n=63)	Korea; 2018	The amounts of bacterial cells were lower and the relative abundances of *Akkermansia muciniphila, Ruminococcus gnavus* and bacterium Lachnospiraceae 2_1_58FAA were lower in babies with AD than in control babies
Patients with AD (n=23), controls (n=58)	Brazil; 2020	*Clostridium difficile* was associated with AD, and less Lactobacillus and more bifidobacterial in patients with AD
Patients with AD (n=44), healthy controls (n=49)	China; 2021	Alpha diversity decreased in patients with AD than in healthy individuals. *Blautia, Parabacteroides , Bacteroides ovatus , Porphyromonadaceae* and *Bacteroides uniformis* were increased, but *Clostridium* and *Prevotella stercorea* were reduced in patients with AD
Patients with AD (n=19), patients with other allergic diseases (n=20)	China; 2021	The relative abundances of *Bacteroidetes, Bacteroides, Bacteroidia, Romboutsia* and *Sutterella* were significantly increased in patients with eczema

Source: Adapted from Fang *et al.* , 2021.

Compared with healthy subjects, gut microbial diversity decreased and the relative abundance of beneficial microbes such as *Lactobacillus* and *Bifidobacterium* decreased significantly, while the proportion of *Escherichia coli*, *Clostridium difficile*, and *Staphylococcus aureus* increased in patients. Colonization and alteration of the gut microbiome were detected prior to clinical manifestation in early life, indicating dysbiosis of the gut microbiome as one of the causes of AD. Infants with lower diversity of the gut microbiome appear to be susceptible to atopic dermatitis, and some studies suggest that bifidobacterial composition, particularly the proportion of *B. teenis*, has particular effects on the development of the allergic disease[9, 17]. Regulating the microbial diversity and composition of the gut in early life can reduce the occurrence and development of allergic symptoms, including AD. Therefore, this is an alternative to reduce the side effects of medications[15].

Toll-like receptors (TLRs), a superfamily of pattern recognition receptors, are involved in innate and adaptive immunity. TLRs are a class of noncatalytic transmembrane proteins and can recognize molecules with conserved structures of microorganisms. These molecules are known as pathogen-associated molecular patterns (PMAPs) such as lipopolysaccharide, peptidoglycan, and zymosan. When TLRs bind to PMAPs, they initiate a signal transduction cascade to activate innate immune responses and eliminate pathogens that penetrate the skin or mucosal barrier. Most TLRs (TLR1, TLR2, TLR4, TLR5, TLR6, TLR10, TLR11, and TLR12) are expressed on the cell surface to recognize PMAPs, but TLR3, TLR7, TLR8, and TLR9 are intracellular and recognize nucleic acids. To date, 13 and 10 members of TLRs have been identified in mice and humans, respectively, and their respective ligands have also been discovered[9].

S. aureus colonizes skin lesions of patients with AD and can be recognized by TLR2 due to its cell wall components. Compared with healthy subjects, TLR2 expression in Langerhans cells (LC) was decreased in patients with AD with high colonization by in situ analysis[15]. The intestinal microbiota and its metabolites can be recognized by TLRs, and interactions between bacteria and TLRs contribute to systemic immunological homeostasis. Disturbances in the intestinal microbiota lead to the invasion of microorganisms and their metabolites into the bloodstream and influence the pathological symptoms of distant local organs such as the brain, liver, kidney, lung, and skin via the signaling pathways of TLRs [9].

As mentioned earlier, the onset and development of AD are closely related to changes in the gut microbiome, and patients lack beneficial bacteria such as Bifidobacterium and Lactobacillus. Taking probiotics can be an effective alternative to provide beneficial bacteria and restore intestinal dysfunction. The gut microbial environment can be reshaped by long-term probiotic intake, contributing to the balance of the gut microbiota and systemic immune response. Probiotics promote the synthesis of nutrients such as amino acids and vitamins in the host and increase the content of short-chain fatty acids (SCFA) in the intestinal lumen. In particular, short-chain fatty acids such as acetate, propionate, and butyrate lead to an intestinal environment with a low pH, which inhibits the growth of pathogens. In addition, probiotics compete with pathogens, including competition for nutrient substrates and ecological niches, and these interactions contribute to the suppression of excessive pathogen proliferation in the gut, affecting gut microbial composition, metabolic functions and immune responses[9, 15].

Table 2 shows the effects of probiotics on the clinical manifestations of patients of pregnant women, infants, children and adults and the potential to relieve AD.

Table 2 – Effects of probiotics on clinical manifestations of AD in different populations

Probiotics	Participants	Result
B. Brief M-16V and *B. longum* BB536	Pregnant women; N=130	Probiotics significantly reduced the risk of developing eczema and AD
L. rhamnosus GG, *B. animal* subsp. *Milk* Bb-12 and L. acidophilus La-5	Pregnant women; N=415	Probiotic intake significantly decreased the proportion of Th22 cells and prevented AD in their offspring
Lactobacillus GG ATCC53103	Pregnant women with a family history of allergy; N=105	*Lactobacillus* GG did not reduce the incidence of AD or alter the severity of AD
L. rhamnosus GG, *L. acidophilus* La-5 and *B. animal* subsp. Bb-12 milk	Pregnant women; N=415	Probiotics reduced the cumulative incidence of AD, but did not affect atopic sensitization
Bifidobacterium infantis, *Streptococcus thermophilus* and *Bifidobacterium lactis*	Premature; N=1099	Probiotics did not affect the incidence of allergic diseases and atopic sensitization
Hn001 Rhamnosus	Babies N=474	*L. rhamnosus* HN001 exerted the protective effect against eczema when administered only in the first 2 years, extending up to at least 4 years of age
B. Brief M-16V and oligosaccharides mixture	Infants <7 months with atopic dermatitis; N=90	No effect on AD markers

L. Rhamnosus MP108	Children from 4 to 48 months with AD; N=66	*L. rhamnosus* MP108 decreased the SCORAD socres
L. acidophilus DDS-1, B. *lactis* UABLA-12 with fructooligosaccharides	Children from 1 to 3 years with moderate to severe AD; N=90	Clinical improvement was associated with the administration of the probiotic mixture
L. plantarum CJLP133	Children from 12 months to 13 years; N=118	*L. plantarum* CJLP133 decreased the SCORAD score and the total eosinophil count. IFN-γ and IL-4 were significantly reduced compared to baseline measurements
L. paracasei and L. yeast	children aged 1 to 18 years with moderate to severe AD	Probiotics significantly improved clinical symptoms of AD
Pentosus lactobacillus	Children from 2 to 13 years; N=82	The probiotic significantly reduced SCORAD scores, but the improvement in clinical symptoms had no difference in the probiotic and placebo groups
Bifidobacterium lactis CECT 8145, *B. longus* CECT 7347 and *Lactobacillus casei* CECT 9104	Children from 4 to 17 years with moderate AD; N=50	SCORAD index and topical steroid use were significantly reduced in the probiotic group compared to the control group
B. animal genome LKM512	Adult patients N=44	*B. animalis* subsp *lactis* LKM512 decreased itching and dermatology-specific quality of life scores via tryptophan quinurenic acid metabolism
L. paracasei K71 killed by heat	Adult patients N=34	*L. paracasei* K71 significantly reduced skin severity scores

Source: Adapted from Fang *et al.* , 2021.

Most probiotics reduced SCORAD scores (scale to assess AD index) and even decreased the risk of developing AD. A study by Kalil et al. (2020) presents a relationship of dosage and results for treatment of AD with probiotics.

Table 3 - Dose ratio and result of oral probiotic use efficacy.

Title	Treatment	Result
A randomized trial of Lactobacillus plantarum CJLP133 for the treatment of atopic dermatitis	Two daily doses of *L. plantarum* $^{5 \times 10^9 UFC}$ for 12 weeks	Reduction of the SCORAD index is significantly higher than the placebo group with reduction of eosinophil count and levels of IFN-gamma and IL-4 at the end of treatment.
Lactobacillus16 plantarum IS-10506 supplementation reduced SCORAD in children with atopic dermatitis	Two daily doses of *L. plantarum* $10 \times 10^9 UFC$ for 12 weeks	SCORAD and IL-4 levels, INF – gamma and IL-17 were significantly lower at the end of the study in the treated group compared to placebo. IgE levels have not changed significantly.
Effects of probiotics on atopic dermatitis: a randomized controlled trial	Two daily doses of *L. fermentum* VRI-033 PCC $1 \times 10^9 CFU$ for eight weeks	Significant reduction in the SCORAD index in the treated group compared to placebo.
Children with atopic dermatitis show clinical improvement after Lactobacillus exposure	A daily dose of *L. paracasei* $2 \times 10^9 UFC$, *L. fermentum* $2 \times 10^9 CFU$ or mixture *of L. paracasei and L. fermentum* $4 \times 10^9 CFU$ for three months	The treated groups showed a significant reduction in the SCORAD index and an improvement in quality of life indexes compared to placebo. There was no significant difference between the groups in reducing IgE levels.

Source: Adapted from Kalil *et al.* , 2020.

According to the "hygiene hypothesis", bacterial stimulation is necessary for the maturation of the intestinal immune system in the first years of life. Most probiotics derived from *Coebium* bacteria in the intestine have been shown to contribute to the formation of immune tolerance and the maintenance of the intestinal immune response[17]. Immunoglobulin (Ig) A is an important antibacterial protein for the defense of the intestinal mucosa. It blocks the adhesion of pathogens to the intestinal epithelium and increases bacterial confinement in the mucus[10].

Bifidobacterium is known to stimulate Peyer's plaques to stimulate IgA production and maintain the integrity of the intestinal barrier. Administration of Lactobacillus GG and Saccharomyces boulardiia affects the release of cytokines and mucosal centre, which increases IgA production in the intestine[3].

Regulating the balance between Th1 and Th2 immune responses is a way to improve clinical symptoms in allergic diseases. B. animalis subspecies lactis Bb12 increased IgA responses in serum and IgG1 and IgG2 responses in ileal fluid in pigs infected with Ascaris suum. Treatment with B. animalis subspecies lactis Bb12 enhanced the expression of genes related to Th1/Th2 cells, inflammatory cells, regulatory T cells (Treg) of the colon, and physiological function in the intestine, and reduced Th2-type immune responses. In allergic mice induced by β-lactoglobulin, *L. plantarum* ZDY2013, *L. plantarum* WLPL04, and *L. rhamnosus* GG increased the differentiation of Th1 cells and inhibited the immune response of Th2[8].

Moreover, differentiation of Tregs not only regulates the Th1/Th2 immune balance but also suppresses the reaction with Th17. *L. paracasei* KBL382 significantly improved pathological features and altered gut microbial composition in AD mice. Regulates immune balance by increasing expression of IL -10 and transformer-β growth factor and enhancing differentiation of CD4+ CD25+ Foxp3+ Treg in mesenteric lymph nodes. *L. sakei* WIKIM30 enhanced the differentiation of Tregs into mesenteric lymph nodes by inducing tolerance to DCs and skin lesions like AD. It increased the level of *Ruminococcus*, which was positively associated with immune responses associated with Tregs and may have contributed to the alleviation of AD[9].

Probiotics also contribute to decrease the expression of proinflammatory cytokines such as IL -13, thymic stromal lymphopoietin (TSLP) and IL -5. Eosinophil differentiation is closely related to allergic diseases such as AD, but IL -5 is the crucial cytokine to increase eosinophil development and survival[16].

Pediococcus acidilactici ingestion decreased IL-4, TNF-α, and IL -13 mRNA expression in dorsal skin and improved clinical severity of AD. The 0 levels of TSLP are increased in the lesions of patients with AD and TSLP is a key protein in the development of AD. TSLP is expressed by epithelial cells of the intestine, lung, and skin and promotes Th2 cell differentiation and Th2-type inflammation by interacting with immune cells such as DCs, natural killer T cells, and CD4+ T cells. In a mouse model with AD, overexpression of skin specific TSLP resulted in an increase in Th2 CD4+ T cells and serum IgE levels. *L. rhamnosus* Lcr35 significantly reduced the expression of IL-4 and TSLP and prevented the development

of AD. Overall, probiotics have great potential to modulate immune function in AD and could be an alternative microbial strategy to improve the AD [9].

Probiotics alter the composition of the gut microbiome while influencing its metabolic activities, which may lead to a lower risk of allergy. Metabolites of B. breve C50 and Streptococcus thermophilus 065 increased the proportion of CD4+ and CD8+ T cells secreting Th1-type IFN-γ cytokines and restored Th1/Th2 immune imbalance in IL-10 deficiency[11].

Short-chain fatty acids (SCFA) are produced by the microbial fermentation of indigestible carbohydrates in the intestine and are closely associated with the alleviation of the clinical manifestations of AD. In addition, SCFA have been shown to regulate the size and function of the Tregs pool in the gut. In a cohort study, the severity of AD was negatively associated with the proportion of butyrate-producing bacteria in infants, suggesting that butyrate plays a potential role in ameliorating AD symptoms. Increased faecal propionate and butyrate levels reduced atopic sensitization in early life, and administration of butyrate reduced the severity of allergic inflammation in mice. Antibiotic-induced dysbiosis of the gut microbiome led to a decrease in SCFA production and an increase in inflammatory cells, and these changes were highly associated with ad-like skin lesions[1].

However, transplantation of fecal microbiome significantly decreased the clinical score of lesions such as AD, increased SCFA levels and regulated the number of immune cells. SCFA contribute to the balance of the intestinal microbiota and are closely related to the number of immune cells. Therefore, increasing SCFA production in the gut by consuming probiotics may be an effective means of alleviating the symptoms of AD. D-tryptophan, a metabolite of Bifidobacterium, Lactobacillus, and Lactococcus, suppressed the expression of CCL17 associated with Th2 in KM -H2 cells. Significantly increased the production of il-10 and decreased IL -12, IL -5 and IFN-g in human DCs. After supplementation with D-tryptophan in mice with allergic airway inflammation, clinical symptoms were alleviated and immune responses with Th2 orientation were significantly reversed. Conjugated linoleic acid (CLA), a natural unsaturated fatty acid, can inhibit the release of histamine, which causes increased vascular permeability and is associated with the development of AD[7].

Bifidobacterium, Lactobacillus, and Roseburia spp. metabolize polyunsaturated fatty acids, including omega-3 and omega-6 fatty acids in CLA. *B. breve* and *B. pseudocatenulatum* are CLA-producing bacteria that have been reported to alleviate colitis by modulating the intestinal microbiota and TLR4/NF-Kb signaling(9).

Fang et al. (2021) and Souza et al. (2010) suggest that consumption of probiotics increases CLA production in the gut and influences the systemic immune response. L. plantarum JBCC105645 and JBCC105683 isolated from salted fermented seafood for their CLA-producing activity significantly alleviated the pathological symptoms of ad by decreasing IL -4 levels and increasing IFN-γ levels. This suggests that CLA may be the substantive basis of probiotics for alleviating AD. Oral administration of CLA significantly attenuated AD type skin lesions by inhibiting

COX -2/5- LOX and TLR4/NF-κB signaling pathways. The results showed that the anti-inflammatory effect of CLA has great potential to alleviate AD.

There are some limitations regarding the effects of probiotics on alleviating symptoms in this review. The efficacy of probiotics in improving the clinical symptoms of AD needs to be more rigorously demonstrated on a larger scale and in clinical trials in different patient groups stratified by age, sex, and concomitant diseases. The interactions between probiotics and the gut microbiota are complex, leading to difficulties in uncovering the exact mechanisms of relief AD. Moreover, the immunomodulation of probiotics is strain-specific and may activate different signaling pathways to improve the clinical manifestations of AD. The basic substance of probiotics to alleviate AD is not yet clarified, whether it comes from the probiotic component itself and probiotic metabolites or the gut microbiota(13).

The most conclusive evidence relates to treatment with Lactobacillus plantarum and Lactobacillus fermentum in children 12 months of age or older. Each probiotic was studied in two separate randomized clinical trials over a 12-month period that showed a reduction in SCORAD score (Scoring Atopic Dermatitis-AD score) when given to patients alone, without other probiotic strains. The improvement was clinically significant, as an improvement of an average of 8.7 points on the SCORAD scale resulted in an improvement of 1.0 point on the overall severity scale, although another study of treatment with *L. plantarum* showed no efficacy. However, this study lasted only six weeks, whereas the other studies lasted 12 weeks, possibly showing the beneficial effect of longer treatments(9, 15).

CONCLUSION

Considering that the use of corticosteroids is recommended on AD but causes adverse effects that affect the patient's health, the use of probiotics as an adjunct to treatment may reduce the need for the use of corticosteroids.

Probiotics have been shown to be effective in the treatment of AD because the ingested strains stimulate the immune system.

The most used strains in AD are Lactobacillus plantarum and Lactobacillus fermentum, according to authors Huang et al. (2017), Fang and coworkers (2021), who found overall satisfactory results in the present study considering the recommended dosage.

The literature showed the effectiveness of the use of probiotics in AD, characterized the most used strains with their respective dosages and it was possible to understand the relationship of the gut microbiota with THE, according to Table 3 of this study.

It can be concluded that the best results in the use of probiotics are more frequent in children.

Acknowledgements

Controversial findings are associated with many factors such as environment and diet, and in the future, larger samples and more accurate experimental designs are needed for clinical trials to verify the efficacy of probiotics in AD.

CONFLICT OF INTEREST

REFERENCES

Rios, A. R., de Miranda, B. A., Pereira, G. R., Costa, H. B., Costa, I. L. B., Cesconetto, J. & Gandra, M. F. (2021). Dermatite atópica: um olhar sobre os tratamentos atuais. Revista Eletrônica Acervo Saúde, 13(6), e7595-e7595.

Torres, T., Ferreira, E., Gonçalo, M., Mendes-Bastos, P., Selores, M., & Filipe, P. (2019). Update on atopic dermatitis. Acta médica portuguesa, 32(9), 606-613.

Vilefort, L. A., de Oliveira Melo, I. V., do Nascimento Cardoso, B., Mohr, A. C., Motta, D. F. B., Atavila, F. P., Xavier, P. H. Z. (2022). Ampla abordagem sobre a dermatite atópica: revisão narrativa. Revista Eletrônica Acervo Científico, 41, e9807-e9807.

Chong-Neto, H. J., Pastorino, A. C., Melo, A. C. D. B., Medeiros, D., Kuschnir, F. C., Alonso, M. L. O., ... & Barreto, B. A. P. (2019). A microbiota intestinal e sua interface com o sistema imunológico. Brazilian Journal of Allergy and Immunology (Bjai),[SL], 3(4), 406.

Kim, J., Kim, B. E., & Leung, D. Y. (2019, March). Pathophysiology of atopic dermatitis: Clinical implications. In Allergy and asthma proceedings (Vol. 40, No. 2, p. 84). OceanSide Publications.

Edslev, Sofie M.; Agner, Tove; Andersen, Paal S. Skin Microbiome in Atopic Dermatitis. Acta Dermato-Venereologica, v. 100, 2020.

Rusu, E., Enache, G., Cursaru, R., Alexescu, A., Radu, R., Onila, O. & Radulian, G. (2019). Prebiotics and probiotics in atopic dermatitis. Experimental and Therapeutic Medicine, 18(2), 926-931.

Fanfaret, I. S., Boda, D., Ion, L. M., Hosseyni, D., Leru, P., Ali, S. & Bumbacea, R. (2021). Probiotics and prebiotics in atopic dermatitis: Pros and cons. Experimental and Therapeutic Medicine, 22(6), 1-8.

Fang, Z., Li, L., Zhang, H., Zhao, J., Lu, W., & Chen, W. (2021). Gut Microbiota, Probiotics, and Their Interactions in Prevention and Treatment of Atopic Dermatitis: A Review. Frontiers in Immunology, 2799.

Torres, T., Ferreira, E., Gonçalo, M., Mendes-Bastos, P., Selores, M., & Filipe, P. (2019). Update on atopic dermatitis. Acta médica portuguesa, 32(9), 606-613.

Kalil, C. L. P. V., Chaves, C., Vargas, A. S. D., & Campos, V. B. (2020). Uso dos probióticos em Dermatologia-Revisão. Surgical & Cosmetic Dermatology, 12(3), 208-214.

Córdova Martínez, A., & Alvarez-Mon, M. (1999). O sistema imunológico (I): Conceitos gerais, adaptação ao exercício físico e implicações clínicas. Revista Brasileira de Medicina do Esporte, 5(3), 120-125.

Reis, A. P., & Aarestrup, F. M. (2019). Imunoterapia e imunobiológicos na dermatite atópica. Arquivos de Asma, Alergia e Imunologia, 3(2), 123-132.

Guillen JS, Fileto MB, Pinto CA, Rosado C, Baby AR, Velasco

MV. Abordagens no tratamento da dermatite atópica. BWS Journal. 2021 Jun 22;4:1-8.

Huang R, Ning H, Shen M, Li J, Zhang J, Chen X. Probiotics for the treatment of atopic dermatitis in children: a systematic review and meta-analysis of randomized controlled trials. Frontiers in Cellular and Infection Microbiology. 2017 Sep 6;7:392.

Park DH, Kim JW, Park HJ, Hahm DH. Comparative Analysis of the Microbiome across the Gut–Skin Axis in Atopic Dermatitis. International Journal of Molecular Sciences. 2021 Jan;22(8):4228.

Petersen E, Skov L, Thyssen JP, Jensen P. Role of the Gut Microbiota in Atopic Dermatitis: A Systematic Review. Acta dermato-venereologica. 2019 Jan 1;99(1).