

# Physiological and Immunological Functions and Therapeutic Importance of Probiotics in Allergic Diseases

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## ABSTRACT

Allergic diseases have been a global problem over the past few decades. The effect of allergic diseases on healthcare systems and society is generally remarkable and is considered as one of the most common causes of chronic and hospitalized disease. The functional ability of probiotics to modulate the innate/acquired immune system leads to the initiation of mucosal/systemic immune responses. Gut microbiota plays a beneficial role in food digestion, development of the immune system, control/growth of the intestinal epithelial cells and their differentiation. Prescribing probiotics causes a significant change in the intestinal microflora and modulate cytokine secretion, including networks of genes, TLRs, signaling molecules and increased intestinal IgA responses. The modulation of Th1/Th2 balance is done by probiotics, which suppresses Th2 responses with shifts to Th1 and thereby prevent allergies. In general, probiotics are associated with a decrease in inflammation by increasing butyrate production and induction of tolerance with an increase in the ratio of cytokines such as IL-4, IL-10/IFN- $\gamma$ , Treg/TGF- $\beta$ , reducing serum eosinophil levels and the expression of metalloproteinase-9 which contribute to the improvement of the allergic disease's symptoms.

**Keywords:** Allergy; Immune system; Immunotherapy; *Lactobacillus*; Microbiota; Probiotic

## INTRODUCTION

Allergic diseases have been a global problem over the past few decades. The prevalence of eczema (atopic dermatitis), food allergies and asthma have increased dramatically during this period, especially in western societies. It is believed that between 20%-30% of people living in Western countries are suffering from at least one type of allergic disease. The effect of allergic diseases on health care systems and society is generally remarkable and is one of the most common causes of chronic and hospitalized illness. Allergic diseases are described with an inadequate immune response of T helper (Th2) cell lymphocytes to environmental or food antigens. Activating this response results in the secretion of Interleukins (IL)-4, IL-5, IL-13 and the production of IgE specifically for allergens. The induction of Th2 cytokine responses also inhibits Th1 activity primarily via

interferon (IFN)- $\gamma$ , which helps maintain an allergic phenotype. The stability of Th1/Th2 balance is governed by the expression of the transcription factors GATA-3 (Th2) and T-bet (Th1) [1].

Several studies have shown that in patients with allergies, the number and function of regulatory T cells (Tregs) is associated with a decrease of the immune response, while the mutation in the FoxP3 Treg transcription factor leads to severe immunosuppression. The mechanisms that cause allergic diseases in early life are not yet fully understood. One of the well-known and very prominent ideas is the impact of intestinal microbiota, where the composition and structure of commensal bacteria are associated with the developing immune system. Such interactions can affect the maturity of the immune system, which potentially results in Th2-type allergic responses. Similarly, preventive or therapeutic strategies targeting intestinal

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**Received:** 03-Oct-2019, Manuscript No. jph-23-2393; **Editor assigned:** 07-Oct-2019, PreQC No. jph-23-2393 (PQ); **Reviewed:** 21-Oct-2019, QC No. jph-23-2393; **Revised:** 30-Nov-2023, Manuscript No. jph-23-2393 (R); **Published:** 26-Mar-2024, DOI: 10.35248/2329-8901.24.12.344

**Citation:** Eslami M, Keikha M, Kobylak NM, Karbalaei M, Yousefi B (2024) Physiological and Immunological Functions and Therapeutic Importance of Probiotics in Allergic Diseases. J Prob Health. 12:344.

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microbiota are the subject of increasing scientific research. In this review, the beneficial effects of probiotics on the prevention and treatment of some allergic diseases are critically discussed [2].

The prevalence of allergic diseases and asthma are increasing worldwide, particularly in low and middle-income countries. Allergic diseases are common in children and adolescents and result in high costs to the health care system, as well as having an adverse impact on the quality of life.

Complexity and severity of allergic diseases include life-threatening anaphylaxis, food allergies, certain forms of asthma, rhinitis, conjunctivitis, angioedema, urticaria, eczema, eosinophilic disorders, include eosinophilic esophagitis and drug and insect allergies continue to escalate particularly in children and young adults, who are bearing the highest burden of these trends.

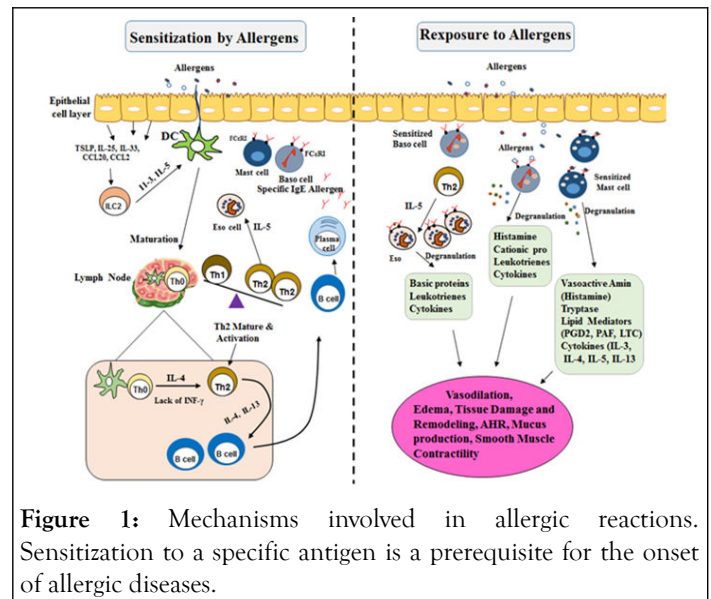
Globally, 300 million people suffer from asthma and about 200 to 250 million from food allergies. Moreover, one-tenth of the population hurts from drug allergies and 400 million from rhinitis. In the United States, the prevalence of asthma is approximately 7%. Allergic Rhinitis (AR) is more prevalent than asthma, ranging from 10% to 20% (500 million) worldwide and in the United States ranging from 10% to 40% [3].

The prevalence of the atopic disease has reportedly been on the rise in the United States and around the world, although rates may have plateaued recently. International study of asthma and allergies in childhood reported that the lifetime prevalence rates of atopic disease stabilized at 20%. This plateau is a mixture of a substantial increase in the prevalence of the atopic disease in Mexico, Chile, Kenya, Algeria and Southeast Asia, with decreases in New Zealand and the United Kingdom, which previously had high rates.

## LITERATURE REVIEW

The increase of urbanization in the developing world may contribute to the higher occurrence of aeroallergic disease in an urban area as compared with rural locations. The hygiene hypothesis by industrialization/urbanization led to reduced microbial exposure and infectious agents (biasing the immune system away from a Th1 immune-mediated response toward to Th2, in early life in contrast to rural societies.

In addition, another risk factor of the aeroallergic disease includes prolonged and high exposure to dust mite populations, cockroach or rodent allergens, lifestyle and obesity, elevated concentrations of air pollution (Figure 1) [4].



**Figure 1:** Mechanisms involved in allergic reactions. Sensitization to a specific antigen is a prerequisite for the onset of allergic diseases.

Differentiation and expansion to Th2 cell subtypes lead to the production of inflammatory cytokines (IL-4, IL-5 and IL-13). They drive Immunoglobulin E (IgE) class-switch in B cells and the recruitment and activation of proinflammatory cells in mucosal target organs. Allergic reactions are triggered when allergens cross-link preformed IgE bound to the high-affinity receptor FcεRI on Mast cells and Basophil cells. In the early phase of allergic reactions alert the local immune cells and induce inflammatory reactions by secreting chemical mediators, leukotrienes and cytokines. Mast cell and Basophile cell degranulation followed by a more constant inflammation, recognized as the late-phase response. This late response includes the employment of other effector cells, particularly Th2 lymphocytes, eosinophils and basophils, which contribute significantly to the immunopathology of an allergic response. These activations contribute to the development of the inflammation and the symptoms of allergic disease.

In the allergic response, the immune system must identify the allergens and induce a dynamic immune response. Sensitization to a specific antigen is an essential part of allergic immune responses mediated by naïve T and B lymphocytes. Primary, recognized and processed allergens presented by Antigen-Presenting Cells (APC) to naïve T cells (Th0). Th2 cell differentiation is linked on the local cytokine environment provided by interactions among the epithelium, resident Dendritic Cells (DCs) and regional lymph nodes. The crucial cytokines responsible for the allergic response include IL-4, IL-5 and IL-13, as well as Innate Lymphoid Cells (ILC-2) which may intensify and preserve local Th2-driven allergic inflammation. These interleukins switched immunoglobulin production by heavy chain gene rearrangement to class IgE in B cells [5].

## Allergy treatment and allergen immunotherapy

Primary and the best way to prevent allergy symptoms and is to avoid allergens as much as possible. This includes removing the source of allergens from your home and other places you spend time. There are many harmless prescription medicines to relieve allergy symptoms. Non-pharmacological treatment of these patients may cause allergy and manifestation of painful

problems such as sinus or ear infections. Some of the allergy medication includes nasal corticosteroids, antihistamines, mast cell stabilizers, corticosteroid and epinephrine.

The third treatment is the immunotherapy as an appropriate therapeutic strategy chosen for some allergy patients. The most common types of immunotherapy are allergy shots and Sublingual Immunotherapy (SLIT). Allergy shots involve giving injections of allergens in an increasing dose over time. The person becomes progressively less sensitive to that allergen. Allergy shots can work well for some people with allergies to pollen, pets, dust, bees or other stinging insects, as well as for asthma. Allergy shots do not usually work well for allergies to food, medicines, feathers or for hives or eczema. SLIT is another way to treat certain allergies without injections. Allergists give patients small doses of an allergen under the tongue. This exposure improves tolerance to the substance and reduces symptoms. SLIT is fairly safe and effective for the treatment of nasal allergies and asthma. SLIT tablets are currently available for dust mites, grass and ragweed. While allergy shots are fairly safe, there is a chance for a severe, life-threatening allergic reaction to the injections, so they must always be given in an allergist's office under observation from a medical professional [6].

### **Merits and demerits of immunotherapy and new strategies for treating allergic diseases**

When oral drugs and allergies are not able to control allergic reactions, allergy shot known as immunotherapy treatment may be the solution to this problem. There are many benefits to patients who get an allergy shot, include some people who do not tolerate oral medication. While the cost of allergy shots is more expensive than oral medications, ultimately, the longer the cost of this treatment is less than the anti-allergic drug and should be spent by these patients who do not choose this treatment. Oral allergy medications treat allergic symptoms, but allergy shots treat the cause of allergic reactions. When immunotherapy is successful, patients are recovered, because shots instead of symptoms cure the underlying causes of allergies, but like other types of medical treatments, the desensitization of allergy also has disadvantages. Some of the common disadvantages of this type of allergy include: Immunotherapy does not affect any type of allergy. Shots do not have a good effect on common allergies such as pet, pollen, dust. Shots are not effective in treating allergies to food and hives. In addition, allergy to insect bites or spider bites cannot be prevented by allergic shots. In some patients, the reactions are reddening, swelling and hypersensitivity of the place of the injection. Losing these opportunities can delay or eliminate the treatment of allergies. Allergy shots will make allergic symptoms worse when the infusion regimen starts. Since allergic shots rarely cause anaphylaxis, patients should wait 30 minutes at the treatment facility to reduce the risk of anaphylaxis.

One of the newest therapeutic approaches is allergenic changes that include the use of recombinant proteins, the combination of antigens with infectious carrier proteins, peptide immunotherapy and genetic vaccines containing code for allergic proteins, including these methods are oral and fecal

immunotherapy, intralymphatic immunotherapy and epicutaneous immunotherapy. The first priority in the treatment of allergic diseases is the therapeutic approach to immunotherapy and the reduction of the risk of side effects and in the second stage, the maintenance of the tolerance and recovery of the individual [7].

### **The effect of microbiota and development of the immune system on allergic diseases**

Reducing exposure to microorganisms in early life is one of the main mechanisms for increasing the prevalence of allergic diseases over the past few decades. Typically referred to as the "Health Hypothesis", which was originally used by Strachan. Today, reducing exposure to microorganisms (increasing allergic conditions) has been pointed out to factors such as diet, antibiotic use, vaccination, households and health improvements. The digestive microbiota provides a significant amount of microbial contamination for infant growth. So that there are more than 10<sup>15</sup> microorganisms which contain 1000 different species that are colonized in the gastrointestinal tract. Under normal conditions, these bacteria play a beneficial role in food digestion, development and growth of the immune system, control and growth of the intestinal epithelial cells and their differentiation. Commensal bacteria also play an important role in the fermentation of dietary fiber, in addition to essential vitamins, a significant amount of Short Chain Fatty Acids (SCFAs) are also released. The colonization of commensal bacteria occurs immediately after birth and during the first years of life. The gastrointestinal microbiota acquisition affects the type of parturition, maternal microbiota, as well as genetic factors, breastfeeding and other environmental factors.

One of the important functions of the intestinal microbiota is to contribute to the development of the immune system. The extensive antigenic stimulation after microbiota acquisition helps to organize the immune system through the development of Gut-Associated Lymphoid Tissue (GALT) and tolerogenic responses to harmless antigens, including food. These responses are performed by sampling and initial detection of antigens by intestinal epithelial cells and intrinsic immune cells through Pattern Recognition Receptors (PRRs). These receptors are bonded to Pathogen-Associated Molecular Patterns (PAMPs), expressed by microorganisms. PAMPs include lipoteichoic acid on gram-positive bacteria and lipopolysaccharide on gram-negative bacteria. Identification of PAMPs by PRRs such as Toll-Like Receptor (TLR)-2 and TLR4, triggers signals that determine the type of immune response, leads to the formation of a combination of regulatory and executive functions by DCs, Treg cells, chemokines and cytokines [8].

The study of Germ-Free (GF) mice confirmed the key role of microbiota and their antigens in the development of GALT and inadequate immune responses. Several studies have shown that GF mice have dramatically reduced the number of intra-epithelial lymphocytes, Peyer's patches with incomplete germinal centers and produce less IgA antibodies by plasma cells in the gastrointestinal lamina propria regions (which is actually the GALT executive region). Restoring different types of microbial species can help rebuild the GALT function in these mice, as

well as the development and growth of the immune system. Additionally, in GF mice, there is no tolerance to prescriptive antigens due to the deficiency of Treg cells. However, oral administration of microorganisms leads to stabilization of tolerance.

## DISCUSSION

### Probiotics

Probiotics are defined as live microorganisms that confer a health benefit on the host when administered in adequate amounts. The history of the use of probiotics with extensive access to them reflects the high degree of safety. These findings highlight the important role of microbiota in immune system developing and its potential role for immune disorders, such as allergies and autoimmune disease, resulting in intestinal dysbiosis. The identification and use of probiotics date back to the early 20<sup>th</sup> century. Generally, probiotic bacteria need to have a set of criteria for inducing their beneficial effects, include:

- Resistance to PH, bile and digestive enzymes.
- Preventing the binding of pathogens and oral antigens to epileptic cells.
- Increasing the probability of biological efficacy in humans.
- Direct effect on toxicity of bacteria, viruses, fungi and parasites.
- Proper tolerance and their importance in clinical use for their safety.

### Safety of probiotics

The human body is colonized (mainly gastrointestinal tract) by 10-100 trillion microbes, including bacteria, archaea, viruses and eukaryotic microbes. The indigenous intestinal microbiota is known to be a principal contributor in maintaining usual physiology, immune homeostasis and energy production during life. Protein products and metabolites of these microbes play an important role in the development and homeostasis of a number of body functions. The communication between these microorganisms and hosts has grown during the entire mammalian evolution, resulting in a distinctive gastrointestinal microbial community in humans. The microbial community remains stable over time, moreover, diet and other environmental factors can affect the microbial community. Commensal microorganisms, in addition to inhibiting invasion of other pathogenic microorganisms; donate fermentation of non-digestible fibers; help to absorption of minerals and produce vitamins, SCFAs and carbohydrates and also regulate inflammatory responses and the immune system. Defect to maintain of the balance among them (commensal microbiota and the host) interrupt the complex homeostasis (defined as dysbiosis) may cause a variety of syndromes (e.g. intestinal, metabolic and immune disorders) [9].

Probiotics are live microorganisms have been regarded as safe because of their long history of use in foods and dairy products for over a hundred years. Commonly probiotics are *Lactobacillus* and *Bifidobacterium*, some strains of *Enterococcus* and *Saccharomyces* species are generally. Because probiotics have been

shown to affect both the innate and adaptive immune systems, a theoretical concern about the potential of probiotics to stimulate the immune response in some individuals, possibly leading to autoimmune or inflammation has not been reported in any human subjects.

The gut acts as an extremely discerning barrier and communication organ between the luminal bacterial environment and the host. Therefore, failure of this communication due to the loss of barrier function or failure of tolerance mechanisms have been associated with diseases, usually as opportunistic infections in some predisposing patients and development of inflammation. In addition, the presence of transferable antibiotic resistance genes, which comprises a theoretical risk of transfer to a less harmless member of the gut microbial community, must also be considered.

Therefore, the safety of probiotics is related to the nature of the specific microbe proposed use, dose and duration. The overall probiotics when administered in adequate amounts consult a health benefit on the host. Agency for Healthcare Research and Quality (AHRQ) in support with National institutes of health and the FDA released report which analyzed 622 studies and clinical trials that used organisms from 6 species (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus* and *Bacillus*) and reveal no evidence of increased risk in these researches [10].

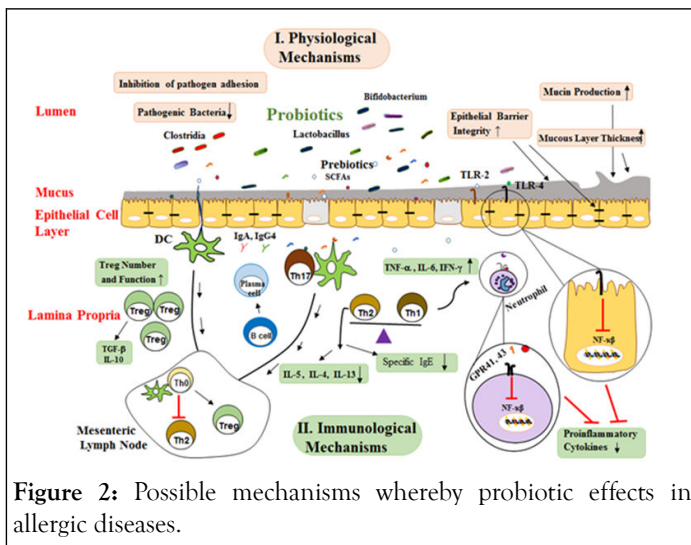
Overall, the evaluation of probiotics safety includes consideration of a variety of factors: Isolation history and taxonomic classification of the applicant probiotic; monitoring of contamination; lack of transferable antibiotic resistance genes; physiological status of the consuming population; dose and method administration (oral or otherwise); lack of allergenic material (for example, dairy proteins) for allergic populations.

### Functional mechanisms of probiotics

Probiotics cause beneficial effects in the host *via* several mechanisms, which are divided into physiological and immunological sections.

**Physiological functions:** Probiotics are capable of modulating the intestinal microbiota. In this regard, studies have shown that probiotic supplements, such as *Lactobacillus rhamnosus* GG (LGG) or *Lactobacillus casei* are capable of modulating the intestinal microbiota that involves the reduction of pathogenic bacteria, including cholesterol and on the other hand, an increase in the level of beneficial bifidobacteria in the neonate with allergies. These limiting physiological changes include the appropriate PH for the growth and reproduction of these pathological bacteria. Probiotics can also prevent invasion by competing with other microorganisms to bind to the host epithelial cells. Treatment with bifidobacteria and Lactobacilli in newborns results in modulation of the intestinal microbiota in early years of newborn life. It also stimulates the growth of other beneficial bacteria and their products in humans and other species. Modifying the colonization by probiotic bacteria can the prolonged presence of harmful pathogens in the intestine lumen and thus facilitate their clearing by the immune system. In

addition, some of these strains prevent the growth of bacterial pathogens by producing bacteriocin. For example, the bacteriocin produced by *Lactobacillus acidophilus* La-14 inhibits the growth of *Listeria monocytogenes* bacteria (Figure 2) [11].



**Figure 2:** Possible mechanisms whereby probiotic effects in allergic diseases.

These mechanisms generally divided into two groups of mechanisms of physiological and immunological mechanisms. SCFAs binding to various GPRs and TLR-2/TLR-4 activate several signaling pathways I. physiological mechanisms include: a) Probiotics create competitive conditions and inhibit bacterial adherence to mucosal layer, b) Enhancement epithelial barrier integrity and Improved barrier function c) Mucus production can also be increased by probiotics that stimulate goblet cells leading to activation of mucin gene expression and therefore altering colonization and persistence condition. II. Immunological mechanisms: a) Probiotics, directly and indirectly, affect the epithelial cells and modulate signaling pathways that lead to a reduced expression of inflammatory cytokines by suppressing NF- $\kappa$ B signaling, b) Primary mode of action of probiotics includes restoration of Th1/Th2 cytokine balance and enhancement of Th2 cytokines (IL-4, IL-5, IL-13), c) Probiotics with their products stimulate dendritic cells might be leading to Treg differentiation induction of CD4<sup>+</sup> Foxp3<sup>+</sup> Treg cells and production of TGF- $\beta$  and IL-10, d) Probiotics changes the cytokine profiles through effects on dendritic cells and so increase the production of secretory IgA and IgG4 by B cell and reduction in allergen-specific IgE by B cells.

Another of the probiotic functional mechanisms is their effect on epithelial barrier integrity and regulation of the expression of the proteins which involved in tight junctions and secretion of mucus. Treatment with *Streptococcus thermophilus* and *Lactobacillus acidophilus* increased transepithelial resistance as well as phosphorylation of proteins involved in cellular tight junction such as actinin and occludin. Probiotics also release a significant amount of SCFAs during the fermentation of food fibers and the induction of strong anti-inflammatory activity. Butyrate is one of these SCFAs that is involved in modulating the expression of tight junction proteins, including cingulin, Zo and occludin which improve the integrity of the epithelial barrier. Another SCFA is acetate, which has beneficial effects in animal models by reducing inflammation in asthma and colitis. Neutrophils interfere with their anti-inflammatory effects by

acting via G Protein-Coupled Receptors (GPR 41, 43) through which they can attach to SCFAs. These effects of SCFAs are accomplished by modulating the NF- $\kappa$ B signaling and the activity of their cytokines network. It also appears that SCFAs have the potential to inhibit histone-deacetylase and alter the structure and function of chromatin and so the downstream signal affects the gene expression.

**Immunological functions:** The activation of TLRs by microorganisms can lead to immune responses that have mucosal and systemic effects. *Lactobacillus* reduces pro-inflammatory responses by regulating NF- $\kappa$ B signaling. Probiotic bacteria also modulate the maturation of DCs towards anti-inflammatory cytokines such as IL-10. Although DCs derived from human monocytes treated with probiotics in culture can release IL-10 that cause differentiation and survival of Treg cells. B. animals and *B. longum* have been shown to induce the release of IFN- $\gamma$  and TNF- $\alpha$  by DCs, while only *B. bifidum* can activate Th17 cells through the release of IL-17. Sufficient evidence indicates that the Th1/Th2 balance modulates by probiotics, thereby preventing inflammatory diseases such as allergies. Peripheral Blood Mononuclear Cell (PBMCs) isolated from allergic patients *in vitro* with several lactic acid bacteria, including *L. plantarum*, *L. lactis*, *L. casei* and *Lactobacillus* GG, before induction with house dust mite, reduced the Th2 responses, which is characterized by reduction of IL-4 and IL-5 production. LGG and *B. lactis* reduce the allergic symptoms of asthma mouse models by inducing TGF- $\beta$  secreting.

## Probiotics function in allergic disorders

Other effects of probiotics that make them suitable for modulation of allergic diseases include stimulating the levels of mucosal IgA, as well as allergen-specific T cells and B cells. These interactions are very complex, including a network of genes, TLRs, signaling molecules and an increase in IgA intestinal responses. Many animal and *in vitro* studies, as well as several human experiments, show the positive effects of probiotics in allergic diseases. Several randomized studies showed that when *Lactobacillus* GG or placebo was given to pregnant mothers with a serious family history of eczema, allergic rhinitis or asthma and after to newborns during the first 6 months from delivery, the incidence of atopic dermatitis in children decreased by 50%, 44% and 36% in 2 years, 4 years and 7 years, respectively.

**Animal studies:** Studies on probiotic effects in allergic diseases in animal models have promising results. In the dermatologic atopic model induced by house dust mite and dinitrochlorobenzene, treatment with probiotic mixture *L. acidophilus*, *L. casei*, *L. reuteri*, *B. bifidum* and *Streptococcus thermophilus*, was associated with an increase in the number of CD4<sup>+</sup>FOXP3<sup>+</sup>Treg cells parallel with the regression of clinical symptoms, including the specific and total IgE level and the amount IL-4, IL-5, IL-13. In mouse Allergic Airway Disease (AAD), which is a human asthma model, the probiotic efficacy has been studied. Hougee et al. demonstrated that six probiotic strains, when administered to Ovalbumin (OVA), induced animal model of AAD lead to improvement of lung function and the number of eosinophils, specific IgE levels, IL-4, IL-5

and IL-10 in the Bronchoalveolar Lavage Fluid (BALF). Specifically, treating rats with *L. casei* and *L. plantarum* before sensitization with OVA prevented the development of Airway Hypersensitivity (AHR) and increased eosinophil count and total IgE levels. *L. reuteri* can significantly reduce AAD and eosinophilia of the respiratory tract, AHR and level of TNF- $\alpha$ , IL-5 and IL-13 in the BALF. It has also been shown that this bacterium can induce Treg CD4<sup>+</sup> CD25<sup>+</sup> FOXP3<sup>+</sup> cells in the spleen and prevent the development of AAD in OVA-sensitive mice.

In animal models, *L. lactis* and *L. plantarum* cause a shift in response to Th1 and reduce the clinical symptoms associated with allergic diseases. *B. bifidum* and *L. casei* reduces the incidence of OVA-induced allergy symptoms. LGG can reduce the expression of Metalloproteinase 9 (MP9) and cell infiltration and in combination with *L. gasseri*, *L. reuteri* and *L. salivarius* reduce the symptoms of allergy. Mixture of LGG with *B. lactis* induces Treg responses along with increased TGF- $\beta$  and lead to inhibition of allergic responses and decreased IgE levels.

*B. longum* and *L. casei* have a role in preventing Th2 responses and allergic diseases. *Streptococcus thermophilus*, *L. acidophilus*, *L. bulgaricus* and *B. Longum* cocktail had an anti-allergic effect which is manifested mainly by increasing the IFN- $\gamma$ /IL-4 ratio and lowering the serum IgE level. In the use of bacteria, *L. casei* Shirota results were variable and it was not found to be beneficial in BALB-c animal model, while in cases of C57BL6, there was a reduction of allergic disease symptoms. Simultaneous use of *B. animalis*, *B. brave*, *L. helveticus* and *L. paracasei* improves allergic responses and alleviates the clinical symptoms of allergic disease [72, 83-85]. *B. infantis* and *L. rhamnosus* also reduce the level of eosinophil and specific IgE antibodies leading to an anti-allergic effect. Also, by increasing the level of IFN- $\gamma$ , it reduces the symptoms of the disease and, by increasing Treg cells, reduces allergic asthma in the BALB-c model.

**Human studies:** Early study demonstrates that administration for 8 weeks of LGG, *Bifidobacterium lactis* Bb12, or *B. breve* M-16V strains lead to improvement of eczema symptoms in infants and children compared to control group. In spite of the studies that were later carried out in this field, the results were poor in patients with eczema. Viljanen in 2005 and Sistek in 2006 studies showed that LGG, *L. rhamnosus* and *B. lactis* had a better scorad in children with atopic dermatitis. Viljanen et al, observe that LGG decrease the IL-6 and C-reactive protein and thereby inflammation. On the other hand, stimulate IL-10 and IgA production which indicates the beginning of repressive responses. The complementary formulation containing *L. acidophilus*, *B. lactis* and Fructooligosaccharides (FOS) after 8 weeks of treatment significantly reduced scorad as compared to the control. Wu et al. demonstrated that treatment of children with *L. casei* for 12 weeks significant decreased scorad scar as compared to placebo. In 2012, Yesilova studied the effect of *B. bifidum*, *L. acidophilus*, *L. casei*, and *L. salivarius* combination for 8 weeks in 1-3 years aged children with eczema. It was observed a decrease in scorad and IL-5, IL-6, IFN- $\gamma$  and IgE total compared to the control group. Although the use of a combination of probiotics, prebiotics and synbiotics, including

*B. breve* M-16 and a mixture of galacto-fructooligosaccharides, was not able to improve the severity of eczema and reduce scorad. In Toh et al. study in children with moderate to severe eczema, the use of the combination of *L. salivarius* and FOS for 8 weeks resulted in a significant reduction in scorad severity compared to FOS alone. In another similar adult study, treatment with *L. salivarius* for 16 months significantly decreased with scorad in comparison with the control group, as well as decreased the level of IFN- $\gamma$ , IL-2 and Th1/Th2 cytokines.

Preventing allergies is one of the major clinical challenges. While there is a lack of evidence, there is a great gap in the use of probiotics in the treatment of allergic diseases. Several Randomized Clinical Trials (RCTs) have been conducted to evaluate the effects of various probiotic strains in children and adults with a history of allergic diseases. The duration of treatment with probiotics seems to be one of the key factors determining their beneficial effects [12].

Among the human studies conducted between 2014 and 2018, strains that can affect AD (Atopic Dermatitis) could be *L. acidophilus*, LGG, *B. animalis*, *L. paracasei*, *L. fermentum* and *L. plantarum*. The combination was generally accompanied by suppressing Th2 responses and improving AD clinical symptoms. In the Cows' Milk Allergy (CMA) studies, the use of LGG, which caused butyrate production, increased the induction of tolerance in CMA children, but no significant effect was observed in the presence of *B. lactis* Bb-12 and *L. casei* on CMA. The improvement of AR symptoms was reported for several strains such as LGG, *L. reuteri*, *L. casei*, *L. salivarius*, *B. Longum*, *B. infantis*, *B. breve*, *B. gasseri*, *B. bifidum* G9-1 and *Lactococcus lactis*, all of which were effective in reducing clinical symptoms. In patients with asthma, the effect of *L. acidophilus*, *L. reuteri*, and *Clostridium butyrate* were evaluated. The *L. reuteri* increased IL-10 and decreased inflammation, leading to symptom improvement in these patients. Probiotics used to prevent and treat allergic diseases in human studies.

## CONCLUSION

Currently, prevention and treatment of allergic diseases are one of the major clinical challenges. The rapid rise in immune system disorders, such as allergic disease, is strongly associated with reduced exposure to early microorganisms. Intestinal microbiota partially stimulates the immune system and the particular composition of the microbiota of the intestine may affect the risk of allergic disease. Therefore, these findings suggest a therapeutic approach for probiotics and prebiotics used in allergic diseases. Probiotics are selectively stimulating a number of beneficial bacteria that are evaluated in allergy treatment studies. In general, probiotics use major mechanisms to improve clinical symptoms in patients with allergic diseases and prevent them, includes (1) suppression of Th2 responses and shift response to Th1 (2) butyrate production and increased induction of tolerance (3) increase of IL-10 and decreased inflammation (4) decreased eosinophil level and serum specific IgE levels (5) increasing the IFN- $\gamma$ /IL-4 ratio (6) increasing Treg cells and inducing their responses (7) increasing TGF- $\beta$  responses and inhibiting allergic responses; and (8) reducing the expression of metalloproteinase 9 and cell infiltration. Finally, it

can be said that the therapeutic approach to immunotherapy and the reduction of the risk of side effects in the treatment of allergic diseases is the first priority of treatment. And the final approach that completes the first priority is maintaining the condition and sustainability of the tolerance along with the recovery of the individual.

## ACKNOWLEDGMENT

Department of immunology, Semnan university of medical sciences, Semnan, Iran and cancer research center, Semnan university of medical sciences, Semnan, Iran.

## CONFLICT OF INTEREST

None to declare.

## FUNDING ACKNOWLEDGEMENT

This research is not supported by a specific project grant.

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