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## REVIEW

### Probiotics in allergy treatment: a literature review

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#### Probiotics in allergy treatment: a literature review

#### KEYWORDS

Probiotics;  
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Rhinitis, Allergic;  
Dermatitis, Atopic;  
Food Hypersensitivity;  
Gastrointestinal  
Microbiome.

#### ABSTRACT

Allergy is an exacerbate response of immune system to a triggering element. A probable cause of allergies is gut microbiota composition. It has strong relationship with development of human immune system and this is formed in intrauterine life and early childhood, crucial periods for formation adequate microbiota. In this sense modulation gut microbiota by probiotics could prevent or help in the treatment of allergic diseases such as allergic rhinitis, asthma, atopic dermatitis and food allergy. Studies published to date are controversial. It is difficult to determine whether the probiotic can be used in the treatment and prevention of allergic diseases.

## Probióticos en el tratamiento de alergias: una revisión

### PALABRAS CLAVE

Probióticos;  
Asma;  
Rinitis Alérgica;  
Dermatitis Atópica;  
Hipersensibilidad a los Alimentos;  
Microbioma Gastrointestinal.

### RESUMEN

La alergia es una respuesta exacerbada del sistema inmunitario a un elemento desencadenante. Una probable causa de las alergias es la composición del microbioma intestinal. Tiene una fuerte relación con el desarrollo del sistema inmunitario humano y se forma en la vida intrauterina y en la primera infancia, períodos cruciales para la formación de la microbiota adecuada. En este sentido, la modulación de la microbiota intestinal por los probióticos podría prevenir o ayudar en el tratamiento de enfermedades alérgicas como la rinitis alérgica, el asma, la dermatitis atópica y la alergia alimentaria. Los estudios publicados hasta la fecha son controvertidos. Es difícil determinar si los probióticos pueden usarse en el tratamiento y prevención de enfermedades alérgicas.

### CITA

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## INTRODUCTION

Allergy is a hypersensitivity reaction initiated by immunological mechanisms. It can be mediated by antibodies or cells<sup>1</sup>. Prevalence of allergy is increasing worldwide<sup>2</sup> such as atopic dermatitis, food allergies, allergic rhinitis and asthma, and childhood is the phase of the beginning<sup>3</sup>. The allergic phenotype is due to the combination of two elements: genetic predisposition and environmental factors interacting with genes<sup>4</sup>.

Hygiene hypothesis may be possible explanation for the increased diagnosis of allergies. It is believed that the increase in care of cleaning and hygiene, reducing the number of family members and reduction of childhood infections decrease bacterial exposure, which is crucial for the development of the immune system in early life<sup>5</sup>. The lack of contact with bacteria in childhood means that there is absence in the conversion of T help 1 (Th1) to Th2, thereby making the individual more susceptible to allergy<sup>6</sup>.

Recently it has been proposed that bacteria habiting the human body, in particular gut microbiota, is associated

with the allergic process by possessing an important role in the construction of the mucosal immune tolerance<sup>7</sup>. Recent evidence shows that the colonization of microbiota occurs during pregnancy at intrauterine life, through contact of maternal microbiota with the fetus through the placenta and amniotic fluid<sup>8</sup>.

Some points are critical in the formation of microbiota and, hence the immune system, such as type of delivery and lactation. Vaginal birth allows the baby have to contact with maternal microbiota<sup>8,9</sup>. In addition breastfeeding plays a key role in the development of newborn microbiota. Studies show that children breastfed contain higher amounts of bifidobacteria in the microflora<sup>8</sup>. Childhood period is where gastrointestinal tract (GIT) undergoes greater influence of environmental factor and it is completely established between 2 and 3 years of age. For this reason, this stage of life is crucial for the proper development of the immune system<sup>10</sup>.

The formation of microbiota is important in development of host defenses against gastrointestinal infections and allergic reactions. Bacteria interact with cells of immune system helping the maturation of these<sup>11</sup>. A study compared the development of immune system in germ-free mice,

which have not microbiota, and conventional mice. Authors found immune system undeveloped in germ-free mice, with reduction of intra epithelial lymphocyte number and small size of Peyer's patches, change in the structure of the crypts and reducing the thickness of the mucus<sup>12</sup>.

Probiotics are live microorganisms able to improve the microbial balance producing beneficial health effects of the individual<sup>13</sup>. Probiotics have revealed adjuvant effects on immune response<sup>12</sup>. They can modulate the gastrointestinal physiology of the host by improving mucosal immunity and intestinal permeability<sup>14</sup>. Thus, the stimulation and maintenance of normal microbiota can increase the beneficial bacterial population, resulting in health of GIT with regular consumption of probiotic bacteria<sup>15</sup>.

The objective of this study was to evaluate the use of probiotics on prevention and treatment of allergic diseases as atopic dermatitis, allergic rhinitis and asthma, and food allergy.

### ALLERGIES: ASTHMA, ALLERGIC RHINITIS, ATOPIC DERMATITIS AND FOOD ALLERGY

Allergy is characterized by increased capacity of B lymphocytes producing immunoglobulin E (IgE) against antigens that enter the body via the airways, skin or GIT. Among allergic diseases can be mentioned atopic dermatitis, asthma, allergic rhinitis and food allergy<sup>1</sup>.

Asthma is a chronic inflammation of the lower airways coming from eosinophils and hyperresponsiveness. It is characterized by coughing, wheezing and dyspnea. This disease is triggered when individual is exposed to elements that initiate inflammation in bronchi, limiting the flow of air in the lungs. Diagnosis is based on history of a disease, clinical examination, pulmonary function and allergy evaluation<sup>16</sup>. Treatment is indicated to prevent and reduce contact allergenic elements; moreover, some drugs can be used, as such:  $\beta$ 2-adrenergic, theophylline, anticholinergics, and corticosteroids.

Allergic rhinitis is a chronic symptomatic nasal disorder triggered by exposure to allergies such as dust, cold air, smoke, odors and pollutants which cause IgE-mediated inflammation in the nasal mucosa. Diagnosis is made by clinical and family history of atopy and, physical and laboratory tests. Treatment of disease can be divided into non-drug and drug. The first include control of allergenic components, reducing objects that may favor the accumulation of dust, such as carpets, curtains, etc.,

avoid the animals and feathers, keep always clean and airy environment. The second is the use of drugs such as antihistamines that inhibits the main allergy mediator; decongestants, promote vasodilation; corticosteroids, control protein synthesis, reducing production of inflammatory mediators<sup>17</sup>.

Atopic dermatitis, also called of atopic eczema, is a chronic disease with clinical manifestations cutaneous. It is originated from the genetic predisposition of the immune system to emphasize IgE-mediated hypersensitivity in response to allergic food and environment. Diagnosis is made by the clinical picture of the disease<sup>18</sup>. Drugs can be used, such as topical steroids, which have anti-inflammatory effect by inhibiting the action of dendritic cells (DC) and lymphocytes; immunomodulators or topical calcineurin inhibitors, which reduce inflammation; systemic immunosuppression indicated for severe cases that do not respond to previous treatments<sup>19</sup>.

Food allergy occurs when an abnormal response is given to food or food additive exposure<sup>20,21</sup>. It may be toxic, which depends on the ingested food or non-toxic dependent on individual predisposition, being or not immune mediated<sup>21</sup>. Diagnosis is made by medical history of the individual and it may be supplemented by laboratory tests, such as determination of specific IgE. Skin tests of immediate hypersensitivity and oral trigger, which is the reliable test to diagnose food allergy. This test consists of exposing the individual to food that is likely to have allergies. Treatment is based on combination of exclusion of food that causes the allergy and drugs that treat allergy symptoms. Among the drugs may be mentioned self-injectable adrenaline, may be used in case of accidental ingestion of food to which it is allergic, when associated anaphylaxis; antihistamines for relief of symptoms of oral allergy syndrome and cutaneous symptoms mediated by IgE; systemic corticosteroids, which triggered reverse the inflammatory symptoms<sup>20,21</sup>.

### MICROBIOTA AND IMMUNE SYSTEM

GIT is composed by microorganisms forming microbiota, which has role in various metabolic activities of host. Microbiota may to help absorption of nutrients, fermentation food, stimulation of the host immune system and protection against pathogens<sup>22</sup>.

The colonization of the host begins in intrauterine life through of maternal microbiota contact by placenta and amniotic fluid with fetus<sup>8</sup>. Some points are crucial for colonization with beneficial bacteria, among which can

be highlighted childbirth and lactation. Vaginally delivery exposes children to bacteria maternal microbiota<sup>8,9</sup>. Breastfeeding promotes colonization of the infant microbiota with bifidobacteria<sup>8</sup>. A study that compared microbiota composition of breastfed babies and those fed with infant formula found that breastfed had greater variety of Bifidobacterium in the composition of their gut microbiota<sup>23</sup>. Two-three years old is essential to microbiota because in this period microbiota suffers a major impact of environmental factors<sup>24</sup>.

The colonization of gut microbiota is essential for proper development of innate and adaptive immune system. It has been found that the colonization of microbiota is critical to the maturation of Th1 and regulatory T (Treg) during childhood<sup>25</sup>, and assist in the development of gut associated lymphoid tissue (GALT) and IgA production<sup>26</sup>. Studies in animal models comparing immune system of germ-free rats and conventional showed that the germ-free has major defects in the immune system with Peyer's patches in quantity and reduced size and fewer lymph nodes centers in the mesentery<sup>12</sup>. Another experimental study on germ-free mice noted that microbiota is important to develop GALT and function of epithelial barrier<sup>27</sup>. Studies were performed in which colonization by bacteria in gut of germ-free rats found restoration of the immune system in this animals<sup>28</sup>.

Immune system is developed with gut microbiota to ensure homeostasis and symbiosis. When commensal and pathogenic bacteria are in balance, there is a constant stimulus in secretion defense mediators by gut epithelial cells such as  $3\gamma$  protein derived islet for regeneration (REGIII $\gamma$ ), lymphopoietin thymic stromal (TSLP), interleukin 33 (IL-33), IL-25 and tumor growth factor- $\beta$  (TGF- $\beta$ ), which are responsible for the tolerability of macrophages and DC<sup>28,29</sup>. DC stimulates the formation of Treg cells by TGF- $\beta$  and retinoic acid, which associated with macrophages and DC are capable of generating an anti-inflammatory environment in the gut lumen<sup>29</sup>. Moreover, there is IgA production by TGF- $\beta$  to cell activation<sup>30</sup>.

In the dysbiosis, which there is an imbalance between commensal and pathogenic bacteria, creating an inflammatory environment, the molecular pattern associated with microbes is increasing, and this stimulates gut epithelial cells differently, activating DC, macrophages and secrete inflammatory cytokines. This latter stimulate Th1 and Th17 culminating in chronic inflammation. Th17 together with the innate immune system cells producing IL-22, which promotes the expression of REGIII $\gamma$  and REGIII $\beta$ , thus interfering in the intestinal microbiota<sup>31</sup>.

In this feeling composition of microbiota plays an important role in allergy development. A systematic review evaluated

the composition of microbiota associated with allergic processes, and identified difference between children with or without allergy. They noted that children with allergy had lower biodiversity in microbiota composition<sup>32</sup>.

## PROBIOTICS AND IMMUNE SYSTEM

Probiotics could be from human origin and undergo a selection considering the following criteria: gender (source, definition, characterization and safe species), stability and security (activity and viability in products; adherence; have resistance to low pH and gastric juices, bile and pancreatic; and colonizing ability) and functional and physiological aspects (adhesion to intestinal epithelium, antagonism to pathogens, stimulation or suppression of immune response and stimulating beneficial bacteria)<sup>33</sup>.

Probiotics have the ability to modulate the digestive physiology of the host, altering mucosal immunity and gut permeability<sup>14</sup>. Thus, it has been studied how to maintain a healthy microbiota to obtain benefits to the host. Furthermore, the daily consumption of probiotic favors the growth of commensal bacteria, thereby reducing pathogens, resulting in health GIT<sup>15</sup>.

The positive effects that these bacteria have on the GIT microbiota occur through antagonistic effects of competition and immunological favoring the gut commensal bacteria, intensified, so natural defenses of host. These effects occur through three possible mechanisms. The first is by deletion of viable cells by competition of nutrients, adhesion cells, production of antimicrobial substances lactic acid, which is able to reduce the intestinal pH, preventing growth of bacteria sensitive to acidic environments, which most often are pathogenic. Since the antibacterial substances kill pathogenic bacteria affecting essential enzymes or cell membrane. In the second microbial metabolism is altered, increasing or decreasing enzyme activity. The third through stimulating host immunity with increased circulating antibodies and macrophage activity<sup>34</sup>.

Compounds of cell wall, DNA and metabolites of probiotics may manipulate the immune system because the host enterocytes have receptors that recognize these bacteria, which bind triggering a signaling cascade and modulating the immune function of the individual. The probiotics modulate immunity through the induction of proinflammatory cytokines and increased production of secretory<sup>35</sup>.

*In vitro* studies show the effects of probiotic exerted on the immune system of the host. These bacteria have the ability to stimulate specific and nonspecific immune response by activation of macrophages and increase of cytokines, natural killer cells, IgA and T lymphocytes<sup>35</sup>. Braat *et al.*<sup>36</sup> observed that supplementation of *Lactobacillus rhamnosus* for 2 weeks is capable of modulating T cell responsiveness *in vivo* and found that the probiotic was able to modulate DC inducing T cell hyporesponsiveness.

Humans and animals studies have showed probable mechanisms of probiotics in modulation of immune system of the host. They act repairing and maintaining the mucosal barrier, which reduces gut permeability; increases TGF- $\beta$  and prostaglandin E2 production in enterocytes, thereby reducing translocation of allergy, enhancing local inflammation and promote tolerance; anti-inflammatory effect through toll-like receptor 9 by inhibiting Th2-type allergic response; DC increased activity in the intestine, which leads to tolerance of these cells; increase in Th1 response with consequent reduction in differentiation of Th2 response; IL-10 production and TGF- $\beta$  to enhance oral tolerance via DCs, IgA and Treg; increase in lymphoid tissue that generates tolerogenic effect; increase in Th1 differentiation and IgA production in other tissues due to effects of GIT T and B cells, respectively<sup>37</sup>.

## PROBIOTICS IN RESPIRATORY ALLERGIES

A systematic review evaluated randomized controlled trials testing use of probiotics on allergic respiratory diseases such as asthma and allergic rhinitis, and found that most studies indicated beneficial effects of probiotics in treatment of rhinitis and reduced severity of symptoms, thereby reducing the use of medications<sup>38</sup>. However they do not define possible probiotics strains and doses benefices. On the other hand, a meta-analysis including studies with intervention of probiotic in asthma and rhinitis allergic did not observe beneficial effect of probiotic on these diseases<sup>39</sup>.

A double blind randomized controlled study administered  $10^8$  CFU of *L. reuteri* in women during pregnancy and their children from birth until 12 months old and accompanied the children until seven years old. There was not reduction in the prevalence of respiratory allergy in preschool period<sup>40</sup>.

A recent meta-analysis evaluated whether probiotics can prevent and treat allergic rhinitis. There is not claim that probiotics should be used in the treatment and prevention of disease, although having showed improve overall in

symptoms<sup>41</sup>. Another meta-analysis did not show beneficial effect on prevention of the development of asthma in children after use of probiotic during pregnancy and early life<sup>42</sup>.

## PROBIOTICS IN ATOPIC DERMATITIS

The literature shows the probiotic as potential effects preventive of atopic dermatitis. Two meta-analysis indicated the use of probiotic as important role in prevention of atopic dermatitis<sup>43,44</sup>. Its use can be in intrauterine life or after birth, including population general and that in risk of allergic<sup>44</sup>.

On the other hand, another study this type showed improves on atopic dermatitis in children and adults individual. The authors suggested the use of probiotic in treatment of this allergy<sup>45</sup>. This contradictory result when comparing with meta-analysis cited before could be the population of study.

A randomized clinical trial administered fermented milk containing  $3 \times 10^9$  CFU of *L. acidophilus* L-92 in children 4-15 years old for 8 weeks. They observed that the probiotic had potential to improve symptoms in atopic dermatitis<sup>46</sup>. Han *et al.*<sup>47</sup> showed effect on treatment of atopic dermatitis in children (18 months-13 years old) when used  $0.5 \times 10^{10}$  CFU *L. plantarum* CJLP133 twice a day during 12 weeks. Another clinical trial with children aged 1-13 years old consuming a mix of probiotic (*Bifidobacterium bifidum*, *L. acidophilus*, *L. casei*, and *L. salivarius*) by 8 weeks found improves in SCORAD index for this disease and any cytokines and IgE<sup>48</sup>.

## PROBIOTICS IN FOOD ALLERGY

There are not many studies conducted in humans to evaluate the effects of different probiotic strains on signs and symptoms allergic to certain foods, which makes it more difficult to determine whether the use of probiotics could help in treatment of this allergy.

A recent meta-analysis assessed whether probiotics can prevent the development of food allergies in children, but could not determine if probiotics are beneficial in this regard<sup>49</sup>. A recent randomized controlled trial evaluated the use of probiotic *L. rhamnosus* CGMCC 13724 ( $2 \times 10^{10}$  CFU) as adjuncts in the treatment of oral immunotherapy in children with peanut allergy and found that there was no allergic response to food<sup>50</sup>.

A randomized clinical trial conducted with children between 3 and 12 months old administered  $1 \times 10^9$  CFU *B. animalis* subsp. *lactis* BB-12 and  $1 \times 10^8$  CFU *Streptococcus thermophilus* TH-4 for a period of 8 weeks and evaluated its effects on gastrointestinal symptoms of allergy to cow's milk. They found that the group receiving the probiotic associated with conventional treatment for allergy to cow's milk had improved gastrointestinal symptoms and lower gastrointestinal clinical manifestations resulting from allergy to milk<sup>51</sup>.

## CONCLUSIONS

Studies have showed conflicting results, which may be due to different methods, doses and strains used in the work, hindering the determination of strain and the quantity that could assist in the treatment and prevention of allergic diseases. However, probiotics seem to have promising effects in supporting of treatment and prevention of allergic diseases, principally respiratory allergies and atopic dermatitis. Well-conducted studies evaluating the use of probiotics in children with allergies should be performed to find out the strains that can be used to treat this disease.

## AUTHORS' CONTRIBUTIONS

LC searched of database and wrote the manuscript. DCG and ELT revised of manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

Authors state that there are no conflicts of interest in preparing the manuscript.

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