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# Immuno-Modulatory Effect Of Probiotics In Allergic Diseases

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***Abstract:*** *Prevalence of allergic diseases tends to increase in global population over the past decade in many countries of the world. Loss of microbial load in gut (gastro-intestine) might involve in the progress of various allergic disorders. Presence of probiotics in the intestinal flora prevents the occurrence of undesirable allergic reaction in the host immune system. In particular with allergy, probiotics seems to show positive effect in reducing Th2 cytokine profile as well as promotion of Th1 cells and Treg differentiation. Probiotics enhances the restoration of microbial in the gut, modulating the immune system by their metabolites which fetch in decline of allergic condition. The focus of this review is on highlighting the powerful effects of this treatment for managing, preventing, and treating allergic diseases.*
***Keywords:*** *allergy, immunomodulation, Th1-Th2 cytokine, probiotics, immune-regulation*

## INTRODUCTION

Allergic diseases are caused mainly due to IgE dependent mediated immune reaction, referred as immediate or type I hypersensitivity, which accounts for 20% of the world's population. The body has its own ways to fight against the allergens but in quite a time it was discovered that good bacteria (probiotics) can also be used to enhance the immune system. Probiotics show anti- allergic reactions by modulating different T- helper cells like $T_h1$, $T_h2$ $T_h3$, Tr) and different cytokines related to the T- helper cells. The probiotics is responsible to shift to a defensive immune response against the allergens. Gram positive bacteria like LAB showed $T_h1$ and $T_h2$ cytokines release whereas Gram negative bacteria showed no much effect on the allergens (Ghadimi et al.,2008). Basic allergic reactions include the mast cells and basophils which releases the cytoplasmic granules containing histamine (White, 1990). Histamine is a key part of mast cells and plays an important role in activating various inflammatory cytokines, leading to allergies and inflammation. It works through four histamine receptors: H1R, H2R, H3R, and H4R. H1R and H4R are especially involved in allergic responses and inflammation (Thangam et al., 2018). Probiotics are live microorganisms that benefit the host and help avoid complications from various diseases (Butel et al., 2014). Probiotics can be given as supplements or through foods that have been tested in controlled trials for preventing allergic diseases. When administered in the right amounts, these probiotics can offer health benefits to the host (Mao et al., 2020). Probiotics regulate several functions, including digestion, metabolism, immune response, blocking pathogens, and communication between the brain and gut. They can also transform different chemical compounds into simpler nutrients like cellulose, hemi-cellulose, pectin, and lignin, turning them into simple sugars that create short-chain fatty acids (like acetate, butyrate, and propionate). These fatty acids are important for maintaining mucosal immune function and are beneficial for clinical and nutritional applications. Probiotics demonstrate humoral, cellular, and non-specific immunomodulatory effects. They can reduce pro-inflammatory cytokine production in the intestines and help manage conditions like irritable bowel syndrome (IBS), colitis, allergic diseases, Type 2 diabetes, and cancer (Markowiak-Kope´c et al., 2020; Hajavi et al., 2019; Azad et al., 2018). A key benefit of probiotics is their ability to interact with the host immune system and alter immune responses during infections and allergic conditions. While they are valuable in preventing many health issues, their overall influence on the immune system is still not completely understood (Yang et al., 2013).

## MATERIALS AND METHODS

PubMed database was carried out for search without limiting the publication time period. The keyword such as "probiotics" in combination with "in allergy", "in cytokine balance in allergic disease", "in immunoregulation", "in clinical trials" were used to collect the data.

## MICROBIOTA IN THE HOST

In the world of all diseases, there are microbes which are beneficial to the host. These beneficial microbes

live in the host itself, some from the birth and some are gradually adapted and incorporated in the host system. The term "probiotics" comes from Greek and means "for life." In simple terms, probiotics are live microorganisms, like bacteria or yeast, that offer health benefits and are often called "good" bacteria. Recently, the most common definition is "probiotics are live microbial feed supplements that positively affect the host animal by improving microbial balance" (Fuller, 1991).Most of them are involved in digestion and some of them are to be participated in the defence mechanism. The term “normal microbiota” mostly refers to the microbes that are on the surface of the skin, deep skin tissue, the oral cavity and the gastro- intestinal tracts.

Some of the common places where we can locate them in a huge concentration are skin, mouth, nose, eyes, respiratory tract, stomach, small intestine, vagina, throat, and urethra.The parts which are exposed to the surrounding are more susceptible to the bacterial from the environment. Each individual has a unique composition of microbiome in their body depending on their habitat, diet and lifestyle (Davenport et al., 2017).

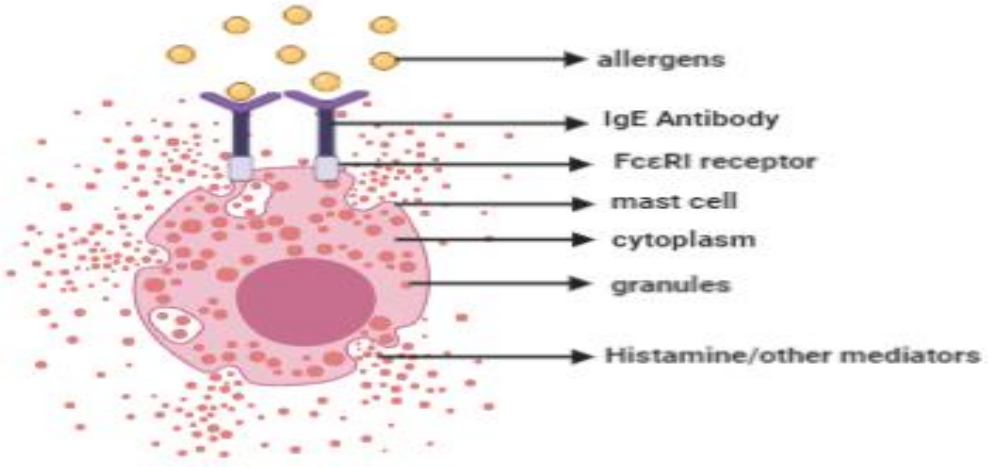
The final function of these beneficial bacteria in the host is to regulate the passage of pathogenic bacteria to get into the host. The microbes in the mucosal layer secrete mucus to form a barrier between the host and the microbes (Y. Belkaid & O.J. Harrison., 2017), which also inhibit some allergies that include the gut immune system. They also communicate with the body's immune system, assist in triggering the cellular processes and leads to creation of various metabolites and constituents.

These beneficial bacteria assist in digestion and supply energy by decomposing the food, solubilizing in giant fatty chains and carbon chains which may be resistant to the host equipment (Nishida et al., 2017). Throughout any allergic reactions, pathogenic invasion or trauma, it regulates the inflammation by keeping the Th1 and Th2 in balance. A number of studies assert that probiotics exhibit anti-inflammatory and anti-allergic activities in in-vitro and in-vivo models by supporting the differentiation of T regulatory cell development that balances Th1-Th2 responses (Mao et al., 2020).

## IMMUNOLOGY OF ALLERGY

Allergic responses are characterized mainly by allergen-specific IgE and Th-2 (T-helper-2) cells that recognize the allergen-derived antigen in the host. Allergens are of two types - the first type involves the non-infectious agent such as environmental substances like dust, mite, animal dander, food products (milk, egg, tree, nuts, shellfish) and venoms of insects and reptiles, which are IgEdependent. Second types of allergens are independent of IgE which are caused by non-infectious substance that promotes the local inflammation induced by the adaptive immune response (Galli et al., 2008)**.** Cascade of allergic reaction is initiated by uptake of allergen by Antigen Presenting Cells (APC) that are present selective peptides on the surface of MHC-II molecules to T-cells thus favoring Th-2 cell response (S.T. Holgate & R. Polosa, 2008)**.**

**Figure 1:** Immunology of Allergy




### Initial Phase Reactions

Development of sensitization phase includes processing of antigen by Antigen Presenting Cells (APC) followed by Th2 production in the presence of IL-4 or IL-13 and induction of IgE switching by B and T

cell interaction. Within few minutes of allergic contact, Crosslinking of IgE antibody takes place on the surface of mast cells and basophils via FcεRI, resulting in the degranulation of cellular contents (Velez et al., 2019). Inflammatory mediators like histamine, cysteinyl leukotrienes (S.T. Holgate, R. Polosa , 2008).and other lipid mediators also trigger the release of various cytokines and chemokines that recruit macrophages, eosinophils and neutrophils to the site of inflammation (S.T. Holgate & R. Polosa , 2008).. Thus, sequentially promotes various factorial events like vasodilation, bronchoconstriction of blood vessels, mucous secretion in respiratory tract and upregulation of vascular adhesion molecules.

**Late Phase Reactions**

When allergens are consistently present, they trigger the release of inflammatory cytokines and activate Th-2 cells. This process results in symptoms such as swelling, pain, redness, and increased sensitivity of the airways. Mast cells release substances that attract immune cells to produce inflammatory cytokines like TNF-α, IL-6, and IL-1β, depending on how long the signaling factors remain active (Galli et al., 2005; Galli et al., 2008). However, there is a counteracting mechanism involving anti-inflammatory responses, including the production of IL-10 and Transforming Growth Factor-β (TGF-β), which helps balance inflammation and promotes immune suppression (Sayed et al., 2008). The late phase reaction lasts from 2 to 6 hours after allergen exposure, peaking between 6 and 9 hours. For example, in human skin allergic reactions, Th-2 cells are recruited first during this late phase, followed by Th-1 cells. This shift alters the cytokine environment, leading to an increase in eosinophils and monocytes, and a decrease in basophils and neutrophils (S. Bonness & T. Bieber, 2007).

Role of Probiotics in Restoration of Th1/Th2 Cytokine Balance

Regulation of Th1/Th2 cytokine-based immunity found to have progressive mode of immune-regulation by probiotics in various allergic disorders. Immuno-modulation activities of probiotics were multilateral and each type of probiotics present in the host tends to affect the immune system in their unique aspect (Hajavi et al., 2018). In allergic disorders, an imbalance in Th1/Th2 cytokines is observed, in which Th2 cytokines activation takes place due to a shift in equilibrium of Th1/Th2 cells. Upon the activation of Th2, release of IL-4, IL-5 and IL-13 in turn triggers inflammatory response in the host and production of IgE antibody as well.

Modulation of Toll-like receptors and proteoglycan recognition surfaces are potentially modified by probiotics leading to the activation of dendritic cells and Th1 response, which results the elevation of Th1 cytokines mediated immune response and suppression of Th2 response, indicating that allergic response is inhibited (Michail S. et al., 2009). Hirotsugu Morita et al showed that administration of Lactobacillus gasseriin subjects with high level of IgE and perennial allergic rhinitis tend to show reduction in IgE levels and enhancement in the production of Th1 immune response thus altering Th1/Th2 balance in the host (Morita et al., 2006). Administration of probiotics such as L. casei, L. reuter, L. acidophilus, Streptococcus thermophiles, and B. bifidiumin combination form tends to reduce the production, stimulation and proliferation of B-cells and T-cells, altering the profiling in cytokine levels of Th1, Th2 and Th17 cells. They also contribute to the regulation of T-regulatory cytokine that maintains the immune response in homeostasis (Michail S. et al., 2009). Experimental studies using lactobacilli and bifidobacterium demonstrated the modulation in production of cytokines by monocytes and lymphocytes via upregulation of IL-10 and down regulation of pro-inflammatory cytokines such as IL-12p70 and TNF-alpha. On the other hand, Th2 cytokine production was decreased on treatment with these probiotics, proving that it can alter immune system in a regulated or tolerant manner (Niers et al., 2005). Many studies reveal the probiotic treatment in atopic children shows the regulation in Th1 response and alteration towards suppression of Th2 cytokine profile as well as production of allergen specific IgE(Michail S. et al., 2009).

**Immunomodulation - Stimulatory and Regulatory Effects of Probiotics in Allergy**

Immunomodulatory activity of probiotics plays a vital role in promoting health benefits in treating various diseases like neurodegenerative disorders, autoimmune disease, allergic and pathogenic infectious disease. Many studies reported the basic mechanism of probiotics such as include enhancing the production of IgA, cytokine balance, production of anti-microbial substances against pathogenic micro-organisms and build-up of tight junction in intestinal barrier as a protective mechanism towards pathogenic bacterial entry to regulate intestinal health. Probiotics involved in immune regulation perform two types of functions-immunostimulation and immunoregulation. They play an immunisitic mechanism such that alteration in the release and suppression of cytokines and chemokines take place. Immunostimulatory activity refers to induction of Th1 cells production (Azad et al., 2018), thereby aids in the release of pro-

inflammatory cytokines such as IL-6, TNF-alpha, IL-12 which act against infection and cancer (Chiba et al., 2009)as well as in allergic conditions like dermatitis, rhinitis and other inflammatory conditions (Hajavi et al., 2018). The immune balance between Th1 and Th2 cells can be changed by the activity of these probiotics. Conversely, immunoregulatory probiotics tend to increase the amount of IL-10 (T-regulatory cytokine), which suppresses hyper-inflammatory events and reduces inflammatory events in conditions like irritable bowel syndrome (IBS), autoimmune disorders, and allergies (Chiba et al., 2009). Lactobacillus and Bifidobacterium strains tend to show protection against pathogenic infection and tumor activity growth in mice by enhancing cell-mediated immune response to promote Th1 cells. On administration of L. casei in OVA- primed mice provokes anti-allergic immune mechanism, showing reduction in IgE antibody response in in vivo studies (M.L. Cross, H.S. Gill., 2000). Moreover, probiotics induce the immune regulation in the host system by maintaining a homeostasis in Th1-Th2 cell population and also promoting anti-inflammatory effect.

**Figure 2:** Immunomodulatory action of Probiotics

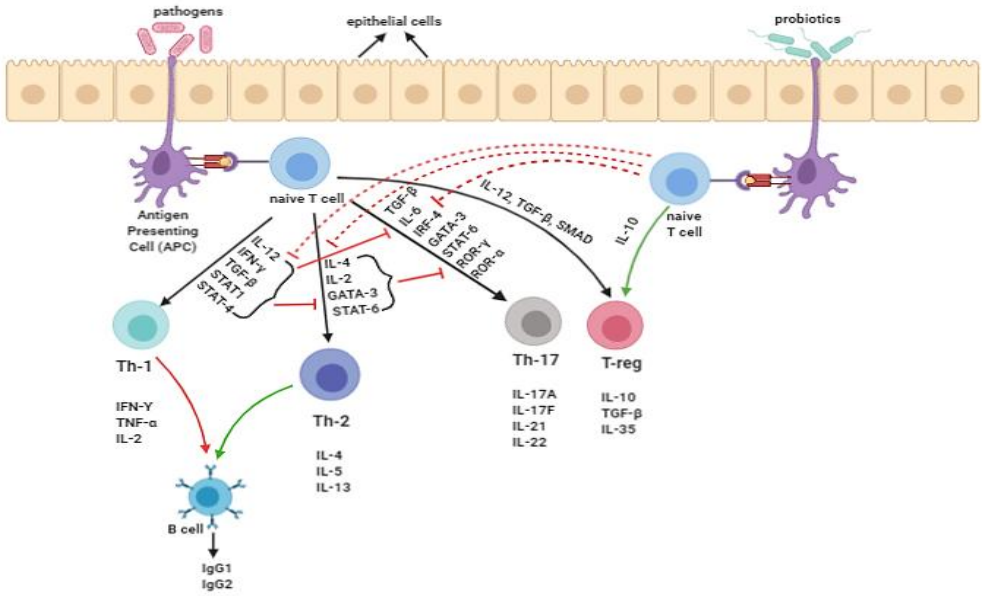



**Table 1:** Immunomodulatory effects of probiotics

| PROBIOTICS | MODE OF MECHANISM | REFERENCE |
|---|---|---|
| LACTOBACILLUS ACIDOPHILUS | Strong IL-12, IL-10, INF-β, TLR-3 genes in dendritic cells | Weiss et al., 2013 |
| L. FERMENTUM | Reduced levels of proinflammatory factors and increase in intestinal macrophages and Peyers patches | Garcia-Castillo et al.,2019 |
| L. PLANTARUM | Homeostasis, regulation of IL-12 and IL-10 | Mujagicet al.,2017 |
| L. CASEI | Act on intestinal macrophages and dendritic cells to release a controlled level of proinflammatory cytokines and TNF-α. | Chiba et al.,2010 |
| L. GASSERI | Reduced level of antigen IgE and increased production of IL-12 | Sashihara et al.,2006 |
| L. PARACASEI | Increased cellular responses for proinflammatory, anti-inflammatory, intra cellular pathogen killing, lymphocyte antagonistic cytokines | Biswas et al.,2013 |
| STREPTOCOCCUS THERMOPHILUS (285) | Induce Th2 cytokines and supress the INF-γ responses | Dargahi et al.,2020 |
| LACTOCOCCUS LACTIS | Improved BAL, IL-4 and IL-10 production (bronchiole infection) | Villena et al.,2008 |

| | | |
|---|---|---|
| **BIFIDOBACTERIA BIFIDUM** | Immunomodulatory effects in Lower GIT, vaginal delivery, breast milk | Westermann et al.,2016 |
| **B. BIFIDIUM W32** | Induces the Regulatory T cells and inhibit the cytokines by Th2 | Chiba et al.,2010 |
| **B. LONGUM W11** | Induce Th1 cytokines production | Medina et al.,2007 |
| **B LONGUM NCIMB 8809 AND BIF53** | Supress Th1 cytokines and increase IL-10 secretion | |
| **B. LONGUM W52** | Inhibition of cytokines by Th2 | Chiba et.al.,2010 |
| **B. ANIMALIS** | Shows pulmonary inflammatory effects and induced Th1 responses | Ezendam et al.,2008 |

Clinical Trials

Probiotics have been known to exhibit immune response in constipation, ulcerative colitis, heart disease and cancer. The microbes present in an individual are enough to control the gut flora and intestinal diseases (Fuller 1991). In aspect of allergic diseases, probiotics tend to show reduction in the inflammatory cytokines in human and murine experimental models. Many randomized and non-randomized controlled studies were performed to figure out the efficacy of probiotics in allergy (Ö. Özdemir & A.Y. Göksu Erol, 2013).

**Table 2:** Probiotics involved in clinical trials of allergic diseases

| PROBIOTICS | MODE OF MECHANISM | REFERENCE |
|---|---|---|
| Lactobacillussalivarius LS01 | Decreases Th2 cytokines and maintains the levels of Th1 cytokines leasing to shift in balance of Th1/Th2 ratio. | Drago et al., 2011 |
| Lactobacillus plantarum CJLP133 | Produces T regulatory cells and regulatory dendritic cells, which release cytokines like TGF-β and IL-10 to lower the levels of IFN-γ, IL-4, and total eosinophils. | Han et al., 2012 |
| Lactobacillus sakei KCTC 10755BP | Decreases serum levels of proinflammatory chemokines CCL17 and CCL27 and downregulatesIgE and IL-4 levels upon allergen sensitization. | Woo et al., 2010 |
| Lactobacillus paracasei-33 (LP-33) | Promoted TGF-β and IL-10 production by inducing CD4+ T cell development thereby downregulatingIgE production | Wang et al., 2004 |
| Bifidobacterium lactis Bb-12 | Alleviate gut inflammation. Causes decline in IL-8, sCD4, IL2, TGF-β production and subsequent inhibition of NFκβ pathway. | **Miraglia et al., 2017** |
| Lactobacillus rhamnosus GG | Reduces inflammatory response via Treg cell promotion which leads to subsequent increase in IL-10. Effective in inducing CD4+, CD25+, Foxp3+, Treg cell mediated tolerance | Pessi et al.,2000 |

**Asthma**

Asthma can be caused by many factors; hence it is called multifactorial airway disease which causes inflammation in the respiratory tract and in lungs (G. Nagarajan & E.B. Thangam, 2020). For treatment and prevention, many studies have been carried out. Probiotics have been used for reducing the usage of synthetic medicines such that the adverse reaction of those medications can be avoided. Birch pollen allergy can be a possible allergen such that it can lead to allergic reaction. In a study, Bifidobacterium-12 exhibited immune response in the airways. A mixture of Lactococcus lactis and Lactobacillus plantarum can help in provoke out the immune system to suppress inflammation in the asthmatic condition. Lactobacillus reuteri can also be administered to treat allergic reaction inflammation of airway disorder (Özdemir, 2010). In another study a mixture of Bifidobacterium and Propionibacterium spp. were

introduced during few months of pregnancy which reduced wheezing (up to 1 year) and prevented some asthmatic symptoms. Oral administration of probiotics has induced $CD4^+$, $CD25^+$ and FOXP3 regulation, T cell regulation and reduced airway hyperresponsiveness(Kim et al., 2013). The study using Lactobacillus casei showed reduced episodes of asthma and allergic rhinitis but these results were inconclusive due to lack of proper statistical evidence (Tang et al., 2015). Lactobacillus rhamnosus (LGG) has shown to suppress this enzyme activity, thereby reducing the airways hyper-responsiveness and decreases the number of infiltrates in the airway. The NO concentration was observed to be reduced in the infants and also involves a set of enzymes that are responsible for cleaving the extracellular proteins in the matrix (Wang et al., 2019). Studies have showed very less treatment plans for allergic asthma but have showed various methods to reduce some symptoms of asthma.

**Allergic Rhinitis**

Although most of the microbes are found in the gut flora, they can exhibit their immune response in the proximal region i.e., the gut as well as in the distal region (endocrine response) such as the nose. These probiotics demonstrate various immune responses; reduces the nasal inflammation of eosinophil in the mucosal layer. Probiotics are not responsible for full recovery but reduce the severity of the allergy (Kim et al., 2013). Another study showed that individual probiotics or mixture of probiotics can show much different response. The peripheral blood monocytic cellsrelease of IL-5, IL-8, and IL-10 was caused by Lactobacillus paracasei.Bifidobacteria longum reduced the eosinophil response and diminished the INF-γ release and maintained the Th2 balance. Lactobacillus rhamnosus and Lactobacillus gasseriare both able to down-regulate the Th2 response with the subsequent release of TNF-α, TNF- gamma, IL-12 and IL-13. In a case of pollen allergy, LGG and L. gasseri demonstrated changes in specific IgG and IgE along with polarization of Th2 and higher levels of IL-4, IL-5, and IL-13 cytokines (Yang et al., 2013).Lactobacillus casei showed reduced rhinitis episodes (Tang et al., 2015). In 2019, a clinical trial was carried out to compare placebo drug and probiotic group among which probiotic group showed better results. The immune response by the probiotics group was more effective in the age group of 5-10-years old. (Wang et al., 2019).

**Atopic Dermatitis**

Three studies were conducted to determine the impact of probiotics on atopic dermatitis. In the first study, Lactobacillus rhamnosus GG (LGG) and Bifidobacterium lactis Bb-12 were used which showed statistically significant lower severity of Atopic Dermatitis in comparison to placebo. The second study was carried out using LGG 190702 and L. reuteri DMS 122460, which showed a significant improvement and increase in the IgE levels. The third study was carried out using the LGG and Bifidobacterium lactis which weren't effective but showed much better results in elevating the IgE levels in the host. few random trials were also carried out using the LGG and the placebo which results better in reducing the symptoms but was not very significant (Michail S., 2009).In later years, studies were carried out where the probiotics were given during the pregnancy and the infants who were born without any distinct characteristic but had a better prevention for the diseases. Oral administration of these probiotics showed better results in reducing inflammatory response by inducing $CD4^+$, $CD25^+$ and FOXP3 and treg cells (Kim et al., 2013). In 2015, studies showed that probiotics had shown improved preventive methods than treatment. It increased the tolerance of the host body and the immune response in the infants of age 1, moreover, the effects had been reduced and they developed a better preventive counter for allergic reactions than adult individuals (Tang et al., 2015).

**Food Allergy**

Food allergy can be in many different types. Food allergy constitutes upto 5-10% of the population. The most common food allergens include cow's milk (0.6%), nuts (0.5%), soy (0.3%), egg (0.2%), peanuts (0.2), wheat (0.1%), fish (0.1%) and shell fish (0.1%) (Satitsuksanoa et al.,2018) Food allergy disrupts the balance of flora with component that weakens state of host. Probiotics are essential as it has a protective function in food allergy. The probiotics attach to the layer of the pathway and significantly limit binding of allergen. By attaching, the probiotics also multiply and produce acids or metabolites to counter the allergens. The adhesion may lead to activation of dendric cells to release Il-10 and Il-12 which leads to the activation of Th1/Th2. Some of the mature dendritic cells may then lead to the activation and proliferation of natural-killer (NK) cells, and the release of IL-12 and IL- 15 which activates the NK-dependent IFN-g that expands Th1 (Kim et al, 2013).

A randomized double-blind placebo-controlled trial had taken place for a cow milk allergy with L. casei and B. lactis Bb12 for 1 year, however had limited results. Lacticacillusrhamnosus (LGG) was given with

extensively hydrolyzed neg casein formula (EHCF) or soy form or hydrolyzed rice form to increase the modulation of the immune system and response of mast cells, DCs and Tregs (Nermes et al., 2013). Other double-blind placebo-controlled study was carried out for peanut allergy, where L. rhamnosus CGMCC1.3724 was used. The probiotics group showed better results than the placebo (Wang et al., 2019). Many plant extracts are also used for food allergy purpose and have shown a productive result.
The clinical studies have shown that the probiotics do not play a very prominent role in treatment of the diseases but complications due to allergens can be prevented. The effect of probiotics is better observed in the infants which can be used for the development of better immune system.

**Probiotics – a Source as Immunotherapy**

Immunotherapy is done to modulate the immune system in such a way that it fulfills the need of the human body (G. Nagarajan & E.B. Thangam, 1998). Allergens are recognized by the T cell receptor, and unlike conformal B cell receptor, they cannot identify and encounter it. The B cell receptors identify the allergen and induce allergen- specific tolerance in Th2 and also induce specific response to Th0/Th1 response (C.A. Akdis& K. Blaser, 2001). Pure recombinant allergen to which epitopes, peptides and structures are formed is Specific Immunotherapy (SIT) (Valenta et al., 2012). Therapeutic Effects have shown better results. Probiotics in conjunction are used and when breast fed, the children have shown to have a better immune system (Kim et al., 2013).
In a clinical trial for bee venom allergy, the venom was treated with peptide immunotherapy, where 3 peptide epitopes of phospholipase $A_2$ ($PLA_2$) was introduced. As an indicative response measure to the allergen, decreased PLA2 proliferation was visualized with decrease release of cytokine IL-4, IL-3, IL-5 and IL-13 (G. Nagarajan & E.B. Thangam, 1998). In another study, development of immunomodulation towards cow's milk allergy was observed, where, recombinant LAB strains were genetically modified to express major cow milk allergen, BLG, as a therapeutic tool. The study further indicated, when treating with r BLG and (shown to restore IgE levels), resulted in improvement of Th1 cytokine (IFN- γ and IL-12) as well as Th2 cytokine (IL-4, IL-5) levels, indicating the increase of Th1/Th2 response ratio. Furthermore, oral administration of rBLG allergen, also increased Th1 response while decreases Th2 response, signifying suppression of allergic event.Moreover, this suggests the route of administration of rLAB to be a critical factor in provoking out immunomodulatory effects (de Azevedo et al., 2013). Hence, more approaches have to be standardized and drawbacks in implementation of recombinant have to be found out to develop immunobiotics as a valuable tool in treatment of allergic and other diseases.

## FUTURE PERSPECTIVES

Many researches have been done using probiotics and their effects on the immune system have been studied to understand the mechanism by which they prevent the disease condition. By oral administration of the probiotics which was given during pregnancy had increased the efficiency of preventive measures in children. The probiotics can be administered in any individual in the form of nanoparticles and as food supplements. In many cases the extent of the allergic response was not predicted appropriately but most of them have gradually showed better results than many of the placebo trials. The probiotics which are administered are already presented in the human body, therefore, the human body are mostly accustomed and habitual to the existance of these probiotics. In future other bacteria or microbes can be used with better effects and negligible adverse effects. Recombinant technology, Microbiological and molecular biological techniques can be used to alter the non-beneficial genes and introduce in the human genome to provoke the immune response against various allergic and non-allergic disease in a better way.

## CONCLUSION

Over decades, probiotics have shown promising effectiveness in the promotion of health consequences in both pathogenic and non-pathogenic diseases. Th2 cytokines are known to be involved in mediating the allergic event in the host, and due to the excessive secretion of Th2 immune response, a majority of allergic diseases are associated with this indicate excessive Th2 immune response. The effect of probiotic in allergic states include the elevation in Th1 production and decrease in the Th2 cell response and also induce the regulation of Treg such as IL-10, TGF-β cytokine.Probiotics play a superficial role in maintenance of Th1-Th2 Balance in immune system regulating the cytokine profile that are responsible for allergic and inflammation, thus proving the immune-modulatory activity. Disturbance in gut microbiota tend to cause imbalance in the cytokine level as well as reduction in production of metabolites that prevent the complications in the host system making a way for various health complications.

Administration of probiotics in optimized range in a daily diet progresses the development of immune system against allergic and non-allergic disorders. The limitations in administration of probiotics have to be studied out by evaluation of probiotic therapy. Even though suitable evidence is not present to completely state that probiotics can be used to treat diseases but there are many evidences to state that probiotics can be used for preventing the severity of the diseases and preventing to result in any fatal conditions.

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**REFERENCES**

[1] D. Ghadimi, R. Fölster-Holst, M. de Vrese, P. Winkler, K.J. Heller, J. Schrezenmeir, Effects of probiotic bacteria and their genomic DNA on TH1/TH2-cytokine production by peripheral blood mononuclear cells (PBMCs) of healthy and allergic subjects, Immunobiology. 213 (2008) 677–692. https://doi.org/10.1016/j.imbio.2008.02.001.

[2] M.V. White, The role of histamine in allergic diseases, J Allergy Clin Immunol. 86 (1990) 599–605. https://doi.org/10.1016/s0091-6749(05)80223-4.

[3] E.B. Thangam, E.A. Jemima, H. Singh, M.S. Baig, M. Khan, C.B. Mathias, M.K. Church, R. Saluja, The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets, Front Immunol. 9 (2018) 1873. https://doi.org/10.3389/fimmu.2018.01873.

[4] M.-J. Butel, Probiotics, gut microbiota and health, Med Mal Infect. 44 (2014) 1–8. https://doi.org/10.1016/j.medmal.2013.10.002.

[5] J. Mao, S. Qi, Y. Cui, X. Dou, X.M. Luo, J. Liu, T. Zhu, Y. Ma, H. Wang, Lactobacillus rhamnosus GG Attenuates Lipopolysaccharide-Induced Inflammation and Barrier Dysfunction by Regulating MAPK/NF-κBSignaling and Modulating Metabolome in the Piglet Intestine, The Journal of Nutrition. 150 (2020) 1313–1323. https://doi.org/10.1093/jn/nxaa009.

[6] P. Markowiak-Kopeć, K. Śliżewska, The Effect of Probiotics on the Production of Short-Chain Fatty Acids by Human Intestinal Microbiome, Nutrients. 12 (2020). https://doi.org/10.3390/nu12041107.

[7] J. Hajavi, S.-A. Esmaeili, A.-R. Varasteh, H. Vazini, H. Atabati, F. Mardani, A.A. Momtazi-Borojeni, M. Hashemi, M. Sankian, A. Sahebkar, The immunomodulatory role of probiotics in allergy therapy, J Cell Physiol. 234 (2019) 2386–2398. https://doi.org/10.1002/jcp.27263.

[8] M.A.K. Azad, M. Sarker, D. Wan, Immunomodulatory Effects of Probiotics on Cytokine Profiles, Biomed Res Int. 2018 (2018) 8063647. https://doi.org/10.1155/2018/8063647.

[9] G. Yang, Z.-Q. Liu, P.-C. Yang, Treatment of allergic rhinitis with probiotics: an alternative approach, N Am J Med Sci. 5 (2013) 465–468. https://doi.org/10.4103/1947-2714.117299.

[10] R. Fuller, Probiotics in human medicine, Gut. 32 (1991) 439–442. https://doi.org/10.1136/gut.32.4.439.

[11] E.R. Davenport, J.G. Sanders, S.J. Song, K.R. Amato, A.G. Clark, R. Knight, The human microbiome in evolution, BMC Biol. 15 (2017) 127. https://doi.org/10.1186/s12915-017-0454-7.

[12] Y. Belkaid, O.J. Harrison, Homeostatic Immunity and the Microbiota, Immunity. 46 (2017) 562–576. https://doi.org/10.1016/j.immuni.2017.04.008.

[13] A. Nishida, R. Inoue, O. Inatomi, S. Bamba, Y. Naito, A. Andoh, Gut microbiota in the pathogenesis of inflammatory bowel disease, Clin J Gastroenterol. 11 (2018) 1–10. https://doi.org/10.1007/s12328-017-0813-5.

[14] S.J. Galli, M. Tsai, A.M. Piliponsky, The development of allergic inflammation, Nature. 454 (2008) 445–454. https://doi.org/10.1038/nature07204.

[15] S.T. Holgate, R. Polosa, Treatment strategies for allergy and asthma, Nat Rev Immunol. 8 (2008) 218–230. https://doi.org/10.1038/nri2262.

[16] T.E. Velez, A.J. Byrne, J.B. Wechsler, R.A. Krier-Burris, K.E. Hulse, P.J. Bryce, Histamine-driven responses are sustained via a bioactive metabolite, J Allergy Clin Immunol. 143 (2019) 2287-2290.e1. https://doi.org/10.1016/j.jaci.2019.01.037.

[17] S.J. Galli, J. Kalesnikoff, M.A. Grimbaldeston, A.M. Piliponsky, C.M.M. Williams, M. Tsai, Mast cells as "tunable" effector and immunoregulatory cells: recent advances, Annu Rev Immunol. 23 (2005) 749–786. https://doi.org/10.1146/annurev.immunol.21.120601.141025.

[18] B.A. Sayed, A. Christy, M.R. Quirion, M.A. Brown, The master switch: the role of mast cells in autoimmunity and tolerance, Annu Rev Immunol. 26 (2008) 705–739. https://doi.org/10.1146/annurev.immunol.26.021607.090320.

[19] S. Bonness, T. Bieber, Molecular basis of atopic dermatitis, CurrOpin Allergy ClinImmunol. 7 (2007) 382–386. https://doi.org/10.1097/ACI.0b013e3282a643c3.

[20] S. Michail, The role of probiotics in allergic diseases, Allergy Asthma Clin Immunol. 5 (2009) 5. https://doi.org/10.1186/1710-1492-5-5.

[21] H. Morita, F. He, M. Kawase, A. Kubota, M. Hiramatsu, J.-I. Kurisaki, S. Salminen, Preliminary human study for possible alteration of serum immunoglobulin E production in perennial allergic rhinitis with fermented milk prepared with Lactobacillus gasseri TMC0356, MicrobiolImmunol. 50 (2006) 701–706. https://doi.org/10.1111/j.1348-0421.2006.tb03842.x.

[22] L.E.M. Niers, H.M. Timmerman, G.T. Rijkers, G.M. van Bleek, N.O.P. van Uden, E.F. Knol, M.L. Kapsenberg, J.L.L. Kimpen, M.O. Hoekstra, Identification of strong interleukin-10 inducing lactic acid bacteria which down-regulate T helper type 2 cytokines, Clin Exp Allergy. 35 (2005) 1481–1489. https://doi.org/10.1111/j.1365-2222.2005.02375.x.

[23] Y. Chiba, K. Shida, S. Nagata, M. Wada, L. Bian, C. Wang, T. Shimizu, Y. Yamashiro, J. Kiyoshima-Shibata, M. Nanno, K. Nomoto, Well-controlled proinflammatory cytokine responses of Peyer's patch cells to probiotic Lactobacillus casei,

Immunology. 130 (2010) 352–362. https://doi.org/10.1111/j.1365-2567.2009.03204.x.
[24] M.L. Cross, H.S. Gill, Immunomodulatory properties of milk, Br J Nutr. 84 Suppl 1 (2000) S81-89. https://doi.org/10.1017/s0007114500002294.
[25] Weiss G, Rasmussen S, Zeuthen LH, Nielsen BN, Jarmer H, Jespersen L, Frøkiaer H. 2010. Lactobacillus acidophilus induces virus immune defence genes in murine dendritic cells by a Toll-like receptor-2-dependent mechanism. Immunology. 131: 268-281.
[26] Garcia-Castillo V, Komatsu R, Clua P, Indo Y, Takagi M, Salva S, Islam MA, Alvarez S, Takahashi H, Garcia-Cancino A, Kitazawa H, Villena J. 2019 Evaluation of the Immunomodulatory Activities of the Probiotic Strain Lactobacillus fermentum UCO-979C. Front Immunol. 10:1376.
[27] de Vos P, Mujagic Z, de Haan BJ, Siezen RJ, Bron PA, Meijerink M, Wells JM, Masclee AAM, Boekschoten MV, Faas MM, Troost FJ. Lactobacillus plantarum Strains Can Enhance Human Mucosal and Systemic Immunity and Prevent Non-steroidal Anti-inflammatory Drug Induced Reduction in T Regulatory Cells. Front Immunol. 2017 Aug 23;8:1000. doi: 10.3389/fimmu.2017.01000. PMID: 28878772; PMCID: PMC5572349.
[28] Sashihara T, Sueki N, Ikegami S. 2006. An analysis of the effectiveness of heat-killed lactic acid bacteria in alleviating allergic diseases. J Dairy Sci. 13: 2846–2855.
[29] Biswas G, .Korenaga H, Nagamine R, Kawahara S, Takeda S, Kikuch Y, Dashnyam B, Yoshida T, Kono T, Sakai M. 2013. Elevated cytokine responses to Vibrio harveyi infection in the Japanese pufferfish (Takifugurubripes) treated with Lactobacillus paracasei spp. paracasei (06TCa22) isolated from the Mongolian dairy product, 2013, fish shellfish immun. 3: 756-765.
[30]Dargahi N, Matsoukas J, Apostolopoulos V, 2020,. Streptococcus thermophilus ST285 Alters Pro-Inflammatory to Anti-Inflammatory Cytokine Secretion against Multiple Sclerosis Peptide in Mice. Brain Sci. 10: 126.
[31] Villena J, Medina M, Raya R, Alvarez S. 2008. Stimulation of respiratory immunity by oral administration of Lactococcus lactis, 2008,Canadian Journal of Microbiology. 54: 630-638.
[32] Westermann C, Gleinser M, Corr SC, Riedel CU. A Critical Evaluation of Bifidobacterial Adhesion to the Host Tissue. Front Microbiol. 2016 Aug 5;7:1220. doi: 10.3389/fmicb.2016.01220. PMID: 27547201; PMCID: PMC4974247.
[33] Medina M , Izquierdo E, Ennahar S, Sanz Y. 2007. Differential Immunomodulatory Properties of Bifidobacterium Logum Strains: Relevance to Probiotic Selection and Clinical Applications. Clin Exp Immunol 150 :531-538.
[34] Ezendam J, Klerk A, Gremmer ER, and Loveren H. 2008. Effects of Bifidobacteriumanimalis administered during lactation on allergic and autoimmune responses in rodents. Clin Exp Immunol. 154 :424–431.
[35] Ö. Özdemir, A.Y. Göksu Erol, Preventative and Therapeutic Probiotic Use in Allergic Skin Conditions: Experimental and Clinical Findings, BioMed Research International. 2013 (2013) e932391. https://doi.org/10.1155/2013/932391.
[36] G. Nagarajan, E.B. Thangam, Effect of H4R Antagonist N-(2-Aminoethyl)-5-Chloro-1H-Indole-2-Carboxamide (Compound A) in a Mouse Model of Allergic Asthma, Immunological Investigations. 0 (2020) 1–14. https://doi.org/10.1080/08820139.2020.1712415.
[37] O. Ozdemir, Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data, Clin Exp Immunol. 160 (2010) 295–304. https://doi.org/10.1111/j.1365-2249.2010.04109.x.

[38] H.-J. Kim, H.Y. Kim, S.-Y. Lee, J.-H. Seo, E. Lee, S.-J. Hong, Clinical efficacy and mechanism of probiotics in allergic diseases, Korean J Pediatr. 56 (2013) 369–376. https://doi.org/10.3345/kjp.2013.56.9.369.
[39] R.-B. Tang, J.-K. Chang, H.-L. Chen, Can probiotics be used to treat allergic diseases?, J Chin Med Assoc. 78 (2015) 154–157. https://doi.org/10.1016/j.jcma.2014.08.015.
[40] H.T. Wang, S. Anvari, K. Anagnostou, The Role of Probiotics in Preventing Allergic Disease, Children (Basel). 6 (2019). https://doi.org/10.3390/children6020024.
[41] L. Drago, E. Iemoli, V. Rodighiero, L. Nicola, E. De Vecchi, S. Piconi, Effects of Lactobacillus salivarius LS01 (DSM 22775) treatment on adult atopic dermatitis: a randomized placebo-controlled study, Int J ImmunopatholPharmacol. 24 (2011) 1037–1048. https://doi.org/10.1177/039463201102400421.
[42] Y. Han, B. Kim, J. Ban, J. Lee, B.J. Kim, B.S. Choi, S. Hwang, K. Ahn, J. Kim, A randomized trial of Lactobacillus plantarum CJLP133 for the treatment of atopic dermatitis, Pediatr Allergy Immunol. 23 (2012) 667–673. https://doi.org/10.1111/pai.12010.
[43] S.-I. Woo, J.-Y. Kim, Y.-J. Lee, N.-S. Kim, Y.-S. Hahn, Effect of Lactobacillus sakei supplementation in children with atopic eczema–dermatitis syndrome, Annals of Allergy, Asthma & Immunology. 104 (2010) 343–348. https://doi.org/10.1016/j.anai.2010.01.020.
[44]M.F. Wang, H.C. Lin, Y.Y. Wang, C.H. Hsu, Treatment of perennial allergic rhinitis with lactic acid bacteria, Pediatr Allergy Immunol. 15 (2004) 152–158. https://doi.org/10.1111/j.1399-3038.2004.00156.x.
[45] M. Miraglia Del Giudice, C. Indolfi, M. Capasso, N. Maiello, F. Decimo, G. Ciprandi, Bifidobacterium mixture (B longum BB536, B infantis M-63, B breve M-16V) treatment in children with seasonal allergic rhinitis and intermittent asthma, Ital J Pediatr. 43 (2017) 25. https://doi.org/10.1186/s13052-017-0340-5.
[46] T. Pessi, Y. Sütas, M. Hurme, E. Isolauri, Interleukin-10 generation in atopic children following oral Lactobacillus rhamnosus GG, ClinExp Allergy. 30 (2000) 1804–1808. https://doi.org/10.1046/j.1365-2222.2000.00948.x.
[47] P. Satitsuksanoa, K. Jansen, A. Głobińska, W. van de Veen, M. Akdis, Regulatory Immune Mechanisms in Tolerance to Food Allergy, Front Immunol. 9 (2018) 2939. https://doi.org/10.3389/fimmu.2018.02939.
[48] M. Nermes, S. Salminen, E. Isolauri, Is there a role for probiotics in the prevention or treatment of food allergy? Curr Allergy Asthma Rep. 13 (2013) 622–630. https://doi.org/10.1007/s11882-013-0381-9.
[49] J. Rolland, R. O'Hehir, Immunotherapy of allergy: anergy, deletion, and immune deviation, CurrOpinImmunol. 10 (1998) 640–645. https://doi.org/10.1016/s0952-7915(98)80082-4.
[50] C.A. Akdis, K. Blaser, Bypassing IgE and targeting T cells for specific immunotherapy of allergy, Trends Immunol. 22 (2001) 175–178. https://doi.org/10.1016/s1471-4906(01)018622.
[51] R. Valenta, R. Campana, K. Marth, M. van Hage, Allergen-specific immunotherapy: from therapeutic vaccines to

prophylactic approaches, J Intern Med. 272 (2012) 144–157. https://doi.org/10.1111/j.1365-2796.2012.02556.x.
[52] M.S.P. de Azevedo, S. Innocentin, F.A. Dorella, C.S. Rocha, D. Mariat, D.S. Pontes, A. Miyoshi, V. Azevedo, P. Langella, J.-M. Chatel, Immunotherapy of allergic diseases using probiotics or recombinant probiotics, J ApplMicrobiol. 115 (2013) 319–333. https://doi.org/10.1111/jam.12174.