

Potentials of Probiotics in the Treatment of Food Allergy – a Review

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Abstract

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Food allergy is an adverse immune response to some proteins in some foods. Probiotic, health promoting bacteria have gained much importance because of their innumerable benefits, particularly in the treatment of diarrhea, hypercholesterolemia, atopic dermatitis, eczema, and gastrointestinal disorders by strengthening the immune system. The current paper reviews recent advances made in the treatment of food allergy through employing probiotic or synbiotic therapy. The results of several reports are very promising suggesting probiotics can influence the immune system to curtail the allergic responses.

Keywords: lactobacillus; food proteins allergen; immunomodulation; peanut

The cultural diversity spanning the length and breadth of the globe is reflected in the multitude of dietary habits and culinary choices among the people. In this diversity, there exists a group of people who have developed an allergic reaction towards some foods. Food allergy is now recognised as a worldwide problem and appears to be on increase because of lifestyle changes in modern times such as the changes in the alimentary habits, living conditions, excessive use of antibiotics contributing to immune-deviation and thus to the development of allergy (VON MUTIUS 2004). Food allergy, defined as an adverse immune response to food proteins, affects as many as 6% of young children and 3–4% of adults (GREER *et al.* 2008). Surprisingly, food allergies are much more common in India as compared to the western countries with a figure reaching 16–20%. In young children the most common casual foods are cow milk (2.5%), egg (1.3%), peanut (0.8%), wheat (0.4%), soy (0.4%), nuts (0.2%), fish (0.1%), and shellfish (0.1%) (WOOD 2003).

The immune system is an integral part of protection against disease; however the normal protective immune mechanisms can sometimes cause detrimental reactions in the host. Such reactions are known as hypersensitivity reactions. Allergy is an immediate

hypersensitivity disorder (type I) of the immune system. Allergic reactions occur to normal harmless environmental substances known as allergens; these reactions are acquired, predictable, and rapid. The risk factors for allergy can be the host and environmental factors. The host factors include heredity, gender, race, and age, with heredity being by far the most significant. However, there have been recent increases in the incidence of allergic disorders that cannot be explained by genetic factors alone. Four major environmental candidates are alterations in the exposure to infectious diseases during early childhood, environmental pollution, allergen levels; and dietary changes (GREER *et al.* 2008). Apart from these, protein in the food is the most common allergic component. Some proteins or protein fragments are resistant to digestion and those that are not broken down in the digestive process are tagged by the IgE. In such circumstances, the immune system triggers an allergic reaction that may range from mild to severe. Allergic responses with any protein may result in dermatitis, gastrointestinal, and respiratory distress including life-threatening anaphylactic responses as biphasic anaphylaxis and vasodilation; these require immediate emergency intervention.

Thus, the individuals with protein allergies should avoid the contact with the problematic protein which is strongly recommended.

Pharmaceutical medicine has been unable to stop the increasing global morbidity and mortality both in acute and chronic allergic diseases. In view of this, there is a growing awareness of the preventive and therapeutic potential of alternative agents in the medical field. Probiotics, among other agents, fall into this category and can have a direct and positive effect on the prevention of allergic disorders (BUTLER 2008). Probiotics are defined as “live microorganisms that confer a health benefit on the host when consumed in adequate amount” (WHO/FAO 2006). Many studies have been performed which indicate that probiotics can temporarily modify the composition of gut microbiota, and potentially these can reduce the susceptibility to allergy (TANNOCK *et al.* 2000; NOVERR & HUFFNAGLE 2004), leading to health benefits for the host. Human consumption of various probiotic bacteria stimulates phagocytic activity and increases the production of T and B lymphocytes and production of antibodies, particularly of immunoglobulins A (IgA), IgM and IgG (TIWARI *et al.* 2012). Furthermore, it is presumed that probiotics can bind with the allergic compounds and modify them or convert them into forms that remain no longer allergic. For example, they can hydrolyse polypeptides or complex proteins into harmless peptides.

Evidence of probiotic treatment in prevention of food allergy

Several strains of lactobacilli and bifidobacteria have been found to influence the immune function through stimulating different immune cells such as erythrocytes, antigen presenting cells, regulatory T cells and/or effector T and B cells in the host. Most studies exploring the role of probiotics in the treatment of allergic diseases have focused on early manifestation of allergy, specifically food allergy including allergy to milk, egg, peanuts, soy, wheat, mashroom, and sea foods (ZUERCHER *et al.* 2006; MORE 2010).

Milk allergy

The milk allergy is a state of intolerance of milk proteins which varies in severity. When the immune system is involved, usually due to reactions mediated by IgE, it is called cow's milk protein allergy (CMPA). Well-known signs of milk allergy are skin rash, sinus

problems, wheezing, asthma attacks, diarrhoea, and gastrointestinal discomfort while in acute condition eczema, autism and eosinophilic esophagitis may occur (MORE 2010).

(i) Autism: The Autism spectrum disorders are more common in the pediatric population. Autism is a disorder of neural development characterised by impaired social interaction, communication, and by restricted and repetitive behaviour. WALFSON *et al.* (2008) stated that probiotic species *S. thermophilus* may be capable of provoking an autoimmune response. Pediatric Autoimmune Neuropsychiatric Disorders (PANDAS) and Autism Spectrum Disorders (ASD) are triggered or exacerbated by the group A beta-hemolytic streptococcus (GABHS) infections. Anti-GABHS antibodies have been found in a person with ASD giving rise to concerns that other streptococcal organisms, including *S. thermophilus* have anti-allergic properties. Although belonging to the same genus as the disease causing GABHS, the examination of the *S. thermophilus* genome reveals a lack of the most important genetic determinants of their pathogenicity (HOLS *et al.* 2005).

(ii) Eczema: It is a form of dermatitis, or inflammation of the epidermis. MARSCHAN *et al.* (2008) performed a clinical study in which mothers were allowed to receive capsules containing a mixture of four probiotic bacterial species, *L. rhamnosus* GG (ATCC 53103) 5×10^9 colony-forming units (CFU), *L. rhamnosus* LC705 5×10^9 CFU, *Bifidobacterium breve* Bb99 2×10^8 CFU, and *Propionibacterium freudenreichii* ssp. *shermanii* JS 2×10^9 CFU. Their infants received the same capsules as the mothers once a day: those given probiotics were mixed with sugar syrup containing 0.8 g of prebiotic sugars (galacto-oligosaccharides). The mothers received these products for 2–4 weeks before delivery, and their infants for the first 6 months. In this clinical study, which included 925 children, the cumulative prevalence of eczema and atopic eczema was reduced by the age of 2 years in the children who received probiotics.

(iii) Eosinophilic esophagitis (EE): An allergic white blood cell, the eosinophil, is responsible for this disease, which is characterised by swelling of the esophagus, and the symptoms of EE can range from severe heartburn, difficulty in swallowing, food impaction in the esophagus, nausea, vomiting, and weight loss. KONIECZNA *et al.* (2011) determined that a probiotic could induce Foxp3 T cells in humans. Volunteers fed with *B. infantis* displayed selective increase in secretion of interleukins and enhanced

Foxp3 expression in peripheral blood. *B. infantis* administration to humans selectively promotes immunoregulatory responses, suggesting that these bacteria may have therapeutic utility in patients with inflammatory disease.

Egg allergy

Hypersensitivity reactions can be caused by dietary substances from the yolk or whites of eggs, causing an overreaction of the immune system which may lead to severe physical symptoms for millions of people around the world (NIAID Allergy Statistics 2005). Egg allergy is mainly caused by three proteins in the egg called ovomucoid, ovalbumin, and conalbumin. Egg allergy is rare in adults, but more common in young children, usually outgrown by the age of 6. However, a female patient developed egg allergy in her 50s (UNSEL *et al.* 2007). Hives and atopic dermatitis (AD) are the most common allergic reactions to egg. Hives, or urticaria, are tiny red rashes that form anywhere on the body, developing within minutes to hours after ingesting egg or food with egg ingredients. A person with egg allergy may also experience swelling of the lips, eyelids, tongue or throat on eating food containing egg. Adults with egg allergies may experience a variety of respiratory symptoms, including hay fever and asthma upon breathing powdered egg ingredients. Nasal symptoms may include itchy, watery eyes, runny or stuffy nose, and headache or sinus pressure. There may also be wheezing, coughing, breathing with difficulty and incurring other asthma symptoms. Asthma may require immediate intervention because mild symptoms of wheezing can quickly progress to severe breathlessness (MONERET-VAUTRIN *et al.* 2005).

GRUBER *et al.* (2008) investigated the therapeutic effect of *L. rhamnosus* GG (LGG) as a food supplement in infants suffering from atopic dermatitis. It was observed that the supplementation of food with lactobacilli may prevent or improve atopic dermatitis as the infants who received lactobacilli pre- and post-natally were less likely to develop atopic dermatitis than the placebo-fed infants (ROSENFELDT *et al.* 2003).

Currently, newborn pigs pretreated orally with *L. lactis* were protected against allergy to ovomucoid (Ovm) and the treatment with this bacterium significantly reduced the subsequent frequency of allergy supporting “Hygiene Hypothesis” (BABU *et al.* 2010). The authors suggested that *L. lactis* may prevent allergy by biasing from type 2 to type 1 immune response.

Peanut allergy

Sometimes body's natural defense system that fights infections and diseases overreacts and can cause a serious, even life-threatening response in peanut allergy. It may lead to the release of chemicals, including histamine into the blood and these chemicals can affect different tissues in the body such as the skin, eyes, nose, airways, intestinal tract, lungs, and blood vessels. The allergic response to peanuts usually occurs within minutes after the exposure and the symptoms range from mild to severe. Peanut allergy symptoms can include: skin reactions such as hives, redness or swelling, itching or tingling in or around the mouth and throat, digestive problems such as diarrhoea, stomach cramps, nausea or vomiting, tightening of the chest, shortness of breath or wheezing and runny or stuffy nose. Peanut allergy is one of the most common causes of anaphylaxis. Some reports may support the role of probiotic strains (such as *L. rhamnosus*) for the protection against peanut allergy.

SKOLNICK *et al.* (2001) had shown that peanut allergy can be outgrown in as many as 21.5% of patients. Some therapeutic modalities were reported which include monoclonal anti-IgE, oral peanut desensitisation and immunotherapy, some Chinese herbal formulas, probiotics, and heat-killed *Listeria monocytogenes* (HKL). The study conducted by KALLIOMAKI *et al.* (2003) is a prospective study dividing newborn infants into two groups receiving either the probiotic *L. rhamnosus* strain GG (ATCC 53103) or placebo. At the age of 4 years, there was a significant decrease in the prevalence of atopic dermatitis in the *Lactobacillus* treatment group, suggesting a role for probiotics in the prevention of the development of AD. However, the number of children with allergic rhinitis and asthma did not differ between the two groups. Therefore, oral administration of probiotics to children with food allergy, some of whom being allergic to peanut, is associated with a decrease in IgE production *in vitro*.

Wheat allergy

Wheat is the dietary staple in many parts of India and other southeast Asian countries. Conversely, in recent years wheat allergy is also prevalent in India, being termed an impending epidemic (RAMAKRISHNA 2011). The disease affects paediatric patients and adults, too. Many foods, such as breads, cakes, breakfast cereals, pasta, crackers, beer, soy sauce

and condiments, such as ketchup contains wheat as a chief base. In wheat, about four different classes of protein including albumin, globulin, gliadin, and gluten have been found to cause allergies. As stated by ŠOTKOVSKÝ *et al.* (2011), 27 potential wheat allergens have been successfully identified. Common symptoms of wheat allergy include eczema, asthma, allergic rhinitis, angioedema (tissue swelling due to fluid leakage from blood vessels), abdominal cramps, nausea, and vomiting. The most severe response is exercise/aspirin induced anaphylaxis attributed to one omega gliadin that is a relative of the protein that causes celiac disease (AKAGAWA *et al.* 2007).

Wheat gliadin induces severe intestinal symptoms and small-bowel mucosal damage in coeliac disease patients. At present, the only effective treatment for the disease is a strict life-long gluten-free diet, although some research reveals the potential of probiotic bacteria against wheat gluten induced allergy. LINDFORS *et al.* (2008) investigated whether probiotics *L. fermentum* or *B. lactis* can inhibit the toxic effects of gliadin in intestinal cell culture conditions. In this study, it was observed that among the probiotics tested, live *B. lactis* can directly counteract the harmful effects exerted by coeliac-toxic gliadin and would clearly warrant further studies of its potential as a novel dietary supplement in the treatment of coeliac disease. The efficacy of different numbers of both *L. fermentum* and *B. lactis* in inhibiting the gliadin-induced increase in Caco-2 cell permeability was assessed by TER measurement. *B. lactis* were able to protect epithelial cells from cellular damage induced by gliadin administration. The addition of *B. lactis* to the cell culture medium together with gliadin was able to counteract the gliadin-induced inhibition of TER recovery.

DE ANGELIS (2006) aimed at showing the capacity of probiotic VSL#3 preparation (10^9 CFU/ml) to hydrolyse extensively wheat flour gliadins as a tool for decreasing the level of toxic or immunogenic epitopes causing celiac disease. Two-dimensional electrophoresis, immunological (R5 antibody), and mass spectrometry analyses showed an almost complete degradation of gliadin during long-time fermentation of wheat flour by VSL#3. Freeze-dried preparation of VSL#3 containing *S. thermophilus*, *L. plantarum*, *L. acidophilus*, *L. casei*, *L. delbrueckii* spp. *bulgaricus*, *B. breve*, *B. longum*, and *B. infantis* was used for dough fermentation and gliadin polypeptides hydrolysis. Other commercial freeze-dried probiotic preparations such as Oxadrop (*L. acidophilus*, *L. brevis*, *B. infantis*, and *S. thermophilus*), Florisia (*L. brevis*,

L. salivarius spp. *Salicinius*, and *L. plantarum*) (all VSL Pharmaceuticals, Inc., Towson, USA), and Yovis (*S. salivarius* spp. *thermophilus*, *B. breve*, *B. infantis*, *B. longum*, *L. acidophilus*, *L. plantarum*, *L. casei*, *L. delbrueckii* spp. *bulgaricus*, *S. faecium*) (Sigma Tau, Industrie Farmaceutiche Riunite S.p.a., Roma, Italy) were also used. Thus, it can be interpreted that probiotics can efficiently help to alleviate the harmful immunological responses caused by specific protein.

Soy allergy

Soy, a product of soybeans, is a common food that can cause allergies and may lead to death in some cases. A team of researchers collected data on all fatal and life-threatening reactions caused by food between 1993 and 1996 in Sweden and found that soy was indeed the culprit (DANIEL 2004).

In many cases, soy allergy starts with a reaction to a soy-based infant formula. Although most of the children eventually outgrow a soy allergy, it may persist into adulthood. At least 16 allergenic proteins of soy are presumed to cause allergic reactions (LALLES & PELTRE 1996), and among them soybean lectin, an antinutrient has been identified as a major allergen. Whenever there is a damaged intestinal lining or “leaky gut”, soy lectin can easily pass into the bloodstream causing allergic reactions (BARNETT & HAWDEN 1987). The symptoms of such allergic response are flushed face, hives, swelling of eyes, face, lips, throat and tongue, diarrhoea, and rhinoconjunctivitis.

CHOURAQUI *et al.* (2008) developed infant formulas containing probiotics and synbiotics for the safety and protection against infant diarrhoea. A standard infant formula contained a mixture of probiotics *B. longum* BL999, *L. rhamnosus* LPR, and *L. paracasei* ST11 with prebiotics galactooligosaccharide (GOS) and short chain fructooligosaccharide (SCFOS). The infants in the group that received the formula containing *B. longum* BL999 and *L. rhamnosus* LPR (BL999 + LPR) had significantly fewer incidents of diarrhoea. It is intriguing that the decrease in the incidence of diarrhoea was observed several months after infants had stopped taking the probiotic-supplemented formula; this confirms the successful colonisation of probiotics in the infants’ gut. Recently, WICKENS *et al.* (2012) demonstrated that the probiotic *L. rhamnosus* HN001, which halves the prevalence of rhinoconjunctivitis at the age of 2 years, continues to have a protective effect until the age of 4 years. Maternal supplementation with HN001 from 35 weeks’ gesta-

tion until 6 months after birth, followed by infant supplementation until the age of 2 years, halves the cumulative prevalence of rhinoconjunctivitis in high-risk infants. The outcomes of different approaches are suggestive of beneficial effects of probiotic or synbiotic preparations in infants.

Blueberry allergy

Blueberries contain “salicylate” which is a naturally occurring chemical compound in plants. Some individuals experience an allergic reaction to blueberries, due to sensitivity to salicylate. One reaction common in this allergy is the swelling of lips, face, tongue and throat called angioedema. IgE-mediated food allergy, a condition that may lead to a fatal outcome or to life-threatening condition, is angioedema (MONERET-VAUTRIN *et al.* 2005). In certain reports anti-allergic effects have also been ascribed to gram-negative probiotics (ZUERCHER *et al.* 2006). LODINOVA-ZADNIKOVA *et al.* (2003) demonstrated that colonisation with a probiotic *Escherichia coli* strain (O83:K24:H31) during the first week of life resulted in a significantly reduced allergy prevalence 10 years (study in pre-term infants) or even 20 years later (full-term infants) later. Such positive outcomes propose a possible role of probiotics as anti-allergic agents.

Furthermore, CIPRANDI *et al.* (1986) reported that the patients receiving adjunctive treatments with *Bacillus subtilis* spores resulted in significant reduction of frequency and severity of symptoms of adult with angioedema manifestations from blueberry allergy. However, the safety of the use of such spores in immune-compromised patients has been brought into a question.

Seafood allergy

Seventy percent of the world's catch of fish and fishery products is consumed as food. Fish and shellfish products represent 15.6% of animal protein supply and 5.6% of total protein supply on a worldwide basis. Seafood-borne allergic disease outbreaks affect consumers by a swollen throat (airway constriction), rapid pulse, shock, and dizziness, causing asthma. There is a high allergic cross-reactivity between different types of fish. This is because of a protein (parvalbumin) that is present in many fish. For this reason, most of the people with an allergy to one fishes are advised to avoid all fishes (GROCE 2008).

KARIMI *et al.* (2009) reported that oral treatment with live *L. reuteri* ATCC 23272 can attenuate the

major characteristics of the asthmatic response in the mouse model of allergic airway inflammation. BALB/c mice were treated daily with *L. reuteri* and, after 9 days of oral treatment, the percentage and total numbers of regulatory T cells (Foxp3+, CD4+ and CD25+) in spleens increased significantly. The airway responsiveness, inflammatory cell influx and cytokine levels in bronchoalveolar fluid of the recipient mouse were assessed and provides evidence that regulatory T cells can attenuate allergic airway response (KARIMI *et al.* 2009).

Mushroom allergy

An allergic reaction after eating mushrooms can be a sign of mold allergy, which is fairly common. The members of the fungus family, mushrooms, and mold trigger similar symptoms, including skin rash and irritation. The symptoms can be worsened in summer, including itchy eyes, mouth and throat, a runny nose, sneezing, swollen eyelids, headaches, breathing trouble, and rash or hives on the skin can develop. Basidiomycetes found in mushrooms are commonly responsible for mushroom allergy (DIAZ 2005).

The impact of a non hydrolysed fermented infant formula containing heat-killed *Bifidobacterium breve* C50 and *S. thermophilus* 065 (HKBBST) was evaluated on the incidence of allergy-like events during the first 2 years of life in children at high risk of atopy (MORISSET *et al.* 2011). The infants used HKBBST or a standard infant formula since birth until one year of age, and were followed at 4, 12, and 24 months after birth. HKBBST decreased the incidence of potentially allergic adverse events in children with respiratory events during the first months of life and even after the formula was stopped, suggesting potential applications of probiotic bacteria in children.

Fat and animal products allergy

Fat and animal products in the diet are known to be responsible for predisposing people to general atopic disorders, or allergies. They cause hives, itching, shortness of breath, swelling, and most severely Irritable bowel syndrome (IBS). The prevalence of IBS in the general population ranges from 3–25%. (CREMONINI & TALLEY 2005). IBS is a chronic condition that severely impacts on the quality of life of the affected individuals, being characterised by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits (CAIN *et al.* 2006).

McFARLAND and DUBLIN (2008) took various strains of probiotic bacteria – *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. reuteri*, *L. rhamnosus*, *Saccharomyces boulardii*, *S. faecium*, and VSL#3, and proved that the symptom of IBS, i.e. abdominal pain decreased, and that there was a global improvement in the syndrome suggesting the perspective application of probiotic strains as therapeutic agents in IBS like contagious diseases.

Food additives and preservatives

Food additives are substances added to food to preserve flavour or enhance its taste and appearance (MORE 2013). A preservative is a naturally occurring or synthetically produced substance that is added to products such as foods or pharmaceuticals to prevent the decomposition by microbial growth or by undesirable chemical changes. Since it is probable that many allergic reactions to food additives and preservatives have not been diagnosed, the exact rates of reactions are still unknown. However, various studies estimate that the rate is probably less than 1% in adults, and up to 2% in children (MORE 2010). There are many types of allergic diseases that can occur as a result of food additives and preservatives – sweating, itching, flushing, abdominal pain, nausea/vomiting, and atherosclerosis leading to cardiac disorder.

JONES *et al.* (2012) carried out a double blind placebo controlled experiment on 114 subjects, aiming to evaluate the cholesterol-lowering efficacy of a yoghurt formulation containing microencapsulated bile salt hydrolase (BSH)-active *L. reuteri* NCIMB 30242, taken per day over 6 weeks by hypercholesterolemic adults. Over the intervention period, the subjects consuming yoghurts which had microencapsulated *L. reuteri* NCIMB 30242 attained significant reductions in LDL-cholesterol, total cholesterol and non-HDL-cholesterol over placebo.

The Food Allergen Labelling and Consumer Protection Act (FALCPA) was passed by the Congress to ensure clearer labelling of food for the millions of people with food allergies. As from January 01, 2006, all food products regulated by the FDA must be labelled in a specific way to identify the eight major food allergens: milk, egg, fish, crustacean shell fish, tree nuts, wheat, peanuts, and soybeans. FALCPA labelling applies to all retail and food-service establishments that package, label, and offer products for human consumption (e.g. vending machines and all packages labelled “for individual sale”). The foods that are sometimes known to cause allergy may be

listed again in a box or highlighted in some way to draw attention to their presence (e.g. this product contains EGG). Some products carry ‘MAY CONTAIN’ warnings on labels to highlight that the food may contain minute traces of foods known to cause allergic diseases. This may be because the food is produced on the same line or in the same factory as other products that contain the food known to cause allergy (www.icmr.nic.in).

CONCLUSION

In summary, many scientific reports clarify the defensive ability of probiotic bacteria against the allergic disorders developed due to egg, wheat, peanuts and other food products. Probiotics also assists normal human body in regulating and maintaining immunological functions and also in reducing allergic responses. They promise to be an effective tool for allergy therapy, however, a careful selection of the probiotic strain(s), the dose standardisation, and thorough knowledge of its beneficial effects over and above the toxic effects is desirable.

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