

PROBIOTIC A NOVEL APPROACH TO TREATING CHILDHOOD ATOPY

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Summary

In theory, increased levels of Probiotics may induce a 'barrier' influence against common pathogens and antigens. The survival issues of Probiotics are associated with their establishment in the competitive gut ecosystem. Since the generation of immunophysiologic regulation in the gut depends on the establishment of indigenous micro flora and the therapeutic interventions based on the consumption of cultures of beneficial live micro organisms that act as Probiotics. Among the possible mechanisms of Probiotics therapy is promotion of a nonimmunologic gut defense barrier, which includes the normalization of increased intestinal permeability and altered gut micro ecology. The role and effect of probiotics in infant feeding, on the mucosal permeability & microbial flora composition and in turn on the stabilization of Th1/Th2 & IgE production has been tested.

Another possible mechanism of Probiotics therapy is improvement of the intestine's immunologic barrier, particularly through intestinal immunoglobulin A responses and alleviation of intestinal inflammatory responses, which produce a gut-stabilizing effect.

Many Probiotics effects are mediated through immune regulation, particularly through

balance control of pro inflammatory and anti-inflammatory cytokines. Probiotics can be used as innovative tools to alleviate intestinal inflammation, normalize gut mucosal dysfunction, and down-regulate hypersensitivity reactions.

There are differences which exist in the immunomodulatory effects of candidate Probiotics bacteria. Specific immunomodulatory properties of Probiotics bacteria should be characterized when developing clinical applications for extended target populations.

1. Introduction

A probiotic is currently defined as a live microbial food supplement with a proved beneficial effect on human health. Probiotics are live microorganisms that occur naturally in the human digestive system.

Probiotics consist of yeast or bacteria, especially lactic acid bacteria, and are available as capsules, powder, fermented milks or yoghurts. Probiotics exhibit strain-specific differences in their resistance to acid and bile, ability to colonize the gastrointestinal tract, clinical efficacy, and benefits to the health of the host.

Probiotics were defined by a group of experts convened by the Food and Agriculture Organization of the United Nations (FAO) as "living non-pathogenic microorganisms administered in adequate amounts which confer a beneficial health effect on the host and disease prevention and/or treatment". Most probiotics are bacteria, which are small, single-celled organisms. Bacteria are categorized by scientists with genus, species and strain names.

One of the major problems when trying to identify and evaluate candidate probiotic strains is our lack of knowledge about their mode of action; several modes of action have been hypothesized or proven.

Activation as well as down-regulation of the humoral and cellular mucosal immune response has been reported in diseases with a defective mucosal barrier, probiotics have been documented to decrease intestinal permeability.

Mucus production increases in response to certain probiotics and cytokine-induced apoptosis of enterocytes may be prevented. Complex interactions between the probiotic microorganism and the host may thus turn out to be more important than the more simple interactions that have been demonstrated with other bacteria.

It is probable that probiotics do not exert their effects by one single mechanism. However, which of the putative modes of action that is relevant when treating a specific disease is still unsettled, although the light is beginning to shine at the end of the corridor. Recent studies have confirmed immunomodulatory and anti-inflammatory properties of probiotics. The beneficial effects of probiotics on the allergic airway response seem to be strain specific.

Due to our incomplete understanding of how probiotics work, in vitro methods are not useful tools for evaluation of probiotics and randomized clinical trials have to be

performed to test the probiotic abilities of each specific strain for each specific condition. However, this is a very tedious task to handle in a systematic way. Although the number of bacterial species with theoretical probiotic potentials is limited, the number of specific bacterial strains within each species is countless. For the time being, we have to lean on data obtained from in vitro studies and animal models, and continue to carry out carefully designed randomized clinical trials.

2. Mechanisms of action of Probiotic

Health benefits attributed to probiotics have been described for decades. They include the treatment and the prevention of gastrointestinal diseases, vaginal and urinary infections and allergies. Furthermore, results obtained in probiotics clinical trials suggest some beneficial effects over placebo in the relief of irritable bowel syndrome symptoms. Probiotics have been shown to decrease the risk of developing atopic dermatitis, reduce incidence of intestinal and upper airway infections in the first year of life.

Molecular and cellular mechanisms of probiotics in therapy are mainly manifested in the following ways.

- Restore Microbiologic balance in the intestine.
- Competition with pathogenic bacteria for specific binding sites on intestinal epithelial cells.
- Protective functions through modulation of immune activity and epithelial function in both the large and small intestine .
- Enhanced phosphorylation of actinin and occludin in the tight junction region epithelial cells.
- Maintenance barrier function by preventing cytokine-induced apoptosis in intestinal epithelial cell models through the inhibition of a tumor necrosis factor.
- Alter action signal transduction pathways in the presence or absence of pathogenic bacteria and cytokines with epithelial and immune cells.
- Epithelial cells respond to whole bacteria and bacterial components in a differential manner, releasing interleukin-8 in response to pathogenic bacteria such as *E. coli* but not to probiotic strains.
- Bacterial DNA recognition in a differential manner by epithelial cells, with pathogenic strains evoking a phosphorylation of the extracellular signal-regulated kinase pathway and activation of activator protein-1.
- Modulation of the nuclear factor- κ B pathway in response to TNF- α .

3. The aims of intervention

To avert deviant micro biota development, impair the gut barrier function, elevate abnormal immune responsiveness, and decrease immune inflammatory reactions.

At an early age, probiotic supplementation aims to provide safe yet sufficient microbial stimulus for the immature immune system, contributing to the anti-inflammatory tone of

the intestinal milieu.

Probiotics are selected from members of the normal healthy intestinal micro biota, most of them belonging to *Lactobacillus* or *Bifidobacterium* species, but new probiotic microbes from other species and genera have recently been introduced. Improved understanding of the host-microbe interaction at different ages will lead to the development of a new generation of probiotics, the action of which could be selected for defined disease-associated aberrancies. Identification of new *Bifidobacterium* and *Lactobacillus* species and strains from the gastrointestinal tract of healthy subjects might then allow us to devise better target- and age-specific probiotics, which might be recognized with risk reduction of human disease in the future. It is well established that different probiotic strains induce distinct responses, and thus specific strains might have specific targets in reducing the risk and treatment of human disease. Probiotic strains selected for their beneficial effects in providing maturational signals for the infant's immune system and propagating oral tolerance induction might be of no use in treating adults. Further research might also substantiate the clinical efficacy of genetically modified probiotic bacteria, as indicated by the initial studies on *Lactococcus lactis* engineered to produce IL-10 locally.

Probiotic research exemplifies that the dietary approach to reduce allergic diseases is evolving from passive elimination diets to supplementation with active immunomodulatory compounds. Still, because of interaction between nutrients, no single supplement can be expected to resolve the challenge of allergic disease, and better understanding of the interaction between nutrients is required.

4. Clinical Context

Probiotics such as *Lactobacillus* species have been theorized to improve the balance of gastrointestinal tract flora and immune function within the gut. Through biopsies of the gastrointestinal tract, researchers have shown that probiotic bacteria can colonize and grow within the gut following oral administration. Moreover, in children with diarrhea due to rotavirus, *Lactobacillus* administration has been demonstrated to improve IgA humoral immunity compared with controls. In addition, several clinical trials have provided evidence of probiotic effectiveness for the treatment and prevention of acute diarrhea and antibiotics-induced diarrhea as well as for the prevention of cow milk-induced food allergy in infants and young children. Probiotics are also effective for the prevention of traveler's diarrhea, relapsing *Clostridium, difficile*-induced colitis and urinary tract infections.

The body's response to probiotic agents can lead to improved clinical outcomes. According to a meta-analysis by Van Niel and colleagues that appeared in the April 2002 issue of *Pediatrics*, probiotics can reduce the symptoms of pediatric diarrhea by 0.7 days and they were also shown to reduce diarrhea episode frequency by a mean of 1.6 fewer stools per day beginning on day 2 of probiotic treatment.

Furthermore, two strain combinations of *Lactobacillus rhamnosus GR-I* and *Lactobacillus reuteri RC14* have proved to be the most effective at restoring and maintaining a normal vaginal microbiota. On the other hand, food sensitivities are

constantly increasing in westernized countries and may pose serious health risks to sensitized individuals, thus the need for safe and effective probiotics strains and food supplements is now emerging clearly. Allergen-free probiotics represent this innovative and safe tool for human health.

5. How Probiotics Work?

To understand how probiotics work, it is important to understand a little about the microbiology and physiology of the human gastrointestinal tract. Probiotic bacteria are normal inhabitants of microflora and may confer several benefits, including prevention against intestinal inflammation. However, the exact mode of action of probiotics is still largely unknown. The origin of micro biota and its development depends on genetics, mode of delivery, early feeding strategies and the hygienic conditions around the child. The native micro biota of an infant gastrointestinal tract is modulated through contact and interaction with the micro biota of the parents and the infants' immediate environment. Modifying this exposure can take place by probiotic bacteria when breastfeeding is not possible. Thus, incorporating specific probiotics may form a beneficial possibility for future infants feeding purposes. Many probiotics have documented strain-specific health-promoting effects, and most of the effects have been demonstrated in infants and children. Live probiotic bacteria and dietary prebiotics oligosaccharides are being used increasingly in infancy and they seem to be safe and increase resistance to respiratory infection during the first two years of life. They are beneficial to the gastrointestinal health of infants, so infants fed formulas containing probiotics or synbiotics showed a similar safety and tolerance. Probiotics maybe useful for prevention of dental carries. Irritable bowel syndrome and inflammatory bowel disease.

Human beings, like all animals, play host to many types and high numbers of microbes on our skin, in our mouths, in women's vaginal tracts, and all the way through our gastrointestinal tract. In fact, it has been estimated that there are more microbes associated with the human body (about 10^{14} , or 100,000,000,000,000 bacterial cells) than there are human cells in it (about 10^{13}). In addition to this very large number of bacteria, there also is a very large diversity of bacteria. It has been estimated that more than 400 different species, or types, of bacteria make their homes on humans.

Taking this into consideration, it is not surprising that microbes have been found to play an important role in human health. Most of these bacteria are not harmful, and in fact contribute positively to normal human growth and development. But some of these bacteria can have negative influences. It is therefore important that the balance of microbes be maintained to favor the beneficial bacteria over the potentially harmful ones as is necessary for digestive and immune health.

The first line of defense against the entry of pathogens is represented by the gut membrane barrier and probiotics may prevent pathogen-induced membrane damage by inhibiting pathogen adhesion and maintaining the correct organization of the tight junction and cytoskeleton proteins. Thus, benefits include prevention of diarrhea, decreased mortality, establishment of a healthy microbiota balance and improved immune function.

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Biographical Sketch

Dr. Aziz Koleilat, born in Beirut 1939, accomplished his premedical studies at the American University of Beirut, Lebanon and in 1966 he graduated from Charles University Prague, Czech Republic - Pediatric Faculty .He pursued his postgraduate studies and training at the Teaching Hospital of Charles University, Prague. He acquired his first and second attestation (board degrees) at the Institute for Postgraduate Medical Studies Prague, Czech Republic.

During 1974-1978 he was appointed the Chairman of the Department of Pediatrics of Berbir Hospital in Beirut, affiliated to Lebanese University & Saint Josef University. During 1978-1984 and 2005-2008 he was the Chairman at The Makassed University Hospital which is affiliated to Lille 2 University, France, the American University of Beirut, the Arab University of Beirut and the Lebanese University. During his 2005-2008 Chairmanship at the Makassed University Hospital he was appointed as the Director of Pediatric Residency Program and joined in training program in Nutrition. He published articles in gastroenterology and was elected the Vice General Secretary of the Pan Arab Pediatric Society of Gastroenterology, Nutrition & Hepatology. He lectured in the field of gastroenterology and nutrition at various congresses and symposia in the Czech Republic and various Arab and Mediterranean countries.

He is a member of many Lebanese, Arab and Czech & Polish medical societies, organizations and advisory committees and he has presided over several Arab congresses.

During his medical career he established several pediatric departments in various hospitals in Lebanon - Berbir Hospital, Makassed Hospital, and Hospital of Mother & Child Care.

Dr. Koleilat was the first one to establish Pediatric Award for the best research paper for pediatric residents in Lebanon.

During the Lebanese civil war he established the Development Society for aiding the population in Beirut, worked with international associations and conducted a survey for TB prevalence among displaced people.