Editorial

Probiotics: concept and applications

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Introduction:

'If gut bacteria are making you ill, can swapping them make you healthy?' This is where the concept of probiotics enters the discussion about microbiota gone awry. The United Nations Food and Agricultural Organization and the World Health Organization define probiotics as "live microorganisms such as bacteria or yeast that are similar to beneficial microorganisms found in the human gut, which when administered in adequate amounts confer a health benefit on the host." There are substantial evidences that probiotics may have a role in treating gastrointestinal illnesses, boosting immunity, and preventing or slowing the development of certain types of cancer[1,2]. They are also called "friendly bacteria" or "good bacteria" and are believed to improve health. Probiotics are derived from traditional fermented foods, from beneficial commensals or from the environment. They are available to consumers mainly in the form of dietary supplements and foods. The idea of taking live bacteria or yeast may seem strange at first. After all, we take antibiotics to fight against bacteria. But our bodies naturally teem with such organisms. The digestive system is home to more than 500 different types of bacteria. They help keep the intestines healthy and assist in digesting food.

About a century ago in 1908, Elie Metchnikoff (a Russian scientist, Nobel laureate, and professor at the Pasteur Institute in Paris) postulated that lactic acid bacteria (LAB) offered health benefits capable of promoting longevity. He suggested that "intestinal auto-intoxication" and the resultant aging could be suppressed by modifying the gut microbiota and replacing proteolytic microbes such as Clostridium, which produce toxic substances including phenols, indoles, and ammonia from the digestion of proteins with useful microbes. He developed a diet with milk fermented with the bacterium he called *Bulgarian bacillus*[3]. The concept of probiotics evolved based on such observations. Etymologically the term probiotic is derived from the Greek language meaning "for life". The term "probiotics" was first introduced in 1965 by Lilly and Stillwell; in contrast to antibiotics, probiotics were defined as microbially derived factors that stimulate the growth of other organisms. In 1989, Roy Fuller emphasized the requirement of viability for probiotics and introduced the idea that they have a beneficial effect on the host.

What are probiotics?

Probiotics are live microbes that can be formulated into many different types of products, including foods, drugs, and dietary supplements. Species of Lactobacillus and Bifidobacterium are most commonly used as probiotics, but the yeast Saccharomyces cerevisiae and some E. coli and Bacillus species are also used as probiotics. Lactic acid bacteria, including Lactobacillus species, which have been used for preservation of food by fermentation for thousands of years, can serve a dual function by acting as agents for food fermentation and, in addition, potentially imparting health benefits. Strictly speaking, however, the term "probiotic" should be reserved for live microbes that have been shown in controlled human studies to impart a health benefit. Fermentation of food provides characteristic taste profiles and lowers the pH, which prevents contamination by potential pathogens. Fermentation is globally applied in the preservation of a range of raw agricultural materials (cereals, roots, tubers, fruit and vegetables, milk, meat, fish etc.).

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Lactobacillus- a model probiotic

As far as nutrition is concerned only the strains classified as lactic acid bacteria are of significance and among them the ones with the most important properties in an applied context are those belonging to the genera Lactococcus and Bifidobacterium. Lactic acid bacteria are Gram-positive, catalase-negative bacterial species able to produce lactic acid as main end-product of carbohydrate fermentation. Lactobacillus is a type of bacterium having lots of different species. These are "friendly" bacteria that normally live in our digestive, urinary, and genital systems without causing disease. Lactobacillus is also used in some fermented foods like yogurt and in dietary supplements. Lactobacillus is used for treating and preventing diarrhea, including infectious types such as rotaviral diarrhea in children and traveler's diarrhea.

It is also used to prevent and treat diarrhea associated with using antibiotics. Some people use lactobacillus for general digestion problems; irritable bowel syndrome (IBS); colic in babies; Crohn's disease; inflammation of the colon; and a serious gut problem called necrotizing enterocolitis (NEC) in babies born prematurely. Lactobacillus is also used for infection with H. pylori and also for other types of infections including urinary tract infections, vaginal yeast infections, to prevent the common cold in adults, and to prevent respiratory infections in children attending daycare centers. Lactobacillus is used for skin disorders such as fever blisters, canker sores, eczema (allergic dermatitis); and acne. It is also used for high cholesterol, lactose intolerance, Lyme disease, hives, and to boost the immune system. Currently it is also being tested to prevent serious infections in people on ventilators. Women sometimes use lactobacillus suppositories to treat vaginal infections.

How do probiotics work?

In vitro studies suggest that probiotics potentially act favorably in the host through several different mechanisms. They have an antimicrobial effect through modifying the microflora, secreting antibacterial substances, competing with pathogens to prevent their adhesion to the intestinal epithelium, competing for nutrients necessary for pathogen survival, producing an antitoxin effect and reversing some of the consequences of infection on the intestinal epithelium, such as secretory changes and neutrophil migration[4,5]. Probiotics are also capable of modulating the immune system[6], regulating the allergic immune cell response of the body[7] and reducing cell proliferation in cancer[8]. The effects of these agents may go beyond the gastrointestinal tract to distant areas, such as the urogenital and respiratory mucosa, and it may not be necessary to administer the intact probiotic organism to achieve benefits.

Probiotics are the subject of increasing basic and clinical research, while also being incorporated into an expanding array of foods, nutritional supplements and pharmaceutical products globally. Researchers believe that some digestive disorders happen when the balance of friendly bacteria in the intestines becomes disturbed. This can happen after an infection or after taking antibiotics. Intestinal problems can also arise when the lining of the intestines is damaged and taking probiotics may help. “Probiotics can improve intestinal function and maintain the integrity of the lining of the intestines. These friendly organisms may also help fight bacteria that cause diarrhea.

Probiotic products and clinical applications

Probiotic bacteria have become increasingly popular during the last two decades as a result of the continuously expanding scientific evidence pointing to their beneficial effects on human health. The range of food products containing probiotic strains is wide and still growing. The main products existing in the market are dairy-based ones including fermented milks, cheese, ice cream, buttermilk, milk powder, and yogurts, the latter accounting for the largest share of sales. Probiotics can also be found as nutritional supplements, drugs and medical foods. Each product has country-specific legal requirements for allowed claims of efficacy, target populations, safety and risk/benefit assessment. Hypothesized future uses for probiotics in modifying the composition or activities of the microbiota for improved health. A range of health and clinical targets for different probiotics have been studied, encompassing intestinal and extraintestinal sites, and over a range of life stages. Mechanisms for observed health effects may not be known, but probably include direct or indirect action on the activities and/or populations of gut microbiota and on the intestinal immune system.

Probiotics have been advocated for the prevention and treatment of a diverse range of disorders, from acute gastroenteritis to intestinal neoplasia. The evidence for their efficacy in many such disorders is not strong, but there are well-established benefits in a small number of conditions. Current insights into the clinical applications for various probiotics include

cardiovascular disease, colon cancer, acute diarrhea, antibiotic-associated diarrhea & radiation associated diarrhea, H. pylori infection, allergic conditions, hepatic encephalopathies, inflammatory bowel diseases, irritable bowel syndrome common infectious disease, necrotising enterocolitis, lactose malabsorption, nonalcoholic fatty liver disease, upper respiratory tract infections, prevention of systemic infections, boosting immune response etc[9].

The literature on the health benefits of probiotics has often focused on disease states using either animal models of such diseases or studies in human populations[10]. More recently, investigators have been asking how to measure the impact of probiotics on healthy individuals, such as reducing the risk of developing disease or optimizing physiological function within normal ranges. The distinction between research aimed at maintaining health and that aimed at treating a disease has important regulatory implications; the former can be applied to foods and supplements, whereas the latter is confined to drugs.

In general, the strongest clinical evidence for probiotics is related to their use in improving gut health and stimulating immune function.

Probiotics and the immune system

There is growing evidence that probiotics help maintain a strong immune system. In societies with very good hygiene, we've seen a sharp increase in autoimmune and allergic diseases. That may be because the immune system isn't being properly challenged by pathogenic organisms. Introducing friendly bacteria in the form of probiotics is believed to challenge the immune system in healthy ways. The most powerful and important aspect of the immune system involves the body's probiotic bacteria. The human body houses more than 32 billion beneficial and harmful bacteria and fungi at any particular time. When beneficial bacteria are in the majority, they constitute 70-80% of the body's immune response. Probiotic colonies work with the body's internal immune system to organize strategies that prevent toxins and pathogenic microorganisms from harming the body. Probiotics communicate and cooperate with the immune system to organize cooperative strategies. They stimulate the body's immune cells, activating the cell-mediated response, the humoral response, and indirectly, the body's exterior barrier mechanisms through immunoglobulin stimulation. Three decades of medical research has indicated that probiotics stimulate T-cells, B-cells, macrophages and NK-cells with smart messages that promote specific immune responses. They also activate cytokines and phagocytic cells directly to coordinate their intelligent immune response.

Further, probiotics produce antimicrobial biochemicals that manage, damage or kill pathogenic microorganisms. In some cases, they will simply overcrowd the invaders with biochemistry and populations to limit their growth. In other cases, they will secrete chemicals into the fluid environment to eradicate large populations. In still other cases, they will insert specific chemicals into the invaders, which will directly kill them. Probiotic mechanisms are quite complex and variegated to say the least. Probiotics also produce acetic acids, formic acids lipopolysaccharides, peptidoglycans, superantigens, heat shock proteins and bacterial DNA-all in precise portions to nourish each other, inhibit challengers and/or benefit the host. Probiotics also produce antibacterial molecules called bacteriocins. Lactobacillus plantarum produces lactolin. Lactobacillus bulgaricus secretes bulgarican. Lactobacillus acidophilus can produce aciophilin, acidolin, bacterlocin and lactocidin. These and other antibacterial substances equip probiotic species with territorial mechanisms to combat and reduce pathologies related to Shigella, Coliform, Pseudomonas, Klebsiella, Staphylococcus, Clostridium, Escherichia and other infective genera[11].

Safety of probiotics

There is considerable interest in probiotics for a variety of medical conditions, and millions of people around the world consume probiotics daily for perceived health benefits. Unique to probiotics is that they are alive when administered, and unlike other food or drug ingredients, possess the potential for infectivity or in situ toxin production. There are 3 theoretical concerns regarding the safety of probiotics: (a) the occurrence of disease, such as bacteremia or endocarditis; (b) toxic or metabolic effects on the gastrointestinal tract; and (c) the transfer of antibiotic resistance in the gastrointestinal flora. Although considerable differences exist in the bioavailability, biological activities, doses and composition among probiotic preparations but there have been many controlled clinical trials on the use of probiotics that demonstrate safe use. But still further studies are necessary to increase understanding of how probiotic agents produce effects on the host as

various strains of probiotic bacteria may work by distinct mechanisms. It is important to recognize that in vitro effects of a probiotic may display opposite behavior in vivo[12]. Although probiotics have an excellent overall safety record, they should be used with caution in certain patient groups—particularly neonates born prematurely or with immune deficiency. Because of the paucity of information regarding the mechanisms through which probiotics act, appropriate administrative regimens, and probiotic interactions, further investigation is needed in these areas.

The future

It seems clear that there is an association of microbiome alterations with a progression from health to disease. However, causality and reversal of disease in response to probiotic-induced microbiome changes still remain to be demonstrated. Until a healthy microbiome is clearly defined, providing a microbiological target for probiotic interventions, probiotic benefits must be described in the context of physiological or clinical improvement. In the future, probiotics developed to address microbiota-associated conditions will probably move beyond the microorganisms commonly used as probiotics today. Genetically modified microorganisms can provide epitopes for efficient oral vaccine delivery, improve vaccine or natural immune responses, or restore antigen-specific tolerance. Probiotic strains with altered cell surface components, such as lipoteichoic acid, provide a potential strategy for the treatment of inflammatory intestinal disorders. Recently, faecal microbiota transplant from non-diabetic donors infused into the duodenum of patients with the metabolic syndrome improved their insulin sensitivity, highlighting the broad potential of this intervention. However, cocktails of defined microbes imparting key functionalities may provide a more acceptable approach. Finally, specific strains with uniquely useful properties, such as Oxalobacter formigines (kidney stones), F prausnitzii (chronic gut inflammation), Bacteroidetes and Fusobacterium (cancer risk), should be more thoroughly studied in well designed clinical trials[13].

More effective probiotic interventions for microbiota-associated conditions require a more complete understanding of the interactions between genetic, microbial and environmental influences within individuals. Such an approach will also facilitate the identification of subsets of patients most likely to respond to manipulations of the gut microbiota and the optimal agents to use in an individual subject. The effect of widespread use of safe and effective probiotic products on society-wide economic and quality-of-life indicators should be assessed with end points such as reduction of common infectious diseases in developing and developed nations. Such information could provide support for sustained research in this field.

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