Probiotics, Prebiotics and Synbiotics: Biologic Therapies For Nutritional Recommendations In Improving Health

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Abstract: ***Live microbial supplementation (yogurt, fermented milk, bacterial lyophilizates, and more recently, infant formula, unfermented milk, juices or candy) have been proposed to control various digestive or extra-digestive diseases. The micro biota management tools of Probiotics, Prebiotics and Synbiotics have been developed and indeed, commercialized over the past few decades. Inrecent years, increasing attention has been focused on the possible beneficial effects of Probiotics, Prebiotics and Synbiotics, such as enhanced resistance to invading pathogens, improved bowel function, anti-colon cancer properties, lipid lowering action, and improved calcium bioavailability, amongst others. Several aspects, including safety, functional and technological characteristics, have to be taken into consideration in the selection process of probiotic micro-organisms. Safety aspects include specifications such as origin (healthy human GI-tract), non-pathogenicity and antibiotic resistance characteristics. Functional aspects include viability and persistence in the GI-tract, immunomodulation, antagonistic and antimutagenic properties. Both probiotics and prebiotics may be helpful in malnutrition, particularly in lactose intolerance and calcium absorption, and in constipation. Increasing evidence suggests that combining several probiotic bacteria into multistrain probiotics will achieve stronger effects than single-strain probiotics. Combining probiotics and prebiotics into "Synbiotics" will further enhance the immune supportive effects. A number of human disease states may benefit from the use of probiotics, most notably, diarrheal illnesses, some inflammatory bowel diseases, certain infectious disorders, and irritable bowel syndrome. Prebiotics promote the growth of "good" bacteria, and although a variety of health benefits have been attributed to their use.***

Keywords: Intestinal Microflora; Probiotics; Prebiotics; Synbiotics.

I. INTRODUCTION

In recent years, the concept of functional foods has been examining food additives that may exert beneficial effects on the composition and/or activity of the host intestinal micro biota and an important class of functional foods has received considerable attention: probiotics and prebiotics.[1, 2]Each person presents a distinct and highly variable intestinal micro biota, at least at the species level; however, a stable core of intestinal colonists (intestinal microbiota-core) and of genes (microbiome-core) are shared by individuals and may be related to the intestinal function.[3] The intestinal microbiota is in direct contact with the intestinal mucosa. Both, along with the mucus, form the so-called mucosal barrier, an important defense system against potentially pathogenic and immunogenic factors present in the lumen. In fact, the mucous membrane separates the lumen containing the microbiota, organic food waste and secretions (salivary, gastric, biliary, pancreatic and intestinal) from the lymphoid tissue associated with the intestines.[4,5] The cells that make up the immune system are mainly concentrated in the lymphatic organs located in the lamina propria of the GIT. The lymphoid tissue associated with the intestine is composed of several follicular structures, Peyer's patches, T lymphocyte aggregates, antigen-presenting cells and B lymphocytes. The classical example of this is antibiotic-associated diarrhea and its deadliest manifestation, *Clostridium difficilecolitis*, which is a scourge of hospitals and nursing homes with the frail and elderly being especially susceptible. This microbial population increases throughout the gastrointestinal tract (GIT) showing approximately 10^3 micro-organisms/ml of the luminal content in the duodenum, 10^8 micro-organisms/g of the ileal content and up to 10^{12} micro-organisms/g of the colonic content.[6,7,8] The immunological interaction between the micro biota is disturbed and the host may, for example, begin to recognize the constituents of the normal micro biota, not as friend but as foe, and may mount an inappropriate inflammatory response that may ultimately lead to conditions such as inflammatory bowel disease. Any injury to the intestine that makes it more leaky will permit bacteria (in whole or in part) to gain access to the sub mucosa or even to the circulation, with the associated potential to cause catastrophic sepsis, a mechanism that is thought to account for many of the infections that occur in the critically ill in the intensive care unit, following major surgery or significant trauma.[9,10,11,12] Most recently, qualitative changes in the micro biota have been invoked in the pathogenesis of a global epidemic: obesity. It has been postulated that a shift in the composition of the micro biota toward a population where bacteria are more avid extractors of absorbable nutrients, thus delivering more calories to the host, could play a major role in obesity.[13,14,15]In 1908, Russian researcher ElieMetchnikoff,

who got a Nobel Prize, firstly proposed the beneficial effects of probiotic microorganisms on human health. Metchnikoff hypothesized that Bulgarians are healthy and long-lived people because of the consumption of fermented milk products which consist of rod-shaped bacteria (*Lactobacillus* spp.). Therefore, these bacteria affect the gut micro flora positively and decrease the microbial toxic activity in human intestine.[16,17,18]Probiotics are live microbial food supplements which benefit the health of consumers by maintaining or improving their intestinal microbial balance and defined as live microbial food ingredients beneficial to health are normal commensal bacteria of the healthy human gut micro flora.[19,20,21]Our current usage of the term probiotic was proposed by Roy Fuller who deleted "other substances" from the definition and defined probiotics as "live microbial feed supplements which beneficially affects the host animal by improving its intestinal microbial balance". Our current definition of probiotics was formulated in 2001 by FAO/WHO as "live microorganisms which, when administered in adequate amount, confera health benefits to the host".[22,23,24,25] In 2002 FAO/WHO subsequently drafted guidelines regarding the evaluation of probiotics in various food products. Prebiotics are indigestible food ingredients that selectively promote the growth or activity of beneficial bacteria, thereby benefiting the host. In Japan, in the early 1930s,Shirota succeeded in isolating strains existing in healthy individuals' intestinal bacteria. [26,27,28] He has used such strains to develop fermented milk and test its effects on patients. He introduced his first product, Yakult, into the market. The isolated bacteria used in this fermented milk were later named *Lactobacillus caseiShirota*.[29,30,31,32Changes] in the diet, including the amount, type and balance of the main dietary macronutrients (carbohydrates, proteins and fats), may significantly affect the intestinal micro biota diversity, which may influence its functional relation with the host. Due to their perceived health benefits probiotic bacteria have been increasingly included in yoghurts and fermented milks during the past two decades. Most commonly they have been lactobacilli such as *Lactobacillusacidophilus* and Bifidobacteria often referred to as 'Bifidus'.[33,34,35]A major development in functional foods pertains tofoods containing probiotics and prebiotics whichenhance health promoting microbial flora in theintestine. There is growing scientific evidence tosupport the concept that the maintenance ofhealthy gut microflora may provide protectionagainst gastrointestinal disorders including gastrointestinalinfections, inflammatory bowel diseases,and even cancer. The useof probiotic bacterial cultures stimulates thegrowth of preferred micro-organisms, crowds outpotentially harmful bacteria, and reinforces thebody's natural defense mechanisms.[36,37,38]. The consumption of probiotic microorganisms and prebiotic ingredients is a promising alternative to beneficially influence the intestinal microbial ecology, maintaining the intestinal homoeostasis and controlling the dysbiosis, and, consequently, improving health.[39,40] Therefore, intestinal micro biota is an important target for interventions with probiotics and prebiotics, administered as supplements or food ingredients, with the specific goal of modulating the microbial community composition, as well as the microbiome functional capacity. Today, plenty of evidence exists on the positive effects of probiotics on human health. However, this has usually been demonstrated in diseased human populations only. Thus there is an urgent need for evidence for probiotic health benefits in average (generally healthy) populations.[41,42,43,44,45] Preterm infants lack adequate intestinal commensal or "healthy" bacterial flora, which regulate natural defense systems by promoting sufficient maturation, inflammatory response, and homeostasis in the underdeveloped gut. Before a probiotic can benefit human health itmust fulfill several criteria: It must have good technological properties so that it can be manufactured and incorporated into food products without losing viability and functionality or creating unpleasant flavors or textures; it must survive passage through the upper gastrointestinal(GI) tract and arrive alive at its site of action; and it must be able to function in the gut environment. To study the probiotic strain in the GItract, molecular techniques must be established for distinguishing the ingested probiotic strain from the potentially thousands of other bacterial strains that make up the gastrointestinal ecosystem.[46,47,48]Additionally, techniques are required to establish the effect of the probiotic strain on other members of the intestinal micro biota and importantlyon the host. This includes not only positivehealth benefits, but also demonstration that probioticstrains do not have any deleterious effects.Armed with this knowledge, the probiotics canthen enter human pilot studies that attempt toassess their health benefits to consumers.[28, 29,30Compared] with probiotics, which introduce exogenous bacteria into the human colon, prebiotics stimulate the preferential growth of a limited number of health-promoting species already residing in the colon, especially but not exclusively lactobacilli and bifidobacteria. galactooligosaccharides have been identified as prebiotics due to characteristics such as resistance to gastric acidity and hydrolysis by mammalian enzymes and they are fermented by gastrointestinal microflora to further selectively stimulate the growth and activity of beneficial microorganisms.[49,50,51]Synbiotics, defined as a combination of a probiotic and a prebiotic, aim to increase the survival and activity of proven probiotics in vivo, as well as stimulating indigenous bifidobacteria and lactobacilli.[52,53,54,55]

Table 1: Probiotic categorization across the Globe

Country	Category	Definition as per country	Regulatory body
India	Functional foods, drugs	Food that has physiological functions, including regulation of biorhythms, the nervous system, the immune.	FSSA, PFA, FDA
China	Functional foods	Functional food has special health functions or is able to supply vitamins or minerals and has the capability to regulate human body functions.	SFDA
Malaysia	Functional Foods	Currently no official definition available for functional food products in Malaysia.	FSQD, the Drug Control Authority, NPCB and the Committee for the Classification of Food-Drug Interface Products
Japan	Functional foods and Nutraceuticals	Food for Specified Health Use, with a specific regulatory approval process separate from food fortified with vitamins, minerals, and dietary supplement not carrying FOSHU claims.	MHLW, FOSHU
Europe	Functional foods	Food that beneficially affects one or more target functions in the body beyond adequate nutritional effects in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease.	FUFOSE
Brazil	Functional foods	Functional foods constitute items to which health ingredients are added due to which have specific physiological function and/or are enhanced with added ingredients not normally found in the product, providing health benefits beyond their nutritional value.	ANVISA
New-Zealand and Australia foods	Functional	Functional foods are products which are supposed to serve physiological roles beyond the provision of simple nutrient requirements.	FSANZ
USA	Dietary supplements	Dietary supplements are intended to supplement the diet; containing one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents and also to be taken by mouth as a pill, capsule, tablet, or liquid; and are labeled on the front panel as being a dietary supplement.	DSHEA

Table 2 Constituents of dietary fiber according to the classification of American Association of Cereal Chemists

Nonstarch polysaccharides and resistant oligosaccharides Cellulose, Hemicellulose, Arabinoxylans, Arabinogalactans, Polyfructoses, Inulin, Oligofructans, Galactooligosaccharides, Gums, Mucilages, Pectins
Analogous carbohydrates Indigestible dextrins, Resistant maltodextrins (from maize and other sources), Resistant potato dextrins
Synthesized carbohydrate compounds Polydextrose, Methylcellulose, Hydroxypropylmethyl cellulose, Indigestable (“resistant”) starches, Lignin
Substances associated with nonstarch polysaccharide and lignin complexes in plants Waxes, Phytate, Cutin, Saponins, Suberin, Tannin

II. THE INTESTINAL MICRO FLORA

Intestinal micro biota, a term used to replace the former name of intestinal microflora, is an ecosystem consisting of different ecological niches composed of a huge diversity of bacterial species and strains. The human gastrointestinal microbiota is a complex ecosystem of approximately 300–500 bacterial species comprising nearly 2 million genes (the "microbiome"). Indeed, the number of bacteria within the gut is about 10 times that of all cells in the human body. At birth, the entire intestinal tract is sterile; bacteria enter the gut with the first feed. One moves along the gut, the number and diversity of organisms that comprise the microbiota increase, and on crossing into the colon, the bacterial concentration and variety of the enteric microbiota change dramatically. Concentrations as high as 10^{12} colony-forming units/mL may be found, comprised mainly of anaerobes such as *Bacteroides*, *Porphyromonas*, *Bifidobacterium*, *Lactobacillus*, and *Clostridium*, with anaerobic bacteria outnumbering aerobic bacteria by a factor of 100–1000:1.3. When components of the normal microbiota are eliminated or suppressed by a course of broad-spectrum antibiotics, the stage is set for other organisms that may be pathogenic to step in and cause disease. The classical example of this is antibiotic-associated diarrhea and its deadliest manifestation, *Clostridium difficilecolitis*, which is a scourge of hospitals and nursing homes with the frail and elderly being especially susceptible. Nutrients and vitamins, such as folate and vitamin K, are produced by enteric bacteria. The relationship between the host's immune system and nonpathogenic constituents of the microbiota is important in protecting the host from colonization by pathogenic species. In this regard, intestinal bacteria produce a variety of substances, ranging from relatively nonspecific fatty acids and peroxides to highly specific bacteriocins, which can inhibit or kill other, potentially pathogenic, bacteria. The main functions of the intestinal micro biota include participation in the intestinal wall formation; colonization resistance against pathogens; production of SCFA; butyrate, propionate and acetate; production of vitamins, especially vitamin B and vitamin K complex; interactions with the mucosal immune system; and degradation of xenobiotics. Human Microbiome Project Launched in 2007 initiated programs to examine the healthy body's microbial environments. Studies found that a delicate balance between commensal and pathogenic bacteria supports normal function, immunology, and homeostasis in the healthy intestine, and disruption of this balance may lead to disease onset. The vast majority of potentially probiotic lactic acid bacteria (LAB) belongs to the phylum Firmicutes, a very diverse group of bacteria with low G+C genomic contents and which includes the Aerococcus, Enterococcus, Lactobacillus, Lactococcus, Leuconostoc, Oenococcus, Pediococcus, Streptococcus, Carnobacterium, Tetragenococcus, Vagococcus and Weissella genera. Lactobacilli are found in a variety of habitats where rich, carbohydrate-containing substrates are available, such as on human and animal mucosal membranes, on plants or material of plant origin, on sewage, and on fermented milk products, fermenting or spoiling food. Bifidobacteria comprise a major part of the normal intestinal microflora in humans throughout life. The number of Bifidobacteria in the colon of adults is 10^{10}-10^{11}cfu/gram, but this number decreases with age.

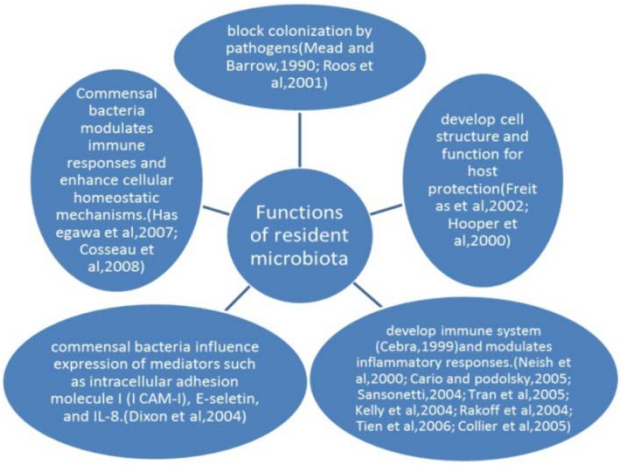

Figure. 1: Functions of the Resident Micro biota

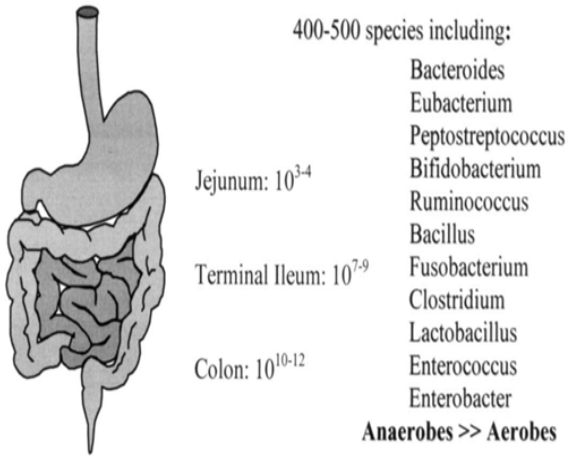

Figure 2. Bacterial flora along the gastrointestinal tract

Fluctuations in the composition of the intestinal ecosystem have been associated with various diseases, including imunnoinflammatory disorders, obesity and cancer. The wide diversity of intestinal micro biota has only recently been recognized because of the development and use of culture-independent molecular methods, which are based on the analysis of the 16S ribosomal RNA. These techniques have indicated that most bacteria in intestinal microbiota from healthy individuals belong to three main phyla: Firmicutes, Bacteroidetes and Actinobacteria.

Probiotics:

Probiotics, derived from Greek and meaning "for life," are defined as live organisms that, when ingested in adequate amounts, exert a health benefit to the host. Probiotics are classified under distinctive classifications in diverse nations. They are named diversely as regular wellbeing items in Canada, dietary supplements, drugs, therapeutic sustenance, live bio therapeutic specialists, natural operators according to their planned use in USA, utilitarian nourishment in Japan, China, Malaysia, as sustenance supplement in Sweden, Denmark and Finland, bio therapeutic or pharmaceuticals European nations like Belgium and Germany. In 1965 the term "probiotic" was first used by Lilly and Stillwell to describe substances which kindle the growth of other microorganisms. Probiotic definition was improved by Parker in 1974. Parker defined "probiotic" as "substances and organisms which contribute to intestinal microbial balance." In 1989, definition for probiotics was improved by Fuller as Probioticmicroorganisms do not act exclusively in the large intestine via affecting the intestinal flora. They also affect other organs, either by modulatingimmunological parameters, intestinal permeability, and bacterialtranslocation or by providing bioactive or otherwiseregulatory metabolites. The broader definitions havebeen suggested by Schrezenmeir and de Vreseby the International Life Sciences Institute (ILSI) Europe,according to which probiotics have been defined as "a viablemicrobial food supplement which beneficially influences thehealth of the host". Several commercially available supplements contain viable microorganisms with probiotic properties. The most common sources of probiotics are yogurt, cultured buttermilk, and cheese. Cultured buttermilk is made with bacteria that produce lactic acid, which makes the product sour. Some cultured cheese use bacteria to finish the maturation of the cheese. Another fermented dairy product is Kefir. Traditionally, yogurt has only one or two bacteria whereas Kefir tends to have several probiotic bacteria.Other foods that are produced by bacterial fermentation are Japanese miso, tempeh, sauerkraut, beer, sour dough, bread, chocolate, kimchi, olives, and pickles. The dominant food vehicles for probiotics are still yogurts and fermented milks, both of which provide a relatively low pH environment in which the probiotic bacteria must survive. However, many studies show that probiotics strains are also found in nondairy fermented substrates. Some of the nondairy probiotic products are cereal, legume, cabbage, maize, pearl millet, vegetable, sorghum, and so forth. The most commonly used probiotics are lactic acid bacteria and nonpathogenic yeasts. Although probiotics have been proposed for use in inflammatory, infectious, neoplastic, and allergic disorders, the ideal probiotic strain, for use in any of these indications, has yet to be identified. In India Amul, Nestle and Mother Dairy are contributing a ton to Probiotic dairy items and acknowledgment amongst urban populace is serving to build organizations center to create Probiotics items. In India, Probiotics are frequently broadly utilized as creature food supplements for dairy creatures like steers, poultry and piggery. Lactobacilli suspension is a case of a probiotic detailing, generally given to pediatric patients in India for wide mixed bag of helpful advantages. ViB act is the most recent and late expansion to the rundown of Probiotics in India (made out of hereditarily changed Bacillus mesentricus), which goes about as another to B-complex containers. Sporulating lactobacilli are created and are sold with a portion of the anti-microbial arrangements in India. The sufficient dose of probiotic micro-organisms to lead to beneficial health effects may vary depending on the strain and the product. In general, products containing probiotic micro-organisms should have a minimum number of viable cells, with proven efficacy established based on human clinical trials, estimated to be between 10^6 and 10^8 colony-forming unitsper gram (CFU/g) of end product or 10^8–10^{10} CFU/d (considering 100 g or 100 ml of the ingested food). Brazilian legislation recommends a minimum probiotic population ranging from 10^8 up to 10^9 CFU/daily serving portion of the food product to obtain a beneficial health effect in the gut(35). A similar number of viable probiotic cells (10^9 CFU) per serving portion, consumed on a daily basis, is also recommended by Health Canada and the Italian Health Ministry.

Commercialization of Probiotics:

In 1906, "Le Fermente" a French Society began marketing a fermented milk product (Lactobacilline) containing *Streptococcusthermophilusand Lactobacillus delbruekii.* In 1919, Isaac Carasso similarly began commercial production of yogurt in Spain. It is whether these organisms were able to survive transit through the upper gastrointestinal tract. Accordingly, Yakult (described above) fermented milk is commonly cited as the first commercially available probiotic. Unclear that these products contained living organisms and, if so, In the earlier part of last century, focus was on the use of fermented milk with probiotics to take care of intestinal infections. Gradually focus has shifted to survival of these bacteria in the gastrointestinal tract and the carrier food to have their beneficial effect on the host. From the late 1930's onward, interest in probiotics gradually decreased as a result of the pressures of the Great Depression, World War II, and the discovery and proliferation of various antibiotics. However, global trends from the 1980's to the present have included increasing antimicrobial resistance, limited pharmaceutical research and development in infectious diseases, skyrocketing costs for new antibiotics, and discrepancies in availability and/or utilization of

routine infection prevention measures. Accordingly, interest in probiotics has again increased as it is widely viewed as a non-antibiotic strategy to prevent and potentially treat a variety of infections. In 1994, passage of the Dietary Supplement Health and Education Act (DSHEA) led to dramatic growth in the sales of products marketed as probiotics. This legislation allowed these agents to be marketed as dietary supplements without the rigorous requirements necessary to approve prescription drugs. Since this time, marketing and sales of probiotic productsin the United States has grown exponentially. The global market of probiotic ingredients, supplements and food was $14.9 billion in 2007 and is expected to reach $19.6 billion in 2013. This represents a compound annual growth rate of 4.3 %. Probiotics can be marketed in several different ways in the U.S. depending on their intended usage. They can be marketed as foods, medical foods, dietary supplements or drugs. Each of these categories has unique requirements in terms of formulation, scientific documentation, and/or FDA approval. In most cases, probiotics are marketed as either a dietary supplement (e.g., products in pill form) or as a food substance (e.g. yogurt). Several of probiotic organisms including *Lactobacillusacidophilus*, *Streptococcus thermophilus*, and *Bifidobacteriumlactis* have "generally recognized as safe" (GRAS) status, meaning that they are permissible additives in food substances. Similarly, these species and many others are contained in products marketed as dietary supplements, which are regulated via the afore-mentioned DSHEA.

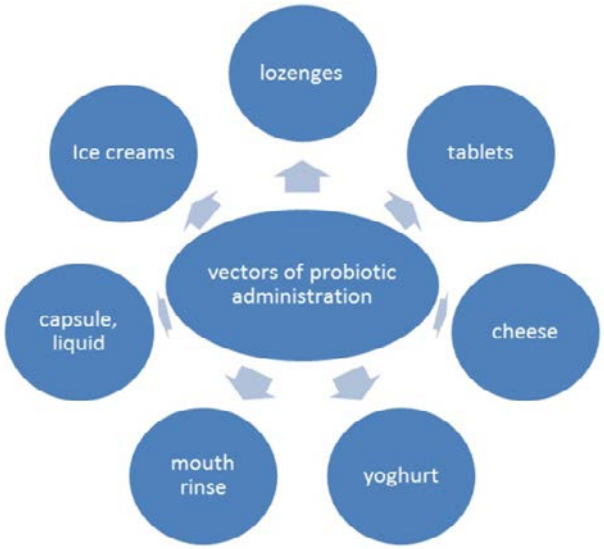

Figure. 3: Probiotic Administration Method

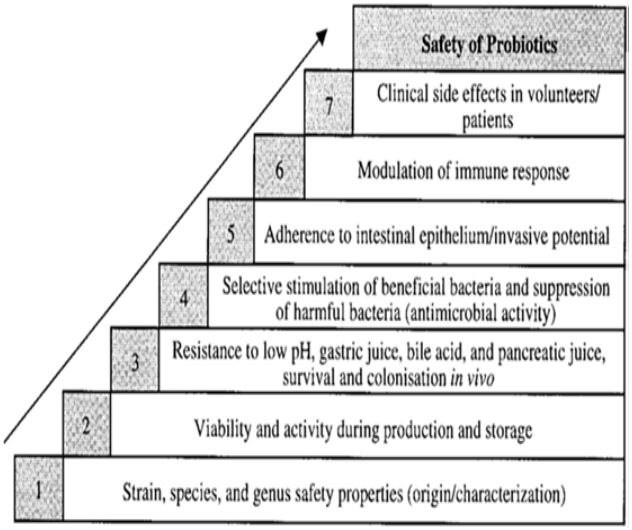

Figure 4. Safety aspects of probiotics

Table 3: Clinical effects of some probiotic strains and yoghurt strains

Strain	Clinical effects in humans	References
*Lactobacillus rhamnosus*GG (ATCC 53103)	Lowering faecal enzyme activities, reduction of antibiotic-associated diarrhoea in children, treatment and prevention of rotavirus and acute diarrhoea in children, treatment of relapsing *Clostridium difficilediarrhoea*, immune response modulation, alleviation of atopic dermatitis symptoms in children	Siitonen et al. (1990), Goldin et al. (1992), Kailaet al. (1992), Hosoda et al. (1994), Isolauri et al. (1991, 1994), Majamaa et al. (1995), Raza et al. (1995), Sepp et al. (1995), Bennett et al. (1996), Malin et al. (1996), Hilton et al. (1997), Majamaa and Isolauri (1997), Shornikova et al. (1997c), Alander et al. (1997, 1999), Kankaanpa¨a¨ et al. (1998), Pelto et al. (1998), Kankaanpa¨a¨ et al. (1998), Pelto et al. (1998),
Lactobacillus johnsonii(*acidophilus*) LJ-1 (La1)	Modulation of intestinal flora, immune enhancement, adjuvant in *Helicobacter pylorireatment*	Link-Amster et al. (1994), Schiffrin et al. (1995), Marteau et al. (1997), Michetti et al. (1999) Donnet-Hughes et al. (1999) Black et al. (1989, 1991), Marteau et al. (1990),
Bifidobacteriumlactis Bb-12	Prevention of traveller's diarrhoea, treatment of viral diarrhoea including rotavirus diarrhoea, modulation of intestinal flora, improvement of constipation, modulation of immune response,	Black et al. (1989, 1991), Marteau et al. (1990), Alm et al. (1993), Link-Amster et al. (1994), Saavedra et al. (1994), Schiffrin et al. (1995), Kankaanpa¨a¨ et al. (1998),

	alleviation of atopic dermatitis symptoms in children	Fukushima et al. (1998)
Lactobacillus reuteri(BioGaia Biologics)	Shortening of rotavirus diarrhoea in children, treatment of acute diarrhoea in children, safeand well-tolerated in HIV-positive adult subjects	Wolf et al. (1995, 1998), Shornikova et al. (1997a,b)
Lactobacillus caseiShirota	Modulation of intestinal flora, lowering faecalenzyme activities, positive effects on superficialbladder cancer and cervical cancer, no influenceon the immune system of healthy subjects	Aso and Akazan (1992), Okawa et al. (1993), Tanaka and Ohwaki (1994), Aso et al. (1995), Spanhaak et al. (1998)
*Lactobacillus plantarum*DSM9843 (299v)	Modulation of intestinal flora, increase in faecalshort-chain fatty acid content	Johansson et al. (1993, 1998)
Saccharomyces boulardii	Prevention of antibiotic-associated diarrhoea, treatment of *Clostridium difficilecolitis*, prevention of diarrhoea in critically ill tube-fed patients	Surawicz et al. (1989), Buts et al. (1993), McFarland et al. (1994), Bleichner et al. (1997)
Yoghurt strains (*Streptococcus thermophilusand*:or*L. delbrueckiisubsp. bulgaricus*)	No effect on rotavirus diarrhoea, no immuneenhancing effect during rotavirus diarrhoea, noeffect on faecal enzymes, weak effect onrespiratory burst activity of blood leuckocytes but not on overall phagocytic activity in healthy adults	Goldin et al. (1992), Majamaa et al. (1995), Donnet-Hughes et al. (1999)

Table 4. Key probiotic micro-organisms reported in the literature

Micro-organism		**Effect on human health**
Lactic acid bacteria	Lactobacillus rhamnosus GG	Reduces the intestinal permeability defects caused by exposure to cow's milk or rotavirus infection. May shorten the course of rotavirus infection causing diarrhoea, traveller's diarrhoea and antibiotic-associated diarrhea
	Lactobacillus casei	Reduces the severity and duration of diarrhoea. Stimulates the immune system of the gut, alleviates the symptoms of Crohn's disease and possesses strong antimicrobial properties
	Lactobacillus caseiShirota	Prevents diarrhoea caused by viruses or bacteria. Has the strongest human health efficacy with respect to management of lactose malabsorption, rotaviraldiarrhoea, antibiotic-associated diarrhoea and Clostridium difficilediarrhoea. Has a preventive effect on the recurrence rate of superficial bladder cancer after surgery
	Lactobacillus acidophilus	Secretes lactic acid that lowers the pH of the intestinal content and helps to inhibit the development of invasive pathogens such as Salmonella spp. or strains of Escherichia coli. Increases antibody responses and seroconversion rates. Lowers serum cholesterol levels
	Lactobacillus acidophilus	
	Lactobacillus plantarum	May reduce density of Helicobacter pylori and inflammation as well as gastritis activity
		Produces short-chain fatty acids that inhibit the generation of carcinogenic products by reducing enzyme activities

Yeasts	Saccharomyces cerevisiaeBoulardii	Prevents traveller's diarrhoea and the development of colitis and enterocolitis of pathogenic origin. Reduces the risk and duration of antibiotic-associated diarrhoeab
Bifidobacteria	Bifidobacteriumbifidum Bifidobacteriumbreve Bifidobacteriumanimalis Bifidobacteriuminfantis	May successfully compete for space and nutrients against pathogenic or putrefactive bacteria. Reduces the incidence of diarrhoea and increases antibody responses and seroconversion rates Activates the humoral immune system by augmenting anti-rotavirus IgA production or anti-influenza virus Normalises the intestinal motility of obstipated subjects. Reduces the risk of acute diarrhoea in children and adults Prevents diarrhoea and constipation

Prebiotics:

Prebiotics are defined as non-digestible, but fermentable, foods that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon. In 1995 the term prebiotic was first used by Gibson and Roberfroid. Lactulose was used 50 years ago as a prebiotic formula supplement to increase the number of *Lactobacillus* strains in infants' intestines. Compared with probiotics, which introduce exogenous bacteria into the human colon, prebiotics stimulate the preferential growth of a limited number of health-promoting species already residing in the colon, especially but not exclusively lactobacilli and bifidobacteria. galactooligosaccharides have been identified as prebiotics due to characteristics such as resistance to gastric acidity and hydrolysis by mammalian enzymes and they are fermented by gastrointestinal microflora to further selectively stimulate the growth and activity of beneficial microorganisms. The number of new compounds which have gut resistant properties and selective ferment ability by intestinal microorganisms are identified and developed as prebiotics. These include oligosaccharides (isomaltooligosaccharides, lactosucrose, xylooligosaccharides, and glucooligosaccharides), sugar alcohols, and polysaccharides (starch, resistant starch, and modified starch). The oligosaccharides in human breast milk are considered the prototypicprebiotic as they facilitate the preferential growth of bifidobacteria and lactobacilli, in the colon, among exclusively breastfed neonates; this phenomenon may well account for some of the immunological and other benefitsthat accrue to breastfed infants. Fermentation of oligofructose in the colon is due to the presence of intestinal micro flora, which confers beneficial effects to humans, which include increasing the numbers of probiotics in the colon, increasing calcium absorption, increasing fecal weight, shortening gastrointestinal transit time, and possibly, lowering blood lipid levels. The only prebiotics for which sufficient data have been generated to allow an evaluation of their possible classification as functional food ingredients are the inulin-type fractions, which are linked by β (2-1) bonds that limit their digestion by upper intestinal enzymes, andfructo-oligosaccharides. dietary sources of prebiotics include soybeans, inulin sources (such as Jerusalem artichoke, jicama, and chicory root), raw oats, unrefined wheat, unrefined barley, and yacon. Both are presenting in significant amounts in many edible fruits and vegetables, including wheat, onion, chicory, garlic, leeks, artichokes, and bananas. Because of their chemical structure, prebiotics are not absorbed in the small intestine but are fermented, in the colon, by endogenous bacteria to energy and metabolic substrates, with lactic and short-chain carboxylic acids as end products of the fermentation.

Table 5. Claimed gastrointestinal effects of prebiotics

Through fermentation in the large bowel
• Production of short-chain fatty acids and lactate Gas, mainly CO2 and H2 • Increase in biomass • Increased faecal energy and nitrogen • Mild laxative properties
On the microflora

• Selective increases in bifidobacteria and lactobacilli in planktonic • and biofilm communities • Reduction in clostridia • Increase in colonisation resistance to pathogens • Potential benefit in preventing pathogen invasion
Small intestine
• Osmotic effect of low molecular weight prebiotics (DP3, 4) which • occasionally causes diarrhoea • Improved calcium, magnesium and iron absorption • Interaction with mucus to change binding sites for bacteria,lectins etc.
Mouth
• Protection against caries
Other effects • Bile acid metabolism–no consistent changes reported • Variable effects on microbial enzymes with potential to affect • Carcinogenesis • Stimulation of apoptosis

Synbiotics:

Synbiotics are the dynamo combination of prebiotics and probiotics. Not only do they provide good food for gut bacteria but they also deliver significant amounts of live bacteria themselves. The probiotics are good, live bacteria for our gut while the prebiotics are the food for our beneficial gastro intestinal bacteria. Synbiotics, defined as a combination of a probiotic and a prebiotic, aim to increase the survival and activity of proven probiotics in vivo, as well as stimulating indigenous bifidobacteria and lactobacilli.The combination of suitable probiotics and prebiotics enhances survival and activity of the organism, for example, an FOS in conjunction with a *Bifidobacteriumstrain* or lactitol in conjunction with *Lactobacillus* strains. Because the word alludes to synergism, this term should be reserved for products in which the prebiotic compound selectively favors the probiotic compound. In this strict sense, a product containing oligofructose and probiotic bifidobacteria would fulfill the definition, whereas a product containing oligofructose and a probiotic *Lactobacillus casei* strain would not. The combination of prebiotic and probiotic has synergistic effects because in addition to promoting growth of existing strains of beneficial bacteria in the colon, synbiotics also act to improve the survival, implantation, and growth of newly added probiotic strains. Examples of Synbiotics are:

- Bifidobacteria and Fructooligosaccharides (FOS),
- *Lactobacillus rhamnosus* GG and inulins,
- Bifidobacteria or lactobacilli with FOS or inulins or galactooligosaccharides (GOS)
- Yogurt, or kefir and honey
- Yogurt, or kefir and honey and acacia gum
- Beans, (legumes), and pickles
- Yogurt, sour cream, or kefir with garlic
- Feta cheese and onions
- Yogurt with oats
- Greens sauté with garlic and sour cream
- Kombucha with Chia seeds
- Kombucha with acacia gum
- Yogurt, or kefir, with acacia gum and honey
- Yogurt, or kefir, with chia seeds, acacia gum and honey
- Sour pickled onions, and pickled garlic
- Sour pickled asparagus

Fermented Milk:

The Vedic hymns of India, written before 2,000 B.C., indicate that Hindu people used fermented milk products in their diet since prehistoric times. Between 2,000 and 3,000 B.C. a multitude of other civilizations (the Egyptians, Greeks and Romans) left many records to indicate that milk, cheese, and butter were commonly used. As an example, Sumerians crossed expanses of deserts with milk carried in bags made from the stomachs of sheep. Credited with

saying "All disease begins in the gut" the Greek physician Hippocrates considered fermented milk both a food product and a medicine with the potential to cure intestinal disorders. Plinius, the Roman historian, stated that fermented milk products could be used for treating gastroenteritis.

Fermented Vegetables:

The peoples of Japan, China and Korea have relied heavily on fermentation as a pickling agent for cabbage, turnip, eggplant, cucumber, onion, squash and carrots over the centuries. Records in China document that cabbage has been fermented for over 6,000 years. Fermented vegetables were regularly provided to Chinese workers during the construction of the Great Wall of China (around 300 B.C.) to promote their health and well-being.

Bread:

The first records of bread-making are contained in ancient Egyptian hieroglyphs. Egyptians discovered that if dough was left untreated for several hours prior to baking, the resulting bread became airy and lighter.

Beer and Wine:

The earliest evidence that beer was produced and consumed comes from China more than 7,000 years ago. The archaeological record shows that as early as 4,000 B.C, yeast was used both as a leavening agent and for brewing ale in Egypt. Centuries later, the Greeks and Romans are known to have used starter cultures to inoculate fresh fruit juice for fermentation.

Table 6. Characteristics of ideal probiotics and prebiotics:

Probiotics
• Be of host origin • Non-pathogenic • Withstand processing and storage • Resist gastric acid and bile • Adhere to epithelium or mucus • Persist in the intestinal tract • Produce inhibitory compounds • Modulate immune response • Alter microbial activities
Prebiotics
• Be neither hydrolyzed or absorbed • by mammalian enzymes or tissues • Selectively enrich for one • or a limited number of beneficial bacteria • Beneficially alter the intestinal microbiota • and their activities • Beneficially alter luminal or systemic aspects • of the host defense system

Table 7. Beneficial effects of probiotics and prebiotics

• Modify intestinal microbiota • Stimulate immune system • Reduce inflammatory reactions • Prevent pathogen colonization • Enhance animal performance • Decrease carcass contamination • Decrease ammonia and urea excretion	• Increase production of VFA • Increase biomass and stool bulking • Increase B vitamin synthesis • Improve mineral absorption • Prevent cancer • Lower serum cholesterol • Lower skatol, indole, phenol, etc

III. CONCLUSION

Future research on probiotic, prebiotic and synbiotic bacteria will center on selecting new and more specific strains for the well-being of the host (age groups, healthy populations, disease specific). Yogurt and fermented milk have been thought to be foods with special benefits for health. More recently, a great deal of interest has developed concerning the many beneficial effects of probiotic microorganisms in a variety of pathological situations. Prebiotics and probiotics are obviously interesting agents in the field of preventive nutrition, and they should therefore have an important development. Given the lack of directed therapy for many clinical disorders of the gut, and the expense involved, both probiotics and prebiotics can offer alternative options. New advances that use the symbiotic effect, target distal colonic activity and include improved functionality. ISAPP recognizes that scientific establishment of the 100-year-old concept of probiotics and prebiotics will require complex and multidisciplinary investigative strategies that integrate microbiology, ecology, immunology, cell biology, genomics, bioinformatics, food science, and medicine. We look forward to combining these disciplines to scientifically advance a new paradigm for probiotics and prebiotics in the maintenance of health and prevention of disease.

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