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Current Developments in Probiotics

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Abstract

Probiotic products have been used worldwide in the last decades. They are significantly gaining popularity and their consumption is associated with increasing levels of health-consciousness and availability in the form of dietary supplements. Probiotics can be defined as microbial cells that have a beneficial effect on the health and wellbeing of the host. The use of probiotics in the treatment of a number of inflammatory conditions is well known, which includes arthritis, pouchitis, Crohn's disease and colitis. Some important actions are also reported such as the control of the intestinal microbiota, decrease of the pathogens population by the production of lactic acids, bacteriocins and other antimicrobial compound forms, prevention or suppression of colon cancer, reduction of cholesterol, improvement of allergic states and treatment of the respiratory tract. In this sense different probiotic products have appeared on the market with different formulations and applications. This paper presents review about probiotics products your use and health benefits.

Keywords: Probiotics; Diseases; Health benefits; Probiotics products

Introduction

The use of probiotics has been reported since olden times, as observed in some products used by the Pharaonic civilization, such as milk, seeds, fish and some other products [1]. However, it might be that Eli Metchnikoff, the Nobel Prize winner in Medicine in 1908, was the first who spotted the effect of what is called now probiotic. He linked the health and longevity of Bulgarian peasants to the ingestion of bacteria (*Lactobacillus bulgaricus* and *Streptococcus thermophilus*) present in yogurt [2,3].

Several studies since then have been performed in order to develop probiotic products. In Japan, in the early 1930s, Shirota succeeded in isolating strains existing in healthy individuals' intestinal bacteria. 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 casei* Shirota [4].

The term 'probiotic' was first used by Lilly and Stillwell in 1965 to describe the 'substances secreted by one microorganism that stimulate the growth of another' [5]. A powerful evolution of this definition was coined by Parker in 1974. He proposed that probiotics are 'organisms and substances, which contribute to intestinal microbial balance' [6]. Then in 1989, Fuller modified the definition to 'a live microbial feed supplement, which beneficially affects the host animal by improving its microbial balance' [7]. Salminen et al. [8], defined probiotics as 'foods that contain live bacteria, which are beneficial to health', whereas Marteau et al. [9], defined them as 'microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being'. Some modern definitions include more precisely the preventive or therapeutic action of probiotics.

Currently, Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) [10] endorsed by the International Scientific Association for Probiotics and Prebiotics [11], define probiotics as "live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host".

Despite these definitions, the practical question arises of whether or not a given microorganism can be considered to be a probiotic. Criteria for designating a strain as a probiotic include its total safety for the host; human origin; acid and bile resistance; survival in the gastrointestinal transit; production of antimicrobial substances; immune modulator activity; adhesion to epithelial cells; inhibition of pathogenic bacteria; resistance to antibiotics, tolerance to food additives and stability in the food matrix [12,13].

The probiotics in use today have not been selected on the basis of all these criteria, but the most commonly used probiotics are strains of lactic acid bacteria such as *Lactobacillus*, *Bifidobacterium* and *Streptococcus* [14], but new probiotic from other species and genera have recently been introduced. 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 [15].

There is some evidence indicating that non-viable microorganisms can confer health benefits. Products containing non-viable microorganisms have been available on the market since 1907 when Pierre Boucard isolated two strains of *Lactobacilli* from human stool, heat-killed them, and marketed them as an antidiarrheal supplement called Lacteol™. The anti-diarrhea benefit was later confirmed in clinical studies [16] and thus, Lacteol™ is still available as over-the-counter medication in a number of countries [17]. Some studies have demonstrated that beneficial effects were achieved not only by live bacteria but also by heat-inactivated or gamma-irradiated bacteria,

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isolated bacterial DNA or even probiotic-cultured media [18].

The use of probiotics has considerably increased and their potential domain of application in human clinical care is extremely wide: oncology, bowel inflammatory diseases or infectious diseases, protection against diarrhea, *H. pylori* infection, allergic disorders, lactose intolerance, hypercholesterolemia, and even against systemic disease. The clinical utility of probiotics may extend to fields such as allergic disease and cancer [19-22]. Probiotics have roles in epithelial cell proliferation and differentiation, and the development and the homeostasis of the immune system [23].

There are several possible functions of probiotics that include the production and secretion of antimicrobial substances, a stimulation of host immune responses and displacement of pathogen colonization [20,24,25].

Secretion of substances such as protein, Short Chain Fatty Acid (SCFA), organic acids, cell surface active components and DNA from these microbes exerts the same therapeutic effect in gastrointestinal disease. These therapeutic agents are known as pharmabiotics or probioactive [26,27].

Another example of substance produced by probiotics is riboflavin. Riboflavin (vitamin B2) is essential for the activity of a wide variety of metabolic enzymes in higher eukaryotes and is not synthesized by higher animals including humans. So humans and animals must obtain riboflavin through dietary sources [28]. Arena et al. [29] assayed the potential probiotic activity of *Lactobacillus plantarum* CECT 8328 and *Lactobacillus fermentum* CECT 8448 testing their riboflavin overproduction ability finding that both strains possess the potential ability to survive the oro-gastro-intestinal tract transit, reach the intestine in a viable state, and there exert various probiotic activities, including the production of vitamin B2 in the body compartment where it can be adsorbed.

The mode of action of probiotics is complex; however there are a number of common mechanisms that are evident in a wide variety of probiotic strains. Some mechanisms studied are the adherence to the intestinal mucosal surface, which prevents colonization of pathogenic bacteria [30] and stimulation of the intestinal immune system [31]. Probiotics are also believed to function via the modulation of cell proliferation and apoptosis [32,33]. Furthermore the mode of action of a given probiotic can differ based on the presence of other probiotics or enteric bacteria, and also eventual diseases to be treated [31,34]. Due to the importance of this topic, this review summarizes some relevant knowledge about probiotics and their health benefits.

Probiotic Products

Consumption of probiotic cells through food products is actually the most popular approach. The global market for functional foods and beverages has grown from $33 billion in 2000 to $176.7 billion in 2013, accounting for 5% of the overall food market. It has been estimated that probiotic foods comprise between 60% and 70% of the total functional food market [35,36].

Probiotic microorganisms are usually available as culture concentrates in dried or deep-freeze form to be added to a food matrix. The most common genera and species are Lactic Acid Bacteria (LAB) from the genera *Lactobacillus* and *Bifidobacterium*, because they are considered as GRAS (Generally Recognized as Safe) [37–39]. *Lactobacillus* and *Bifidobacterium* species are also dominant inhabitants in the human intestine (*Lactobacillus* in the small intestine and *Bifidobacterium* in the large intestine) [38]. However, bacterial species belonging to the genera *Lactococcus*, *Enterococcus* and *Propionibacterium*, yeasts (e.g. *Saccharomyces cerevisiae* and *Saccharomyces boulardii*) and filamentous fungi (e.g. *Aspergillus oryzae*) are also used as probiotics due to their health-promoting effects [35,40–42]. In addition some authors suggest that dairy probiotic products supplement with multispecies can have a more specifically targeted function in the human alimentary tract [43].

Viability maintenance of probiotic cells throughout food-processing and gastro-intestinal transit is important for the microorganisms to reach the intended site of action in sufficient numbers (10^8 cells/gram). Following the consumption of a probiotic there is a considerable loss of viable cells due to passage through the low pH environment of the stomach and high bile salt conditions in the intestine [44]. One possible solution for this problem is microencapsulation [42,45–47]. Encapsulation is a mechanical or physicochemical process that traps a potentially sensitive material and provides a protective barrier between it and the external conditions. The spray-drying, emulsion and extrusion techniques are well known encapsulation methods for the production of microcapsules containing probiotics [44].

The probiotic effect and survival is strain dependent, therefore it must be perfectly identified (phenotypic and genotypic identification) and characterized [16,48]. In terms of robustness of probiotic organisms, *Lactobacilli* are generally stronger than *Bifidobacteria*, more resistant to low pH and have better adaptation to milk and other food substrates [35].

Depending of the matrix that carries the probiotic bacteria, probiotic products can be classified as: dairy probiotic products and non-dairy probiotic products. Dairy beverages are produced from milk or its derivatives, with or without the addition of other ingredients, in which the dairy base represents at least 51% (vol/vol) of the formulation, and can be submitted to a fermentation process using yogurt cultures [49]. The most common dairy probiotic products are: fermented milks, ice cream, various types of cheese, baby food, and milk powder, frozen dairy desserts, whey-based beverages, sour cream, and buttermilk, normal and flavored liquid milk [44,50].

Milk and dairy products are abundant sources of minerals that play a variety of roles in the human body [51-53]. However, the availability of minerals from cheeses and cheese-like products is lower than that from other dairy products, due to the high content of saturated fatty acids. Alejewicz and Cichosz [54] determined the effect of the *Lactobacillus rhamnosus* HN001 probiotic culture on the increase of calcium, magnesium, zinc, phosphorus and potassium in cheese like products finding that the addition of *Lactobacillus rhamnosus* HN001 increase the availability of divalent metal cations.

In addition, some technologies and methodologies can be implemented to developed dairy probiotic products. Schäffer et al. [55], used an isotherm differential scanning calorimetry method to identify the probiotic microbes in probiotic products, the products developed are now commercial in Hungry, they are: Probiotic kefir (Symbiofir), probiotic sour cream, probiotic butter cream, poultry meat products complemented with calcium and bakery products complement with calcium, the last two were developed motivated in the increment of osteoporosis disease. Castro et al. [56] demonstrated that the optimal concentration of constituents like whey in probiotic dairy beverages could be determined employing mathematical models like survival analysis, minimal significant difference, and mean global acceptance.

Because of the high prevalence of lactose intolerance, different

non-dairy probiotic products such as vegetarian-based products, cereal-based products, fruit juices, soya-based products, oat-based desserts, confectionary products, breakfast cereals and baby foods have been developed in recent years [38,57,58].

Technological advances have made possible the change of some structural characteristics of fruit and vegetables matrices by modifying food components in a controlled way. This could make them ideal substrates for the culture of probiotics [59]. On the other hand, cereal grains are one of the most important sources of protein, carbohydrates, vitamins, minerals and fiber; strains of *Lactobacillus* are fastidious microorganisms that require these sources for growth. Moreover, cereals may act as prebiotics because they can be used as sources of non-digestible carbohydrates, promoting the growth of *Lactobacilli* and *Bifidobacteria* present in the colon [60].

Another good raw material to be used as an alternative for non-dairy probiotic carrier is soy, which has some sugars and amino acids in its composition that are used as substrates by lactic acid bacteria to produce aroma compounds. However, soy consumption is limited because of its undesirable beany flavor and the presence of oligosaccharides (stachyose and raffinose) that often lead to flatulence and stomach discomfort. One way to improve the sensory quality of soymilk and also to mask undesirable compounds is through lactic acid fermentation, which can be combined with supplemental sucrose, glucose, and lactose [57,61]. Matias et al. [57] developed a probiotic soy – based product similar to petit – Suisse cheese.

Bakery products including breads are staple foods composed by several major components (complex carbohydrates, insoluble dietary fibre, proteins, lipids, minerals and vitamins) in varying proportions and with varying physical interactions and structures. Soukoulis et al. [50] developed probiotic bread through the use of air dried probiotic edible films with the addition of the bacteria *Lactobacillus rhamnosus* GG.

Meat can be another source of probiotic products. The buffering capacity of meat may be due to a raised pH of the microenvironment of bacteria living on its surface. Furthermore, meat has been found to protect LAB against the lethal action of bile [38].

Several probiotic products formulations, commercial names, companies, probiotic cultures, compositions and applications are presented in Table 1.

Generally, the majority of these products are dairy probiotic products. The first commercial probiotic product was developed by Yakult Honsha Co. in 1935 [63]; It is a probiotic drink composed by water, sugar, skim milk powder, glucose, natural and artificial flavors. Today, companies such as Danone and Nestlé are the main producers of yogurt probiotic products. It is important to continue the research for the development of new non-dairy probiotic products which could have a big market because of the high prevalence of lactose intolerance and vegetarianism.

Therapeutically Use of Probiotics and Their Health Benefits

Several health benefits are associated to the consumption of products containing probiotics, among them it is possible to mention the improvement of the intestinal transit of the foods making the digestion easier, relieve of the lactose intolerance symptoms, increase of the immune response, decrease of the diarrhea episodes, control of the intestinal microbiota, stabilization of the intestinal microbiota after the usage of antibiotics, decrease of pathogens population by the production of lactic acid, bacteriocins and other antimicrobial compounds, prevention or suppression of colon cancer, reduction of the blood cholesterol, improvement of allergic states and in the treatment of infections of the respiratory tract [51-53].

Modulation of Intestinal Microbiota by the Action of Probiotics

In the development of efficient probiotics a promising feature is the enlarged resistance against pathogens reinforcing the natural organism defense mechanisms [64]. According to Guarner and Malagelada [30], the intestinal microbiota modulation by probiotic microorganisms occurs through a mechanism named as "competitive exclusion".

This mechanism blocks the colonization of intestinal mucous membrane by pathogens that compete for adhesion to sites, nutrients and production of antimicrobial compound forms [30,65].

In this way, probiotics help to renew the intestinal microbiota by the adhesion and colonization of the intestinal mucous membrane, an action that blocks the adhesion and subsequent production of toxins or invasion of the epithelial cells by pathogenic bacteria [30,66]. Competition by nutrients among probiotics and undesirable bacteria also occurs. There is a relation between the nutrients supplied by the host and their necessity by intestinal bacteria. This symbiotic relation and balance block an excessive production of nutrients, which could favor the establishment of pathogens in intestinal tract [65,66].

Besides this the probiotics produce antimicrobial substances, mainly the bacteriocins that exclude the multiplication of competing bacteria [66]. Another mechanism investigated is the relationship between the regular activities throughout the brain-gut axis. Clinical studies in humans have shown that the consumption of fermented milk containing probiotics can modulate a wide ceberal network, making a connection in the gut-brain axis, but further study is needed [67,68]. The instability of intestinal microbiota causes the installation of diseases such as diarrhea, associated to infections or antibiotic therapy, food allergies, atopic eczema and intestinal inflammatory diseases. Probiotics therapy passes through the balance of the microbiota [15].

In the irritable bowel syndrome it is observed the alteration of the intestinal microbiota promoting abnormal fermentation in the colon. However, it is not elucidated if there is a casual relation in this sense or if the altered microbiota is a consequence of an intestinal dysfunction. Even so, the restoration of this microbiota balance by the administration of probiotics can result in therapeutic benefits [69].

Chronic intestinal inflammatory diseases, such as Crohn's disease and ulcerative colitis, generally are identified in young adults. The etiology and pathogenesis of the intestinal inflammatory diseases are not fully understood, but there are substantial evidences pointing to the intestinal microbiota. It was also observed that this disease is more frequently detected in the intestine areas more densely colonized by microorganisms [70,71]. Studies with probiotic strains of *Lactobacillus plantarum* 299v in animal models prevent or attenuate the intestinal inflammatory diseases; the anti-inflammatory effect can be mediated by several different mechanisms, including the mucins production, the interference with cytokines production and the standardization of the intestinal barrier integrity [71-73].

The lactic bacteria of the intestinal microbiota show a vital function with the production of β-D-galactosidase, which help with lactose break in the intestine in individuals with lactose intolerance. These people are

Product (company)	Probiotic culture	Composition	Application
Yakult® (Yakult Honsha Co. Ltd.)	*Lactobacillus casei* Shirota, *Bifidusregularis*	Water, sugar, skim milk powder, glucose, natural and artificial flavours	Probiotic beverage, intestinal flora reposition, improve digestion
Align (Procter y Gamble)	*Bifidobacterium infantis*35624	Probiotic strain:, contains 1×109 colony-forming units (1 billion) (4 mg) when manufactured and provides an effective level of bacteria (1×107), microcrystalline cellulose, hypromellose, sucrose, magnesium stearate, sodium caseinate, titanium dioxide, trisodium citrate dihydrate, propyl gallate (antioxidant preservative),	One capsule once a day, help to maintain the digestive balance fortifying the digestive system with healthy bacteria
Bioflorin (Cerbios – Pharma)	Enterococcus LAB SF 68	Probiotic active ingredient. Hard gelatin capsules	Prevention and treatment of intestinal disorders
Mutaflor (Ardeypharm)	*Escherichia coli* Nissle 1917	Probiotic supplemet (2.5–25×109 viable cells (CFU)), Talc, Methacrylic acid-methyl methacrylate copolymer (1:1), Macrogol, Dibuytl phthalate, Glycerol, Titanium dioxide, Iron (III) hydroxide oxide monohydrate, Gelatin, Beeswax (yellow), Carnauba wax, Shellac, Purified water	Colonize the gut, biologically fit and active against disease-causing agents known as pathogens1, strain has been shown in scientific studies to be of benefit for both inflammatory bowel as well as functional bowel disease
URO VAXOM® (Apsen)	*Escherichia coli*	*Escherichia coli*bacterial lysate (6 mg). Excipient: propyl gallate anhydrous, monobasic sodium glutamate, mannitol, starch, magnesium silicate, magnesium stearate, red iron oxide, yellow iron oxide, titanium dioxide, gelatin	immunotherapy, prevention recurrent infections of the lower urinary tract,
Ginophilus® (Probionov)	*Lactobacillus casei* rhamnosusLcr 35	341 mg lyophilized culture, measuring at least 109 cells per gram. Excipient: lactose monohydrate.	lowers the local pH in the vagina, preventing harmful pathogenic bacteria from colonizing and proliferating
Activia® Yogurt (Danone)	*L. bulgaricus, S. thermophilus*	Varies (strawberry, natural, peaches, vanilla) Presented in the form of milk, buttermilk, yogurts, fermented milks, daily dose drinks, juices, berry soups, cheese and capsules	Help regulate digestive system
SVELTY® Gastro Protect (Nestlé)	*Lactobacillus johnsonii*La1	A fermented drink milk, flavor, sugars	Controls *H. pylori* infection and stomach discomfort
LC1 Yogurt® (Nestlé)	*Lactobacillus johnsonii* La1 and acidophilus bacteria	A probiotic yogurt, fermented milk, flavours, sugars	Regulates digestion, protection against pathogens
Actimel® (Danone)	*L. casei*(Defensis)	Milk, sugar, flavours	Protection against pathogens
Flora FIT® (Danisco A/S)	*Bifidobacterium breve*Bb-03, *B. lactis* Bi-07, *B. lactis* Bl-04, *B. longum* Bl-05, *Lactobacillus acidophilus* La-14, *L. bulgaricus* Lb-64, *L. brevis* Lbr-35, *L. casei* Lc-11, *Lactococcuslactis* Ll-23, *L.plantarum* Lp-115, *L. paracasei* Lpc-37, *L.rhamnosus* Lr-32, *L. salivarius* Ls-33, *Streptococcus thermophilus*St-21		Food and beverages
HOWARU® Premium Probiotics (Danisco A/S)	*L. acidophilus* NCFM™		A probiotic product that can be applied in beverages, confectionery, dairy, dietary supplements and frozen desserts
Yógourmet Products (Lyo-San,Inc.)	*L. casei, B. bifidus, L. acidophilus*		Starters for yoghurt manufacture
Biorich® (Chr. Hansen A/S)	*L. acidophilus*LA-5 and *Bifidobacterium* BB-12		Starters for yoghurt manufacture
Probiotic Chewy Cereal Bars	Ganeden BC30	5 g fibre, 2 g protein, prebiotics, omega-3 fatty acids	
Chocolate Probiotic Bars Chocolate Crisp®ATTUNE	*L. acidophilus, L. casei, Bifidobacteriumlactis*	Milk Chocolate Coating (evaporated cane juice, chocolate, cocoa butter,inulin, non-fat milk, calcium carbonate, anhydrous milk fat, soy lecithin, vanilla), organic brown rice crisps (organic brown rice flour, organic molasses, calcium carbonate)	
XoBiotic™ squares (MXI Corp.™)	*L. helveticus*R0052 and *B. longum*R0175	Dark Chocolate (unsweetened chocolate, sugar, cocoa powder, lecithin, vanilla extract), antioxidant blend (natural cocoa, açaí, blueberry powders) and probiotics	
Heini`s Yogurt Cultured Cheese (Bunker Hill Cheese Company)	*L. acidophilus, L. casei, B. lactis*	Milk, yogurt cultures, coagulants, probiotic cultures and salt	

Adapted from Yamaguishi et al. 2011 [62]

Table 1: Probiotic products that are commercially available, probiotic cultures, composition and its applications.

incapable of digesting it adequately resulting in abdominal discomfort. So the action of these bacteria is fundamental. Several studies show that lactic bacteria strains consumption promotes the relief the lactose intolerance symptoms [74,75].

The efficacy of probiotics in clinical studies in humans is related to several factors such as genetics, ethnicity, age, health status, environmental factors, and cultural traditions or geographical. Another important factor is diet, which may contribute to the action of probiotics or can hinder the survival and even lead to death of probiotics [68,76].

Probiotics in Control of Dyslipidemias

The dyslipidemias are directly related to several cardiovascular problems, diseases that attack a big part of the population. Several studies with probiotics confirm that their continuous consumption helps to keep the level of total cholesterol, LDL-cholesterol and triglyceride in normal levels [77-79].

The cholesterolemia modulation by probiotics consumption occurs through several mechanisms that act on the lipids metabolism, such as the reduction of the cholesterol intestinal absorption, increase of the fecal steroids excretion, and cholesterol synthesis locking by the organism [80]. Other extremely important mechanism of action is that several probiotic bacteria, including *Lactobacillus*, produce the enzyme called bile salt hydrolase (BSH) and through this enzyme the microorganisms are able to hydrolyze the bile salts that affect the cholesterol levels [77,80]. Bile acids separated by BSH, which is released by probiotics, absorb low quantities of gastrointestinal tract lipids, increasing the cholesterol excretion in coprostanol form and decreasing its absorption in the intestine [78,80]. Once separated, bile acids are eliminated and a high quantity of cholesterol is then required for the synthesis of new bile salts in the liver, reducing the levels of serum cholesterol [81].

The probiotic bacteria ferment the non-digestible carbohydrates originated from the intestine food. The short chain fatty acids resulted from fermentation possibly cause reduction of the hepatic cholesterol systemic concentration and the cholesterol redistribution from plasma to the liver [79].

Probiotics and Respiratory Diseases

Recently probiotics have being used in the prophylaxis of different respiratory tract diseases. Probiotics action mechanisms are directly related to their effect on the pathogen microorganisms. In this way, probiotics improve the immunomodulation, reinforce the epithelial barrier functions and produce substances with antimicrobial activity acting directly in the pathogen bacteria [82].

The superior tract respiratory diseases, such as sinusitis, rhinosinusitis, pharyngitis, laryngotracheobronchitis, otitis, were already studied with relation to probiotics. The strains of *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus fermentum* VRI-003, *Bifidobacterium breve* 99, *Bifidobacterium longum* SP 07/3 among others were used in a combined or single treatment of respiratory infections showing satisfactory results the reduction of acute episodes of the diseases mentioned above as well as a reduction in the duration of the episode in chronic diseases [83,84].

In the case of cystic fibrosis it is common the occurrence of bronchopneumonia episodes and the administration of probiotics such as *Lactobacillus rhamnosus* GG significantly decreased the frequency of infection in patients. Other study evaluated the use of *Lactobacillus rhamnosus* GG for 6 months, and it was verified the reduction of exasperated pneumonia episodes in patients with cystic fibrosis that are chronically colonized by *Pseudomonas aeruginosa* [85].

Some works demonstrate that the constant use of probiotics can prevent nosocomial pneumonias [51,86]. This kind of pneumonia is associated to the respiratory tract colonization by pathogenic bacteria, mainly *Pseudomonas aeruginosa* and the presence of probiotic strains such as *Lactobacillus plantarum* and *Lactobacillus rhamnosus*, which were important in the disease prophylaxis [86].

In the respiratory tract diseases more studies are needed to better explain the probiotics action mechanisms in the prophylaxis, as well as in the diseases treatment [87]. It is also necessary to establish the best way of administration of these probiotics because some authors suggest the administration by oropharyngeal way or nasogastric ingestion. Contrarily, some studies have no mention relating to the way of administration used [88].

The Role of Probiotics in Cancer

Cancer is one of the main causes of human deaths [89], and colon cancer is one of the most prevalent forms of cancer [90]. There are some studies that demonstrate that the gut microbiota may mediate the effects of diet as a modifier of colon cancer risk [91–93] and gastrointestinal cancer risk, additionally, there are a few studies indicating that probiotics have a suppressor effect on superficial bladder cancer [94]. Generally, there is no evidence showing cancer suppression in man as a result of the consumption of probiotics. However, experimental evidence suggests that probiotics might have beneficial effect on the toxicity of anticancer therapy and the prevention of this disease [95–97].

There are *in vitro* studies of the cytotoxic effect of some Lactic Acid Bacteria (LAB) strains in cancer cell lines [98]. Nami et al. [99] evaluated the anticancer activity of *Lactobacillus* acidophilus 36YL on breast, stomach, cervical and colorectal cancer cell lines, finding that the metabolites secreted by this strain exhibited the most potent cytotoxic effect against human colorectal cancer cells (HT-29) and Human Cervical Cancer Cells (HeLa). Liu et al. [98] explored the effects of *Lactobacillus casei* 01 cell fractions, including heat-treated cells, crude cell walls, intracellular extracts and Exo polysaccharides (EPSs), on the genotoxicity of 4-nitroquinoline N-oxide (4-NQO), and the proliferation of human colon cancer cell HT-29 finding that EPS exerted a higher inhibitory effect on the viability of HT-29. Wang et al. [90] found that 10 *Lactobacillus* strains isolated from the traditional fermented foods of minority nationalities or infant feces exerted anti-proliferative activity and higher adhering capability on HT-29 cells. In addition, it was selected cell wall extracts from three strains (X12, M5 and K14 strains) whose anticancer effect might be mainly due to the induction of mitochondrial membrane potential loss. Nonetheless, there is a selective effect of LAB with cancer cell lines. Shyu et al. [100] found that *Lactobacillus* spp isolated from Bear Brand, Nido and Yakult do not have a significant cytotoxic effect on normal HDFn and THP-1 leukemia cells but were significantly cytotoxic for the HT-29 and HCT116 colon cancer cell lines.

Other Beneficial Effects Attributed to Probiotics

Some probiotic cultures are being used in food allergies prevention mainly in children. Many times the etiology is not clarified. Evidences indicate that in children with allergic symptoms the species of *Bifidobacteria* differs from that found in healthy children [101].

It was observed that a significant improvement occurs in the skin condition and a decreasing of inflammation systemic marker after supplementation with probiotics in children with atopic eczema [22]. However it was not observed any symptoms improvement after ingestion of *Lactobacillus* GG in adults with allergy [102]. So the probiotic action seems to be efficient only in prevention and treatment of atopic disease in childhood, but not later in life [103, 104].

The probiotics usage in atopic dermatitis treatment is promising; in cases of pediatric atopic dermatitis, 20% to 24% of the incidence reduction is related to the administration of strains of *Lactobacillus* in the first months of the child life, demonstrating the prevention capacity [105,106].

The possible mechanisms of probiotics related to contact dermatitis treatment and prevention are associated to immunologic response as inhibition of the response of TH2 cells, stimulation of the response of TH1cells and regulation of T cells [107]. These mechanisms can also be associated to the intestinal microflora by probiotic bacteria, reduction of fermentation products and inhibition of *Staphylococcus aureus* [108].

Acne is a skin inflammation that attacks mainly adolescents, but also children and adults. The pathophysiology of this skin disease involves the excess of skin oiliness, the follicular hyperkeratinisation, hyper colonization by *Propionibacterium* acnes and skin inflammation [109]. These factors can become worst when unbalancing of microbiota intestinal level of colonization of undesirable bacteria is altered, intestinal transit stagnation, intestinal barrier committal, stress, which can change the intestinal revetment and cases of constipation [110].

Some studies have showed that 80% of the patients with acne that used probiotics had a reduction of acne inflammation, decreasing the inflammatory cytokines release and activation of regulating T cells due to the increase of ceramide production, but mainly to the maintenance of the intestinal microbiota balance [111,112].

The urogenital tract infectious diseases are related to pathogenic bacteria that enter predominantly through colon and rectum by perineum. Based on this knowledge it is possible to deduce that probiotic bacteria, when in colon, may change the microbiota favorably and some strains can migrate to the vagina and the urogenital tract promoting colonization [113,114]. So there is an improvement in woman urogenital health, whose infections can be attributed to colon bacteria. In this way, the presence of probiotic strains in colon induces the microbiota balance in the region and a reduction of infections incidence at urogenital tract [115].

Obesity is a growing problem in the population and affects all age groups and is considered a public health problem and treated as a disease. Some obesity may be related to the gut microbiota, by several mechanisms involving increased intestinal permeability and also the production of metabolic endotoxin [116-119]. There are several studies that make a direct relationship between abdominal fat deposition and the imbalance of the gut microbiota. Therapeutic efforts indicate that probiotics help maintain the balance of intestinal microflora and are recommended in the treatment of obesity-related disorders following the nutritional and pharmacological treatments [120-122].

Currently several therapies with probiotics have being evaluated trying to prevent determined diseases and also help the treatment of clinical signs already identified. In Table 2 different probiotic strains are listed with their possible application.

Kefir-Probiotic Microorganisms and Their Health Benefits

Kefir is a naturally carbonated fermented milk beverage with a slightly acidic taste, yeasty flavor and creamy consistency [130]. Kefir was originally made in Balkans, Eastern Europe and the Caucasus [131]. Due to the composition of kefir grains (lactic acid bacteria, acetic acid bacteria, yeasts) kefir is considered a probiotic beverage [132] and a possible source of probiotic strains [133,134]. Statistical data suggest that probiotic bacteria in the gut of kefir consumers are abundant and diverse, and microbial communities in the gut are closely correlated with health [135].

Countless studies have being done with isolated microorganisms from different kinds of kefir, always aiming to evaluate the benefit activity to the health in order to classify these microorganisms as probiotics. Table 3 shows a list of microorganisms found in kefir with

Disease	Strain	Study	References
Hypercholesterolemia	*Enterococcus faecium; Lactobacillus plantarum* PH04	Randomized into two groups, oral application; For 14 days, the mice were fed a high-cholesterol diet. Subsequent 14 days, doses of probiotic were orally administered to half the mice/feed of mice	[123]; [124]
Traveller's diarrhea	*Lactobacillus casei* DN-114 001, *L. plantarum*	Patients were randomly assigned to a probiotic drink or placebo, in a double-blind fashion	[125]
Gastroenteritis	*Lactobacillus casei*	For the elderly was introduced probiotic fermented milk containing *Lactobacillus casei* strain Shirota (LcS-fermented milk) in an open case-control study of its effect of (1 bottle a day) on winter-time norovirus gastroenteritis	[126]
Irritable bowel syndrome (IBS)	*Bifidobacterium infantis* 35624	362 primary care IBS patients, with any bowel habit subtype, were randomized to either placebo or freeze-dried, encapsulated *B. infantis*	[127]
Urogenital tract infection (UTI)	*Lactobacillus rhamnosus* GR-1 *L. reuteri*RC-14	Was assessed in a pilot twopatient study in which probiotic were administered to one patient and placebo to another, both along with antibiotics	[128]
Eczema	*Bifidobacterium bifidum B. lactis Lactococcuslactis*	In a double-blind, randomized, placebo-controlled trial, a mixture of probiotic bacteria selected by in-vitro experiments was prenatally administered to mothers of high-risk children and to their offspring for the first 12 months of life	[129]
Immunity	*Lactobacillus plantarum* DSMZ12028	In vitro study, adhesion to intestinal epithelial cells was evaluated using two cell lines, CaCo-2 and HT-29, through the plate dilution method	[23]

Table 2: Different probiotic strains and their application in disease control.

Organism of interest	Origin	Bioactivity	References
Lactobacillus plantarum MA2	Tibetan kefir	Hypocholesterolemic effect	[133]
Lactobacillus plantarum Lp27	Tibetan kefir	Inhibition of cholesterol absorption	[134]
Lactobacillus plantarum CIDCA 83114	Kefir grains	Inhibition of *Shigellasonnei* growth *in vitro*and of *C. difficile* toxin cytotoxicity on eukaryotic cells	[135]
Lactobacillus kefir CIDCA 8348	Kefir grains	Inhibition of *Shigellasonnei* growth *in vitro* and of *C. difficile*toxin cytotoxicity on eukaryotic cells	[135]
Lactobacillus plantarum ST8KF	Kefir grains	Bactericidal effect on *Lactobacillus casei Lactobacillus salivarius Lactobacillus curvatus Listeria innocua*	[136]
*Lactobacillus kefiranofaciens*K1	Kefir grains-Taiwanese Milk	Antiallergic effect	[137], [138]
*Lactobacillus kefiranofaciens*M1	Kefir grains-Taiwanese Milk	Immunoregulatory effects-Anticholitis effects	[139], [140]
Lactobacillus lactis CIDCA 8221	Kefir grains	Inhibition of *Shigellasonnei* growth *in vitro*and of Clostridium difficile toxin cytotoxicity on eukaryotic cells	[135]
*Saccharomyces cerevisiae*CIDCA 8112	Kefir grains	Inhibition of *Shigellasonnei* growth *in vitro*and of Clostridium difficile toxin cytotoxicity on eukaryotic cells	[135]
Lactobacillus lactis cremoris	Kefir grains-India	Activity against food spoilage bacteria	[141]

Table 3: Bioactivity of some bacteria isolated from different types of Kefir.

their origin a respective benefit activity, such as hypocholesterolemic effect, antiallergic effect, immunoregulatory effect, and inhibition of various microorganisms, among other beneficial actions.

Conclusions and Future Perspectives

Many studies have shown the health benefits of probiotics such as improving the intestinal transit, increase of the immune response, prevention or suppression of colon cancer, cholesterol reduction, and improvement of allergic states and in the prophylaxis of different respiratory tract diseases. Although several action mechanisms have been proposed, the therapeutic potential of probiotics in humans is not completely elucidated and needs future clinical studies.

Besides the efforts to elucidate the mechanisms of action of probiotics with therapeutic purpose, technological advances in getting new products contribute significantly to the expansion of this market. As in the case of the spray-drying technique, a well-known encapsulation method, for the production of microcapsules containing probiotics, is required. Microencapsulation of probiotics enables storage of viable bacteria at room temperature and may allow incorporation of probiotics into a wide range of food products. The large variety of probiotic products is also due to the possibility of different food matrix for these products. These products can be dairy and non-dairy probiotic products. Specific techniques are used to change some structural characteristics of fruit and vegetables matrices by modifying food components in a controlled way.

Future work, mainly related to in vivo studies and techniques that enable the action of probiotic microorganisms should guarantee new applications and the development of different products.

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