

REVIEW

The market of probiotics

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Abstract: The advertising of probiotics in dairy products on the market has claimed several health-improving properties, including prevention and treatment of obesity, cardiovascular diseases and cancer prophylaxis, osteoporosis and arthritis treatment, diabetes management and control of hypercholesterolemia. Therefore, it is reasonable to emphasize the perspective of a new self-care and integrative medicine season, where food industry is turned to research-oriented management with putative clinical goals to be achieved. We searched Pubmed/Medline using the terms “probiotics” and “market”. Selected papers until 2013 were chosen on the basis of their content (clinical evidence-based quality). We performed an accurate investigation on the so-called “probiotic market”, leading to better understanding the role of nutraceutical products in the human clinical nutrition physiology. As nutraceutical products are sold all over the world, information, provided by this review may be useful to evaluate their potential impact on human health.

Keywords: Probiotic, market, health, clinical nutrition.

INTRODUCTION

Probiotics are a series of lactic acid bacteria, *bifidobacteria*, *enterococci*, *propionibacteria* and even yeasts, which promote healthy effects when ingested. They are delivered on market in capsules, powders, enriched yogurts, yogurt-like products and milk. Most probiotic strains can be spontaneously found either in the human body, as part of the commensal flora or in dairy products worldwide. The World Health organization (WHO) and the Food and Agriculture Organization (FAO) concluded that probiotics can be generally regarded as safe (Hoesl and Altwein, 2005). However, referring to some literature reports (fig 1) (Salminen *et al.*, 1998, Borriello *et al.*, 2003), such organizations do not exclude that probiotics may be responsible for possible side effects such as: 1) systemic infections (Mackay *et al.*, 1999, Oggioni *et al.*, 1998, Rautio *et al.*, 1999, Richard *et al.*, 1988, Mastro *et al.*, 1990, Sire *et al.*, 1992); 2) deleterious metabolic activities (Zhang *et al.*, 2008, Marteau and Seksik, 2004); 3) excessive immune response soliciting in susceptible individuals (Boyle *et al.*, 2006) and 4) gene transfer (Franz *et al.*, 2011). Untoward effects have been mainly registered in immunocompromised patients, however surveillance of possible rare cases of probiotic infection should be reinforced.

The minimum effective dose of a probiotic is approximately 10^8 - 10^9 cells per day (Shiby and Mishra, 2013) but there is no evidence-based consensus on the optimal concentration of bacteria pro-dose. Generally, human-gut recovered lactic acid bacteria are declared safe

because they may steadily colonize the intestinal tract and remove other pathogenic microorganisms from the gut environment. This goal can be due also to the growth inhibiting pathogenic bacteria by producing bacteriocins (Jack *et al.*, 1995). Even if the effects of some strains have not been satisfactorily evaluated yet, no firm guidelines exist for safety testing (Lee and Salminen, 1995). The clinical reliability of all commercially available probiotics is mandatory, as most of the nutraceutical products do not hold efficient clinical data about the real bioavailability and health benefits (Das *et al.*, 2012). For instance, most of the available probiotics in the world market are unable to survive the acid gut environment and the bile concentration (Sendra *et al.*, 2008). Bile acids can inhibit both Gram-positive bacteria, such as *bifidobacteria* and *lactobacilli*, and Gram-negative organisms (*Neisseria*, *Pasteurella* and *Helicobacter pylori*) but, unfortunately, with almost no effect. As stated by Khan *et al.*, probiotics are gaining place in the “functional food” area, where food-containing probiotics is a subset, where the aim is not only to promote health but also provide basic nutrition (Khan and Ansari, 2007). Probiotics, however, have to be distinguished from prebiotic, non digestible food ingredients which beneficially affect what can selectively stimulate both the growth and/or the activity of one or more bacteria in the colon, thus promoting the host health (Gibson and Roberfroid, 1995).

Global market overview

The term “functional food”, or nutraceutical, is generally used to describe foods enriched with health-promoting ingredients (Stanton *et al.*, 2001). The area of probiotic products belongs to the functional foods, where research

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efforts to develop new dairy products are always under way. The market leaders in nutraceuticals include USA (>400\$ billion), Europe (>200\$ billion) and Japan (<100\$ billion) (Das *et al.*, 2012). Functional food ingredients, such as probiotics, prebiotics, vitamins and minerals can be found in fermented milk and yogurt, sport drinks, sugar-free and baby foods and even chewing gums (Sanders, 1998). Between 2007 and 2008, the global probiotic market increased from \$14.9 billion to \$15.9 billion with an expected value of \$19.6 billion by 2013 (Anonymous, 2013). Recently, the world probiotic market has been estimated at \$15 billion, with a growing rate of 5%-30% depending on the country and product type (Bhadoria and Mahapatra, 2013). Recently, Balaji and coworkers claimed that the Indian probiotic industry, where multinational corporations, such as Nestle and Danone, are present with their dairy products, is valued at \$2 million and is expected to exceed \$8-10 million in the next 3-4 years (Balaji and Kantha, 2011). Currently, the Real-Time Sampling (RTS) market research has valued the European functional food sales at €8 billion and in excess of €10 billion by 2010 (RTS Resource, 2012). Consumers are becoming more interested in health and, in particular, in its relationship with food. Many of them consumers continually seek to optimize their performance and wellness and reduce the risk of cardiovascular diseases (Saini *et al.*, 2010), cancer (de Moreno de LeBlanc *et al.*, 2007) and osteoporosis (Scholz-Ahrens *et al.*, 2007). Moreover, due to both aging of European populations and increase in disposable income, there is spreading desire for convenience. This has prompted both the demand and the development of new functional foods. It is worth noting that in this functional food market the largest share is led by drinks, which occupy around 50% of all sales, these are followed by probiotics (mainly dairy products) and prebiotics, (mainly dairy products, cereals and baked goods) (RTS Resource, 2012). Moreover, it has been estimated that the European probiotic industry accounts for more than €1.4 billion according to retail price index, whereas the prebiotic industry is valued at €0.9 billion (RTS Resource, 2012). A 2012 BCC Research report estimated a growth of the total global market for microbes and microbial products from \$144 billion in 2010 to \$259 billion in 2016 (Anonymous, 2012). Moreover, BCC report pointed out a projection of microbe market from \$4.9 billion in 2011 to \$6.8 billion in 2016 (Anonymous, 2012).

Clinically effective probiotics on the market

Probiotic dairy products belong to the evolving area of European functional food market, in particular yogurt and milk, and the possibility that these products are marketed directly to consumers or that they are qualified as food or dietary ingredients depends on their safety. The main European probiotic brands are fermented dairy drinks from Danone, Yakult and Nestlé LC1. Yakult was the first probiotic drink to be launched in Europe in 1996,

followed by Nestle's LC1 "Go" and Danone's Actimel in 1999. In tab. 1, the most common sold probiotic products are listed.

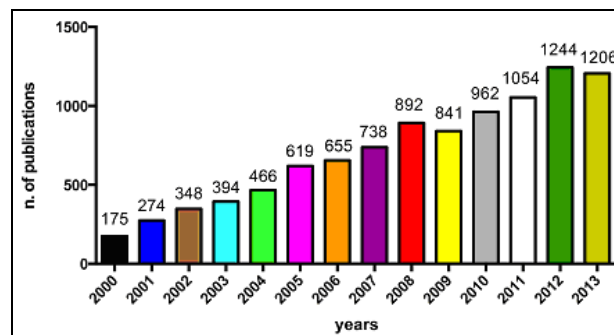


Fig. 1: Schematic representation of the increasing medical literature in the field of probiotics in terms of publication numbers in the last thirteen years

CONCLUSIONS

Our review focused on the most widespread probiotics used in the world on the basis of a proved success in terms of consumer's choice, commercial formula, and subjective symptomatic outcome on bowel habits or other gastrointestinal tract imbalances. The literature about each strain gave us some information about the potential therapeutic benefits in different potential pathologic areas, such as immunological impairment, cancer prevention, helicobacter eradication, pancreatic or digestive insufficiency, metabolic (lipid metabolism) imbalance, etc. In the last five years, one of our main focuses has been the nutraceutical impact in terms of genomic and proteomic induction in the prevention and treatment of medical illnesses. Therefore, it is important to promote the development of large and cost-effective investigations supported by the food industry in the medical area. The use of the web and telephone interviews in monitoring wide cohorts of individuals is becoming widespread, as it is very helpful to perform clinical studies, cut the costs and achieve, on a reasonable time schedule, useful data on the functional and fitness advantages of prolonged probiotic ingestion. Actually, most of the companies manufacturing this kind of dairy products advertise their administration declaring generic benefits related to regular bowel function, relieve of abdominal discomfort and improvement of the symbiotic bacterial flora without claiming any further action mechanism in preventing specific systemic or localized diseases. The reasons of this advertising understatement is obvious: no company wants to be upgraded into the pharmaceutical specialty area both for financial/management reasons and regular medical monitoring requirements. In our perspective we think that public institutions should undertake the follow-up in the long-term use of this market products on a wide epidemiological basis, identifying possible major benefits in the clinical setting and disease prevention.

Table 1(A): Summary of clinical studies of commercially available probiotics

Product Name	Producer	Content	CFUs	Beneficial Claims
Yo-Plus yogurt	Yoplait Inc	<i>B. animalis subsp lactis</i> Bb-12 in addition to <i>S. thermophilus</i> and <i>L. bulgaricus</i> plus prebiotic plus inulin 3 g per serving	> 5 billions	<ul style="list-style-type: none"> - Gut survival (Marteau <i>et al.</i>, 1992) - Activity in pancreatitis (Besselink <i>et al.</i>, 2008) - Activity against <i>Helicobacter pylori</i>. (Kim <i>et al.</i>, 2008, Sheu <i>et al.</i>, 2006) - Activity against pathogens bacteria and viruses (Yang <i>et al.</i>, 2009) - Antioxidant activity (Amaretti <i>et al.</i>, 2013) - Cholesterol lowering activity (Lin <i>et al.</i>, 1989) - Antitumor activity (Borowicki <i>et al.</i>, 2011, Aso and Akazan, 1992) - Mucosal adhesion (Moussavi and Adams, 2010)
Yakult cultured milk	Yakult Honsha Co.	<i>L. casei Shirota</i> plus 11 g of sugar	8 billions	<ul style="list-style-type: none"> - Immunomodulatory activity (Ivory <i>et al.</i>, 2008, Zhang <i>et al.</i>, 2012) - Activity against both pathogens bacteria and viruses (de Waard <i>et al.</i>, 2002, Asahara <i>et al.</i>, 2011) - Cancer prevention and treatment (Yasutake <i>et al.</i>, 1999, Matsuzaki, 1998)
Ultimate Probiotic Formula	Swanson Health Products	<i>B. lactis</i> , <i>B. longum</i> , <i>L. plantarum</i> , <i>L. acidophilus</i> , <i>L. casei</i> , <i>Kyo-Dophilus blend</i> , <i>L. salivarius</i> , <i>L. rhamnosus</i> , <i>L. bulgaricus</i> , <i>L. sporogenes</i> plus 100 mg of prebiotic NutraFlora short chain FOS	60 billions	<ul style="list-style-type: none"> - Antitumor activity (Goldin and Gorbach, 1984, Zhang <i>et al.</i>, 2012, Ohigashi <i>et al.</i>, 2011, Le Leu <i>et al.</i>, 2005, Challa <i>et al.</i>, 1997, Singh <i>et al.</i>, 1997) - Cholesterol lowering activity (Lin <i>et al.</i>, 1989) - Activity against pathogens bacteria and viruses (Yang <i>et al.</i>, 2009, Singh <i>et al.</i>, 1997, Jebur, 2010, Teanpaisan <i>et al.</i>, 2011, Zabihollahi <i>et al.</i>, 2012) - Immunomodulatory activity (Yesilova <i>et al.</i>, 2012) - activity against IBD (Gionchetti <i>et al.</i>, 2000) - gut survival properties (Marteau <i>et al.</i>, 1992) - Activity in pancreatitis (Besselink <i>et al.</i>, 2008) - liver steatosis reduction (Xu <i>et al.</i>, 2012) - Activity in arthritis (So <i>et al.</i>, 2011) - Mucosal adhesion (Tuomola <i>et al.</i>, 1999)
StonyField Farm yogurt	Stonyfield Farms, a subsidiary of Dannon Inc.	<i>L. rhamnosus</i> HN001, <i>B. lactis</i> , <i>L. acidophilus</i> and <i>L. casei</i> in addition to <i>S. thermophilus</i> and <i>L. bulgaricus</i>	15 billion	<ul style="list-style-type: none"> - Activity in pancreatitis (Besselink <i>et al.</i>, 2008) - Antitumor activity (Zhang <i>et al.</i>, 2012, Le Leu <i>et al.</i>, 2005) - Activity against pathogens bacteria and viruses (Yang <i>et al.</i>, 2009) - Activity against <i>Helicobacter pylori</i> (Sheu <i>et al.</i>, 2006) - Cholesterol lowering activity (Lin <i>et al.</i>, 1989)
Good Belly fruit drink	NextFoods	<i>L. plantarum</i> 299v	20 billion	<ul style="list-style-type: none"> - Activity against both pathogens bacteria and viruses (Michail and Abernathy, 2002) - Oral mutants streptococci and <i>Candida albicans</i> (Hasslof <i>et al.</i>, 2010) - Activity against pancreatitis (Mangiante <i>et al.</i>, 1999)
Gerber Good Start Protect Plus powdered infant milk formula	Nestle	<i>B. lactis</i> Bb-12	10 billion	<ul style="list-style-type: none"> - Adhesion Mucosal. (Moussavi and Adams, 2010) - Antitumor activity (Borowicki <i>et al.</i>, 2011, Raftar <i>et al.</i>, 2007)
DanActive cultured milk (in Europe as Actimel)	Dannon Inc	<i>S. thermophilus</i> and <i>L. bulgaricus</i> in addition to <i>L. casei</i> DN-114 001. The latter is also marketed as <i>L. casei Defensis</i> or <i>Immunitas</i>	10 billion	<ul style="list-style-type: none"> - Activity against pathogens bacteria and viruses (Yang <i>et al.</i>, 2009) - Activity against <i>Helicobacter pylori</i> (Sheu <i>et al.</i>, 2006) - Cholesterol lowering activity (Lin <i>et al.</i>, 1989)

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Table 1(B): Summary of clinical studies of commercially available probiotics

Product Name	Producer	Content	CFUs	Beneficial Claims
VSL#3 saket	Sigma-Tau Pharmaceuticals	<i>B. breve</i> , <i>B. infantis</i> , <i>B. longum</i> , <i>L. acidophilus</i> , <i>L. bulgaricus</i> , <i>L. casei</i> , <i>L. plantarum</i> and <i>S. thermophilus</i>	450 billion	<ul style="list-style-type: none"> - Antitumor activity (Goldin and Gorbach, 1984, Zhang <i>et al.</i>, 2012, Ohigashi <i>et al.</i>, 2011) - Cholesterol lowering activity (Lin <i>et al.</i>, 1989) - Activity against pathogens bacteria and viruses (Yang <i>et al.</i>, 2009, Jebur, 2010) - Immunomodulatory activity (Yesilova <i>et al.</i>, 2012) - Activity against IBD (Gionchetti <i>et al.</i>, 2000) - Gut survival properties (Marteau <i>et al.</i>, 1992) - Activity in pancreatitis (Besselink <i>et al.</i>, 2008)
OWP probiotics	One Wellness Place	<i>B. longum</i> , <i>B. brevis</i> , <i>B. infantis</i> , <i>L. plantarum</i> , <i>L. rhamnosus</i> , <i>L. acidophilus</i>	15 billion	<ul style="list-style-type: none"> - Antitumor activity (Zhang <i>et al.</i>, 2012, Challa <i>et al.</i>, 1997, Singh <i>et al.</i>, 1997, Bertkova <i>et al.</i>, 2010) - Activity against IBD (Gionchetti <i>et al.</i>, 2000) - Liver steatosis reduction (Xu <i>et al.</i>, 2012) - Activity against pathogens bacteria and viruses (Teapaisan <i>et al.</i>, 2011, Zabihollahi <i>et al.</i>, 2012, Hugo <i>et al.</i>, 2008) - Immunomodulatory activity (Yesilova <i>et al.</i>, 2012) - Gut survival properties (Marteau <i>et al.</i>, 1992) - Activity in pancreatitis (Besselink <i>et al.</i>, 2008)
Culturelle capsules	Amerifit Nutrition, Inc	<i>L. rhamnosus</i> GG	10 billion	<ul style="list-style-type: none"> - Antitumor activity (Borowicki <i>et al.</i>, 2011, Rafter <i>et al.</i>, 2007) - Activity against toxins (Skopinska <i>et al.</i>, 2012) - Antioxidant activity (Sun <i>et al.</i>, 2010) - Activity against both pathogens bacteria and viruses (Yang <i>et al.</i>, 2009, Huang <i>et al.</i>, 2009) - Activity against <i>H. pylori</i> (Kim <i>et al.</i>, 2008, Zhang <i>et al.</i>, 2012, Myllyluoma <i>et al.</i>, 2007) - Immunomodulatory activity (Ghadimi <i>et al.</i>, 2010) - activity against IBD (Gupta <i>et al.</i>, 2000)
Bio-K+ probiotic capsules	Bio-K+ International Inc	<i>L. acidophilus</i> CL1285 and <i>L. casei</i> LBC804	30 billion	<ul style="list-style-type: none"> - Antitumor activity (Baldwin <i>et al.</i>, 2010) - Activity against pathogens bacteria and viruses (Karska-Wysocki <i>et al.</i>, 2010)
Bio-K+ cultured milk based probiotic	Bio-K+ International Inc	<i>L. acidophilus</i> CL1285 and <i>L. casei</i> LBC804	50 billion	<ul style="list-style-type: none"> - Antitumor activity (Baldwin <i>et al.</i>, 2010) - Activity against pathogens bacteria and viruses (Karska-Wysocki <i>et al.</i>, 2010)
Attune nutrition bars	Attune Foods	<i>L. acidophilus</i> NCFM, <i>L. casei</i> Lc-11 and <i>B. lactis</i> HN019	6.1 billion	<ul style="list-style-type: none"> - Antitumor activity (Rao <i>et al.</i>, 1999)
Align capsules	Proctor & Gamble	<i>B. infantis</i> 35624	1 billion	<ul style="list-style-type: none"> - Immunomodulatory activity (Sheil <i>et al.</i>, 2006)
Adult Formula CP-1	Custom Probiotics Inc	<i>L. Acidophilus</i> , <i>L. Rhamnosus</i> , <i>L. Plantarum</i> , <i>B. Lactis</i> and <i>B. Bifidum</i>	50 billion	<ul style="list-style-type: none"> - Activity against IBD (Gionchetti <i>et al.</i>, 2000) - Gut survival properties (Marteau <i>et al.</i>, 1992) - Activity in pancreatitis (Besselink <i>et al.</i>, 2008) - Antitumor activity (Goldin and Gorbach, 1984, Zhang <i>et al.</i>, 2012, Ohigashi <i>et al.</i>, 2011) - Cholesterol lowering activity (Lin <i>et al.</i>, 1989) - Activity against pathogens bacteria and viruses (Yang <i>et al.</i>, 2009, Jebur, 2010, Teapaisan <i>et al.</i>, 2011, Zabihollahi <i>et al.</i>, 2012, Hugo <i>et al.</i>, 2008) - Immunomodulatory activity (Yesilova <i>et al.</i>, 2012) - Mucosal adhesion (Tuomola <i>et al.</i>, 1999)
Activa yogurt	Dannon Inc	<i>B. animalis</i> DN-173010 and <i>B. regularis</i> in addition to <i>S. thermophilus</i> and <i>L. bulgaricus</i>	10 billion	<ul style="list-style-type: none"> - Activity against pathogens bacteria and viruses (Yang <i>et al.</i>, 2009) - Activity against <i>Helicobacter pylori</i> (Zhang and Ohta, 1993) - Cholesterol lowering activity (Lin <i>et al.</i>, 1989)

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Table 1(C): Summary of clinical studies of commercially available probiotics

Product Name	Producer	Content	CFUs	Beneficial Claims
Gefilus juice	Valio Ltd, Helsinki, Finland	<i>L. Rhamnosus</i> GG	5 milion	<ul style="list-style-type: none"> - Antitumor activity (Borowicki <i>et al.</i>, 2011, Rafter <i>et al.</i>, 2007) - Activity against toxins (Skopinska <i>et al.</i>, 2012) - Antioxidant activity (Sun <i>et al.</i>, 2010) - Activity against both pathogens bacteria and viruses (Yang <i>et al.</i>, 2009, Huang <i>et al.</i>, 2009) - Activity against <i>Helicobacter pylori</i> (Kim <i>et al.</i>, 2008, Zhang <i>et al.</i>, 2012, Myllyluoma <i>et al.</i>, 2007, Corcoran <i>et al.</i>, 2007) - Immunomodulatory activity (Ghadimi <i>et al.</i>, 2010) - Activity against IBD (Gupta <i>et al.</i>, 2000)
Kefir drinks	Lifeway foods Inc	<i>L. acidophilus</i> , <i>Lb. Brevis</i> , <i>L. casei</i> , <i>Lb. casei subsp. Rhamnosus</i> , <i>Lb. casei subsp. Pseudoplatantum</i> , <i>Lb. paracasei subsp. Paracasei</i> , <i>Lb. delbrueckii subsp. Lactis</i> , <i>L. kefiranoformis subsp. kefirgranum subsp. Nov</i> , <i>L. lactis</i> , <i>L. plantarum</i> , <i>L. lactis var. diacetylactis</i> , <i>L. lactis subsp. Cremoris</i> , <i>S. lactis</i> , <i>Enterococcus</i> , <i>L. mesenteriodes</i> , <i>C. pseudotropicalis</i> , <i>C. tenuis</i> , <i>K. marxianus var. marxianus</i> , <i>K. Bulgaricus</i> , <i>K. Fragilis/marxianus</i> , <i>S. subsp. Torulopsis holmii</i> , <i>S. lactis</i> , <i>S. Carlsbergensis</i> , <i>S. Unisporus</i> , <i>D. hansenii</i> , <i>Z. rouxii</i>	7-10 billion	<ul style="list-style-type: none"> - Antitumor effect (Tannock <i>et al.</i>, 2000, Suarez-Quiroz <i>et al.</i>, 2005, Petzinger and Ziegler, 2000) - Cholesterol lowering effect (Xie <i>et al.</i>, 2011) - Activity against pathogens bacteria and viruses (Teanpaisan <i>et al.</i>, 2011, Karska-Wysocki <i>et al.</i>, 2010, Castillo <i>et al.</i>, 2013, Tsai <i>et al.</i>, 2008) - immunomodulatory effect (Lyons <i>et al.</i>, 2010, O'Riordan <i>et al.</i>, 2001, Vesa <i>et al.</i>, 2000) - Gut survival (Xu <i>et al.</i>, 2012) - Activity against <i>Helicobacter pylori</i> (Sykora <i>et al.</i>, 2005) - Activity in pancreatitis (Jureen <i>et al.</i>, 2002)

This spontaneous investigation, also enclosing healthy status, lifestyle, age and sex of the consumers, might fill the gap between the experimental preclinical studies of many investigated probiotics (table 1) and the real clinical impact on fitness and wellness in the long run. In conclusion, this review supports the challenging endorsement of a deeper insight of probiotic use in therapeutics with the possible focus on more specific dose/administration schedule protocols especially in disease prevention (like tumors and/or cardio vascular disease area). New studies are required to achieve a better understanding of probiotic therapeutic applications and improved protocols.

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