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Review

The use of probiotics and safety concerns: A review

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Probiotics are defined as ''live microorganisms which when administered in adequate amounts confer a health benefit on the host''. Most probiotics fall into the group of organisms' known as lactic acid-producing bacteria and are normally consumed in the form of yogurt, fermented milks, cereal or other fermented foods. Many of the products currently available in the market are not clearly tied to research documenting beneficial effects. Probiotics are regulated by FDA and several reports are available now for mislabeling the product claiming health benefits. As live microbial products, probiotics are potential sources of risk and there exists skeptical attitude among medical professionals and consumers who have less than optimal experiences with probiotics. This review outlines information regarding probiotics, overview of proposed regulatory guidelines and commercial probiotic products available in the market considered as safe for humans.

Key words: Probiotics, health benefits, safety, dosage, applications.

INTRODUCTION

The term 'probiotics' was derived from the Greek word, meaning "for life" (Reid et al., 2003). An expert panel commissioned by Food and Agriculture Organization (FAO) and World Health Organization (WHO) defined probiotic as "live micro-organisms," which, when administered in adequate amounts confers a health benefits on the host (FAO/WHO, 2006). Recently, there is an increasing scientific and commercial interest in the use of beneficial microorganisms for the prevention and treatment of diseases (Figure 1). The use of microorganisms to restore or maintain health is the basis of probiotics which is one of the largest segments of the functional foods (FF) market. The global sales of probiotic supplements were predicted to rise 48% from $2.7bn in 2011 to $4bn in 2016 (www.nutraingredients.com/Consumer-Trends). In US, per capita spending on probiotic supplements is expected to nearly double by 2016 and overtake Japan. Indeed, the market of probiotics and healthy food has great potential to grow, especially in Asia. However, the European market is now saturated, and growth of probiotic market is likely to occur mainly in non-dairy food areas and novel applications (Rivera-Espinoza and Gallardo-Navarro, 2010). The different bacterial genera most commonly used in probiotic preparations are *Lactobacillus, Bifidobacterium, Escherichia, Enterococcus, Bacillus, Streptococcus and Pediococcus (*Adam et al., 2012*)*. Some fungal strains belonging to *Saccharomyces* (*Saccharomyces boulardii*) are now used as a "drug" to prevent or treat recurrent *Clostridium difficile* infection (CDI), particularly in critically ill patients (Gupta and Garg, 2009; Mc Farland, 2009). This review focuses on highlighting the current regulatory framework, risks associated, dosage and probiotic products currently available in the market for human consumption for various treatments.

Occurrence and action of probiotics

Most existing probiotics have been isolated from the human gut microbiota. This microbiota plays an important role in human health, not only due to its participation in the digestion process, but also for the function it plays in the development of the gut and the immune system (Sanchez et al., 2012). The human gastrointestinal (GI) tract is "home" to a complex consortia of trillions (approximately 1×10^{13} to 1×10^{14}) of microbes, thousands of bacterial phylotypes, as well as hydrogen-consuming methanogenic archaea, colonizing the entire

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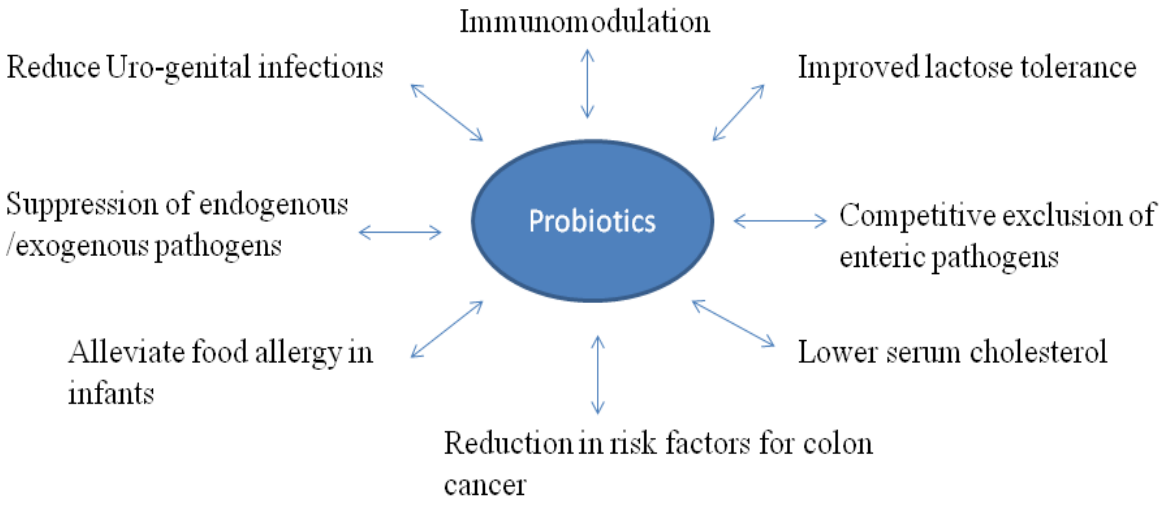

Figure 1. Health benefits of probiotics.

length of the gut with a collective genome (also termed as microbiome) that contains at least 100-times as many genes as our own genome (Cho and Blaser, 2012; Wei et al., 2008). Cutting edge research and vast accumulating data indicates that the gut microbiota is instrumental in energy metabolism and immune function of the host, and has a crucial role in the development of numerous conditions including obesity (Clarke et al., 2012; Ley et al., 2006) diabetes (Bergman et al., 2006), non-alcoholic fatty liver disease (Dumas et al., 2006), inflammatory bowel diseases (Quigley, 2012; Strober et al., 2008), and cancer (Parvez et al., 2006). Mechanism of action of probiotics is not completely understood, however as general include 1) Adherence and colonization of gut, 2) Suppression of growth of pathogenic bacteria, 3) Production of antimicrobial compounds, 4) Improved intestinal barrier function, 5) Stimulation of mucosal and systemic host immunity, 6) Controlled transfer of dietary antigens (Sharma et al., 2012).

Registering probiotic product

Regulatory issues are of prime focus for those involved in the development and marketing of probiotic products. The European Food Safety Authority (EFSA) recently determined that none of the claims for specific probiotic strains submitted to date were adequately substantiated by the scientific data that were provided as evidence of support (EFSA, 2009). Health Canada recently provided industry guidance on probiotic-containing foods (http: //www.hc-sc. gc.ca) and is developing guidance for probiotic natural health products. The Indian Council of Medical Research (ICMR) is developing guidelines for India that would require probiotic strains to be backed by clinical trials preferably conducted in local population, if they are to be marketed (Gokhale and Nadkarni, 2007). Recently, Shane et al. (2010) developed a guide for the design of well performed, randomized, controlled clinical studies in human participants in order to provide acceptable evidence to support a probiotic claim.

Although the concept of probiotics is not new, the advent of commercial products has refocused attention on their potential uses and applications. However, in the last few years new probiotic products have been introduced onto the market, with the inevitable competition for the consumers' disposable income. Additionally, the products have been introduced to health care professionals with a variety of therapeutic claims for health and benefit, often with extrapolated clinical evidence of efficacy (Elliott and Teversham, 2004).

Probiotics in the United States could potentially be regulated in a variety of different product range depending on the intended use either as Conventional foods (For consumption by general population), Dietary supplements (A subcategory of foods, the dietary supplement category was created in 1994 by the Dietary Supplement Health and Education Act- the products are meant to be used as oral supplements to the diet, and are not to be represented as meals), Medical foods (Foods used under medical supervision for patients needing special dietary support for medical condition), Feed additives (Termed "Direct fed microbials" by the USDA) or as Drugs (www.usprobiotics.org). According to the Food and Drug Administration (FDA) definition, a drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (FDA, 2009). If a probiotic is intended for use as a drug, then it must undergo the regulatory process as a drug, which is similar to that of any new therapeutic agent. Sanders (2009), in effectively choosing a product by both health care providers and consumers recommends that any new

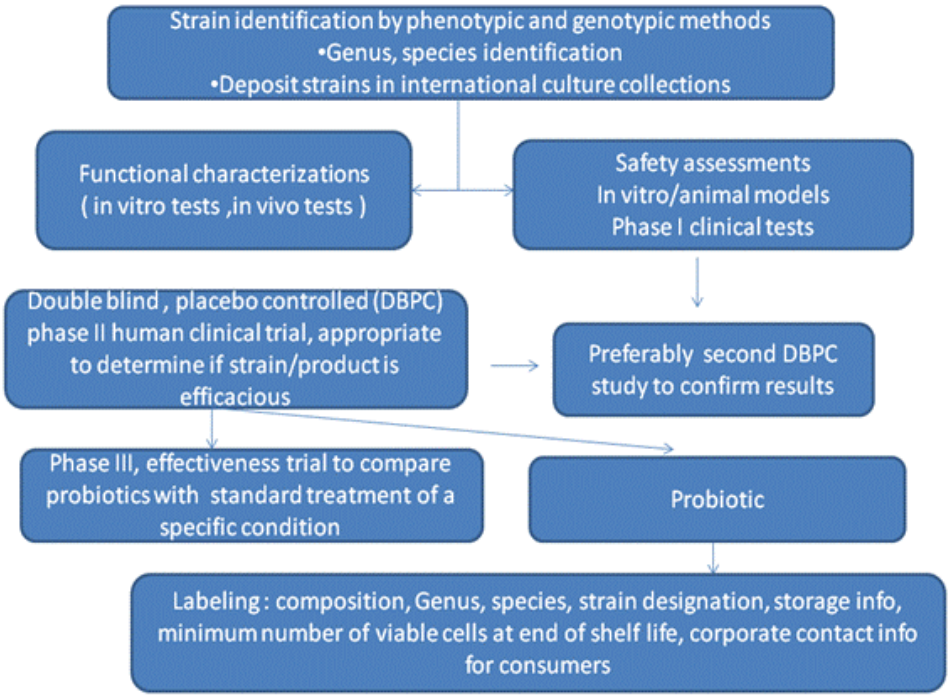

Figure 2. FAO/WHO Guidelines for the evaluation of probiotics for food use.

drug under investigation must be submitted and approved by FDA as safe and effective before an investigational or biological product can be administered to humans.

In an attempt to standardize the global requirements needed to make health claims regarding probiotic agents, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics developed guidelines for evaluating probiotics in food that could lead to the substantiation of health claims. The recommended evaluation of probiotics for food use is shown in Figure 2. Consensus on uniform regulations is desirable to ensure identity, quality manufacturing processes, accurate labeling, proven safety and efficacy for a product that will carry the label “probiotic”.

Safety of probiotics

The absolute essence of Probiotics to be considered as safe is the absence of pathogenicity and infectivity. Safety criteria for successful probiotics have been well defined in several studies (Forssten et al., 2011; Pineiro and Stanton, 2007; Mattila and Saarela, 2000; Saarela et al., 2000).

The fact to prove that the probiotic bacteria are infective is difficult, especially in anaerobes, which are generally considered to have no infectivity. Even if the bacteria are administered orally, infection does not normally occur in healthy animals; this is particularly so for bacteria with weak infectivity. Even with strongly infective bacteria, it is not easy to establish infection by using a single species, and various techniques are necessary to establish infection, such as the use of various pre-treatments in the experimental system or the use of mixed infection. Adverse effects of probiotics, if they occur, are usually mild and affect the digestive system in children (e.g., abdominal discomfort or flatulence) with short gut syndrome (Oliver and Reid, 2009; Kligler et al., 2007). However, as viable and potent microorganisms, probiotics have the potential to cause invasive infections in hosts who may have compromised mucosal epithelia. Invasive infections have primarily been noted to occur in immunocompromised adults. It is advisable to avoid probiotics in these patients or to be aware of risk of sepsis.

Lactobacillus species are a rare but well-recognized cause of endocarditis in adults (and other forms of sepsis in children) in the absence of probiotic supplementation. Several reports have directly linked cases of *Lactobacillus* and other bacterial sepsis to the ingestion of probiotic supplements. The reader is suggested to consult Boyle et al. (2006) for in-depth review of this subject. A proposed scheme for safety assessment of probiotics is presented in Table 1. Most stringent studies have to be completed for genetically modified strains intended for human consumption before commercialization (Choi et al., 2012; Sorokulova, 2008; Salminen et al., 1996).

Table 1. Important studies for safety assessment of probiotic lactic acid bacteria (LAB) and other bacteria (Donohue and Salminen, 1996).

Type of property studied	Safety factor to be assessed
Intrinsic properties of lactic acid bacteria	Adhesion factors, antibiotics resistance, existence of plasmids and *Tra* genes, harmful enzyme profiles
Metabolic products	Concentrations, safety and other effects
Toxicity studies	Acute and subacute effects of ingestion of large amounts of tested bacteria
Mucosal effects	Adhesion, invasion potential, intestinal mucus degradation, infectivity in immunocompromised animals
Dose response effects	Dose response studies by oral administration in volunteers
Clinical assessment	Potential for side effects, careful evaluation in healthy volunteers and disease specific studies
Epidemiological studies	Surveillance of large populations following introduction of new strains and products

Table 2. Probiotic preparations.

Probiotic strain	Recommended daily dosage	Preparations
Lactobacillus rhamnosus GG	10 billion CFUs	Capsules (Culturelle) Therapeutic yogurts and fermented milks
Lactobacillus sp./ *Bifidobacterium* sp	100 million to 35 billion CFUs, depending on preparation	Capsules (Align, Primadophilus) Powder (Primal Defense) Capsules or powder (Fem-Dophilus, Jarro-Dophilus) Therapeutic yogurts and fermented milks (Activia, Danactive, Yo-Plus)
Saccharomyces Boulardii	250 mg to 500 mg	Capsules (Florastor)
Bacillus sp	10^7-10^8 spores g^{-1}	Powder (Bibactyl)

[a] CFU= colony-forming unit, [b] Most commercial brands contain a mixture of strains that may include *Lactobacillus acidophilus, L. rhamnosus, Lactobacillus bulgaricus, Bifidobacterium bifidum, Bifidobacterium longum,* and others. Exact combinations of strains vary among brands (www.usprobiotics.org).

The right dosage

Probiotics are generally sold as capsules, powder, tablets, liquid, or are incorporated into food. The specific number of colony forming unit (CFUs) contained in a given dose or serving of food can vary between brands (Kligler and Cohrssen, 2008). Patients should be advised to read products label carefully to make sure that they are getting the right dose. Interestingly, probiotics are available over the counter and are not regulated by FDA but generally regarded as safe. Because probiotics are not regulated by the FDA, there are no standard dosage recommendations for probiotics. Providers typically use half the adult dose for pediatric patients and a one-fourth dose for infants (Cabana et al., 2006). A recent study analyzed a range of brands of probiotics and found that of the 19 brands examined, five did not contain the number of live microorganisms stated on the label (http://www.consumerlab.com/results/probiotics.asp).
Because some labels are unreliable, physicians should recommend specific brands known to be of reasonable quality or encourage patients to research brands before purchasing a specific product. Guidance on probiotics can be found at http://www.usprobiotics.org and at the National Center for Complementary and Alternative Medicine's Web site, http:// nccam.nih.gov/health/probiotics/.

Presently, a wide range of dosages for *Lactobacillus* sp. and other probiotics have been studied in clinical trials and are available, ranging from 100 million to 1.8 trillion CFUs per day, with larger dosages used to reduce the risk of pouchitis relapse. Most studies examined dosages in the range of 1 to 20 billion CFUs per day, although exact dosages for specific indications varied within this range. Generally, higher dosages of probiotics (that is, more than 5 billion CFUs per day in children and more than 10 billion CFUs per day in adults) were associated with a more significant study outcome. The dosages of *S. boulardii* in most studies range between 250 and 500 mg per day (Table 2).

Probiotic products

Fermented dairy products enriched with probiotic bacteria have developed into one of the most successful

Table 3. Commercial probiotic products in market (Cutting, 2011; Suvarna and Boby, 2005)*.

Product name	Species	Company	Applications
Nesvita	*LAB*	Nestle, India	Gut Probiotic
Vizyl	*LAB*	Unichem, India	Gastrointestinal Health
ViBact	*Bacillus mesentricus, Clostridium butyricum, Streptococcus faecalis, Lactobacillus sporogenes*		Lamb Performance
Provisacc		Vetcare India Pvt. Ltd, India	Vaginal Infections, Gastrointestinal health
Improval	*Saccharomyces cerevasie, lactobacillus sporogenes*	Cadila, India	Vaginal infections
Econova		Glenmark, India	Gastrointestinal health
Amul	*Lactobacillus acidophilus,*	Amul, India	Diabetics
Binifit	*Streptococcus faecalis, Clostridium butyricum, Bacillus mesentricus LAB*	Ranbaxy, India	Antibiotic associated Diarrhoea (AAD)
Actimel®	*Lactobacillus casei DN 014001*	Danone, France	Immune booster
Yakult ®	*Lactobacillus casei*	Yakult Honsha Co., Ltd, Japan	Gastrointestinal health
Proviva	*Lactobacillus plantarum*	Probi, Lund	Gastrointestinal health
Gefilus	*Lactobacillus GG*	Valio Ltd, Finland	Gastrointestinal health
Bifilac	*JPC, Clostridium butyricum, Bacillus mesentricus, Lactobacillus sporogenes*	Tablets India Pvt Ltd, India	Irritable bowel syndrome, Diarrhoea.
LC1	*Lactobacillus johnsonii*	Nestle	Gastrointestinal health
Flora Grow	*Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium bifidum*	Arise & Shine Herbal Products Inc, USA	Gastrointestinal health
Biosporin®	*Bacillus subtilis* *Bacillus licheniformis*	Biofarm, Dniepropetrovsk, Ukraine Garars, Russia	Pyo-speticpost operational complications, bacterial vaginitis,
Enterogermina®	*Bacillus clausii*	Sanofi Winthrop SpA, Milan, Italy	Bacteriotherapy and bacterioprphylaxis of gastrointestinal disorders
Biostart		Microbial Solutions, Johannesburg, South Africa	Aquaculture

Table 3. count

Lactospore ®	Labeled as *Lactobacillus sporogenes*but contains *Bacillus coagulans*	Pharmed Medicare, Bangalore, India http://www.pharmedmedicare.com	Gastrointestinal health
Florastor®	*Saccharomyces boulardii*	Biocodex, USA	Gastrointestinal Health
LG21	*Streptococcus thermophilus* 1131	Meiji milk products, Tokyo	Gastrointestinal health
BioGaia®	*Lactobacillus reuteri SD2112*	BioGaia, North Carolina	Gastrointestinal health
Florafit®	*Lactobacillus acidophilus* NCFM	Rhodia, Madison	Gastrointestinal health
Biopromulti™	*Lactobacillus acidophilus*	Akacia Health Care (Pty) Ltd, South Africa	Immune booster
Morinaga Bifdus milk	*Bifidobacterium longum* BB536	Morinaga Milk Industry Co., Ltd., Japan	Gastrointestinal health
PoultryStar®	*Enterococcus, Pediococcus, Lactobacillus, Bifidobacterium*	Biomin, Herzogenburg, Austria	Improved weight gain, decreased mortality, inhibition of enteric pathogens
Mitomax®	*Pediococcus acidilactici, Saccharomyces boulardii*	Imagilin Technology, USA	Supports digestive system, Reduces stress, Reduces diarrhea, Reduces vomiting, Relieves constipation, Decreases body odor, Enhances immune response

*****partial list

categories of functional foods. They gave rise to the creation of a completely new category of probiotic products like the daily-dose drinks in small bottles, yoghurt, ice creams, milk based desserts, powdered milk for infants, butter, mayonnaise, cheese, products in the form of capsules or fermented food of vegetable origin. Although there are several dozen products in the market that claim to have probiotic activity representatives of only a handful of species dominate the market or have been used in multiple clinical trials. Some of them are listed in Table 3. These include strains of *L. casei, L. johnsonii, L. rhamnosus and L. plantarum*, which are all of human origin and are known under defined brand names. It has been estimated that there were approximately 70 probiotic-containing products marketed in the world (Shah, 2004), and the list is continuously expanding.

Moreover, probiotic products containing *Bacillus* species have been in the market for at least 50 years with the Italian product known as Enterogermina® registered in 1958 in Italy as an OTC medicinal supplement (Cutting, 2011). Of the species that have been most extensively examined are *B. subtilis, B. clausii, B. cereus, B. coagulans* and *B. licheniformis*. Spores that are being heat-stable have a number of advantages over other non-spore formers such as *Lactobacillus* spp., namely, that the product can be stored at room temperature in a desiccated form without any deleterious effect on viability. A second advantage is that the spore is capable of surviving the low pH of the gastric barrier (Spinosa et al., 2000; Barbosa et al., 2005) which is a limitation for all species of *Lactobacillus* (Tuohy et al., 2007).

CONCLUSION

Probiotics are foods that contain live microorganisms.

These microorganisms on metabolite production will give these probiotics their health promoting properties such as boosting immune system, prevent allergies, stop eczema and heal the intestine. Presently the scientific community is at the crossroads, firstly in determining whether probiotics are safe and effective in the treatment of many conditions for which they are already in use. This necessitates addressing basic issues such as dosing, safety and mechanisms of actions of these agents. Other major concern about probiotics is prior use for human consumption alone is insufficient to support clinical studies for registering if this does not match intended use as drug. Finally there exist very few large scale, long term clinical trials conducted on probiotics to support them as “drug”. However, available data from medical literature and clinical studies clearly indicate that probiotics have great health potential particularly to overcome threat of use of antibiotic

over dose and prevalence of antibiotic resistant microorganisms. The future probiotic research should essentially focus and provide more precise information on mechanisms by which probiotics exert their beneficial effects in vivo in various gastrointestinal related diseases and greater acceptance by the medical community.

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