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Probiotic Therapy: Review

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Abstract

Background Although the concept of probiotics was known since the era of Elie Metchnikoff for more than one century ago, the attention of probiotic therapy as effective approach to prevent and treat a wide range of diseases and disordersis increased in the recent years. Probiotic therapy is the treatment of diseases by use live micro-organisms known as probiotics and the aim of this therapy is to increase the numbers of microbiota and enhance their activities until such time that microbiota can be rebalanced. In this review; the definition and properties of probiotics, their types and mechanisms of action, as well as their health beneficial effects and safety have been reported.

Key words Probiotics, Bacteriotherapy, Safety, LAB, GRAS

Introduction

The concept of probiotics comes back to the times of the Ukrainian professor of biology, Elie Metchnikoff (1845-1916) [(1)]. He proposed that the consumption of lactic acid bacteria offered health benefits to the human host [(2)]. The word "probiotic" is derived from the Latin and Greek languages (Latin *pro* meaning "for" and Greek *bios* meaning "life") [(3,4)], it was used for the first time by Kollathin1953; he coined probiotics as "probiotika" to indicate active substances that are essential for a healthy life [(5)].

In 1965 the word probiotic introduced for the first time into scientific literature by Lilly and Stillwell [(6)] to describe "substances secreted by one microorganism which stimulates the growth of another", but Parker in 1974 is considered the first one who used this term as we know it today [(3)]. Fuller [(7)] defined probiotics as "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance." Salminen *et al* [(8)] redefined the probiotics as "microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being of the host".

However, there are many definitions of probiotics but the most widely used and accepted one is that proposed by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) in 2001, they defined probiotics as "Live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host" [(9,10)].

Probiotics are considered one of the preventative and therapeutic potential of alternative agents in the pharmaceutical field [(6)]. Probiotics represent one agent of bacteriotherapy, which consists of three agents; Prebiotics, probiotics and synbiotics. Prebiotics are non-digestible compounds that selectively enhance the growth and activity of intestinal microbiota while synbiotics are probiotics and prebiotics together [(11)]. The treatment by use probiotics called probiotic therapy and its goal is to increase the numbers and activities of those microorganisms with health-promoting properties until such time

that the normal flora can be reestablished [12]. Because the importance of probiotic therapy, this review focused on properties of probiotics, their types and mechanisms of action, their health beneficial effects as well as their safety.

Properties of probiotics

The microorganisms that are used as probiotics must have the following properties:

- They should remain viable and stable after culture, during use and storage before consumption [2].
- Able to survive in the intestinal tract under gastric conditions [13] by exhibiting acid and bile tolerance [14] as well as pancreatic digestion [2].
- Able to adhere to intestinal epithelial surfaces, proliferate, and colonize the gut [13-15].
- They should be nonpathogenic, nontoxic, and generally recognized as safe [6].
- The host should gain direct and indirect beneficial effects from the probiotics after consumption [16] such as; anti-carcinogenic activities, reduced intestinal permeability, stimulate immune system [6], and antimicrobial activity [15].
- They should have resistance to antibiotics.
- They should be isolated from the same species as its intended host, and have good sensory characteristics [6].

In addition to these properties, some authors have suggested that probiotic bacteria should be of "human origin" [2].

Types of probiotics

The microorganisms that are used as probiotics are strains of different bacterial species belong to gram positive bacteria includes lactic acid bacteria (*Lactobacillus*, *Lactococcus*, *Streptococcus, Enterococcus*, *Pediococcus* and *Leuconostoc*), *Bifidobacterium, Bacillus*, and *Propionibacterium* as well as Gram negative bacteria *Escherichia* and nonpathogenic yeast Saccharomyces [16-20] (table 1) but the commonly used probiotics are *Lactobacillus* and *Bifidobacterium* [5,20] as well as nonpathogenic yeast [4,21]. However, the most studied probiotics are; *Lactobacillus rhamnosus*, *Bifidobacteriumlactis*, and *Streptococcus thermophilus* [22]. Some of probiotics are of human origin and others are nonhuman strains used in the dairy industry [23]. The different strains at the same species may show different effects and thus may exhibit overlapping or specific therapeutic actions to different organs [3,24].

Mechanisms of action

The beneficial effects of probiotics on host may be direct or indirect [25]. The mechanisms of action of probiotics are still a significant question regarding clinical use of them [26], the broad-based definition of probiotics makes the study of their mode of action difficult [27], but the scientists during the last decades have studied the mechanisms of action of probiotics [28] and proposed many mechanisms of action for them [12]. Guarner *et al* [19] recorded immunologic and non-immunologic mode of action, whereas Patel and DuPont [11] proposed three general mechanisms of action; antimicrobial activity, immune modulation, and improvement of mucosal barrier integrity (Fig. 1). On the other hand, Binns [4] suggested two main modes of action; Impact of microorganisms or their metabolites on the gastrointestinal tract and microbiota, and interaction with the cells and immune system of the host. However, depending on the function involved, each one of the mechanisms could be further subdivided [27].

The proposed mechanisms of the effect of probiotics on host health to prevent or cure the different diseases could be summarized as follows:

1- Production of antimicrobial agents

Probiotics produce many antimicrobial agents such as organic acids, hydrogen peroxide and antimicrobial peptides known as bacteriocins [12] that can inhibit the growth both of Gram positive and Gram negative bacteria, as well as the other pathogens [25]. Also, probiotics

produce hydrolytic enzymes which contribute increasing amounts of acids and this leads to reduce pH value and thus inhibition of pathogenic bacteria due to the acidic environment [11], the effect of the *Lactobacillus* spp. on *Helicobacter pylori* infection of the gastric mucosa is one of the important examples on the antimicrobial effect of probiotics [27].

Table 1. The microorganisms that are used as probiotics

Microorganism		
Gram +ve bacteria	Lactic acid bacteria	*Lactobacillus*; including: *L. acidophilus*, *L. rhamnosus*, *L. plantarum*, *L. johnsonii*, *L. crispatus*, *L. paracasei*, *L. casei*, *L. gasseri*, *L. fermentum*, *L. salivarius*, *L. delbrueckii*, *L. helveticus*, *L. gallinarum*, *L. mylovarus*, *L. reuteri, L. brevis*, *L. bulgaricus*, *L. cellobiosus, L. crispatus*, *L. curvatus*, *L. lactis*, *L. sporogenes* and *L. sakei*
		Lactococcuslactis
		Streptococcus; including: *S. thermophiles*, *S. salivariussubsp. thermophiles*, and *S. diaacetylactis*
		Enterococcus including: *E. faecium and E. durans*
		Pediococcuspentosaceus
		Leuconostoccremoris
	Bifidobacterium including: *B. infantis*, *B. adolescentis*, *B. animalis* subsp *animalis*, *B. animalis* subsp. *lactis*, *B. longum*, *B. breve, B. thermophilum* and *B.bifidum*	
	Bacillus including: *B. subtilis*, *B. coagulans*, *B. licheniformis*, *B. clausii* and *B. cereus*	
	Propionibacterium freudenreichii subsp. shermanii	
Gram –ve bacteria	*Escherichia coli* Nissle 1917 (EcN)	
Nonpathogenic yeast	*Saccharomyces* including: *S. cerevisiae, S. bayanus*, *S. florentinus* and *S. boulardii*	

2- Competition with pathogens on adhesion sites and nutrients

Competitive inhibition of pathogen and toxin adherence to the intestinal epithelium is one of the mechanisms of probiotic action [26], probiotics strengthening the barrier effect of the intestinal mucosa and release of gut-protective metabolites and thus prevent the adherence of the pathogenic bacteria to the host cells [25]. Walker [28] reported that the effect of probiotics on the activation and secretion of mucus in the intestine was directly correlated with the inhibition of pathogenic *Escherichia coli* attachment and of damage to the intestinal tract. However, the mechanism of adherence is still under investigation [25]. On the other hand, probiotics digest food and compete with pathogens and other microbiota for the nutrients, although there is no evidence that this occurs *in vivo* but probiotics may consume nutrients otherwise utilized by pathogens [12,19].

3- Immunological effects

The most complex proposed mechanisms of action of probiotics are the interaction with gastrointestinal tract immune cells and lymphoid tissue to modulate the immune and inflammatory responses of the host [4]. Probiotics affect directly and indirectly ways the function of lymphoids cells [27], they effect on dendritic cells, monocytes, macrophages,

lymphocytes, T cells, regulatory T cells, immunoglobulin A–producing B cells, and natural killer cells [11,29]. According to the animal studies, probiotics can modulate both mucosal and systemic immune system [25]. They can modulate cytokine profiles, induce hyporesponsiveness to food antigens, and activate local macrophages [19]. However, it's clear that not all the probiotics have the same immunomodulating characteristics [25].

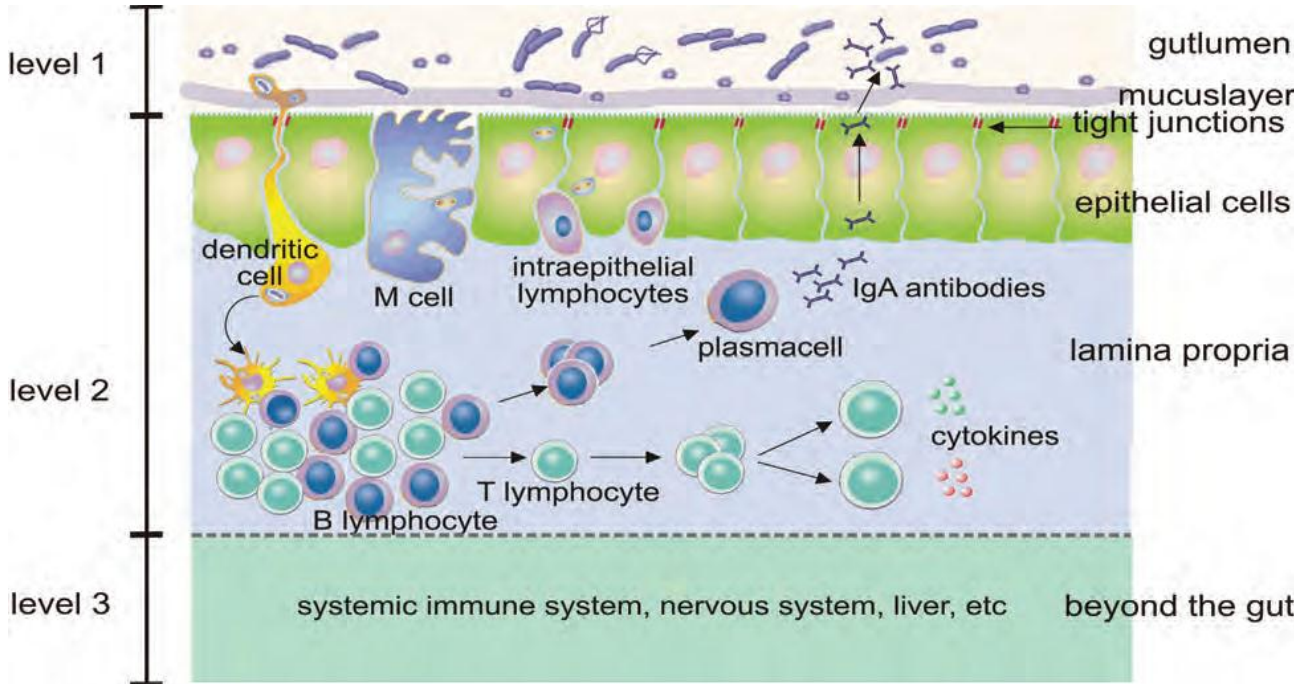

Fig. 1: The three levels or mechanisms of action of probiotics [4]

Health beneficial effects of probiotics

The beneficial effects of probiotics are strain specific [30]. However, there are many evidences that numerous probiotics may have similar function with respect to their health effects [31]. Recently, there is great interest in probiotic therapy as alternative to antibiotic therapy in many health disorders [12].

Depending on the results of animal models studies, probiotics can be used for treatment or prevention wide range of human diseases and disorders [6] such as; cryptosporidiosis [32], urinogenital infections in women [5] such as vaginosis and vaginitis [33], *Helicobacter pylori* infections [34], allergic diseases [2] such as, food allergy [35], and eczema [33], hypertension [36], inflammatory bowel disease [33], irritable bowel syndrome [20] and other diseases. Also probiotics can be used to promote emotional behavior and may influence underlying brain mechanisms [24]. Heikkilä *et al* [37] reported that probiotics can be used to remove the microbial toxins from solutions, such as; aflatoxins, ochratoxin A, Shiga toxin, microcystin-LR and cholera toxin.

However, actually the clinical benefits of probiotic treatment based upon many factors, such as the probiotic strain, its dose, age the host, his diet and period of treatment [9].

Probiotics' safety

The most important requirement for probiotics is safety [8]. In fact, the safety of probiotics has not been studied scientifically [6]. However, probiotics are divided into two groups depending on their risk to health; Risk group 1 and Risk group 2, the first group has no risk, while the other one has small risk [5]. There is no requirement to demonstrate purity, safety, or potency for probiotics before marketing, because they regulated as dietary supplements rather than as biological products or pharmaceuticals [23].

Most LAB strains used in the food supply are nonpathogenic, nonvirulent, and nontoxigenic microorganisms [2]. To date, the products that contain probiotics seem to be safe for human health [22]. Saavedra [2] reported that more than 70 clinical studies involving more than four thousands infants and children consuming products containing probiotics, with no reports of adverse or side effects of probiotics that used in these products.

The potential of health risk of probiotics must keep in mind before pharmaceutical factories adding them into the products [5] and assessment of risk must be made before use the probiotic products for hospitalized patients [6]. However, any probiotic that used for treatment or prevent the disease need Food and Drug Administration review and approval because it is classified as biological product [22]. Probiotics can be prepared as fermented or pelleted feed, powder, capsules, granules, and paste [16]. Finally, the suitable description of a probiotic product as reflected on the label should include; genus and species identification, strain designation and viable count of it, recommended dose, precise description of the physiological effect, recommended storage conditions, safety under recommended use conditions, and contact information for post-market surveillance [19].

In conclusion, the well and full understanding of probiotics and their mechanisms of action will support development new methods to prevent and treat a wide range of diseases.

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