Probiotics and therapeutic effect in clinical practice – Review

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NICOLETA MAFTEI ARON¹, MONICA (GĂUREANU) BOEV², GABRIELA BAHRIM²*
¹ Department of Pharmaceutical Sciences, Faculty of Medicine and Pharmacy, “Dunarea de Jos” University of Galati, 35 A.I. Cuza Street, 800010, Galati, Romania
² Department of Food Science, Food Engineering and Applied Biotechnology, Faculty of Food Science and Engineering “Dunarea de Jos” University of Galati, Street: Domneasca No. 111, 800201, Galati, Romania
*Corresponding author: gabriela.bahrim@ugal.ro

Abstract

A review regarding the relationships between probiotics and the health is presented. After a brief historical introduction, the main mechanisms and beneficial effects of probiotics, the immune system, probiotics like microorganisms and beneficial effects of probiotics on health are presented. Clinical studies with probiotics are discussed in detail. Many experimental studies have found that probiotics are specific effects for all diseases studied and discussed in this review. This review underlines the potential interest in probiotics for the management of diseases pathology.

Keywords: probiotics, mechanism, health, diseases

1. Introduction

The meaning of the term “probiotic” is “for life.” In analogy to antibiotics, “probiotic” is a general term for different species and strains with a diverse range of clinical and immunological capacities. The Food and Agriculture Organization (FAO)/World Health Organization (WHO) defined the probiotics as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host,” and launched guidelines regarding the evaluation of probiotics. The most commonly used probiotics are lactobacilli and bifidobacteria, but other microorganisms have been used as probiotics including the yeast Saccharomyces boulardii. Some examples of bacteria used in probiotics formulations are Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus salivarius, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus sporogenes, Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium infantis, Streptococcus thermophilus and Homeostatic Soil Organisms (HSO’s) [1]. A good probiotic must possess the following requirements: 1) being able to adhere to cells; 2) excluding or reducing pathogenic adherence; 3) being able to persist, multiply and produce acids, hydrogen peroxide and bacteriocins antagonistic to pathogen growth; 4) being able to be safe, noninvasive, noncarcinogenic and non-pathogenic; 5) being able to co-aggregate in order to form a normal balanced microbiota [2].

Prebiotics are nondigestible, fermentable food ingredients that selectively stimulate the growth and the activity of beneficial bacteria in the colon. The combination of prebiotics and
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probiotics is termed as synbiotics. In this combination, the prebiotic substrate may promote the growth of both the probiotic and other “beneficial” endogenous species [3].

Some of the potential benefits of probiotics include prevention of constipation, colon cancer, lactose intolerance, infantile diarrhea, travellers’ diarrhea, antibiotic induced diarrhea, hypercholesterolemia, vaginitis and intestinal infections [4, 5].

For an adequate amount of health benefits, a dose of 5 billion colony forming units (CFU) has been recommended for at least 5 days (5·10^9 CFU/day) [6]. Lactobacilli, bifidobacteria, and lactococci are all included in the category of organisms that are “generally regarded as safe (GRAS)”, a category in which the spore-forming bacteria, enterococci, streptococci and Bacillus spp. are not included. Different probiotics have been administered to a considerable number of individuals under controlled conditions, both infants and adults, suffering from different conditions, and have been proven to be without associated risks. In some of these trials, combinations of probiotics have been used. Furthermore, all kinds’ of products containing these bacteria are sold over the counter and without control to large segments of population without any undesirable affects [7]. However, concerns persist as cases of sepsis are reported periodically in the medical literature [8].

The objectives of this review are as follows: 1) different issues of probiotics especially in reference to pharmaceutical aspects, 2) mechanism of action 3) beneficial effects of probiotics on health.

2. Proposed mechanisms of beneficial effects of probiotics

In recent years enormous efforts have been made to unravel the mechanisms of probiotic actions and various experimental approaches have been used for characterizing the molecular basis of probiotic effects [9]. The mechanisms of beneficial effects of probiotics on human body have been proposed to be mediated via a number of pathways. Several probiotic strains antagonize enteropathogens and the mechanisms (although not fully determined yet) may involve competition for receptor sites and nutrients, aggregation with bacterial pathogens and production of hydrogen peroxide, presence of antimicrobial substances and stimulation of the immune system [10, 11]. Prescott and Björkstén (2007) [12] reported that probiotics may have effects on gut microbial composition, either directly or by effects on microbial products, host products or food components or by modulation of the host’s immune system. However, lactobacilli and bifidobacteria strains have been variously shown to influence immune function via effects on enterocytes, regulatory T cells, effectors T and B cells and antigen-presenting cells (and this includes both circulating monocytes and local dendritic cells) [12]. On the other hand [13] proposed as a mechanism of ingestion of nondigestible carbohydrates which enter the colon and they are fermented by colonic bacteria. The production of short-chain organic acids, lactic and butyric, which lower the colonic pH, increase in biomass, and an environment less conducive to the growth of pathogenic bacteria are the result. In addition, the lower pH aids ion absorption. There is an increase in intestinal epithelial cells, particularly goblet cells whose mucus secretion coats the intestinal wall providing a thicker coat of protection. The length and width of intestinal crypts is increased, providing an enlarged area for absorption for both macro- and micronutrients. This process alters the energy metabolism, gene expression and lipid and cholesterol levels, and the interaction between microbiota and lymphatic cells is critical for the optimal functioning of the immune system [13]. Instead, [2] suggest that probiotics are responsible for competitive exclusion of enteric pathogens from the gut lumen. The inhibitory mechanism should be the production of lactic acid and bacteriocins and they restore the normal intestinal flora during an antibiotic therapy, trigger cytokines synthesis from enterocytes attaching to their surfaces, produce toxic metabolites like
hydrogen peroxide and synthesize butyric acid which increases the turnover of enterocytes and neutralizes dietary carcinogens [2]. The researchers believe that probiotics are responsible of several immunomodulatory functions acting on cellular and humoral responses and they can stimulate Type 1 Helper T Cells (Lb. casei), mononuclear cells leading to increased clearance of circulating pathogenic bacteria (Lb. acidophilus), macrophages to produce TNF-alpha, IL-6 and NO production, increase clearance of circulating pathogenic bacteria by Kupffer Cells and they can produce antirotaviral IgA and antinfluenza IgG antibodies (B. breve).

Marco and Tachon (2013) [14], proposed another mechanism of probiotic which conferred health benefits. This mechanism includes modulation of immune response pathways, strengthening the epithelial barrier and (in) direct effects on human pathogens. Also, in medical literature it was reported other emerging mechanisms which include regulating activity along the gut brain axis [15]. Chen et al. (2012) [16] suggest that the mechanism includes energy homeostasis as well as functions which might apply to probiotics administered at other locations on the human body [17]. In recent years, significant progress has been made toward the identification of the probiotic cell components responsible for these effects [18].

West et al. (2012) [19] thinks that the above observations translate into clinically relevant effects needs further study. However, it is not known to what degree effects of a specific probiotic strain are relevant for other strains, even of the same species. Therefore, effects should be considered strain-specific at this stage. In conclusion, in future evaluating the effects of probiotics in clinical trials is very important because immune stimulating effects of probiotics in in vitro studies can be divergent from those observed in vivo [19].

3. Probiotic microorganisms

Probiotic microorganisms used in food must be able to survive the passage through the gut; i.e., they must have the ability to resist gastric juices and the exposure to bile [20]. Also, they must be able to proliferate and colonise the digestive tract. In addition, they must be safe and effective, and maintain their effectiveness and potency for the duration of the shelf-life of the product [21]. Holzapfel et al. (2001) [22] reported that most commonly micro-organisms used as probiotics belong to the heterogeneous group of lactic acid bacteria (genera Lactobacillus and Enterococcus) and to the genus Bifidobacterium. Each group involves different species (Lactobacillus acidophilus, Bifidobacterium bifidus etc.) which include different strains. Today many other microorganisms are known as probiotics [23, 1]. Lactobacilli are Gram-positive lactic acid producing rod-shaped bacteria. They are part of but not the dominant species of the normal microbiota of the mouth, the lower small bowel, colon and vagina in some but not all individuals. Lb. acidophilus and bifidobacteria constitute 90% of the colonic organisms in breast-fed infants. Lb. casei significantly enhances the immune system and stimulates the production of Immunoglobulin A (IgA). The fermentation of the non digestible carbohydrates constitutes their principle source of energy production and, notably Lb. acidophilus and Lb. johnsonii, contain proteinases and are able to degrade the harmful bacteria polypeptides. Lactobacilli are important in the food industry where they are used in the pickling process and for cheese and yogurt production [13]. Ma et al. (2004) [24] suggest that Lb. reuteri has anti-inflammatory properties, as demonstrated in animal and human in vitro studies. The researchers reported that Lb. reuteri prevents TNF-α− induced IL-8 expression in murine epithelial cells. Then diminishes inflammatory bowel disease in murine models [25], and after that induces human IL-10 producing regulatory T cells by modulating dendritic cell function [26].
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Bifidobacteria are Gram-positive, nonmotile, nonspore forming, catalase negative, polymorphic rods in a Y or V shape and hence the name ‘bifid.’ They are compulsory anaerobes though some can tolerate low levels of oxygen. Ingested bifidobacteria can pass through the stomach’s acid and the unfriendly bile salts and once in the colon, they bind to the epithelial cells and to the intestinal mucin. Their density in the human GIT varies with age, diet, lifestyle, and activity [13]. High quantities of *Bifidobacterium* spp. cells and the recent evidence indicate that *Ruminococcus* spp. also colonizes in abundance the colons of breast-fed infants. Newborns on formula have a varied microbiota but far less of these friendly bacteria. The intestinal microbiota of adult organisms consists of enterobacteria and coliforms and fewer numbers of lactobacilli and bifidobacteria. Bifidobacteria species are able to ferment oligosaccharides and other complex nondigestible carbohydrates such as resistant starches, raffinose, lactulose and intestinal mucins [13].

Up to 30 different bacterial species have been reported, isolated from sewage, human and animal feces, rumen of cattle, dental caries and honey bees. The most frequently reported *Bifidobacterium* spp. as having health benefits is *B. longum*. Protective functions include competing with harmful bacteria for nutrients, colonization numbers and adherence to the intestinal epithelium. Control of epithelial cell proliferation and differentiation and homeostatic regulation of the immune system are tropic functions. Bifidobacteria expand the number of mucosal lymphocytes, the size of germinal centers in lymphoid follicles and there is some research indicating a role in the induction of regulatory T cells in lymph follicles [13].

Other less commonly used probiotic microorganisms are strains of: *Streptococcus* spp., *Bacillus* spp. and *Saccharomyces* spp. *Streptococcus thermophilus* has been used in probiotics to enhance digestion of lactose in intolerant subjects [27].

*Saccharomyces boulardii* is considered probiotic yeast but is not a normal or usual resident of the gastrointestinal tract (GIT) ecosystem. If used, it must be given continuously as within 6 h after the last dose because it cannot be found in the intestinal lumen [13].

Probiotics microorganisms are available in food and dietary supplements (for example, capsules, tablets and powders) and in some other forms as well. In foods and supplements, the bacteria may have been present originally or added during preparation. Probiotics microorganisms must survive of the gastric and bile acids in order to reach the intestinal tract colonize the host epithelium and exhibit a beneficial effect [23].

4. **Probiotics and immune system**

One of the environmental factors that may influence the risk of developing different disease is the gut microbiota. Wohlgemuth *et al.* [9] proposed that probiotics exert their effect by modulating gut microbiota composition and a considerable number of studies support this assumption by demonstrating changes in a number of bacterial groups in response to the consumption of probiotics. Yamano *et al.* (2006) [28] observed that the numbers of bifidobacteria and lactobacilli increase in healthy subjects after ingestion of *Lb. casei Shirotia* or *Lb. johnsonii* La1 while those of numbers of enterobacteria or clostridia decrease.

Kuhbacher *et al.* (2006) [29], reported that the probiotic preparation VSL#3 which consists of four *Lactobacillus* spp. (*Lb. acidophilus, Lb. plantarum, Lb. paracasei* and *Lb. delbrueckii* subsp. *bulgaricus*), three *Bifidobacterium* spp. (*B. breve, B. longum and B. infantis*) and *Streptococcus thermophilus* are effective in elevating the number of total gut bacteria and in restoring the intestinal microbiota diversity in pouchitis patients. Also, VSL#3 increases caecal bifidobacteria numbers and modifies the metabolic activity of caecal bacteria in mice with chronic colitis induced by dextran sulphate sodium (DSS) [30].
Herrick and Bottomly (2003) [31] believe that oral tolerance is present from the first hours after birth and not only gives way to the suppression of immune response against proteins, introduced with nourishment, but also acts against the microbiota that can modulate the immunologic aspect, favoring tolerance itself. Also, oral tolerance to an allergen can block immunologic response outside the gastrointestinal environment, such as in respiratory and cutaneous apparatus. Noverr and Huffnagle (2004) [32], reported that immunologic tolerance, including oral tolerance, is likely mediated by a large group of T cells originated from dendritic cells (DCs), which show antigen (antigen-presenting cell). Then immature DCs, which have not received inflammatory stimuli, mature also in the intestinal mucosa and originate regulator DCs, DC type 1, and DC type 2, with regard to the interactions among pathogenic, different, and/or microbial products [33, 34]. They can originate also regulatory T cells, through interleukin (IL) 10 and/or transforming growth factor-β, and type 1 (Th1) and type 2 (Th2), through the production of cytokine [32].

For humans, [12] suggest that the gut-associated lymphoid tissue (GALT) accounts for two-thirds of the immune system, reflecting the enormous immunological challenge conferred by the intestinal luminal contents especially in early infancy when this is established. Also, gut microbiota confer specific immune-protective effects that are likely to be mediated through complex pathways within and even beyond the GALT. This encompasses effects on local IgA production, induction of tolerogenic dendritic cells and regulatory T-cell populations with the production of immunomodulatory cytokines such interleukin 10 (IL-10) and transforming growth factor beta (TGF-b). The mechanisms described above need further study, because they appear to modulate local inflammation, maintain gut barrier mechanisms and consequently reduce the risk of maladaptive systemic immune responses [3].

Lammers et al. (2005) [35] studied the mucosal gene expression of the pleiotropic proinflammatory cytokines (interleukin (IL)-1beta, IL-6), TH1 cytokines (interferon-gamma (IFN-gamma), TNF-alpha, IL-12), regulatory cytokines (IL-10, transforming growth factor-beta) and the chemokine IL-8. Also, it was evaluated the presence of polymorphonuclear cells in the mucosal tissue. The researcher reported that probiotic treatment is able to regulate the mucosal immune response reducing mucosal levels of neutrophil chemoattractant IL-8 and tissue influx of polymorphonuclear cells, and may further act as an inhibitor for the inhibit T cells activation, reinforce the barrier function and keep a tight control of the potent proinflammatory cytokine IL-1beta.

Another study consisting in a randomized double-blind study was designed by [36]. Probiotic bacteria or placebo were administered for 1 month before delivery to mothers and for 6 months to infants with a family history of allergy. Study by [36] highlights the role of chronic microbial exposure as an immune modulator protecting from allergy.

Makino et al. (2010) [37] studied two independent groups involved 142 elderly individuals who were given either yogurt (90 g) fermented with Lb. delbrueckii or milk (100 mL) daily over an 8–12-week period. The researchers observed an increased in natural killer cell activity in the yogurt group (p=0.028) and their risk for catching the common cold was 2.6 times lower than in the milk group [37].

Abrahamsson et al. (2012) [38], suggest that a high gut microbial diversity might be more important than the absence or presence of specific genera or species in the context of immune system maturation and subsequent development of allergic disease. In conclusion, it can be assessed that there is evidence which certifies that normal immune regulation relies on “optimal” gut microbiota and may be influenced by differences in early colonization patterns. This has been the logical basis for the concept of probiotics in treatment and prevention of disease [3].
5. Beneficial effects of probiotics on health

In recent years a variety of pharmaceutical and medicinal applications have been identified though, probiotics were explored in the beginning for the ‘beneficial health effects’. On the basis of different microbial characteristics, various forms of formulations are being developed for variety of clinical conditions. Differential species with variable characteristics are indicated for different clinical conditions [39]. Unfortunately, investigators who have used probiotics as intervention in treatment of the same disease or conditional though they have not used the same species of bacteria but often different combinations of organisms, different quantities and varied lengths of therapy. This has often resulted in conflicting results and difficulties in interpreting the degree of benefits to health. In selecting which probiotic might be appropriate for a given study several criteria are important, namely [13]:

- Survival of the ingested beneficial bacteria depends on the degree of tolerance to acids and bile.
- Survival of harmful bacteria is influenced by which bacteria have the greater ability to metabolize nutrients not digested by the host and which bacteria can better adhere to intestinal cells.
- Also, survival in the competitive environment is dependent on which probiotics produce bacteriocins, a proteinaceous antimicrobial compounds that protect against pathogenic bacteria and which bacterium is a better scavenger of iron and can thus deprive other bacteria of this vital mineral.

On the basis of different microbial characteristics, differential species and various forms of formulations for variety of clinical conditions various diseases where used probiotics for treatment are described as follows:

Skin disease
Wilson (2008) [40] mentions that the skin is the largest human organ and is in direct contact with the environment; it is inhabited by and constantly exposed to microorganisms in the environment. The resident skin microbiota interacts with other microbes, with human cells and with the human immune system in multiple ways that mediate risk of disease.

The microbial diversity present in and on humans is associated with several infectious and non-communicable diseases. Changes in resident microbial communities have been shown to be associated with skin conditions such as acne, atopic dermatitis and psoriasis [41, 42]. Even more broadly, The Human Microbiome Project has inspired exciting new studies demonstrating how changes in resident microbial communities play a role in disease, including antibiotic-associated diarrhea, bacterial vaginitis, human immunodeficiency virus, obesity and cardiovascular disease [43, 44].

Atopic dermatitis
Baquerizo Nole et al. (2014) [45] reported that probiotics appear to be effective in reducing the incidence of atopic dermatitis in infants, but their role in atopic dermatitis treatment is controversial. Their role in acne, wound healing and photoprotection is promising, but larger trials are needed before a final recommendation can be made.

In medical literature data exist showing the protective effect of probiotics in the incidence of pediatric atopic dermatitis (PAD), there is less convincing information about their effects as treatment [45]. However, [46] reported that Lb. plantarum strain was used for 12 weeks in treatment of 83 children with PAD and showed a reduction of 9.1 in scoring atopic dermatitis (SCORAD index) at week 14, compared with a 1.8 reduction in SCORAD index in the
placebo group. Also, [47] found that a probiotic mixture reduced SCORAD index of 38 patients with moderate to severe atopic dermatitis (AD) and similar results in 48 AD patients reported [48]. Also, [49] studied the effects of probiotics in AD in a randomized double-blind study. A number of 27 infants (mean age, 4.6 months) who presented with AD during exclusive breast-feeding was divided into 3 groups: probiotic-supplemented, *B. lactis* Bb-12 strain or *Lb. rhamnosus* GG (LGG) strain and extensively hydrolyzed whey formulas or the same formula without probiotics. A significant reduction in SCORAD index was seen after 2 months for the probiotic-supplemented groups as compared with the unsupplemented group (P = .002).

The conclusion is that existing studies on the potential therapeutic effect of probiotics are generally promising, but all scientific researcher agree that there is not enough evidence to reliably assess the possible role of probiotics in the treatment of skin allergic disorders and that further studies should be done with a higher number of patients to get more reliable results [50].

Gerasimov *et al.* (2010) [51] performed a single trial that involved 90 children between 1 and 3 years of age with moderate-to-severe AD. The experimental group received *Lb. acidophilus* and fructo-oligosaccharide as supplements for 8 weeks. The children who received symbiotic therapy decreased their SCORAD by 33.7% as compared to the control group whose score decreased 19.4% and the symbiotic group used less topical corticosteroids. These changes were also associated with a change in lymphocyte subsets. However, the daily administration of LGG for 4 weeks decreased SCORAD in the children with high IgE levels [52]. On the other hand, no improvement of SCORAD and of inflammatory parameters was observed in infants less than 5 months of age who received a hydrolyzed, whey-based formula alone or supplemented with LGG or with *Lb. rhamnosus* strain for 3 months [53].

**Acne**

The main factors involved in acne are: excess sebum production, follicular hyperkeratinization, *Propionibacterium acnes* hypercolonization and inflammation [54]. Wang and Wu (2005) [55] observed that these factors may be aggravated with stress. Stress can also alter the intestinal lining, by encouraging bacterial over growth, stagnating intestinal transit time and thereby compromising the intestinal barrier [55]. One of the potential benefits that systemic probiotics may offer is the reduction of inflammation in acne, probably caused by the down regulation of gene expression related to the release of inflammatory cytokines and the recruitment of pathogenic CD8 T cells while activating Treg cells [56]. Kim *et al.* (2010) [57] observed at significant improvement (statistically) in inflammatory lesion count, total lesion count and clinical grade of acne after daily consumption of *Lactobacillus* spp, for 12 weeks compared to fermented milk (placebo) consumption. Also, Di Marzio *et al.* (1999) [58] reported that the application of topical probiotics, such as *S. thermophilus*, increased ceramide production when applied for 7 days as a cream.

**Eczema**

Several studies have been published using probiotics in medical literature and majority of studies evaluated *Lactobacillus* strains alone or in combination with other probiotic species. Woo *et al.*, (2010) [59] demonstrated that *Lb. fermentum* and *Lb. sakei* strain can to reduce SCORAD index significantly.

In two other studies it has been observed that probiotics are only effective in children with food sensitization. In a Finnish randomized controlled study, LGG was effective in preventing the development of eczema in a breast-fed child when the mother was given LGG 4 weeks prenatally and 6 months postnatal. In a double-blind, prospective, randomized study
with breast-fed children and cow's milk allergy, a significant increase of interferon-γ was measured [49]. Zhu et al. (2010) [60] carried out a meta-analysis on 12 RTC trials, seven of which reported that lactic acid bacteria but only when used in combination with other probiotics had a positive effect on the prevention of eczema; compared to the placebo, the relative risk (RR) was 0.79. When mothers were given LGG prior to delivery and during lactation (23 vs 46% in the probiotic and placebo groups, respectively) a decrease of atopic eczema in infants from atopic families was observed [61].

**Gastrointestinal diseases**

*H. pylori* is considered as the etiological factor for gastro duodenal ulcers and a risk factor for gastric cancer, due to the early colonization process and an important factor in determining the development of gastric cancer later in life [62].

In the medical literature was reported that in the treatment and prevention of *H. pylori* infection lactobacillus species and bifidobacteria help and make a direct, non-specific, bacteriostatic activity, increased Ig A production or have an inhibitory effect on attachment of *H. pylori* [39]. Zou et al. (2009) [63] reported that using *Lactobacillus* spp. probiotic strains as the supplements to triple therapy identified eight Randomized controlled trials (RTCs) with a total of 1372 patients. This probiotic was more effective than the control group in improving the eradication rate of *H. pylori*; 82.26% versus 76.97%. As with *S. boulardii*, diarrhea was less in the group that received the *Lactobacillus* spp. [64] tested *Lb. johnsonii* NCC533 alone or combined with cranberry juice and reported an eradication of *H. pylori* in 14.9 and 22.9%, respectively, of colonized children. Also, in a randomized, double blind place to controlled trial carried out in asymptomatic colonized children, it was shown that 4-weeks administration of *Lb. johnsonii* NCC533 significantly decreased *H. pylori* colonization compared with the placebo (65).

All studies reported above suggest that some probiotics may be useful to maintain low levels of *H. pylori* and to decrease the chronic inflammatory processes in the gastric antrum of colonized children. Also, better designed studies with adequate sample sizes are necessary to obtain more solid conclusions [62].

Ulcerative colitis (UC) and Crohn’s disease (CD) are the two most frequent causes of this chronic inflammation of the gastrointestinal tract; these are lifelong diseases characterized by recurrent episodes of diarrhea, frequently with blood in the feces, abdominal pain, fever, malaise and weight loss [62].

Also, studies have shown some promise for probiotics in the treatment of ulcerative colitis (UC). Kruijs et al. (2004) [66] used the probiotic strain *E. coli* Nissle 1917 (ECN) at low dose of 1.5 g/day and observed that was as effective as mesalazine (intestinal anti-inflammatory) in maintaining the recovery of the ulcerative colitis for a period longer than one year. Also, in another study, *Lb. rhamnosus* GG exhibited a beneficial effect equivalent to mesalazine in terms of remission of UC patients [67]. Pronio et al. (2008) [68] showed that the administration of VSL#3 for patients with ileal pouch-anal anastomosis for ulcerative colitis had significantly increases the number of mucosal regulatory T cells, indicating a potential beneficial immuno-regulatory mechanism of probiotic strains in this disease.

Instead, [69] have reported that combination of the probiotic product VSL#3 (at 6 g/day) with the intestinal anti-inflammatory, mesalazin (4 g/day) in 40 patients have reduced to 10% the post-operative recurrence of Crohn’s disease (CD) as compared to 40% in patients treated with antibiotic only. In a randomized controlled trial (98 patients) the ineffectiveness of *Lb. johnsonii* LA1 for prophylaxis of post-operative recurrence in Crohn’s disease was studied by...
Cancer

Probiotics play a protective role through the binding and/or degradation of carcinogens, many of them originating from the western type diet, rich in red meats processed by broiling. Many studies in mice indicate that the use of some lactobacilli reduce the uptake of mutagens by different tissues. After observations in human volunteers [72] showed that consumption of preparations containing lactobacilli reduces the urinary and fecal excretion of mutagenic compounds.

Pool-Zobel and Sauer (2007) [73] performed in vitro and in vivo investigations, the SYNCAN project, in both animal models and human clinical trials. B. lactis Bb12 and Lb. rhamnosus GG and the combination of both (synbiotic) were incubated with a prebiotic mixture of oligofructose and inulin (Synergy). The fermentation supernatant contained a large quantity of butyrate and was placed in a tube with human HT2 cancer cells. Survival of tumor cells was impaired and proliferation of cells was inhibited. Rats given colon carcinogens and fed inulin-type fructans showed a marked reduction in the incidence of colon cancer. Humans with colonic polyps given a synbiotic regimen showed a clear reduction in cellular DNA damage. These authors propose long-term prospective trials to determine if such a dietary change can reduce the rate of colon cancer [73].

Although the evidence for beneficial effects of probiotics in human tumorigenesis is indirect, there is an accumulating body of information from experimental models that suggests that they have anti-neoplastic effects [62].

Bacterial vaginitis

Lactobacillus spp, are the prominent microbial factors that governs the presence, growth, colonization and persistence of non-endogenous microorganisms in vagina. As the Lactobacillus spp. count decreases, the protection provided by them against uropathogens also decreases. It is also proposed that lactobacilli produce biofilms, which cover the urogenital cells [39].

Anukam et al. (2006) [74] treated 40 women diagnosed with bacterial vaginitis (BV) (it is particularly common condition in black women and in Nigeria it is often caused by mycoplasma, as well as Atopobium spp., Prevotellas pp. and Gardnerella spp.) by discharge, fishy odor, sialidase positive test and Nugent Gram stain scoring. Patients were randomized to receive either two dried capsules containing Lb. rhamnosus GR-1 and Lb. reuteri RC-14 strains each night for 5 days, or 0.75% metronidazole gel, applied vaginally twice a day, in the morning and evening. The follow-up at day 6, 15 and 30 showed a significant cure for BV in probiotic lactobacilli treated subjects compared to metronidazole treatment. This is the first report of an effective (90%) cure for BV using probiotic lactobacilli. The researchers conclude that, given the correlation between BV and HIV and the high risk of the latter in Nigeria, intravaginal use of lactobacilli can provide women with a self-use therapy, similar to over-the-counter anti-yeast medication, for treatment of urogenital infections [74]. Also, Oduyebo et al. (2009) [75] studied 24 RCTs that involved 4422 participants with the
experiment group receiving antibiotics with or without probiotic *Lactobacillus* spp. When given vaginally as a gelatin tablet, this probiotic was more effective than oral metronidazole with a relative risk (RR) of 0.20. When given orally in combination with oral metronidazole, the RR was 0.33 as compared with metronidazole alone.

Larsson *et al.* (2008) [76] investigated firstly if supplementary lactobacilli treatment could improve the initial cure rate after vaginal clindamycin therapy. In secondly step, it was studied if the lactobacilli as repeated adjunct treatment during 3 menstrual cycles could lengthen the time to relapse after initial cure. A 100 BV diagnosed women were offered vaginal clindamycin therapy followed by vaginal gelatin capsules containing either 109 freeze-dried lactobacilli or identical placebo capsules for 10 days during 3 menstrual cycles in a double-blind, randomized, placebo-controlled trial. The researchers observed that supplementary treatment, combining two different strains of probiotic lactobacilli, does not improve the efficacy of BV therapy during the first month of treatment, but for women initially cured, adjunct treatment of lactobacilli during 3 menstrual cycles lengthens the time to relapse significantly (more women remained BV free at the end of the 6-month follow up) [76].

**6. Conclusions**

As supplements different probiotics have been administered under controlled conditions to a large number of patients, both adults and infants, suffering from a variety of diseases and it have been proven to be without any associated risk. In the medical literature many studies are reported on the potential therapeutic effect of probiotics and these being generally promising. However, all scientific and medical researchers agree that there is not enough evidence to reliably assess the possible role of probiotics in the treatment of all health disorders and that further studies should be done with a higher number of patients to get good and more reliable results for health patients.

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