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BRIEF NOTES

Use of probiotics in medical devices applied to some common pathologies

Maria Verrucci[1]*, Angelo Iacobino[2]*, Lanfranco Fattorini[2], Roberta Marcoaldi[1], Antonino Maggio[1] and Giovanni Piccaro[1]

[1]*Organismo Notificato 0373, Unità Operativa Dispositivi Medici, Istituto Superiore di Sanità, Rome, Italy*
[2]*Dipartimento Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy*
**Equal contribution*

Abstract
Probiotics, defined as "living microorganisms that, whether ingested in useful amount, may have beneficial effects on human body", are widely used in various products for human use, such as dietary supplements, medical devices and pharmaceutical products. The European Directive on medical devices (MDs) (DDM 93/42), also includes those MDs containing live microorganisms, particularly probiotics, that may have various destinations of use, including that of assisting the therapy of several human pathologies. In this brief note we analyzed the use of probiotics in MDs and how probiotics administration could represent one of the new frontiers of scientific research on the prevention and treatment of various diseases. We'll analyze the literature on probiotics based MDs, to review their major targets in the therapy of some of the most common human pathologies: bacterial vaginosis and vaginitis, atopic dermatitis, infantile colic, obesity, type 2 diabetes, and pharyngotonsillitis.

Key words
- probiotics
- microbiota
- medical devices
- lactobacilli
- bifidobacteri

INTRODUCTION

Inside the human body, a large number of commensal microorganisms reside, which mainly colonize gastrointestinal tract, skin and mouth. The entire population of microorganisms (Bacteria, Viruses and Fungi) that live inside each individual's organism or part of it is called "microbiota"; "human microbiome" refers instead to the collective genomes of these microbes [1].

Probiotics are defined as "living microorganisms that, whether ingested in useful amount, may have beneficial effects on human body" [2]. In the gastrointestinal tract, hundreds (100-1000) of different bacterial species of probiotics have been isolated [3]: among them, *Bifidobacterium* and *Lactobacillus* are the most studied genera.

Probiotics play their beneficial role by several mechanisms, including production of antibacterial compounds, such as organic acids and bacteriocins, enhancement of the epithelial gut barrier function, competitive exclusion. Moreover, this bacteria can exert their role by modulation of the host innate and adaptive immune responses: they can suppress intestinal inflammation via the downregulation of toll-like receptors expression, secretion of metabolites that may inhibit TNF-a from entering blood mononuclear cells and inhibition of NF-kB signaling in enterocytes. The activity of probiotics could have an important role to elicit measured antimicrobial responses with minimal inflammatory tissue damage [4].

Probiotics are used as active component in pills, beverages, oral or vaginal capsules, or as ingredients in several food products, like yogurt [3]. Hence, probiotics could have several usages depending on the product which they are part of: pharmacological, medical device (MD) or dietary supplement.

The European Directive on medical devices (DDM 93/42) [5], also includes those MDs containing live microorganisms, particularly probiotics.

The uses of living microorganisms-based MDs or probiotic-based MDs (PbMDs), as currently sold in the EU, are several. In this brief note, we'll focus on their major targets in the therapy of some of the most common human pathologies: bacterial vaginosis and vaginitis, atopic dermatitis, infantile colic, obesity, type 2 diabetes, and pharyngotonsillitis.

BACTERIAL VAGINOSIS AND VAGINITIS

The vaginal microbiota (namely, the population of microorganisms which naturally live in the vagina) is a dynamic population able to adapt itself to changes of any physiological conditions, e.g. during menstrual cycle or pregnancy. Where the physiological conditions undergo to alteration, due to a number of possible causes (e.g. constipation, use of aggressive hygienic vaginal products), a variation in the vagina microbial population composition may occur. This may lead either to the migration of microbes from the intestine, or to the

Address for correspondence: Giovanni Piccaro, Organismo Notificato 0373, Unità Operativa Dispositivi Medici, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: giovanni.piccaro@iss.it.

entrance of external pathogens, capable to colonize the vaginal environment. In such clinical conditions, the PbMDs seem to act by disinfecting and reducing the growth of pathogens like *Candida albicans*, *Gardnerella vaginalis* and others, which colonize the female urinary tract, providing acidification and hypoxia in the vaginal environment [6].

In women affected by vulvovaginal candidiasis, *lactobacilli* often coexist in the vaginal epithelial together with *C. albicans*, while in women affected by bacterial vaginosis such coexistence between *lactobacilli* and pathogens is reduced [7]. Clinical and *in vitro* studies showed the efficacy of some *lactobacilli* strains against *C. albicans*. Some species, as *L. acidophilus, L. rhamnosus GR-1 e L. fermentum RC-14*, can be used as effective preventive agents in women frequently affected by *C. albicans* vulvovaginitis (more than three times per year), instead of antifungal agents which cannot be used due to their side effects. On the contrary, lactobacilli do not show any contraindications [8].

Bacterial vaginosis is caused by the uncontrolled proliferation of some anaerobic bacteria, as *G. vaginalis*, *Prevotella bivia* spp., *Bacteroides* spp., *Peptostreptococcus anaerobius*, *Mobiluncus*. In healthy women, different species of aerobic bacteria of the genus *Lactobacillus*, and in particular *L. plantarum*, *L. rhamnosuse* and *L. acidophilus* are predominant, while the above mentioned anaerobies are present in a stable and controlled number.

The antagonistic properties of *Lactobacillus* strains, isolated from the vagina of healthy women against the majority of pathogens responsible for bacterial vaginosis, have been evaluated. Almost all *Lactobacillus* strains showed antagonistic activity against anaerobic bacteria such as *G. vaginalis*, *Prevotella biviae*, *P. anaerobius*, while only a few demonstrated the capability to inhibit the growth of aerobic Gram-positive cocci such as *Enterococcus faecalis* or *Staphylococcus aureus* [9].

In a recent study, the *L. fermentum* SK5 strain isolated from the vagina of a healthy woman, was tested *in vitro* to evaluate its probiotic potential. *L. fermentum* SK5 showed to have an antagonist activity towards *Escherichia coli* and *G. vaginalis* [10].

In another *in vivo* study on a murine vaginal model of *G. vaginalis*, it was shown that the growth of *G. vaginalis* was inhibited in animals when locally treated with a 10^9 CFU (colony-forming units)/mL dose of *L. fermentum* L23. Therefore, *L. fermentum* L23 could be considered as a potential biotherapeutic agent for the eradication of such bacterium [11].

Thus, such lactobacilli strains can be regarded as very good candidates to be used as probiotics for the restoring of the normal microbial communities of the vaginal ecosystem [12].

Clinical trials were performed to assess the efficacy of oral administration of *Lactobacillus paracasei* subsp. *paracasei* F19, in association with vaginal suppositories containing *L. acidofilus*, in the treatment of bacterial vaginosis and in the prevention of recurrent vaginitis. Sixty healthy women, aged 18 to 40, with suspected or confirmed bacterial vaginosis were recruited. The involved subjects were randomly divided into 2 groups: group A, which was treated with vaginal ovules containing *L. acidophilus,* and group B, which received the vaginal ovules plus an oral probiotic containing *L. paracasei* F19. Patients were examined at the end of the 3 months therapy, then after a further 3 months. At the end of therapy, both groups showed a significant reduction in vaginal pH and improvement in subjective symptoms. However, for all group A patients, improvement progressively decreased during the 3 months follow-up, while the positive effects were maintained for group B even after the 6 months of treatment. Overall, this study showed that the use of probiotics is crucial for treatment of bacterial vaginosis as alternative to conventional antibiotic therapies [13].

The dominance of lactobacilli in healthy vaginal microbiota and its depletion in vaginitis has given rise to the concept of oral or vaginal therapeutic or preventive use of them. Indeed, the preferred route of delivery for probiotic lactobacilli is intravaginal. However, some authors delivered lactobacilli orally to repopulate the vagina, based on the observation that pathogens can pass from the gut into the urogenital system, and that orally administered *Lactobacillus* strains were recovered from the vagina. It is noteworthy that the capability of lactobacilli to colonize the vagina after oral ingestion is strictly dependent on their viability and ability to resist to gastric acid and bile salts [14].

ATOPIC DERMATITIS

Atopic dermatitis is a skin inflammation due to both hereditary and external factors such as cold weather, synthetic clothing, irritating foods.

In children, it is characterized by generally highly pruriginous skin lesions, with chronic-relapsing diseases, usually appearing for the first time in infants, spontaneously healing around 3 years' age or almost always within puberty (rarely lasts until adulthood).

Characteristics and locations of lesions may vary depending on age: in younger child, they may appear as red and exudative (i.e.) round patches, located in the face (excluding mouthpiece) and in the limbs extensory areas, while they may show as yellowish-brown on scalp and face. In the older children, dermatitis is located at legs and arm folds or around mouth and eyelids, while skin appears dry.

Atopic dermatitis may be based on a constitutional predisposition, ever if some triggers may occur (e.g., cold climate, synthetic or wool garments, dust, saliva, irritating foods like tomatoes and citrus fruits), altering skin barrier and then causing dryness, itching and hyperactivity.

To understand the beneficial effects of probiotics over atopic dermatitis, several clinical trials have been performed.

One of these trials was performed to evaluate the efficacy of *L. paracasei* , *L. fermentum* alone and in combination, on disease evolution, quality of life and atopic dermatitis immune biomarkers. A randomized double-blind study was carried out on 220 subjects, aged between 1 and 18, affected by moderate/severe atopic dermatitis. The subjects randomly took *L. paracasei* , *L. fermentum*, both and placebo for 3 months. The results

showed that *L. paracasei* and *L. fermentum* LF probiotics mixtures supplemented diet, lead to an improvement in the disease [15].

According to another trial, the efficacy of a *L. salivarius* LS01 (DSM 22775) supplemented diet for the treatment of dermatitis in children was evaluated. As atopic dermatitis is a chronic inflammatory and itchy skin disease with multifactorial etiopathology, some studies suggest that probiotics performances can be enhanced by an immune system modulating through the improvement of intestinal bacterial flora composition. Forty-three subjects, aged between 0 and 11 (ratio M/F = 1:1), were treated or not treated with *L. salivarius* strain LS01 probiotic. Clinical efficacy of probiotic therapy evaluation was based on the assessment of changes in the itching index and SCORAD (Scoring Atopic Dermatitis), a score indicating atopic dermatitis severity. Four weeks after the onset of treatment, patients treated with probiotics showed a significant improvement in clinical parameters (i.e., SCORAD and itchy values) compared to untreated ones. Hence, *L. salivarius* LS01 seems to improve the quality of life of children with atopic dermatitis [16].

In this view, a recent review reported that atopic conditions are associated with immunoglobulin E-mediated immune responses, and that probiotic related improvements generally have multiple targets. Indeed, it is known that probiotic supplementation alters the intestinal microbiome in a way that improves skin permeability and barrier functions, thus modulating the immune response [17].

INFANTILE COLIC

Infantile colic (IC) is a syndrome that occurs during the first four months of life, characterized by paroxysmal, excessive and inconsolable crying in healthy children without identifiable cause. According to some studies, the prevalence of colic in infants ranges from 3% to 40% [18].

IC causes are still unknown and no effective protocol for their treatment has been planned, yet. Many causal hypotheses have been prepared, which can be summarized in organic and/or behavioral causes (perhaps, related to mothers' excess anxiety). Organic causes might be attributable to abnormalities in gastrointestinal function or allergic disorders. In the latter case, the most frequently used measures are the use of hydrolyzed proteins added milk (hypoallergenic milk), the use of herbal infusions or a specific pharmacological therapy. A further approach to this problem could be identified in synbiotics, as the result of the synergistic combination of probiotics and prebiotics.

In 1995, prebiotics were defined by Gibson and Roberfroid as non-digested food components which, through the stimulation of growth and/or activity of a single type or a limited amount of microorganisms residing in the gastrointestinal tract, improve the health condition of a host [19]. In 2004, the definition was updated and prebiotics were defined as selectively fermented components allowing specific changes in the composition and/or activity of microorganisms in the gastrointestinal tract, beneficial for host's health and wellbeing [20]. Finally, in 2007, FAO/WHO experts described prebiotics as a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota [21].

Prebiotics may be used as an alternative to probiotics or as an additional support for them. However different prebiotics will stimulate the growth of different indigenous gut bacteria. Prebiotics have enormous potential for modifying the gut microbiota, but these modifications occur at the level of individual strains and species and are not easily predicted *a priori*. Many reports on the beneficial effects of prebiotics on human health are available.

Scientific studies have shown prebiotics ability to improve probiotics, providing a specific substrate for already existing intestinal bacterial flora. In a double-blind, randomized clinical trial, the efficacy of synbiotics was evaluated against the reduction of average baby's crying time over a 30 days' period from the start of treatment. The synbiotic administered contained 10^9 CFUs of: *L. casei*, *L. rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *L. acidophilus*, *Bifidobacterium infantis*, *L. bulgaricus* and fructo-oligosaccharides (FOS). No adverse effect were reported. It was found that the use of a blend of seven probiotic strains plus FOS significantly reduced colic symptoms, instead of those subjects who took placebo [18].

Safety of probiotics and synbiotics in newborns

Another double-blind, randomized clinical trial, evaluated the food safety of synbiotics in infants, by giving then the synbiotics during the last four weeks before their birth, then by feeding their mother until the sixth month of life of the newborn baby. Recruiting of subjects were made considering pregnant mothers whose children were highly likely to develop food allergies. Pregnant mothers, randomly took either a blend of 4 probiotic species (*L. rhamnosus GG, L. rhamnosus* LC705, *Bifidobacterium breve* BB99 and *Propionibacterium freudenreichii* ssp. *shermanii*) or a placebo, plus 0.8 g of galacto-oligosaccharides or a placebo daily. Safety data were obtained from clinical trials and interviews in follow-up visits to 3, 6, 12, and 24 months. Growth data were collected for each item. Growth was normal for all newborns. During 6 months of intake, newborns in the synbiotics group had to take less antibiotics than the placebo group (23% *vs* 28%). During the follow-up period, respiratory infections occurred less often in the group that took synbiotics. The authors conclude that feeding infants with synbiotics may be retained as safe and seems to increase resistance to respiratory infections during the first 2 years from childbirth [22].

OBESITY

It is known to be a correlation between alteration of the microbial flora and obesity [23]. Consequently, among the therapeutic strategies useful as obesity treatment adjuvants, there are probiotics, which help to maintain the composition balance of the intestinal microbial [24].

A randomized, double-blind, placebo-controlled trial was carried out to evaluate the effects of probiotics

when combined with Bofutsushosan (BTS), a Japanese herbal drug, widely used in East Asia as anti-obesity treatment of overweight patients. Probiotics were used to test their ability to modulate intestinal flora, intestinal permeability, and endotoxin levels, factors that may be related to obesity. Bofutsushosan was administered in the form of plant extracts (Tsumura & Co., Japan). Probiotics were taken orally in capsules of Duolac 7 (Cell Biotech, Gimpo, Korea) containing 5×10^9 CFUs total of: *S. thermophilus* (KCTC 11870BP), *L. plantarum* (KCTC 10782BP), *L. acidophilus* (KCTC 11906BP), *L. rhamnosus* (KCTC 12202BP), *B. lactis* (KCTC 11904BP), *B. longum* (KCTC 12200BP) and *B. breve* (KCTC 12201BP). Fifty patients with a high body mass index (> 25 kg/m^2) and a waist circumference (> 85) cm were recruited. Subjects were randomly assigned to receive Bofutsushosan and probiotic (n = 25) or Bofutsushosan and placebo (n = 25) for 8 weeks. At early trial stage and after eight weeks of treatment, relevant parameters such as body composition, metabolic markers, endotoxin levels, intestinal permeability and number of fecal bacteria in the feces were evaluated.

Correlation between the composition of intestinal microbial flora and change in body composition indicates that probiotics can affect energy metabolism in obesity. Moreover, the correlation between endotoxin levels and body weight reduction indicates that probiotics can play an important role in preventing the accumulation of endotoxins, which can lead to intestinal dysbiosis associated to obesity [25].

TYPE 2 DIABETES

Intestinal microbiota, that is, the bacterial microflora that inhabits our intestine as a true human microbial organ, acts as a useful and important system for our body, but whether affected by anomalies or alterations, it can be related to the onset of diabetes mellitus type 2. Recent studies have found a relationship between diabetes and intestinal microbiota [26].

Intestinal bacteria have been shown to play a role in the genesis of obesity, diabetes, and cardiovascular disease. It is known to be a close association between obesity and type 2 diabetes. Many studies have found that both overweight and type 2 diabetes are characterized by an intestinal dysbiosis.

A double-blind, randomized clinical trial, was designed to determine the influence of multiple-species probiotic supplements on certain metabolic parameters such as hs-CRP (high sensitivity C-reactive protein) and stress oxidative in diabetic patients. Fifty-four diabetic patients, aged 35 to 70, were recruited and randomly administered with either a multi-species probiotic or a placebo (27 patients each) over 8 weeks. The synbiotic multiple-species consisted of 7 strains of lyophilized vital probiotics: *L. acidophilus* (2×10^9 CFU), *L. casei* (7×10^9 CFU), *L. rhamnosus* (1.5×10^9 CFU), *L. bulgaricus* (2×10^8 CFU), *B breve* (2×10^{10} CFU), *B. longum* (7×10^9 CFU), *S. thermophilus* (1.5×10^9 CFU), and 100 mg of fructo-oligosaccharides.

Blood samples were taken as fasting and after probiotics intake to measure metabolic parameters, hs-CRP, and oxidative stress biomarkers, including total antioxidant plasma capacity and total glutathione (GSH). Compared to placebo, an eight weeks multiple-type synbiotic intake by diabetic patients prevented an increase in fasting glycemia and resulted in a decrease in serum hs-CRP and an increase in GSH in total plasma [27].

PHARYNGOTONSILLITIS

Acute pharyngotonsillitis are very common diseases, mainly caused by viruses (adenovirus, influenza virus, parainfluenza viruses, rhinovirus, and synthetic respiratory virus). Among bacteria, Beta-hemolytic streptococci (GABHS) or *Streptococcus pyogenes* are the most common cause of acute pharyngeal tonsillitis, which accounts for about 15-30% of cases in children and 5-10% of cases in adults. The aims of antibiotic therapy against GABHS pharyngotonsillitis in adult are to prevent complications, to shorten the clinical course and the duration of disease's infectivity. Due to the increased bacterial resistance to antibiotics, the therapeutic use of probiotics could be very interesting.

Recent clinical studies showed that probiotics can be effective in the treatment of allergic rhinitis [28], eczema and allergies [29, 30].

A meta-analysis of ten randomized controlled trials showed that use of probiotics is advantageous compared to placebo for the prevention of acute upper respiratory tract infections [31].

The most commonly used genera include *Lactobacillus* and/or *Bifidobacterium*, but the list of probiotic microorganisms is continuously growing, including a non-pathogenic strain of *Escherichia coli* (*E. coli* Nissle 1917), *Clostridium butyricum*, *Saccharomyces boulardii* (a non-pathogenic yeast strain), and *Streptococcus salivarius*. *S. salivarius* is the predominant bacterial species of the oropharyngeal tract of adults [32]. The presence of *S. salivarius* inhibits the colonization and proliferation of pathogenic and competing microorganisms [33]. In pediatric patients, frequently suffering by throat infections, *S. salivarius*, isolated from nasopharynge, was shown to produce bacteriocins with anti-*Streptococcus pyogenes* activity [33, 34]. *S. salivarius* was shown to be safe for ingestion [35].

CONCLUSIONS

Although probiotics have been deeply studied, many aspects still need to be clarified, such as competition for energy substrates and intestinal wall adhesion sites. Obviously, like all substances that are administered to humans, probiotics must have specific characteristics that make them suitable for use.

First of all, a probiotic must be safe for humans. According to safety analysis carried out by EFSA (European Food Safety Authority), a list of safe species has been drawn up. Then, a probiotic must reach the intestine alive and vital and here it must be able to multiply. It is important to emphasize that characteristics and mechanisms of action are different from one strain to another. Therefore, to choose a probiotic suitable to each particular need, the specific effects (assessed by appropriate clinical trials) of the different strains available must be known.

In conclusion, the administration of probiotics may be probably considered as the new frontier of scientific research on prevention and treatment of various diseases, ranging from children's respiratory and allergic disorders to severe metabolic manifestations such as adult's insulin-dependent diabetes mellitus.

Of course, new studies are required in order to assess which probiotics strains and species should be used, depending on the type of manifestations and timing of intervention (i.e. prenatal, neonatal, weaning, early childhood, adolescence); nevertheless, probiotics seems to be a really promising remedy for health.

Author contribution statement

MV, GP and AI conceived and wrote the study; LF, RM and AM critically revised the manuscript.

Conflict of interest statement

None.

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