

Probiotics Intervention in Woman Health: Unexpected Acquaintance



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Abstract

There is growing interest in health promoting benefits of probiotics as bio therapeutic agents. Probiotics are used to treat recurrent urinary tract infections, diabetes, diarrhoea, vulvovaginal candidiasis and bacterial vaginosis in women. Probiotics exert their positive effects through various mechanisms, including lowering intestinal pH, decreasing colonization and invasion by pathogenic organisms, and modifying the host immune response. There is no agreement about the minimum number of microorganisms that must be consumed to obtain a beneficial effect; however, a probiotic should typically contain several billion microorganisms to increase the chance that adequate gut colonization will occur. This review presents mechanisms of action of probiotics and briefly examines the recent developments in use of probiotics in treating both infectious and non-infectious diseases in relation to women's health. We conclude with suggestions for future work and possible applications probiotic research.

Keywords: Lactobacillus; Probiotic; intervention; vaginal diseases; Woman health

Introduction

The World Health Organization's (WHO) 2001 defines probiotics as live micro-organisms that, "...when administered in adequate amounts, confer a health benefit on the host [1]". The term came into more common use after 1980. Human probiotics market size is anticipated to surpass USD 5 billion by 2024 [2] owing to its application outlook in foods & beverages, dairy & non-dairy products and fermented meat products to enhance the immunity system and improve the digestive health. These products help in curing immune response, pathogen inhibition, urogenital infections and digestive disorders in adults and nosocomial infections in infants. The outline of the concept (but not the term) is generally attributed to Nobel laureate Élie Metchnikoff, who postulated that yogurt-consuming Bulgarian peasants lived longer lives because of this custom [3]. Medical conditions that have been reportedly treated or have the potential to be treated with probiotics include diarrhoea, gastroenteritis, irritable bowel syndrome, and inflammatory bowel disease (Crohn's disease and ulcerative colitis), cancer, depressed immune function, inadequate lactase digestion, infant allergies, failure-to-thrive, hyperlipidemia, hepatic diseases, Helicobacter pylori infections, genitourinary tract infections, and others [4,5]. Today, we live in an era of potentially

tragic microbiological resistance to antibiotics [6]. With our progressively greater understanding of the influence of probiotics upon inflammation and the immune system, we have entered an era where an ideal climate prevails for the clinical extrapolation of *in vitro* experimentation to *in vivo* trials and treatments [7]. This review will endeavour to focus the use of probiotics in both infectious and non-infectious diseases in relation to women's health. The content of this review was obtained using the search terms probiotic(s), pregnancy, women's health and gynaecology within the Mendeley, PubMed, MEDLINE, EMBASE and Google Scholar data base.

Mechanisms of Action of Probiotics

The detailed mechanisms influencing the crosstalk between the microbe and the host are not completely understood, but there is growing evidence to suggest that the functioning of the immune system at both a systemic and a mucosal level can be modulated by bacteria in the gut [8]. In gut mucosa, pathogenic bacteria induce an inflammatory response, whilst commensal bacteria cohabit without inducing an inflammatory response [9]. A balancing act needs to be achieved between over and under stimulation of the inflammatory response. Interestingly, one of the probiotic

bactericidal mechanisms via high hydrogen peroxide levels is also self-inhibitory upon the growth of lactobacilli. Orally administered strains of lactic acid bacteria (LAB) increased the number of immunoglobulin A (IgA)-producing cells in the small intestine without a concomitant increase in the CD4+ T-cell population, indicating that some LAB strains induce clonal expansion only of B cells triggered to produce IgA [10]. In a separate study [11], the cytokines released by primary cultures of intestinal epithelial cells (IEC) in animals fed with *Lactobacillus casei* CRL 431 or *Lactobacillus helveticus* R389 concluded that the small intestine is the place where a major distinction would occur between probiotic LAB and pathogens. This distinction comprises the type of cytokines released and the magnitude of the response, cutting across the line that separates IL-6 necessary for B-cell differentiation, which was the case with probiotic lactobacilli, from inflammatory levels of IL-6 for pathogens.

According to the hygiene hypothesis, the increasing incidence of allergy in Westernized societies over the last decades may to some extent be explained by a reduced microbial load early in infancy [12] resulting in too little Th1 cell activity and therefore an insufficient level of IFN- γ to cross-regulate optimally Th2 cell responses. On opposing, according to the view of Classical Hygiene hypothesis, traditional commensals (lactobacilli) and other transient but harmless organisms (including saprophytic mycobacteria and helminths) induce maturation of dendritic cells (DCs) that induce Treg specific for allergens, commensals and self-antigens, that are target antigens in three groups of chronic disorders [13]. Nevertheless, probiotics do not have to be alive and whole to exert influences upon the host. Fragments of bacterial DNA, oligonucleotides, are capable of eliciting a host immune reaction [14] dead, whole or fragmented bacteria act through the same presumed mechanisms as that of live bacteria. This latter effect is at a much lower level than that seen for live bacteria [15].

Probiotics in Treatment of Bacterial Vaginosis

Bacterial vaginosis (BV) is the most common cause of vaginal infection in women of childbearing age, characterised by imbalance of the vaginal microbiota with a notable reduction of lactobacilli species, an overgrowth of a mixture of mostly endogenous obligate anaerobic bacteria spp. and elevated pH level in the vagina [16]. There seems to be an association between the absence of, or low concentrations of, vaginal lactobacilli and the development of BV. Many studies have suggested that the presence of H₂O₂-producing vaginal lactobacilli may protect against BV, although some studies do not support this hypothesis [17]. Clinical trials showed that intra-vaginal administration of *Lactobacillus acidophilus* for 6–12 days, or oral administration of *L. acidophilus* or *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14 for 2 months, resulted in the cure of BV (defined as a 0–1 positive score according to Amsel's criteria), and/or reduced the recurrences of BV, and/or caused an increase in vaginal lactobacilli and restoration of

a normal vaginal microbiota, significantly more frequently than did a placebo, acetic acid or no treatment. Though, some trials have found no significant difference in the cure rate of BV and in the number of vaginal lactobacilli after intra-vaginal instillation of lactobacilli when compared with the effect of a placebo or oestrogen. Therefore, although the available results concerning the effectiveness of the administration of lactobacilli for the treatment of BV are mostly positive (Table 1), it cannot yet be concluded definitively that probiotics are useful for this purpose. Further, in a study [18] to compare the efficacy of combined probiotic and antibiotic therapy with antibiotic therapy alone in treatment of bacterial vaginosis, combined therapy is significantly more effective when compared with antibiotic therapy alone for the treatment of bacterial vaginosis. However, some other studies on larger sample size are required to validate these findings

Table 1. Clinical studies of Probiotics showing beneficial effects in treatment of vaginal disorders [28].

Microflora	Mode of Action	Reference
<i>L. casei</i> DN_114001	Shown to control diarrhea	[29]
<i>L. acidophilus</i> LA02 (DSM 21717)	Hinders the persistence of an infection caused by <i>Candida</i>	[30]
Florisia® [<i>L. brevis</i> (CD2), <i>L. salivarius</i> subsp <i>salicinius</i> (FV2) and <i>L. plantarum</i> (FV9)]	Treatment of symptomatic bacterial vaginosis	[31]
EcoVag® [<i>L. gasseri</i> (Lba EB01-DSM 14869) and <i>L. Rhamnosus</i> (Lbp PB01-DSM 14870)]	Bacterial vaginosis	[32]
<i>L. reuteri</i> SD2112	Useful in treating rotavirus diarrhoea	[33]
Kramegin® (<i>L. acidophilus</i> + lactic acid and <i>Krameria triandra</i> extract)	Abnormal cervical cytology	[34]

Probiotics in Treatment of Recurrent Urinary Tract Infection

Recurrent urinary tract infections (UTI) are common among young healthy women even though they generally have anatomically and physiologically normal urinary tracts. Women with recurrent UTI have an increased susceptibility to vaginal colonization with uropathogens, which is due to a greater propensity for uropathogenic coliforms to adhere to uroepithelial cells [19]. Common risk factors for recurrent UTI include sexual intercourse, use of spermicidal products, having a first UTI at an early age, and having a maternal history of UTIs [20]. Since lactobacilli dominate the urogenital flora of healthy premenopausal women, the use of probiotics, especially lactobacilli, has been considered for the prevention of UTIs. Recently, in a double-blind

study [21], phase 1 trial of the safety and tolerance of Lactin-V in women with rUTI, shown that *L. crispatus* CTV-05 can be given as a vaginal suppository with minimal adverse effects to healthy women with a history of rUTI. Lactin-V (Osel) contains a carefully selected H₂O₂+ *Lactobacillus crispatus* strain CTV-05 isolated from a healthy woman's vagina and was developed as a vaginal probiotic for use in patho physiological states characterized by detrimental alterations in vaginal flora, such as bacterial vaginosis (BV) [22], rUTI and potentially others. A prospective study by Yang Bob and Foley [23] suggested that bacterial vaccine Uromune® is safe and effective at preventing UTIs in women. Further research is required in larger groups of patients for longer treatment times.

Adverse Effects of Probiotics

Probiotics are mostly considered to be safe. However, some species of microorganisms that are used as probiotics have recently been isolated from infection sites, causing some concerns regarding the safety of these products [24]. Bacteremia caused by lactobacilli is rare, and data on its clinical significance is based only on case reports or data in abstract form [25]. Immuno compromised patients generally are more vulnerable to infection with pathogens and have a higher incidence of opportunistic infections [26]. However, there is no published evidence that consumption of probiotics that contain lactobacilli or bifidobacteria increases the risk of opportunistic infection among such individuals. In addition, 2 clinical studies have been conducted to assess the safety of probiotics in small groups of specific immune compromised patients (e.g., patients with HIV infection), and the findings of these studies support the safety of probiotics consumed by such groups [27-34].

Conclusion

Several *in vitro* and *in vivo* studies support the beneficial effect of some strains of lactobacilli on the restoration of the vaginal flora and the prevention of recurrent UTIs. Probiotics use do not represent a complete cure, but evidence is accumulating that the use of proven probiotic strains and manipulation of the host's own intestinal and vaginal/urethral microbiota will provide valuable opportunities to help restore and maintain urogenital health. Once appropriate product formulations with supporting clinical data become available, it will be up to the physician to determine their place in patient management.

Conflict of Interest

Author declares no conflict of interest.

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