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Dairy Probiotic Foods and Bacterial Vaginosis: A Review on Mechanism of Action

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1. Introduction

Bacterial vaginosis (BV) is the most common urogenital disease in women, affecting about 19-24% of them in reproductive ages. 10-26% of pregnant women in the United States have been reported to suffer from BV. The prevalence of BV varies in different parts of the world and is higher in developing countries. The disease has been found in 12 to 25 percent of women in routine clinic populations, and accounts for 32 to 64 percent of women in clinics for sexually transmitted diseases; however, there is still some controversy about whether or not BV is a sexually transmitted disease (STD) in the “traditional” sense. Current data indicate that the overall prevalence of BV is much higher among STD clinic attendees and commercial sex workers [1]. BV is believed to occur as a result of an imbalance in the normal vaginal microbiota [2] when the normal *Lactobacillus* bacteria in the vagina are disrupted and subsequently replaced by predominantly anaerobic bacteria including *Gardnerella vaginalis*, *Mycoplasma hominis*, *Prevotella*, and *Peptostreptococcus* [3]. Other bacteria such as *Escherichia coli* from the rectum have also been shown to cause the disease. *Lactobacilli* bacteria, by producing a natural antibacterial, hydrogen peroxide, keep the healthy normal balance of vaginal microorganisms. Factors that upset this balance in the vagina are not well-understood. However, the activities or behaviours that have been related with BV incidence include having a new sex partner or multiple sex partners and douching [4, 5]. BV is mainly followed by irritating symptoms mainly foul, fish-like or musty odor which is sometimes stronger after a woman has sex, watery or foamy, white (milky) or gray vaginal secretions, itching on the outside of the vagina and Burning or discomfort during urination [6]. It is also known that BV is associated with potentially severe gynaecological and obstetric complications. Current data suggest a causal association between BV, pelvic inflammatory disease and tubal factor infertility [7]. Pregnant women with BV have a higher risk of adverse outcomes such as late miscarriage, chorioamnionitis, premature rupture of

membranes, preterm birth and postpartum endometritis; they are more susceptible to having babies of low birth weight as well [8, 9]. BV has been identified as a risk factor for herpes virus type 2 infections and increased viral shedding in infected women [10, 11]. It has also been suggested that the presence of BV increases the risk for human immunodeficiency virus infection [12]. It is noteworthy that many women with BV do not show any symptoms [13], pelvic inflammatory disease [14], infections following gynecological surgery [15] and pre-term birth. BV is not transmitted through toilet seats, bedding, swimming pools, or touching of objects. Women, who have not had sexual intercourse, hardly develop BV [16].

Typically, a cure for BV refers to resolution of symptoms and maybe a repeat BV-negative screen. We know from clinical studies that BV has both an unprompted resolution and repetition [13]. As many as 30 percent of women relapse within 1 month of treatment, with unprompted relapse occurring more commonly among women treated with topical compared with systemic antibiotics [17]. The most common oral treatment for BV in both pregnant and non-pregnant women is metronidazole and clindamycin [18]. The individual cure rate given a 7-day, twice-daily course of 500 mg of metronidazole ranges from 84 percent to 96 percent, and the cure rate given a 2 g single dose of metronidazole is 54-62 percent [19]. The second systemic treatment for BV is oral clindamycin. The one known clinical trial conducted describing the efficacy of oral clindamycin reported that a 300-mg, twice-daily course of clindamycin for 7 days resulted in a 94 percent cure rate [15]. The two topical treatments for BV include metronidazole 0.75 percent vaginal gel and clindamycin 2 percent vaginal cream [5].

Probiotics have been documented to be beneficial in curing BV as well as reducing its recurrence and have been administered both orally and vaginally [20]. Oral administration introduces the beneficial bacteria directly into the vagina; probiotics consumed orally are believed to ascend to the vaginal tract after they are excreted from the rectum. Mechanism through which probiotics play a role in BV treatment include: [1] occupation of specific adhesion sites at the epithelial surface of the urinary tract; [2] maintenance of a low pH and production of antimicrobial substances like acids, hydrogen peroxide and bacteriocins; [3] degradation of polyamines; and [4] the production of surfactants with antiadhesive properties [21]. Probiotics have been shown to exert the beneficial effects both in foods such as yoghurt [22], ice cream [23, 24], and supplements [25]. However, foods may be preferred by patients since BV is not considered a disease by public and the affected women may not want to be prescribed supplements.

The purpose of the present chapter is to review recent research into aspects influencing the impact probiotics have on bacterial vaginosis. All papers published between 1990 and 2011 were searched in Pubmed and Science Direct, using probiotic, bacterial vaginosis and urinary tract infections (UTI) as key words; only clinical trials were included.

2. Probiotics

2.1. History

The expression “probiotic” was probably first defined by Kollath in 1953, when he suggested the term to denote all organic and inorganic food complexes as “probiotics” in

contrast to harmful antibiotics, for the purpose of upgrading such food complexes as supplements [26]. In 1998, probiotics were described as “live microorganisms which, when ingested in adequate amounts, confer a health benefit”. The term “probiotic” is an etymological hybrid derived from Greek and Latin meaning “for life” [27]. The original observation of the positive role played by some selected bacteria is attributed to Eli Metchnikoff, who extolled the virtues of consuming fermented dairy products and postulated his “Longevity without aging” theory, in which he claimed that lactic bacteria by replacing the harmful bacteria indigenous to the intestines, prolong life. The Russian born Nobel Prize recipient, working at the Pasteur Institute at the beginning of the last century suggested that the dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes [28].

2.2. Definition

Presently, there is general agreement that a “probiotic” refers to viable microorganisms that promote or support a beneficial balance of the autochthonous microbial population of the gastrointestinal tract [29, 30]. Probiotics are defined as live microorganisms which, when consumed in appropriate amounts, confer a health benefit on the host, by FAO/WHO [31]. When ingested, some of these probiotic microorganisms are able to resist the physicochemical conditions prevailing in the digestive tract [32]. The strains most frequently used as probiotics belong to the genera *bifidobacterium* and *Lactobacillus* [33]. Some of the species used in probiotic products are: 1) Lactic acid producing bacteria (LAB): *Lactobacillus*, *bifidobacterium*, *streptococcus*; 2) Non-lactic acid producing bacterial species: *Bacillus*, *propionibacterium*; 3) Nonpathogenic yeasts: *Saccharomyces*; 4) Non-spore forming and non-flagellated rod or coccobacilli [31].

2.3. Health benefits

Some mostly documented health effects of probiotics are: relieving diarrhea, improving lactose intolerance, relief of respiratory and urinary tract infections and its immunomodulatory, anticarcinogenic, antidiabetic, hypocholesterolemic and hypotensive properties [25, 34, 35]. LAB also have some other advantageous effects such as vitamin synthesis, improvement of mineral and nutrient absorption, deprivation of antinutritional factors, and/or modulation of GI physiology and reduction of pain perception. Special probiotic strains may induce the expression of receptors on epithelial cells that locally control the transmission of nociceptive information to the GI nervous system [36]. By reducing inflammatory responses, probiotics have been shown to correct insulin sensitivity and reduce development of diabetes mellitus [34]. A beneficial effect of “lactic acid producing” microorganisms on vaginal microflora has also been suggested more than 100 years ago [37]. There are differing degrees of evidence supporting the verification of such effects, and the consultation recognizes that there are reports showing no clinical effects of certain probiotic strains in specific situations [38].

3. Probiotic and bacterial vaginosis

Since antimicrobial treatment of urogenital infections is not constantly effectual and problems remain due to bacterial and yeast resistance, recurrent infections as well as side effects, it is no wonder why alternative remedies are sought for, by patients and their caregivers [39, 40]. The basis for use of probiotics in BV treatment emerged in 1973, when healthy women with no history of UTI were reported to have lactobacilli in their vagina [39]. Lactobacillus organisms that predominate in the vagina of healthy women spread from their rectum and perineum and form a barrier to the entry of uropathogens from vagina into the bladder [41].

Probiotics are believed to protect the host against infections by means of several mechanisms including: [1] occupation of specific adhesion sites at the epithelial surface of the urinary tract; [2] maintenance of a low pH and production of antimicrobial substances like acids, hydrogen peroxide, and bacteriocins; [3] degradation of polyamines; and [4] the production of surfactants with antiadhesive properties [21, 42].

There are important issues to which a great attention must be paid regarding the effects of probiotics on BV treatment and prevention. Probiotics have been administered both orally and vaginally; however it is still not clear as to which route is more efficient. Foods and supplements have been used as carriers when oral administration was aimed; no studies have compared the efficacy of these two vehicles. Not all strains have exerted the desired effects in the patients; poor colonization of some strains in the vagina could be a reason [39, 40, 43]. The most profitable dose and treatment duration must be taken into consideration as well.

3.1. Route of administration

Probiotics must colonize the vagina to confer the benefits claimed for them; therefore they have to reach the organ intact. Vaginal probiotic capsules have widely been used, by the means of which, the probiotic bacteria are directly introduced into the vagina; however, in an attempt to come up with a more practical route which could also prevent BV in healthy women as well as presenting the consumer with other health benefits of these beneficial microorganisms, probiotics were administered orally [41, 43]. Researchers assumed that, similar to pathogenic bacteria with colonic origin which cause urogenital disorders, probiotic bacteria must be capable of ascending to the vaginal tract after being excreted from the rectum (Figure 1). This application is also justified by observations that the normal vaginal microflora colonizes from an intestinal origin which means that microbial ascension is a natural process actually contributing to the development of a healthy vaginal microflora in the host [39]; this has been shown by a number of clinical trials as well [41, 44]. Thus far, no clinical trials have compared the efficacy of probiotics when administered vaginally versus orally. In tables 1-2, clinical trials performed in this regard have been summarized. It appears that vaginal administration has no predominance to oral consumption of probiotics, when it comes to treating BV.

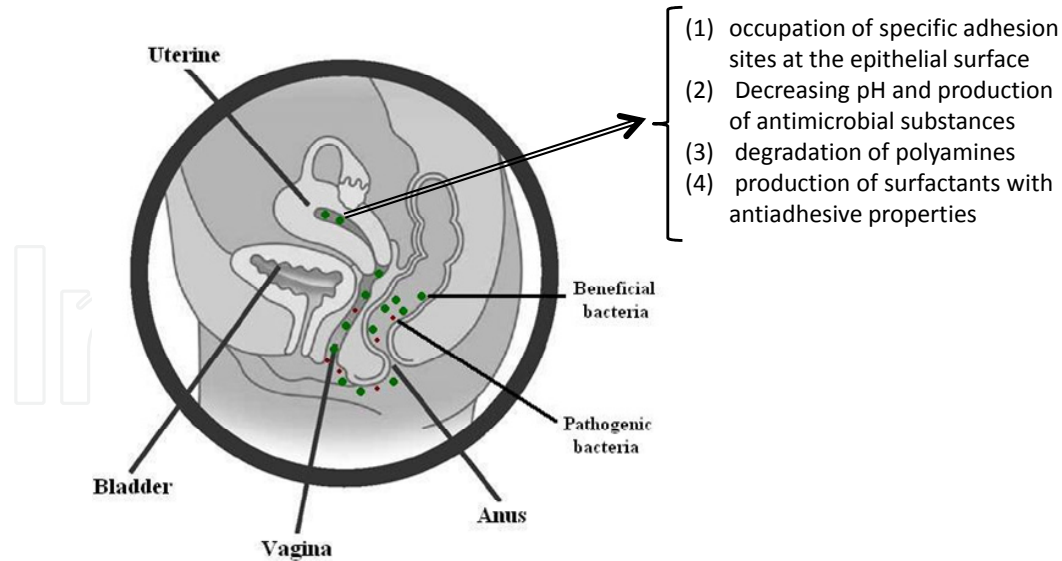


Figure 1. Capability of pathogenic and probiotic bacteria to ascend the vagina after being excreted from rectum

Type	Strain	Dose	Period	Health condition	Effect	Ref.
Yoghurt	Lactobacillus acidophilus	1.0×10^8 CFU	Once daily for 2 month	Bacterial vaginosis, candidiasis	Reduction in BV episodes at 1 mo was 60% for probiotic yoghurt vs 25% for pasteurized	[45]
Capsules	Lactobacillus rhamnosus GR-1 plus Lactobacillus fermentum RC-14 or L. rhamnosus	10^8 CFU	Each day for 28 days	Bacterial vaginosis	Normal vaginal flora was restored using specific probiotic strains administered orally	[41]
Skim milk	Lactobacillus rhamnosus GR-1 and Lactobacillus fermentum RC-14	10^9 CFU	Given twice daily for 14 days	Bacterial vaginosis	Treatment correlated with a healthy vaginal flora in up to 90% of patients	[46]
Capsule	1- L. rhamnosus GR-1/ L. fermentum RC-14 2-L. rhamnosus GR-1/L. fermentum RC-14 3-L. rhamnosus GR-1/L. fermentum RC-14	8×10^8 CFU 1.6×10^9 CFU 6×10^9 CFU	Day orally for 28 days	History of BV	Through 6 weeks after treatment with probiotics, Nugent score decreased, indicative of BV resolution	[43]
Capsule	L. rhamnosus GR-1 + L. fermentum RC-14	$>10^9$ CFU	Once-daily for 60 days	Bacterial vaginosis	Probiotics colonized the vagina properly and the Nugent score normalized after the treatment	[47]
Capsules	Lactobacillus rhamnosus GR-1 and Lactobacillus fermentum RC-14	10^9 CFU	60 days	Urogenital infections	Lactobacilli counts increased while yeast and coliforms decreased significantly after supplementation	[48]
Capsule	Lactobacillus reuteri RC-14 Lactobacillus rhamnosus GR-1	10^9 CFU	Twice daily from days 1 to 30	Bacterial vaginosis	88% were cured in the antibiotic/probiotic group compared to 40% in the antibiotic/placebo group [$p < 0.001$]. High counts of Lactobacillus sp. Colonized the vagina properly	[49]
Capsules	Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14	1.0×10^9 CFU	BID for 30, after 500 mg metronidazole BID PO for 7 d	Bacterial vaginosis	BV cure rate was 88% in probiotic group vs. 40% in placebo group	[42]
Capsules	Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14	2.5×10^9 CFU	14 days	Bacterial vaginosis	The median difference in Nugent scores between baseline and the end of the study was 3 in the intervention group and 0 in the control group	[50]

Table 1. The effects of oral administration of probiotics on BV, performed between 1990 and 2011

Type	Strain	Dose	Period	Heath condition	Effect	Ref.
10–15 mL yoghurt, vaginal douche	<i>L. acidophilus</i>	1.0×10^8 CFU	BID for 7 d	First trimester of pregnancy with BV diagnosis	BV cure rate was 88% probiotic group at 4 and 8 w and 38% in control group	[51]
Vaginal tablets	<i>L. acidophilus</i> and oestriol 0.03 mg	10^6 CFU	Once daily or twice daily for 6 days	Bacterial vaginosis	Microbiological cure [Nugent criteria] and clinical cure were observed on days 15 and 28 post intervention	[1]
Tampons	<i>L. gasseri</i> , <i>L. casei</i> var <i>rhamnosus</i> & <i>L. fermentum</i>	10^8 CFU	5 tampons during menstruation	Bacterial vaginosis	Microbiological cure was observed based on Nugent score and Amsel criteria	[2]
Vaginal tablet	<i>Lactobacillus acidophilus</i> , 0.03 mg oestriol and 600 mg lactose.	$> 10^7$ CFU	Daily for 6 days	Vaginal infections	Vaginal flora was enhanced significantly by the probiotic administration in combination with low dose oestriol	[52]
Capsules	<i>L. rhamnosus</i> GR1, <i>L. reuteri</i> RC14	1×10^9 CFU	Bedtime for 5 consecutive days	Bacterial vaginosis	Microbiological cure at days 6, 15 and 30 and clinical cure at days 6, 15, and 30 were reported	[42]
Vaginal tablet	<i>Lactobacillus rhamnosus</i>	$> 4 \times 10^4$ CFU	Once a week at bedtime for two months	Bacterial vaginosis	Significant difference between the two treatment groups were seen at day 90	[53]
Vaginal tablets	<i>L. brevis</i> , <i>L. salivarius</i> subsp <i>salicinius</i> , and <i>L. plantarum</i>	10^9 CFU	7 days	Bacterial vaginosis	All of the patients in the probiotic group were free of BV, showing a normal or intermediate vaginal flora	[4]
Vaginal application	40 mg of <i>Lactobacillus rhamnosus</i>	$> 4 \times 10^4$ CFU	for 6 months	Prevent the recurrence of bacterial vaginosis	The vaginal administration of the probiotic allows stabilization of the vaginal flora and reduces BV recurrence	[54]
Vaginal Capsules	<i>L. gasseri</i> LN40, <i>Lactobacillus fermentum</i> LN99, <i>L. casei</i> subsp. <i>rhamnosus</i> LN113 and <i>P. acidilactici</i> LN23	Between 10^8 and 10^{10} CFU	Five days, after conventional treatment of bacterial vaginosis	Bacterial vaginosis, vulvovaginal candidiasis	LN had a good colonization rate in the vagina BV patients and women receiving LN were cured 2–3 days after Administration	[55]
Vaginal capsule	<i>Lactobacillus rhamnosus</i> , <i>L. acidophilus</i> , and <i>Streptococcus thermophiles</i>	10^8 CFU	21 days, for 7 days on 7 days off, and 7 days on.	Prophylaxis bacterial vaginosis	Probiotic prophylaxis resulted in lower recurrence rates for BV women	[3]

Table 2. The effects of vaginal administration of probiotics on BV, performed between 1990 and 2011

3.2. Administration vehicles

As for administration route, no studies by now have investigated the efficacy of foods versus supplements in exerting the benefits expected from the probiotics. Supplements have been used in a greater number of studies in BV patients and the number of studies in which foods were opted as probiotic vehicles are limited. Consumption of fermented milk containing lactobacilli has been found to reduce BV episodes [45]. Supplements have been used in a variety of forms including oral capsules, vaginal tablets and vaginal capsules. Clinical trials in which patients were administered oral capsules, reported a positive effect of the treatment on BV [39, 41–43, 49, 56]. Vaginal probiotic tablets were reported to be effective in alleviating BV symptoms and decreasing its recurrence [1, 4, 52, 53]. Vaginal capsules have also been reported to efficiently ease BV symptoms in some studies [3, 42, 50, 55].

3.3. Appropriate strains for treatment of bacterial vaginosis

Various in-vitro studies have shown that specific strains of lactobacilli inhibit the growth of bacteria causing BV by producing H₂O₂, lactic acid, and/or bacteriocins and/or inhibit the adherence of *G. vaginalis* to the vaginal epithelium [52]. According to a general theory a probiotic must have two criteria to be selected as an efficient strain in the treatment of urogenital infections: 1] It must be able to colonize the host without any adverse side effects and 2] It must be capable of inhibiting urogenital pathogens [57]. According to Reid and colleagues [43] different probiotic bacteria have varying capabilities to colonize the vagina of different patients; this indicates the importance of using a combination of strains in probiotic products. Oral administration of *L. acidophilus*, or intra-vaginal administration of *L. acidophilus* or *L. rhamnosus* GR-1 and *L. fermentum* RC-14, have been documented to most efficiently increase the numbers of vaginal lactobacilli, restore the vaginal microbiota to normal, and cure women of BV [52].

3.4. Appropriate dose for treatment of bacterial vaginosis

Researchers have tried different dosages in their attempts to treat BV with probiotics, many of which have resulted in positive outcomes. There is strong evidence that BV is most appropriately treated when over 10⁸ viable organisms per day is used [41]. However, the minimum dose which can generally confer the favored benefits in women must to be determined.

3.5. Effect of treatment duration

What BV patients and their caregivers are mostly looking for, is a treatment protocol to get them rid of the recurrence of the infection. Probiotics are a good option to fulfill this goal, provided that they are properly colonized in the vagina. Parent and colleagues [1] found that cure was more common, and the number of vaginal lactobacilli was significantly higher, in women with BV at both 2 and 4 weeks after the start of a 6-day treatment with *L. acidophilus* and oestriol, when compared to women with BV who received a placebo. However, most clinical trials have reported that 2 months of oral administration of *L. acidophilus*, *Lactobacillus rhamnosus* GR-1 and *L. fermentum* RC-14 can be more effective in preventing recurrences of BV and/or increasing vaginal colonization with lactobacilli, thus restoring the normal vaginal microbiota [58].

4. Conclusion

This study confirms the potential efficacy of lactobacilli as a non-chemotherapeutic means to restore and maintain a normal urogenital flora, and shows that probiotic bacteria especially *L. acidophilus*, *L. rhamnosus* GR-1 and *L. fermentum* RC-14 when administered over 10⁸ CFU for 2 months can most appropriately normalize vaginal flora, help cure the existing infection and prevent recurrence of BV. Longer periods of probiotic administration may be useful for long term control of BV relapses after conventional therapy with metronidazole.

Probiotics have been reported useful when used either vaginally or orally; foods and supplements have both been shown to be efficient vehicles as well; however, since BV is a common disorder for the prevention of which, the vaginal flora needs to be normal and devoid of pathogens by the help of beneficial bacteria, suggesting women to consume probiotic foods will not only protect them against BV, but will also reward them with other health benefits of probiotics.

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