

The Role of Probiotics in Preventing Recurrent Bacterial Vaginosis and Vulvovaginal Candidiasis: A Literature Review

Andiva Nurul Fitri^a, Nadira Putri Nastiti^a, Eighty Mardiyani Kurniawati^{b*}, Sundari Indah Wiyasihati^c

*Corresponding author (eighty-m-k@fk.unair.ac.id)

^aFaculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

^bDepartment of Obstetric and Gynecology, Faculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

^cDepartment of Physiology, Faculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

Abstract

Bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) are the most common vaginal infections that cause vaginal discharge in women. An imbalance of the normal vaginal microbiota can make it easier for the vagina to become infected with bacteria and fungi. The recurrence rate for both diseases is 40–60%. Therefore, alternative therapies are needed to prevent the recurrence of these two diseases. Probiotics are believed to be able to maintain a normal microbiota balance in the vagina. This study aims to determine the role of probiotics in BV and VVC therapy, to prevent recurrence of these two diseases. A literature search was performed on two databases namely PubMed and Science Direct, using several keyword combinations to obtain relevant results. There were 12 studies that met the inclusion and exclusion criteria. There are six studies explaining the role of probiotics in BV and VVC, respectively. The use of probiotics intravaginally or orally can significantly reduce the recurrence rate of these two diseases, restore normal vaginal conditions in BV as well as improve clinical symptoms in VVC. The combination of antibiotics and probiotics can increase the effectiveness of the therapy.

Keywords: Probiotics, Bacterial Vaginosis, Vulvovaginal Candidiasis, Recurrence, Lactobacillus

1. Introduction

Vaginal discharge is the second most common complaint after menstrual cycle complaints in women of reproductive age. [1] Vaginal discharge is basically a normal thing as the body's defense mechanism to keep the vagina moist as well as protection against infection. [2] Changes in amount, color, and smell can be caused by an imbalance of bacteria in the vagina, which causes vaginitis. [3] The prevalence of vaginal infections is 40–50% in BV, 20–25% in VVC, and 15–20% in Trichomoniasis, respectively. [4]

1.1. Normal Vaginal Microbiota

Normal vaginal microbiota conditions are dominated by *Lactobacillus* microorganisms. [5] There is a classification system to describe the composition of the vaginal microbiota based on the predominance of bacteria. This classification is called Community State Types (CST) which consists of CST I, II, III, IV, and V. Each CST is dominated by *L. crispatus*, *L. gasseri*, *L. iners*, polymicrobial flora, and *L. jensenii*, respectively. In healthy women, the types of CST that are often encountered are CST I, II, III, and V. [6] Meanwhile, CST IV is classified into CST IV-A and IV-B. CST IV-A consists of a moderate proportion of *Lactobacillus* bacteria and small amounts of *Anaerococcus*, *Corynebacterium*, *Fingoldia*, or *Streptococcus*. Meanwhile, CST IV-B was dominated by a high proportion of *Atopobium*, *Prevotella*, *Parvimonas*, *Sneathia*, *Gardnerella*, *Mobiluncus*, *Peptoniphilus*, and other anaerobic bacteria associated with the occurrence of BV. [7]

1.2. Bacterial Vaginosis

Bacterial vaginosis is a condition in which there is a decrease or loss of *Lactobacillus* bacteria which produce lactic acid which is then replaced by an increase in the growth of pathogenic bacteria, namely *Gardnerella spp.*, *Atopobium spp.*, *Prevotella spp.*, and *Mobiluncus spp.* [8] The prevalence of BV ranges from 23–29% worldwide. [9] BV is often also called *Gardnerella vaginitis* associated with the bacteria that causes this disease. The presence of *G. vaginalis* bacterial infection forms a biofilm which then becomes a place for the growth of other opportunistic bacteria. [10] In this condition, damaged vaginal defenses will increase the immune response by secreting proinflammatory cytokines such as IL-6, IL-8, IL-1a, IL-1b, TNF-a to fight biofilm-forming bacteria. [11]

The diagnosis of BV is made clinically and also by supporting examinations in the form of a vaginal swab in the cervical region or vaginal fluid which is then made into a wet smear on a glass object. BV is generally diagnosed based on the Amsel criteria. BV is declared positive if at least 3 of the 4 criteria are found. The first criterion is vaginal discharge with a thin consistency, yellowish white in color, homogeneous and clue cells are found. Furthermore, the vaginal pH was > 4.5 and the whiff test smelled fishy after being given 10% KOH to the specimen. This Amsel criterion has a sensitivity of 70% and a specificity of 94%. The diagnosis of BV can also be determined based on the Nugent score on gram stain, a Nugent score > 7 indicates the presence of BV. However, it is rarely used today. [11] First-line therapy of BV includes oral metronidazole 500 mg twice daily for 7 days, 2% clindamycin cream 5g intravaginally for 7 days or metronidazole gel 0.75% 5g intravaginally once daily for 5 days. The recurrence rate of BV is 50% in 6–12 months. Recurrent BV is characterized by the occurrence of $BV \geq 3$ times in 12 months. [12]

1.3. Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is a vaginal infection primarily caused by the fungus *Candida albicans* and a small proportion of non-*Candida albicans* (*Candida glabrata*) which are the normal microbiota of the vagina. VVC is the second most common cause of vaginitis after BV. It is estimated that 70–75% of

women worldwide have experienced VVC, and 40–50% of them have recurrent VVC. [13] VVC can occur when *Candida* fungi invade the vaginal mucosa and cause an inflammatory response. The mechanism of inflammation is still unknown, but inflammatory cells are dominated by PMN cells and macrophages. VVC sufferers will complain of thick, sticky vaginal discharge, accompanied by excoriations, dysuria, itching, burning, and swelling. [14]

The diagnosis of this disease is established by finding budding yeast, blastospores, or *Candida spp* pseudohyphae. on wet smears with 10% KOH, gram stain, or cultures from vaginal fluid specimens. [15] The treatment commonly used today is the administration of antifungal drugs in the form of intravaginal clotrimazole cream for 7–14 days or a single dose of fluconazole 150 mg orally. [16] Recurrent VVC is characterized by episodes of VVC ≥ 4 times a year as evidenced by culture. In recurrent VVC, given a single dose of fluconazole 150 mg orally for 3 days, then continued administration once a week for 6 months. However, 50% of women will experience a recurrence within 3–4 months. [17]

1.4. Probiotics

The term probiotic was first put forward in 1965, which was defined as microorganisms that can enhance the growth of other microbes. [18] Based on the consensus in 2014, the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) define probiotics as live microorganisms that can provide beneficial health for the host if given in adequate amounts. [19] The types of probiotics include *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, *Escherichia*, and *Bacillus*. Probiotics are widely used to maintain the microbial balance in the vagina. *Lactobacillus* is the most researched probiotic, because it is believed to protect the vagina from BV and VVC. The mechanism of action of *Lactobacillus* is described in Figure 1. [18]

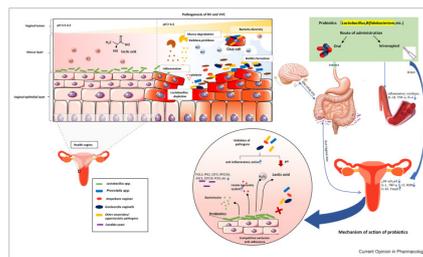


Figure 1. Mechanism of Action of *Lactobacillus*

Lactobacillus produces lactic acid which can destroy pathogens by lowering vaginal pH to 3.5–4.5 which also contributes indirectly to inhibiting pathogens by cervical mucus secretions. *Lactobacillus* also produces bacteriocins which are AMPs (Antimicrobial Peptides) and proteins, in response to an imbalance of the vaginal microbiota, to protect the host from microbial invasion. Then blocking the colonization of pathogenic bacteria as a result of the transfer of *Lactobacillus* bacteria. In addition, *Lactobacillus* also enhances the immunomodulation mechanism by stimulating the innate immune system to produce hydrogen peroxide (H₂O₂) thereby stimulating anti-inflammatory action. [18]

2. Methods

This is secondary research conducted in the form of a literature review. A literature search was conducted through two databases, namely PubMed and Science Direct, using several keywords such as

probiotics, lactobacillus, recurrence, bacterial vaginosis, and vulvovaginal candidiasis according to the MeSH term and adding a boolean operator to obtain relevant results. The literature was then selected according to the year of publication (2012–2022), with study designs including randomized controlled trials, clinical trials, and observational studies. Literature was excluded if the study was conducted in a population of pregnant women.

3. Discussion

3.1. Role of Probiotics in Bacterial Vaginosis

Based on the literature search that has been done, there are six studies that explain the role of probiotics in bacterial vaginosis. Four studies administered probiotics intravaginally while the other two studies administered probiotics via the oral route. Administration of probiotics containing *L. crispatus* for 3–4 months after antibiotic therapy can reduce the recurrence rate of BV. Recurrence rates ranged from 20.5–30%, while the average time to relapse was 3.75 ± 0.16 months. [20,21] Another type of probiotic, namely *Lactobacillus plantarum*, is also known to reduce the risk of BV recurrence. However, statistically, this result is not significant. [22] Probiotic therapy with *Lactobacillus rhamnosus* can also be used in groups of high-risk women safely and without side effects. [23]

The use of probiotics given via the oral route has also shown significant results in preventing BV recurrence. A mixture of *L. crispatus* LMG S-29995, *L. brevis*, and *L. acidophilus* can significantly reduce the percentage of BV relapse and extend the time of BV relapse. [24] In addition, a mixture of lactobacilli (*L. acidophilus* GLA-14 and *L. rhamnosus* HN 001) combined with bovine lactoferrin is a safe and effective alternative therapy to restore a healthy vaginal microbiota in preventing BV recurrence. [25] The overall BV recurrence rate ranged from 18.3–33.33% in the 4th month with an average recurrence time of 97.3 (26.7) days. [24,25]

3.2. Role of Probiotics in Vulvovaginal Candidiasis

Based on the literature search that has been done, there are 6 studies that explain the role of probiotics in bacterial vaginosis. There were 3 studies each giving probiotics intravaginally and orally. Studies using intravaginal probiotics concluded that continued therapy with *L. plantarum* could increase the effectiveness of clotrimazole in preventing recurrence of VVC, reducing complaints of vaginal itching or burning as well as improving vaginal pH. [26,27] Other types of probiotics, namely *L. fermentum* LF10 and *L. acidophilus* LA02 are also known to be able to create and maintain biofilms in the vagina that can inhibit persistent infections caused by *Candida sp.* [28] The use of probiotics is associated with a 3-fold reduction in the risk of recurrence of VVC with a recurrence freedom rate of 72.4–72.83%. [26,28]

In studies that gave probiotics orally, the results showed that the consumption of a probiotic mixture (*L. acidophilus* GLA-14 and *L. rhamnosus* HN 001 combined with bovine lactoferrin) could be an adjuvant therapy of the azole class of antifungal drugs that was safe and very effective in reducing the recurrence rate of VVC. [29] Other effective mixtures are *L. acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*. [15] Administration of oral probiotic *Lactobacillus plantarum* P17630 increased colonization of vaginal lactic acid bacteria and prevented episodes of vulvovaginal candidiasis. [30] The VVC recurrence rate was 7.2–29.2% after 6 months of treatment. [15,29] In addition, probiotic therapy can also improve symptoms of itching, redness, swelling, and vaginal discharge in VVC. [29,30]

4. Conclusion

The use of probiotics can significantly reduce the recurrence rate of bacterial vaginosis and vulvovaginal candidiasis, restore normal vaginal conditions in BV as well as improve clinical symptoms in VVC. The combination of antibiotics and probiotics can increase the effectiveness of the therapy. However, further research is needed regarding the proper dosage and method of administration in administering these probiotics.

References

1. Venugopal S, Gopalan K, Devi A, Kavitha A. Epidemiology and clinico-investigative study of organisms causing vaginal discharge. *Indian J Sex Transm Dis AIDS*. 2017 Jan-Jun;38(1):69-75
2. NHS. Vaginal discharge [internet]. The National Health Service; 2022 [cited 2022Nov7]. Available at: <https://www.nhs.uk/conditions/vaginal-discharge/>
3. Gor HB. Vaginitis [Internet]. Practice Essentials, Pathophysiology, Etiology. Medscape; 2021 [cited 2022Nov7]. Available at: <https://emedicine.medscape.com/article/257141-overview>
4. CDC. Bacterial vaginosis - STI treatment guidelines [Internet]. Centers for Disease Control and Prevention; 2021 [cited 2022Nov7]. Available at: <https://www.cdc.gov/std/treatment-guidelines/bv.htm>
5. Laniewski P, Herbst-Kralovetz M. Vagina. In: Skinner MK, editor. *Encyclopedia of Reproduction*. 2nd ed. Academic Press; 2018. p. 353-359.
6. Chee WJ, Chew SY, Than LT. Vaginal microbiota and the potential of lactobacillus derivatives in maintaining vaginal health. *Microbial Cell Factories*. 2020;19(1).
7. Gajer P, Brotman RM, Bai G, Sakamoto J, Schütte UM, Zhong X, et al. Temporal Dynamics of the human vaginal microbiota. *Science Translational Medicine*. 2012;4(132).
8. Muzny CA, Taylor CM, Swords WE, Tamhane A, Chattopadhyay D, Cerca N, et al. An updated conceptual model on the pathogenesis of bacterial vaginosis. *The Journal of Infectious Diseases*. 2019;220(9):1399-405.
9. Peebles K, Velloza J, Balkus JE, McClelland RS, Barnabas RV. High global burden and costs of bacterial vaginosis: A systematic review and meta-analysis. *Sexually Transmitted Diseases*. 2019;46(5):304-11.
10. Kairys N, Garg M. Bacterial Vaginosis. [internet] Treasure Island, Florida: StatPearls; 2022. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK459216/>
11. Onderdonk AB, Delaney ML, Fichorova RN. The human microbiome during bacterial vaginosis. *Clinical Microbiology Reviews*. 2016;29(2):223-38.
12. Bradshaw CS, Sobel JD. Current treatment of bacterial vaginosis—limitations and need for Innovation. *Journal of Infectious Diseases*. 2016;214(suppl 1).
13. Gonçalves B, Ferreira C, Alves CT, Henriques M, Azeredo J, Silva S. Vulvovaginal candidiasis: Epidemiology, Microbiology and Risk Factors. *Critical Reviews in Microbiology*. 2015;42(6):905-27.
14. Jeanmonod R, Jeanmonod D. Vaginal Candidiasis. [internet] Treasure Island, Florida: StatPearls; 2022. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK459317/>
15. Davar R, Nokhostin F, Eftekhari M, Sekhvat L, Bashiri Zadeh M, Shamsi F. Comparing the recurrence of vulvovaginal candidiasis in patients undergoing prophylactic treatment with probiotic and placebo during the 6 months. *Probiotics and Antimicrobial Proteins*. 2016;8(3):130-3.
16. CDC. Vulvovaginal Candidiasis - STI treatment guidelines [Internet]. Centers for Disease Control and Prevention; 2021 [cited 2022Nov7]. Available at: <https://www.cdc.gov/std/treatment-guidelines/candidiasis.htm>

17. Sobel JD. Recurrent vulvovaginal candidiasis. *American Journal of Obstetrics and Gynecology*. 2016;214(1):15–21.
18. Han Y, Ren Q-ling. Does probiotics work for bacterial vaginosis and Vulvovaginal Candidiasis. *Current Opinion in Pharmacology*. 2021;61:83–90.
19. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. The International Scientific Association for Probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology & Hepatology*. 2014;11(8):506–14.
20. Bohbot JM, Darai E, Bretelle F, Brami G, Daniel C, Cardot JM. Efficacy and safety of vaginally administered lyophilized lactobacillus crispatus IP 174178 in the prevention of bacterial vaginosis recurrence. *Journal of Gynecology Obstetrics and Human Reproduction*. 2018;47(2):81–6.
21. Cianci A, Cicinelli E, De Leo V, Fruzzetti F, Massaro MG, Bulfoni A, et al. Observational prospective study on lactobacillus plantarum P 17630 in the prevention of vaginal infections, during and after systemic antibiotic therapy or in women with recurrent vaginal or genitourinary infections. *Journal of Obstetrics and Gynaecology*. 2018;38(5):693–6.
22. Cohen CR, Wierzbicki MR, French AL, Morris S, Newmann S, Reno H, et al. Randomized trial of lactin-V to prevent recurrence of bacterial vaginosis. *New England Journal of Medicine*. 2020;382(20):1906–15.
23. Parma M, Dindelli M, Caputo L, Redaelli A, Quaranta L, Candiani M. The role of vaginal Lactobacillus Rhamnosus (Normogin®) in preventing Bacterial Vaginosis in women with history of recurrences, undergoing surgical menopause: a prospective pilot study. *European Review for Medical and Pharmacological Sciences*. 2013;17(10):1399–403.
24. Reznichenko H, Henyk N, Maliuk V, Khyzhnyak T, Tynna Y, Filipiuk I, et al. Oral intake of lactobacilli can be helpful in symptomatic bacterial vaginosis: A randomized clinical study. *Journal of Lower Genital Tract Disease*. 2020;24(3):284–9.
25. Russo R, Karadja E, De Seta F. Evidence-based mixture containing lactobacillus strains and lactoferrin to prevent recurrent bacterial vaginosis: A double blind, placebo controlled, randomised clinical trial. *Beneficial Microbes*. 2019;10(1):19–26.
26. Palacios S, Espadaler J, Fernández-Moya JM, Prieto C, Salas N. Is it possible to prevent recurrent vulvovaginitis? the role of lactobacillus plantarum i1001 (CECT7504). *European Journal of Clinical Microbiology & Infectious Diseases*. 2016;35(10):1701–8.
27. De Seta F, Parazzini F, De Leo R, Banco R, Maso GP, De Santo D, et al. Lactobacillus plantarum p17630 for preventing candida vaginitis recurrence: A retrospective comparative study. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2014;182:136–9.
28. Murina F, Graziottin A, Vicariotto F, De Seta F. Can lactobacillus fermentum LF10 and lactobacillus acidophilus LA02 in a slow-release vaginal product be useful for prevention of recurrent vulvovaginal candidiasis? *Journal of Clinical Gastroenterology*. 2014;48(Supplement 1).
29. Russo R, Superti F, Karadja E, De Seta F. Randomised clinical trial in women with recurrent vulvovaginal candidiasis: Efficacy of probiotics and lactoferrin as maintenance treatment. *Mycoses*. 2019;62(4):328–35.
30. Vladareanu R, Miha D, Mitran M, Mehedintu C, Boiangiu A, Manolache M, et al. New evidence on oral L. plantarum P17630 product in women with hHistory of recurrent vulvovaginal candidiasis (RVVC): a randomized double-blind placebo-controlled study. *European Review for Medical and Pharmacological Sciences*. 2018;22(1):262–7.