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Application of Prebiotics and Postbiotics in Vaginal Infections

Jietong Yang

Department of Dermatology, The First Affiliated Hospital of Jinan University, Guangzhou Guangdong, 510630, China

Abstract: Vaginal health is crucial for women's overall well-being. Decades of research have established that colonization and dominance by Lactobacillus species are fundamental characteristics of a healthy vaginal microbiota. Susceptibility factors, including menstruation, pregnancy, sexual activity, antibiotic overuse, and vaginal douching, can disrupt this microbial community. Such disturbances may lead to pathogenic overgrowth, resulting in common infections like bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC). The dominance of vaginal Lactobacillus is essential for preventing these conditions. Recently, the use of prebiotic and postbiotic preparations to support the growth of vaginal lactobacilli has gained considerable interest. Although research on their vaginal application is still in its early stages, growing evidence suggests that prebiotics and postbiotics can help regulate the vaginal microbiota by promoting beneficial probiotics and inhibiting pathogens, thereby maintaining vaginal health. This review compiles published evidence on the use of prebiotics and postbiotics in managing vaginal infections, aiming to overcome the limitations of existing treatments and provide insights for clinical practice.

Keywords: Prebiotics; Postbiotics; Vaginal Infections; Bacterial Vaginosis; Vulvovaginal Candidiasis.

1. Introduction

1.1. Vaginal Infections

The vagina hosts a complex microecosystem comprising billions of microorganisms, collectively known as the vaginal microbiota, which reside on the squamous epithelium. A healthy microbiota is essential for maintaining vaginal homeostasis by coordinating immunomodulatory responses and secreting antimicrobial substances. In healthy women, lactobacilli dominate the vaginal environment, constituting over 70% of the bacterial population. More than 120 Lactobacillus species have been identified, with L. crispatus, L. gasseri, L. jensenii, and L. iners being the most prevalent in the vagina. These species play a critical role in protecting against reproductive tract infections.

Vaginal infections arise from dysbiosis, characterized by a disruption of the healthy microbial balance and overgrowth of pathogens. For instance, a shift from lactobacilli to a mixed flora dominated by Gardnerella vaginalis and anaerobes, accompanied by a vaginal pH >= 4.5, defines bacterial vaginosis (BV). Clinical manifestations of BV include a pungent, fishy-smelling discharge, and discomfort or burning during urination. Statistically, BV is the most common vaginal infection among reproductive-aged women, with a prevalence of approximately 19%–24%. Vulvovaginal candidiasis (VVC) is the second most common infection; studies indicate that 75% of women will experience at least one episode in their lifetime. A weakened immune system, elevated estrogen levels, diabetes, and prolonged antibiotic use are key risk factors for VVC. Typical symptoms include vulvar burning, irritation, swelling, and a "cottage cheese-like" discharge, usually without a strong odor.

1.2. Prebiotics

The concept of prebiotics was first introduced by Gibson and Roberfroid in 1995, who defined them as "non-digestible food ingredients that selectively stimulate the growth and/or activity of one or a limited number of bacteria in the colon, thus conferring benefits to the host." As research on gut microbiota advanced, the understanding of prebiotics evolved. In 2017, the International Scientific Association for Probiotics and Prebiotics (ISAPP) updated the definition to emphasize selective utilization and demonstrated health benefits, defining a prebiotic as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" [1].

Prebiotics are typically plant-based compounds, such as polysaccharides (e.g., inulin, fructooligosaccharides(FOS), galactooligosaccharides (GOS) or other non-sugar molecules with a low degree of polymerization (2–20 units). Based on the number of monomeric units, prebiotics can be classified as disaccharides, oligosaccharides (3–10 units), or polysaccharides, with common monomers including glucose, galactose, fructose, and/or xylose [2]. They are naturally present in foods like tomatoes, bananas, asparagus, garlic, onions, chicory, oats, flaxseed, wheat, and honey, as well as in novel sources such as seaweed and microalgae [3]. Dairy products, particularly yogurt, are also valuable sources, containing phosphates, lactose, oligosaccharides, glycomacropeptide (GMP), and lactoferrin (LF), all of which exhibit prebiotic properties [4].

Prebiotics are generally categorized into three groups: established, emerging, and candidate prebiotics. Established prebiotics, such as inulin, FOS, GOS, and lactulose, have a long history of safe use and well-documented health benefits. Notably, inulin, FOS, and GOS have been recognized as safe food components by the European Food Safety Authority (EFSA) for over two decades. Emerging prebiotics include xylooligosaccharides (XOS), isomaltooligosaccharides (IMO), arabinoxylan oligosaccharides (AXOS), transgalactooligosaccharides (TOS), soybean oligosaccharides (SBOS), raffinose, stachyose, β-glucans, and resistant starch. Candidate prebiotics encompass pectin, human milk oligosaccharides (HMOs), mannan oligosaccharides (MOS), and even non-carbohydrate substances like plant polyphenols, conjugated linoleic acid, and polyunsaturated fatty acids (PUFAs) [5-7].

1.3. Postbiotics

The concept of "biogenics," equivalent to postbiotics, was first proposed by the Japanese scholar Mitsuoka in 1998, referring to non-viable forms of lactobacilli or bifidobacteria used in foods. In the early 21st century, as research on probiotics and their metabolites deepened, scientists began exploring the health benefits of inactivated microorganisms and their components. By around 2015, the term "postbiotics" gained traction in academic literature. In 2021, ISAPP formally defined postbiotics as "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host," specifying that they must be administered on host surfaces (e.g., oral cavity, gut, skin, urogenital tract) and excluding injections [8].

Postbiotics include inactivated microbial cells, cell components (e.g., lipoteichoic acid, teichoic acid, peptidoglycan, cell membrane proteins, intracellular and extracellular polysaccharides), and microbial metabolites (e.g., vitamins, lipids, enzymes, peptides, organic acids like lactic acid, short-chain fatty acids [SCFAs], bile acids) [9]. They are primarily produced through the fermentation of live probiotics or derived from their reproductive environments (e.g., a probiotic-dominated vaginal tract), and can also be synthesized in laboratory settings.

Common preparation methods involve reviving, culturing, and fermenting probiotics to generate metabolites, followed by inactivation through heat (e.g., pasteurization, sterilization) or non-thermal methods (e.g., ultraviolet light, ionizing radiation, ultrasound, high pressure, dehydration, pH alteration). The cell-free supernatant is then obtained via centrifugation. The choice of inactivation technique is crucial, as it influences the profile of cellular metabolites and, consequently, the biological activity of the postbiotic. Heat treatment remains the most commonly used method in current research [10], with optimal temperatures and exposure times varying by strain, typically ranging from 60°C to 120°C [11].

2. Role of Prebiotics and Postbiotics in the Vagina

2.1. Role of Prebiotics in the Vagina

Prebiotics are substrates that can be selectively utilized by beneficial bacteria in the vagina. The antimicrobial effects of prebiotics in the female reproductive tract have been confirmed through laboratory tests, animal studies, and clinical trials. Research indicates that prebiotics can positively impact female vaginal health through various mechanisms. For instance, prebiotics can selectively stimulate the growth and activity of probiotics (mainly lactobacilli) in the vagina, thereby increasing the number and activity of these beneficial bacteria, enhancing lactic acid production, consequently lowering vaginal pH, creating an environment unfavorable for pathogen growth, and maintaining or restoring the microbial balance within the vagina. Prebiotics can enhance the immune response of vaginal epithelial cells, improve local immune defense capabilities, help resist pathogen invasion, and thus play an important role in preventing and treating vaginal infections and maintaining overall reproductive health.

In vitro studies have shown that prebiotics like FOS, GOS, and lactulose significantly promote the growth of vaginal lactobacilli (e.g., L. crispatus, L. gasseri), lower pH, and increase lactic acid levels, while showing no significant promotion of pathogens such as Candida albicans and Gardnerella vaginalis [12,13]. For instance, mannan oligosaccharides combined with lactobacilli synergistically inhibit C. albicans growth [14]; konjac glucomannan outperforms other polysaccharides in promoting lactobacilli and bifidobacteria [15]; and pectin not only stimulates lactobacilli proliferation but also significantly inhibits Escherichia coli and C. albicans [16].

Preclinical studies have further validated the potential of prebiotics. Isomaltooligosaccharide gel demonstrated significant preventive and therapeutic effects in a rat VVC model [14-17]; konjac glucomannan combined with L. reuteri alleviated symptoms in a BV mouse model and improved the microbial microenvironment [18]; β-glucan promoted vaginal tissue repair and modulated microbiota composition [19]; sucrose and maltose gels induced a shift toward Lactobacillus dominance in a rhesus monkey BV model [20]; and topical pectin application significantly increased vaginal lactobacilli counts in rats [21].

In clinical studies, various prebiotic formulations have shown efficacy. Vaginal gels containing inulin and FOS improved BV treatment outcomes [22]; a gynecological gel with isomaltooligosaccharide significantly increased clinical cure rates and reduced recurrence [23]; konjac glucomannan gel reduced C. albicans counts and promoted a healthy microbiota [24]; lactoferrin preparations (e.g., vaginal creams, suppositories) showed positive effects against both VVC and BV [25, 26]; and sucrose gel was superior to metronidazole gel in restoring normal microbiota, with comparable long-term efficacy [27]. Furthermore, oral inulin supplements significantly reduced the recurrence rate of recurrent VVC, suggesting potential for systemic application [28].

For example, one clinical trial evaluated the effect of an oral inulin dietary supplement (sourced from Jerusalem artichoke root) on the vaginal microbiota of patients with recurrent VVC. The results indicated that the group receiving the inulin supplement experienced a recurrence rate three times lower than that of the group receiving standard fluconazole treatment alone, highlighting the potential of inulin to improve vaginal microbial community status [29].

2.2. Role of Postbiotics in the Vagina

Postbiotics are bioactive substances and probiotic metabolites released during microbial fermentation. Due to their significant antimicrobial, antiviral, and immunomodulatory activities, they have the potential to become effective therapies for treating vaginal dysbiosis and establishing probiotic conditions, as well as activating signaling pathways directly related to establishing vaginal homeostasis. One of the main biological roles of postbiotics is related to their ability to lower pH (to 3.8-4.4) and their antimicrobial activity, which significantly inhibits the growth of most pathogenic bacteria. Furthermore, through studies on probiotic strain variation, resistance to Candida species, and hindering biofilm formation, postbiotics have demonstrated the ability to prevent and cure BV and VVC. However, there are currently few reports on the role of postbiotics in vaginal infections, and their role warrants further exploration.

It is reported that lactic acid produced by the vaginal microbiota possesses antimicrobial and immunomodulatory activities. Lactic acid is an organic acid and a major metabolite of vaginal lactobacilli, responsible for maintaining the vaginal pH environment. In the vagina of healthy women, glycogen is anaerobically glycolyzed by lactobacilli to produce lactic acid, acidifying the vaginal environment (average pH 3.5). The high content of lactic acid in the vagina enhances the integrity of the epithelial cell barrier, thereby preventing pathogen invasion [30-32]. For example, lactic acid at physiological concentrations (55 - 111 mM) and pH 4.5 can inactivate 17 different BV-associated anaerobes (BVAB) without affecting the viability of the four main vaginal lactobacilli. Treatment of vaginal epithelial cells (VK2) with lactic acid, a metabolite derived from vaginal probiotics, demonstrated the anti-inflammatory effect of lactic acid and its specific protective effect on barrier integrity [33]. One clinical trial showed that lactic acid vaginal gel as an adjunct to metronidazole had better long-term therapeutic effects in treating bacterial vaginosis [34].

Cell-free supernatants are produced by microbial fermentation and include nutrients from the growth medium not absorbed by the microorganisms and any metabolites left by microbial development, such as organic acids, diacetylenes, carbon dioxide, and bacteriocin-like substances, typically secreted by lactic acid bacteria and yeast. They possess antimicrobial, anti-biofilm, anti-inflammatory, antioxidant, anticancer, and vaginal microbial homeostasis-maintaining effects. Among them, lactic acid and acetic acid, along with other substances, are primarily responsible for the antimicrobial effect [35]. In vitro test results showed that Lactobacillus culture supernatants at low pH (3.8-4.0) could inhibit the growth and hyphal formation of C. albicans [36]. Lactobacillus-conditioned supernatants prepared from lactobacilli isolated from healthy women were demonstrated in a mouse vulvovaginal candidiasis in vivo model to effectively inhibit the proliferation of C. albicans [37].

3. Conclusion

The vaginal ecosystem is crucial for maintaining vaginal health. This functional balance helps provide a barrier against the recolonization of pathogenic organisms or the overgrowth of commensal microorganisms. Lactobacilli can stabilize the vaginal flora through their ability to adhere and compete for adhesion sites within the vagina, as well as by producing antimicrobial factors such as lactic acid, bacteriocin-like substances, and H2O2. Currently, the primary treatments for BV and VVC are antibiotics and antifungal medications. However, long-term use of antimicrobials for vaginitis can lead to the development of resistance. Numerous studies have shown that vaginally administered probiotics can help treat vulvovaginal infections, facilitating the recolonization of lactobacilli without concerns about transfer or survival at the target site. Compared to the long-term benefits of oral probiotics, vaginal administration can provide direct, rapid, and targeted colonization activity to restore the altered vaginal flora. However, uninformed and inappropriate use of probiotics may lead to adverse effects, and the efficacy of probiotics remains a controversial topic.

Compared to probiotics, the advantages of prebiotics and postbiotics mainly lie in their high safety and stability, ease of storage and production, long shelf life, well-defined chemical structures, avoidance of the potential risk of live bacteria transferring resistance genes, and reduction of antibiotic resistance. That is, as non-viable components, prebiotics and postbiotics offer a safe, stable, and effective approach to promoting and maintaining a healthy vaginal microbiota, particularly suitable for those concerned about using live bacteria. The in vitro and in vivo research results summarized in this review indicate that certain prebiotics and postbiotics can positively impact female vaginal health through mechanisms such as stimulating the growth of beneficial vaginal bacteria and inhibiting pathogens, holding potential for treating vaginal infections as alternatives to traditional methods. However, despite scientific evidence, the mechanisms of action and efficacy of different types of prebiotics and postbiotics are not fully elucidated, thus requiring more research to determine their safety, effectiveness, and prospective applications in the treatment and prevention of vaginal infections.

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