Advances in Pharmacology and Therapeutics Journal
Shahid Sadoughi University of Medical Sciences, Yazd, Iran

SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES

Review Article

Recent Treatment Advances in Bacterial Vaginosis (BV) and Vaginal Candidiasis (VC): Herbal Medicine, Antibiotics, and Probiotics

Running Title: Recent Advances in BV and VC Treatment

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ARTICLEINFO

Received: 05/30/2026

Accepted: 08/02/2026

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Abstract

The vaginal microbiota is a dynamic ecosystem that changes throughout the menstrual cycle and the life course. Disruption of the healthy vaginal environment can lead to infection and inflammation, most notably bacterial vaginosis (BV) and vaginal candidiasis (VC), two common vaginal diseases affecting women of reproductive age worldwide. BV arises from an imbalance in the vaginal flora, characterized by reduced *Lactobacillus* abundance and the overgrowth of anaerobic bacteria such as *Gardnerella* and *Mobiluncus*. BV presents with symptoms such as abnormal discharge and an unpleasant odor; more importantly, it increases the risk of complications such as pelvic inflammatory disease (PID), adverse pregnancy outcomes, and sexually transmitted infections (STIs). Various factors, including hormonal fluctuations, sexual behavior, poor hygiene, and antibiotic use, influence the stability of the vaginal flora and susceptibility to BV. VC is mainly caused by *Candida albicans*, but it is increasingly associated with non albicans species and results in inflammation of the vulva and vagina. Its hallmark symptoms include itching, burning, redness, and thick, white discharge. Although VC is treatable with antifungal agents, recurrent or untreated infections can lead to cervicitis, PID, or infertility. Risk factors such as diabetes, pregnancy, immunosuppression, and excessive antibiotic use contribute to the high recurrence rates, negatively affecting women's physical comfort and mental health. Both BV and VC are closely linked to disturbances in the vaginal microbiota. Understanding their microbial and immunological mechanisms is crucial for effective prevention and treatment. Current therapies include conventional antibiotics and antifungal agents, as well as emerging interventions such as probiotics and microbiota modulating strategies to restore balance. Herbal medicine approaches are also gaining attention for their potential to complement conventional treatments through herbal formulations and external applications. By integrating modern medical and traditional perspectives, researchers aim to develop more personalized and microbiome targeted treatments, thereby improving women's reproductive and overall health.

Keywords: Bacterial Vaginosis, Vaginal Candidiasis, *Lactobacilli* Spp, *Candida albicans*, Herbal Medicine, Probiotics.

Citation: Norouzi M, Kardan R, Malekmohammad S, Hemmati J. Recent Treatment Advances in Bacterial Vaginosis (BV) and Vaginal Candidiasis (VC): Herbal Medicine, Antibiotics, and Probiotics. Adv Pharmacol Ther J. 2026;6(1): 14-23.

Introduction

Vaginosis, encompassing a broad spectrum of vaginal infections and inflammatory disorders, represents one of the most prevalent clinical challenges among women of reproductive age (1). These conditions range from bacterial vaginosis (BV), vaginal candidiasis (VC), and trichomoniasis (a sexually transmitted infection, STI) to non-infectious disturbances such as atrophic vaginitis secondary to estrogen deficiency (2). In addition to causing bothersome symptoms such as abnormal discharge, itching, burning, and malodor, the high prevalence of these infections can lead to more severe sequelae (3).

BV is characterized by an imbalance in the normal vaginal microbiota, with a reduction in vaginal microbiota and an overgrowth of pathogenic bacteria (4). BV has been associated with an increased risk of pelvic inflammatory disease (PID), infertility, ectopic pregnancy, and heightened susceptibility to HIV infection (5). Furthermore, BV is a well-established risk factor for preterm birth, premature rupture of membranes, adverse pregnancy outcomes, and postpartum infections (6). BV is the most common reproductive tract infectious disease among women of reproductive age. It is characterized by an increase in anaerobic bacteria and a decrease in *Lactobacillus* spp., a condition known as vaginal dysbiosis. It is estimated that approximately $5 billion is spent annually on its treatment, and 20% to 30% of women worldwide are affected by BV (7, 8). BV is a treatable disease with a high cure rate and many effective treatment methods. Commonly used clinical treatments, including herbal medicine, antibiotics, and probiotics, are mainly aimed at anti-inflammatory and antibacterial effects and restoration of the vaginal environment (9).

VC, typically caused by Candida albicans, is the second most frequent cause of vaginitis and presents with symptoms such as intense itching, burning, and thick, cottage-cheese-like discharge. VC is a common inflammatory disease of the vulva and vagina in women, caused by Candida spp. in the absence of other sources of infection (10).

Although VC rarely leads to serious long-term consequences, pelvic inflammatory disease (PID), which can result in ectopic pregnancy, infertility, and chronic pelvic pain, is primarily caused by sexually transmitted organisms such as Chlamydia trachomatis and Neisseria gonorrhoeae, as well as bacterial vaginosis-associated pathogens (11).

Therefore, early treatment of VC is very important. In general, VC treatment mainly involves antifungal agents such as topical azoles or oral fluconazole (10). However, conventional antifungal drugs have limitations, including inconvenient administration, incomplete antifungal effects, and poor local efficacy (12). Accordingly, many scholars have developed new drugs, new materials, and new dosage forms for VC treatment, such as vaginal suppositories, gels, and vaginal membranes loaded with antifungal agents and probiotics. The development of these new methods has improved the clinical efficacy of VC treatment (12).

Given the widespread nature of these disorders and their significant impact on women's health, accurate diagnosis and effective management of vaginosis are of paramount importance (2). In recent years, alongside standard antibiotic and antifungal therapies, there has been a growing interest in alternative and

  DOI: https://doi.org/10.18502/aptj.v6i1.22269

complementary treatment approaches, including probiotic-based interventions (13) and herbal medicine (14). This review article presents recent advances in the treatment of BV and VC, offering effective approaches for future clinical applications.

Bacterial vaginosis (BV)

➢ Herbal medicine: Herbal medicines and natural compounds offer several advantages, including multi-target and multi-component mechanisms of action, and have shown promise in the clinical management of BV (15). Emerging evidence indicates that natural molecules possess intrinsic antibacterial, antibiofilm, and immunomodulatory properties, can enhance biofilm permeability, and help restore vaginal microbial balance (15, 16). Current therapeutic modalities include dietary therapy, oral administration, and topical applications. Key herbs in these prescriptions contain antimicrobial compounds that can inhibit or eradicate BV-causing bacteria. Herbal medicine has emerged as a complementary and integrative approach in the management of gynecological disorders, including vaginitis (17). According to the guidelines for the clinical application of herbal medicines in the treatment of vaginitis, several herbal formulations are considered valuable adjuncts to modern medical therapy (18). Among anti-inflammatory and antimicrobial herbs, Sophora *flavescens* has been identified as a principal agent for treating BV due to its strong detoxifying, heat-clearing, and antipruritic effects (19). Pharmacological studies also indicate that the Honghe Wash Solution, derived from a single herb, *Crataegus pinnatifida* (hawthorn seed), can serve as a single-herb formulation for managing vaginitis. Additionally, the acidic components of C. *pinnatifida* exhibit detoxifying, antipruritic, and antiprotozoal effects, which collectively contribute to improved vaginal mucosal health and reduced recurrence of infections (20). Furthermore, matrine and sophoraflavanone G, active constituents of S. *flavescens*, possess broad-spectrum antibacterial and anti-inflammatory properties, supporting the therapeutic use of this herb in BV (21). Nevertheless, caution is warranted given the potential for local irritant reactions. Mild pruritus and hypersensitivity to hawthorn seed extracts have been reported in a small subset of patients (22). Topical herbal medicine treatments act directly on the lower reproductive tract, effectively suppressing pathogenic bacteria and promoting the dominance of *Lactobacillus* species. They improve local vaginal conditions, reduce inflammation, and help prevent antibiotic overuse, thereby addressing limitations observed in conventional medical treatments. Although numerous reports have been published on the efficacy of herbal medicine compound prescriptions and their preparations for treating BV, it is noteworthy that the multi-component nature of herbal medicine may pose unknown adverse effects on human health (23, 24). Therefore, further research is imperative to thoroughly investigate the potential adverse reactions of these herbal remedies. Overall, herbal interventions such as *S. flavescens* and C. *pinnatifida* formulations show promise as safe and effective alternatives or adjuncts to conventional therapies for BV when applied under appropriate clinical supervision.

➢ Antibiotics: According to the American College of Obstetricians and Gynecologists Practice Bulletin,

the recommended treatments for BV in non-pregnant patients include vaginal metronidazole gel, oral metronidazole, or vaginal clindamycin cream (25). The guidelines recommend administering antibiotics as the first-line treatment for BV. Topical administration of metronidazole has been shown to quickly attenuate local inflammatory responses by significantly lowering the concentrations of pro-inflammatory cytokines, chemokines, and soluble biomarkers associated with epithelial barrier damage, including Interleukin-1β (IL-1β), IL-6, IL-8, matrix metalloproteinase-9 (MMP-9), macrophage inflammatory proteins-1 and 3 (MIP-1 and MIP-3), and E-cadherin (26). Oral metronidazole has been the standard treatment for 25 years and has a cure rate of up to 85% after one month of administration. Although antibiotics such as metronidazole can achieve short-term clinical resolution of BV, with reported cure rates approaching 90%, treatment adherence may be compromised by drug-related adverse effects. Moreover, recurrent or prolonged courses of antibiotic therapy substantially increase the risk of developing antimicrobial resistance (27). Persistent exposure to these agents creates selective pressure that enables resistant bacterial strains to emerge and proliferate over time, thereby diminishing the long-term effectiveness of standard treatments. Furthermore, despite their initial effectiveness, antibiotic regimens have not prevented recurrence. BV relapse remains highly prevalent, with rates ranging from 70% to 80% within 12 months, further complicating long-term disease management (28).

In BV, antimicrobial resistance is an emerging concern that extends beyond biofilm-mediated protection. A recent large-scale genomic analysis identified 11 distinct genospecies within Gardnerella vaginalis, with six genospecies showing high-level metronidazole resistance (MIC ≥ 32 μg/mL) (29). Notably, these highly resistant genospecies remained susceptible to clinically relevant concentrations of clindamycin (29). This finding suggests that metronidazole treatment failure in some women with recurrent BV may be attributable to infection with specific resistant Gardnerella genus species rather than inadequate drug exposure or poor adherence. Conversely, clindamycin resistance has also been documented and is often mediated by plasmid-encoded genes, limiting therapeutic options for recurrent cases. According to one study, current treatment strategies for BV are associated with recurrence rates exceeding 50% over 3-6 months, with biofilm persistence and antimicrobial resistance identified as major contributing factors (30). The authors emphasize that the complex pathophysiology of BV underscores the need for individualized, multifaceted management approaches (30). Furthermore, emerging evidence from the vaginal microbiome suggests that both vaginal epithelial cells and bacteria possess enzymes that metabolize antibiotics and that transporter proteins can expel drugs, rendering them ineffective. This drug-microbiome interaction, which is well characterized in the gut but poorly understood in the vaginal microenvironment, may significantly reduce antibiotic efficacy and increase the risk of persistent and recurrent BV (31).

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➢ Probiotics: The vaginal microbiota of healthy women of reproductive age is dominated by *Lactobacillus* spp. The World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations define probiotics as "live microorganisms that, when given in adequate amounts, provide health benefits to the host." *Lactobacillus* spp. with probiotic characteristics can combat pathogenic microorganisms through different mechanisms of action. Currently, there is increasing interest in the in vitro selection of promising probiotic strains and in vivo assessment of their ability to treat and prevent vaginal microbiota imbalances. Their efficacy has recently been confirmed, and unlike antibiotic treatment, no adverse reactions have been reported. Probiotics such as *L. casei* and *L. reuteri* have shown significant effects in treating common vaginal infections in non-pregnant women, either alone or in various combinations (32). In addition, the results of one study showed that vaginal microbiota transplantation or probiotic combinations can significantly reduce the levels of tumor necrosis factor α (TNF-α) and IL-1β in vaginal tissue and restore the disturbed vaginal microbiota to normal levels, with decreased numbers of pathogenic bacteria such as *Mobiluncus*, *Gardnerella*, and *Enterococcus* and increased numbers of *Lactobacillus* spp. Another study suggests that oral or vaginal administration of strains significantly reduced pathogen counts after 10 days and maintained a healthy vaginal state for 1 month after treatment (33, 34). However, to date, there is not enough research to confirm that the therapeutic effects of probiotics are superior to those of other therapeutic agents. Therefore, more effective ways to treat BV still need to be explored.

➢ Biofilm-Mediated Recurrence in Bacterial Vaginosis: A crucial driver of BV recurrence is the formation of bacterial biofilms (35). Current evidence suggests that G. *vaginalis* functions as a keystone pathogen, initiating a polymicrobial biofilm on the vaginal epithelium (35). This biofilm acts as a physical shield, helping bacteria evade both the host immune response and systemically administered antibiotics (36). Mechanistically, this explains the high clinical failure rate of standard first-line treatments, metronidazole and clindamycin, with recurrence exceeding 50% within six months of therapy (36). In response, contemporary research has increasingly focused on therapeutic approaches that go beyond simply eradicating planktonic (free-floating) bacteria. These studies aim to actively disrupt pre-existing Gardnerella-associated biofilms (37). Emerging anti-biofilm strategies include plant extracts and essential oils, selected probiotics, biofilm-disrupting enzymes such as DNase, and biosurfactants (37,38). For example, some natural compounds and probiotics have been shown to inhibit Gardnerella biofilm formation and reduce epithelial cell adhesion (38, 39). A particularly promising approach is the use of endolysins, engineered enzymes that specifically target the cell wall of individual bacterial genera. One study evaluated BNT331-endolysin in vaginal samples from 49 women with BV (40). Ex vivo treatment with BNT331-EL reduced viable Gardnerella by ≥94% at 20-50 µg/mL over 19 hours, effectively disrupted Gardnerella biofilms, and was active against

metronidazole-resistant Gardnerella strains (40). Notably, this endolysin treatment spared L. crispatus, which was present in substantial amounts, offering a targeted approach that preserves beneficial vaginal microbiota (40).

Vaginal candidiasis

➢ Herbal medicine: Herbal medicine has shown a potential therapeutic effect on VC. Among these approaches, the application of detoxifying, insecticidal, heat-clearing, and dampness-removing herbal medicines appears to be the most effective (41). In this regard, Cnidium monnieri, Phellodendron chinense, and S. *flavescens* can significantly reduce vulvar itching and other vaginal discomforts. S. *flavescens* and C.monnieri are the most commonly used herbs in combination for the treatment of VC (42), and studies have confirmed that their extracts can inhibit the proliferation of Candida and the release of virulence factors. It has also been shown that S. *flavescens* and C. monnieri extracts can be effectively used to treat VC by downregulating inflammatory factors and altering vaginal mucosal immune indicators, ultimately protecting the vaginal mucosal barrier in mouse models of VC (42). Another study found that acupoint embedding, combined with modified Zhidai Decoction, can rapidly alleviate clinical symptoms of VC, particularly in recurrent VC (43). In addition, studies have shown that the n-butanol extract of Pulsatilla chinensis decoction can reduce the number of fungal hyphae in the vagina of mice, decrease the fungal load, reduce the levels of inflammatory mediators and pro-inflammatory factors such as IL-8 and CXC chemokine ligand 2, improve mucosal tissue damage, and repair the epithelial barrier (41, 44). These findings indicate that the effective components of herbal medicine can exert antibacterial effects and remodel the vaginal mucosal epithelial barrier by reducing immune-mediated inflammatory damage and inhibiting the release of inflammatory factors (44).

➢ Antifungal drugs: For patients with uncomplicated VC, the main drugs currently used are azole agents, including fluconazole and clotrimazole, as well as other first-line topical drugs (45). As antifungal agents, these drugs primarily inhibit fungal cell wall metabolism, thereby exerting their effects. In addition to traditional azole agents, newer antifungal drugs are continually emerging, including caspofungin, an echinocandin that inhibits fungal cell wall synthesis and has significant activity against azole-resistant Candida spp. In addition, dequalinium ammonium chloride, a local antiseptic, has been shown in numerous studies to exhibit broad antibacterial and antifungal activity and to treat vaginal infections such as VC (46). For severe or recurrent VC, oral antifungal drugs such as fluconazole are commonly used options (47). It is worth noting that ibrexafungerp has been shown to have similar efficacy in clinical cure and fungal eradication in patients with fluconazole-resistant and fluconazole-sensitive Candida albicans, and it is well tolerated (48). The results of another study indicate that flucytosine, topical boric acid, and gentian violet also have good therapeutic effects against both BV and VC (49). In recent years, novel oral antifungal drugs, including isaconazole, have shown good efficacy and safety in clinical trials and are expected to provide new treatment options. For recurrent VC,

  DOI: https://doi.org/10.18502/aptj.v6i1.22269

individualized treatment is emphasized; treatment approaches should be tailored to each patient's risk factors, onset frequency, and pathogen type. It has also been shown that long-term use of low-dose antifungal drugs can maintain remission and reduce the recurrence rate.

In the context of VC, the emergence of azole-resistant Candida species represents a growing clinical challenge. One study reported that fluconazole-resistantC. Candida is a growing and perplexing problem following years of indiscriminate drug prescription and unnecessary fluconazole exposure (50). The same study noted that although the azole class of drugs has expanded, new classes of antifungal drugs have not been forthcoming, limiting effective treatment options for patients with azole-resistantVC (50). Non-albicans Candida species, particularly C. glabrata and C. krusei, often exhibit reduced susceptibility to fluconazole, which remains the most commonly prescribed oral antifungal agent for VC. A study investigating 594 Candida isolates from the reproductive tracts of pregnant women found that 64.5% of isolates showed intermediate susceptibility or resistance to at least one antifungal agent, including fluconazole, itraconazole, voriconazole, and amphotericin B (51). Among 215C. Among glabrata isolates, 81.4% showed intermediate susceptibility or resistance to at least one antifungal, and 10% showed multidrug resistance (51). The mechanisms underlying azole resistance include overexpression of efflux pumps (e.g., CDR1, CDR2, and MDR1), target-site alterations in the ERG11 gene, and biofilm formation by Candida species themselves (50).

➢ Probiotics: By regulating vaginal microecology, probiotics effectively reduce the risk and recurrence rate of VC (52). Furthermore, they can be used as a supplement to standard antifungal methods for VC treatment (53). As the predominant species in women's vaginal flora, *Lactobacillus* spp. can produce lactic acid in a low-oxygen, acidic environment, thereby maintaining vaginal acidity. These bacteria can regulate the host immune response and inhibit the growth and reproduction of harmful bacteria,thereby protecting the vagina and helping to prevent and treat VC. It has also been shown that the metabolites of *Lactobacillus* spp., including lactate, hydrogen peroxide, butyrate, bacteriocins, and biosurfactants, contribute to antifungal activity and VC treatment (54). In addition, another study showed that lactic acid-producing bacteria could be used as probiotics to treat VC, noting that these bacteria not only have strong therapeutic effects but also reduce the adverse consequences of VC infection and lower treatment costs (55). The results of one study showed that *Lactobacillus* spp. can produce 1-acetyl-β-carboline (1-ABC), thereby inhibiting the DYRK1 family kinase Yak1, blocking the formation of Candida albicans biofilm and its yeast-to-filament transformation (56).

Conclusion

As a polymicrobial condition, BV is characterized by substantial microbial diversity, underscoring the urgent need for improved diagnostic methods, more effective treatments, and further investigation into antibiotic resistance. Conversely, VC is a common gynecological infection that presents with symptoms such as increased vaginal discharge and itching,

severely affecting daily life and psychological well-being. Conventional treatments relying on antibacterial and antifungal medications, while effective, may disrupt the vaginal microecosystem with prolonged use, leading to recurrence. Future research should therefore focus on restoring microbial balance. Research into novel therapeutic approaches, including herbal medicine and probiotics, is progressing, and optimizing integration with conventional treatment plans, alongside exploring the pathogenesis mechanisms, defines future research directions.

Declarations

Acknowledgments: We hereby thank the Clinical Research Development Unit of medical school for their kind cooperation.

Conflict of Interest: There isn't competing interests concerning authorship and/or publication of this article.

Funding: No funding was received for this work.

Ethical considerations: No human participants, animals, or identifiable personal data were involved in this work; therefore, ethical approval was not required.

Authors' contribution: JH, and MN designed the research; SM, RK, MN conducted the library search and wrote the manuscript; and MN, RK, and JH participated in editing the manuscript. All authors read and approved the final manuscript.

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  DOI: https://doi.org/10.18502/aptj.v6i1.22269