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THE THERAPEUTIC EFFECT OF AZOLE AND PROBIOTIC COMBINATION ON VULVOVAGINAL CANDIDIASIS: A LITERATURE REVIEW

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ABSTRACT

One of the most prevalent vaginal infections in the world is vulvovaginal candidiasis. Due to numerous reported cases of antifungal resistance, a combination treatment with synergistic effect is needed. We aimed to examine the effects of combination therapy involving the administration of azoles and probiotics for treating vulvovaginal candidiasis. A comprehensive search of databases (Google Scholar, PubMed, Wiley, Taylor and Francis, ScienceDirect, and SAGE) using ("Candida" OR "candidiasis") AND ("azole") AND ("probiotic" OR "Lactobacillus") AND ("combination therapy" OR "adjunct treatment") as keywords was performed. Titles and abstracts were reviewed for relevance, followed by full-text screening, without any time limitation (until June 20th, 2025). The inclusion criteria was study published in English about women with vulvovaginal candidiasis receiving azole and probiotic combination as medical treatment. A total of 10 included studies were clinical trials [RCT (n=7) and quasi-experimental (n=3)]. All studies were published between 2015 and 2024. The most commonly used azoles are fluconazole (n=5), clotrimazole (n=4), miconazole (n=1), and the dominant probiotics are Lactobacillus rhamnosus (n=5) and Lactobacillus acidophilus (n=6). Included studies used different azole drugs; most studies used fluconazole orally, either a single dose of 500 mg or 50 mg once daily. Each study combined these azole drugs with probiotics containing several strains via either peroral or pervaginal. The combination of azoles and probiotics can enhance the antifungal effects against candidiasis. Probiotics not only enhance the therapeutic efficacy of vulvovaginal candidiasis treatment but also contribute to reducing the risk of azole resistance.

Keywords: azole; candidiasis; probiotic; vulvovaginal

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INTRODUCTION

One prevalent and pervasive vaginal infectious illness is vulvovaginal candidiasis (VVC). VVC typically manifests clinically as vulvar erythema, oedema, ulcers, fissures, and a white, cheese-like discharge. 85% to 90% of VVC cases are caused by the opportunistic fungus infection Candida albicans (C. albicans). Numerous risk factors, including uncontrolled diabetes, recurrent or prolonged antibiotic exposure, and bad lifestyle choices, contribute to the incidence of VVC.(Zeng et al., 2023) Clinical examination and diagnostic procedures, such as vaginal wet prep, pH testing, and cultures to rule out other causes of vaginal discharge and infection (such as bacterial vaginosis and gonococcal and chlamydial illness), are the main methods used to diagnose the disorder.(Jeanmonod R et al., 2025) When Candida spp. create an inflammatory reaction after superficially penetrating the vaginal mucosa, the result is Candidal vulvovaginitis. The predominant

inflammatory cells are usually macrophages and polymorphonuclear cells. Vaginal discomfort, excoriations, dysuria, itching, burning, dyspareunia, or swelling are all symptoms of the inflammatory reaction (Yano et al., 2019).

The majority of VVC patients are treated primarily with azole antifungals. Azoles prevent the production of the fungal-specific membrane sterol ergosterol by inhibiting the enzyme 14-α-sterol demethylase, which is encoded by the ERG11 gene. Azoles are categorized into triazoles (fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole) and imidazoles (clotrimazole, miconazole, ketoconazole, etc.). Fluconazole is the antifungal most often recommended for C. albicans infections.(Whaley et al., 2017) Single dosage of 150 g of fluconazole is given orally as part of therapy. After six months, VVC recurs in around 50% of patients receiving fluconazole treatment. Azole-resistant Candida spp. may become more likely to occur if oral fluconazole and/or topical clotrimazole are used for an extended period of time.(Satora et al., 2023) Numerous studies have shown that Candida spp. may become highly resistant to azole antifungals, most likely as a result of their fungistatic properties, leading to treatment failures.(Gerges et al., 2023) The type of resistance and virulence that Candida spp. display in response to conventional VVC therapy is mostly determined by the growth of the fungal biofilm. An extracellular matrix-encased microbe that adheres to a surface is called a biofilm. As a result, the pathogens are less susceptible to antimicrobial treatments. Due to differences in their pathogenicity and profiles of resistance to current antifungal drugs, studies describing innovative treatment strategies for azole-resistant Candida spp. have been conducted recently (Satora et al., 2023)

Probiotics, particularly Lactobacillus spp., can impede the proliferation of Candida spp. by generating lactic acid and competing for adhesion sites. The use of Lactobacillus spp. for treating fungal diseases is predicated on the notion that specific Lactobacillus species provide a protective effect in vivo by diminishing fungal adhesion to the vaginal mucosa, producing organic acids and beneficial metabolites, and augmenting the immune defense mechanisms of vaginal epithelial cells.(Zangl et al., 2020a) Additional proposed ways by which Lactobacillus spp. strains positively influence vaginal health involve the release of bacteriocins, which eliminate a broad spectrum of potentially harmful pathogens by permeabilizing the target cell membrane.(Wang et al., 2024). Until now, there has been no literature review that specifically discusses the role of azole with probiotics combination in vulvovaginal candidiasis. This study aims to provide a more comprehensive understanding of the current scientific evidence regarding the potential of azole and probiotic combination treatment. This study is expected to be a further reference for researchers in conducting clinical trials.

METHOD

References from Google Scholar, PubMed, Wiley, Taylor & Francis, ScienceDirect, and SAGE were used in the literature search. Keywords ("Candida" OR "candidiasis") AND ("azole") AND ("probiotic" OR "Lactobacillus") AND ("combination therapy" OR "adjunct treatment") were used to search the literature without any time limitation (until June 20th, 2025). Titles and abstracts were reviewed for relevance, followed by full-text screening. The following were the requirements for inclusion: (1) Original article; (2) Literature evaluating the role of probiotics and azoles together in treating candidiasis; (3) Preclinical and clinical research. The extracted data were as follows: (1) The name of the first author and year of publication; (2) Study design; (3) Subjects; (4) Intervention combination (azole; probiotics; duration); (5) Outcomes (disease status; microflora composition), (6) Adverse effects.

The full texts of included studies were examined, and their appropriateness for the inclusion criteria was evaluated. The search results were reviewed by five authors (UA, SAP, JH, EG, and AA). One author (MMS) mediated any disagreements amongst the authors. Through discussion, the writers addressed any diversity and distinctions that prompted a fresh perspective on the problem, the focus, the validity, and the clarity.

RESULT

A total of 10 included studies (Table 1) were clinical trials [RCT (n=7) and quasi-experimental (n=3)]. All studies were published between 2015 and 2024. The most commonly used azoles are fluconazole, followed by clotrimazole, miconazole. The dominant probiotics are *Lactobacillus rhamnosus* and *Lactobacillus acidophilus*. Included studies used different azole drugs; most studies used fluconazole orally, either a single dose of 500 mg or 50 mg once daily. The second most used drug is clotrimazole topical 2%, 500 mg single dose intravaginally, and oral 100 mg once daily. One study administered miconazole 400 mg orally once daily. Each study combined these azole drugs with probiotics containing several strains via either oral or per vaginal. Most of these studies compared 2 separate groups with azole + probiotics and azole-only with the same therapy period; some also added a probiotics regimen several days after standard therapy was administered. The most significant result was seen in a study by Guglielmo et al., which combined topical clotrimazole and 2 daily doses of a probiotic supplement containing *Saccharomyces cerevisiae* for 15 days. This study shows higher clinical and microbiological cure in the azole + probiotics group compared to the azole-only group; a similar result was seen in symptomatic recurrences. On the contrary, a study by Molllazadeh-Narestan et al. (2023)(Mollazadeh-Narestan et al., 2023) shows that a single dose of 150 mg oral fluconazole plus a probiotics capsule containing *L. acidophilus* for 60 days gives lower symptom resolution and lower negative culture frequency than the fluconazole-only group.(Mollazadeh-Narestan et al., 2023)

Table 1.
Characteristic of included studies

Author (Year)	Study Design	Subjects	Intervention Combination			Outcomes		Adverse Effects
			Azole	Probiotics	Duration	Disease Status	Microflora Composition	
Zeng et al. (2023)(Zeng et al., 2023)	Quasi-experimental	Women with a normal vaginal flora (n=27) and uncomplicated vulvovaginal candidiasis (n=15)	Single dose of 500 mg clotrimazole tablets intravaginally	*Lacidophilin* Vaginal Capsules (n=2)	7 days	Eventually, 72.73% (8/11) of patients were healed, followed by 46.67% (7/15) at the second visit and 61.54% (8/13) at the third.	The control group's bacterial composition was incredibly diverse and dominated by *Lactobacillus*, particularly *L. crispatus*. *L. iners*, *L. jensenii*, and *Gardneralla*. VVC group showed a low bacterial makeup, predominated with *L. iners*.	N/A
Stabile et al. (2021)(Stabile et al., 2021)	Quasi-experimental	Women (n=40) with uncomplicated VVC; 18-55 years old; not menopausal	Topical clotrimazole 2%	Unilen® Microbio+ supplement (*L. acidophilus* GLA-14, melatonin, and *S. cerevisiae* live strains)	For six days, apply 2% clotrimazole topically (before bed). For 15 days, Unilen® Microbio in a night and day formula: In the morning, take one *S. cerevisiae* tablet. - One melatonin and GLA-14 tablet in the evening.	Compared to 8 women (40%) in the clotrimazole-alone group, only 4 women (20%) in the Unilen® Microbio+ group experienced symptomatic recurrences during the 3-month follow-up period.	Compared to 16 women (80%) in the group treated with topical clotrimazole alone, 18 women (90%), in the Unilen® Microbio+ group, showed clinical and microbiological improvement at 15 and 30 days.	N/A
Russo et al. (2019)(Rus	Randomised controlled	Women (n=48); premenopausal	Clotrimazole (100 mg	Respecta® [*Lactobacilli*	Participants were	The clinical overall cure rate during the	The investigational drug reduced the	N/A

Author (Year)	Study Design	Subjects	Intervention Combination			Outcomes		Adverse Effects
			Azole	Probiotics	Duration	Disease Status	Microflora Composition	
so et al., 2019)	trial	adult women (ages 18–50); positive cultures for Candida spp.; anamnestic history of recurrences documented	once a day; 7 days)	mixture (5 × 109 CFU per capsule) including *L. acidophilus* GLA-14 and *L. rhamnosus* HN001 in combination with bovine lactoferrin RCX™ (50 mg)]	randomly randomized to receive either Verum (Respecta ®) or a placebo during the study's induction phase. During the premenstrual phase, participants took one capsule of Respecta ® or a placebo every day for ten days in a row.	maintenance phase was higher with the investigational medicine, indicating the absence of any symptoms (e.g., vaginal discharge or itching). from swabs, demonstrating a significant difference between the two study groups at T4 and T5. At the end of follow-up (T5; **P < 0.01 Respecta® vs. placebo), the intervention group's overall cure rate was 70.8% vs. 0%, and at T4, it was 66.7% vs. 8.3%.	number of the culture-identified yeasts during the maintenance phase.	
Kovachev et al. (2015)(Kovachev & Vatcheva-Dobrevska, 2015)	Randomized controlled trial	Women with vulvovaginal candidiasis (n=436)	Single dose of 150 mg fluconazole oral + Single dose of 600 mg fenticonazole vaginal globule	*Lactobacillus acidophilus, L. rhamnosus, Streptococcus thermophilus*, and *L. delbrueckii subs. bulgaricus* are present in this vaginal probiotic.	Single dose fluconazole + fenticonazole were given on the first days, followed by 10 doses of vaginal probiotic agent started on fifth day	Clinical symptoms include itching, vaginal and vulva erythema, dyspareunia, and dysuria considerably decreased by 29% on days 35–40 (p=0.005).	Slides with *lactobacillus*-dominated vaginal microbiota rose from 35.3% to 91.79% in the azole therapy group alone, and more than 30% of patients had *C. albicans* resistance. In contrast, the azole + probiotic group showed a decrease in *C. albicans* from 99.5% to 4.8% and an increase in *Lactobacilli* from 23.9% to 98.7%.	N/A
Pendharkar et al. (2015)(Pendharkar et al., 2015)	Randomized controlled trial	Women with recurrent vulvovaginal candidiasis (n=19)	Fluconazole (daily; 50 mg)	EcoVag capsules per vaginal (contain *L. rhamnosus* and *L.gasseri*)	Fluconazole 50 mg daily for 28 days and EcoVag® vaginal capsules for 10 days between days 18 and 28	By the 6-month follow-up, all nine of the women in group 2 who were receiving EcoVag® and fluconazole for a Candida infection had recovered. Eight of the women in this group were still cured (89% cure rate) when they returned to the clinic for a second follow-up 12–18 months following the first therapy.	While non-EcoVag® *Lactobacillus* strains dominated the *Lactobacillus* microbiota, EcoVag® strains were recovered from eight out of nine (89%) of the women in the *Candida*-infected patients at some point during the research. Other *Lactobacillus* species that were isolated included *L. gasseri, L. crispatus, L. iners, L. jensenii, L. vaginalis, L. reuteri, paracasei, L. plantarum, L. rhamnosus, L. fermentum, L. acidophilus,* and *L. salivarius.*	N/A
Theko et al. (2024)(Thekho et al.,	Randomised Controlled Trial (non-blinded)	Individuals (n=60) between the ages of 18 and 50 who had	Fluconazole (Per oral; 150 mg; single-dose)	Oral probiotic capsules with 1 billion	Take two pills a day for two weeks,	Clinical symptoms and indications did not differ statistically	The mycological evaluation revealed that one patient (3.3%) in group A	No side effects were observed

Author (Year)	Study Design	Subjects	Intervention Combination			Outcomes		Adverse Effects
			Azole	Probiotics	Duration	Disease Status	Microflora Composition	
2024)		recently received a diagnosis of VVC according to clinical signs, positive microscopic findings, or a positive vaginal culture for candida Group A: a single dosage of 150 mg of oral fluconazole Group B: 150 mg of oral fluconazole given as a single dosage along with oral probiotic capsules that contained 1 billion CFU of L. crispatus, 1 billion CFU of L. rhamnosus, 0.3 billion CFU of L. gasseri, and 0.2 billion CFU of L. jensenii.		CFU of *Lactobacillus crispatus*, 1 billion CFU of *L. rhamnosus*, 0.3 billion CFU of *L. gasseri*, and 0.2 billion CFU of *L. jensenii*	then one pill per week for two months.	significantly between the two groups (P > 0.05).	had Candida, while there were no cases in group B. Clinical symptoms, indicators, and mycological outcomes did not change statistically significantly between the two groups (P > 0.05).	in both groups
Vahedpoor et al. (2021)(Vahedpoor et al., 2021)	Randomized, placebo-controlled Trial (double-blind)	Women (n=40) with VVC; aged 18–48 years	Fluconazole 150 mg	*Lactobacillus acidophilus*, *L. plantarum*, and *L. rhamnosus* 1×10^9 each are among the vaginal probiotics (Lactovag) supplements. 1×10^9 colony-forming units of *L. gasseri* each day for 14 nights and oral probiotic supplements (Lactofem), such as *L. plantarum*, *L. acidophilus*, *L. gasseri* , and *L. fermentum*, 1×10^9 colony-forming units each per day for 30 days	14 nights for vaginal probiotic and 30 days for oral probiotics	Probiotic supplementation significantly reduced burning, discharge, and itching symptoms (OR 6.21, 7.38, and 13.82). pH significantly dropped in the group using probiotic supplements (P=0.021)	Although the two groups' mycological cures (negative cultures) did not differ significantly (P=0.184), the probiotic supplement group had a higher mycological cure rate (68.4%) than the placebo group	No side effects were observed in patients with VVC following probiotic supplementation.
Pane, M and Chisari, E (2024)(Pane & Chisari, 2024)	Randomized controlled trial (single-blind)	All 100 women between the ages of 19 and 61 had a clinical and microbiological culture diagnosis of VVC.	Miconazole (400mg daily before sleep)	Vaginal capsule containing *Limosilactobacillus fermentum* LF5 (I-789) (109 CFUs/dose)	3 days	Both groups experienced low and comparable recurrence rates within two weeks after treatment (10% for LF5 and 17% for miconazole). The recurrence rate	Both treatments demonstrated significant percentages of *Candida spp.* microbiological eradication on day three (LF5 = 96% and miconazole = 94%).	When compared to LF5 (4%, two instances), the frequency of local adverse events

Author (Year)	Study Design	Subjects	Intervention Combination			Outcomes		Adverse Effects
			Azole	Probiotics	Duration	Disease Status	Microflora Composition	
						of LF5 was found to be considerably reduced (p=0.372).		was three times higher with miconazole (12, six cases).
Palacios et al. (2016)(Palacios et al., 2016)	Clinical open-label, prospective study of two non-randomized parallel cohorts	55 sexually active women aged 18–50 years old with acute VVC	Clotrimazole (500 mg; single-dose; per vaginal)	*Lactobacillus plantarum I1001* (CECT7504). Each tablet contained a minimum of 1×10^8 colony forming units (CFU)	60 days	The adjusted risk of VVC recurrence was shown to be three times lower when probiotic use (L. plantarum I1001) was included. P = 0.033 and the Hazard Ratio (HR) was 0.30 (95% CI: 0.10–0.91). At three months, the probiotic group's adjusted recurrence-free survival was 72.83%, while the clotrimazole-only control group's was 34.88%. For women taking the probiotic, this indicates an increase in adjusted survival of +108.6%. Similar results were shown at 6 months in women with a history of RVVC, with probiotic usage associated with an adjusted HR for symptomatic recurrence of 0.30 (95%CI: 0.10–0.89; P = 0.03)4. In this RVVC subgroup, the probiotic group's adjusted survival was 63%, whereas the control group's was 22%.	The study primarily focuses on the clinical outcome of symptomatic recurrence While the study emphasizes the role of *Lactobacilli* in restoring vaginal microbiota and producing lactic acid, it does not explicitly report quantitative changes in vaginal pH or specific microbiological culture results beyond the primary outcome of symptomatic recurrence. It mentions that *L. plantarum I1001* has been shown to achieve adequate vaginal lactobacilli concentration and successful colonization in prior studies	Edema and erythema were the only moderate adverse effects reported by one subject.
Mollazadeh-Narestan et al. (2023)(Mollazadeh-Narestan et al., 2023)	Randomized controlled trial (triple-blinded)	80 married women between the ages of 18 and 49 who had VVC were diagnosed clinically and in a lab.	Fluconazole (150 mg; single-dose)	1×10^9 CFU/g *L.acidophilus LA-5* in probiotic capsule	30 days	In the first and second follow-ups, the fluconazole group exhibited noticeably less pruritus, vulvovaginal erythema, and abnormal discharge than the probiotic group. At 35–40 and 60–65 days, the fluconazole group experienced fewer cases of severe discharge and erythema. Burning, frequent urination, dysuria, and dyspareunia did not differ statistically significantly between the groups at either follow-up ($p > 0.05$).	Before the intervention, the probiotic group's mean vaginal pH was marginally higher than that of the fluconazole group, according to the study. However, after 30 to 35 days or 60 to 65 days following therapy, there was no discernible difference. Although the two groups experienced negative culture rates at comparable rates, fluconazole was more effective in halting VVC recurrence. At baseline, Candida albicans was the most commonly	Flatulence (n=1) and nausea (n=1) in the probiotic group Fluconazole group: gastrointestinal issues (n=1) and nausea (n=1)

Author (Year)	Study Design	Subjects	Intervention Combination			Outcomes		Adverse Effects
			Azole	Probiotics	Duration	Disease Status	Microflora Composition	
						Supplementing with Lactobacillus acidophilus was found to be similar to fluconazole in curing the majority of VVC symptoms, although it was less successful than fluconazole in avoiding recurrence. Patient Contentment: Thirty-five to forty days after beginning therapy, the fluconazole group's degree of satisfaction with treatment was considerably higher (p = 0.020).	isolated species, and it was still the most prevalent at 60–65 days.	

Several studies have shown a synergistic effect between azoles and probiotics in inhibiting the growth of *Candida*, such as the study by Zeng et al. (2023).(Zeng et al., 2023) The data indicated that using Clotrimazole Vaginal Tablets (500 mg) in combination with Lacidophilin Vaginal Capsules is an effective approach for treating uncomplicated vulvovaginal candidiasis (VVC). Over the course of treatment, the overall cure rate for simple VVC increased, reaching 72.73% (8/11), 46.67% (7/15) at the second visit, and 61.54% (8/13) at the third.(Zeng et al., 2023) Similarly, research by Guglielmo et al. showed that azole treatment alone was less successful than azole plus Unilen® Microbio+, a medication that contains melatonin, GLA-14, and Saccharomyces cerevisiae. Microscopic wet mount tests conducted at one and three months demonstrated a significant decrease in polymorphonuclear cells and an increase in lactobacillus levels in the group receiving Unilen® Microbio+.(Stabile et al., 2021)

According to a study by Pendharkar et al., the recurrence rate of Candida infections can be decreased by taking probiotics and azole together. At the 6-month follow-up, women who had both fluconazole and EcoVag® were still cured, and at the second follow-up, which was 12–18 months after the first therapy, 89% of them were still symptom-free. However, 30% of women who had fluconazole alone experienced a relapse prior to the 12-month follow-up, even though all of them were cured at 6 months.(Pendharkar et al., 2015) Another study by Theko, A. et al. found that patients who took oral probiotic capsules containing *Lactobacillus rhamnosus, L. crispatus, L. gasseri,* and *L. jensenii* along with a single 150 mg dose of oral fluconazole, a standard antifungal treatment, had a lower recurrence rate than those who took fluconazole alone.(Thekho et al., 2024) Studies from Pane and Chisari (2024)(Pane & Chisari, 2024) shows lower recurrence rate in patient receiving vaginal capsule containing Limosilactobacillus fermentum LF5 (I-789) (109 CFUs/dose). similar studies from Palacios S, et al. shows that A three-fold decrease in the adjusted risk of recurrence was linked to probiotic administration in patients with acute symptomatic VVC.(Palacios et al., 2016) Research by Vahedpoor et al. (2021)(Vahedpoor et al., 2021) showed that the group taking probiotic supplements had a marked decrease in symptoms like burning, discharge, and itching (Vahedpoor et al., 2021)

Generally indicating good tolerability for probiotic interventions, though with varying specifics and comparisons to azole antifungals. In the study by Palacios et al. (2016)(Palacios et al., 2016), only one subject in the *Lactobacillus plantarum I1001* probiotics group showed a moderate intensity side effect (edema and erythema), which slightly impacted her satisfaction.(Palacios et al., 2016) Gynaecologists in this study rated the probiotics' tolerability as "very good" or "good" in 100% of cases, and overall, patients expressed high satisfaction with its efficacy, lack of side effects, and convenience. Mollazadeh-Narestan et al. (2023)(Mollazadeh-Narestan et al., 2023) reported side effects in the *Lactobacillus acidophilus LA-5* probiotic group as nausea (one person) and flatulence

(one person). In comparison, their fluconazole group also had two individuals reporting adverse effects, specifically nausea (one person) and a stomach problem (one person). This source also points out that a review of numerous studies found probiotics to be generally well tolerated, with no statistically significant increase in the relative risk of general side effects, such as infection or gastrointestinal issues, when compared to placebo in randomized controlled trials. However, some case studies may have connected probiotic use to bacteremia.(Mollazadeh-Narestan et al., 2023).

Lastly, Pane and Chisari (2024)(Pane & Chisari, 2024) found that the probiotic *Limosilactobacillus fermentum LF5* demonstrated a significantly lower incidence of local side effects at 4% (two cases) compared to miconazole, which had a 12% incidence (six cases). These reactions in both groups were described as mild to moderate in severity, and were attributed to mild local intolerance, possibly from the probiotic's metabolic activity causing local acidification or general intolerance to the vaginal capsule application, but were minor and rapidly reversible, with no systemic adverse reactions observed. Hematological and biochemical safety testing revealed no adverse effects, and both therapies in this research demonstrated high clinical tolerability.(Pane & Chisari, 2024)

DISCUSSION

Our literature review consists of 10 studies, indicating that the combination of azoles and probiotics can enhance the antifungal effects against candidiasis, supported by the study by Zangl et al., 2019.(Zangl et al., 2020b) Lactic acid and acetic acid are among the short-chain aliphatic organic acids produced by Lactobacilli. The disruption of the plasma membrane structure of yeast cells by these lactic and acetic acids can enhance the absorption of azole into yeast cells. Probiotics and azoles together typically provide encouraging results in treating candidiasis, both directly and by boosting the mucosal immune response.(Wang et al., 2024)

Azole antifungals and probiotics have different mechanisms of action. Azole antifungals work by preventing the 14-α-demethylase enzyme from functioning. Azoles achieve this by attaching themselves to the enzyme's group, which is necessary for the transformation of lanosterol into ergosterol. Thus, azoles cause a buildup of hazardous precursors and induce ergosterol shortage in the fungal cell membrane to produce their fungistatic action. The cytochrome P450 (CYP) family includes the 14-α-demethylase (CYP51A1).(Sahadevan, 2021) By improving intestinal barrier functioning, producing neurotransmitters, immunomodulating the host's body, and competitively excluding pathogens, probiotics may have a favorable effect on the human body. Probiotics hinder pathogen survival in the gut by competing with them for resources and receptor-binding sites. Probiotics also produce bacteriocins, hydrogen peroxide, organic acids, and short-chain fatty acids (SCFA), which reduce dangerous bacteria in the gut and give them antibacterial qualities. Probiotics also affect B and T cells, dendritic cells (DC), and macrophages, which regulates the innate and adaptive immune response. Additionally, probiotics attract macrophages and mononuclear cells, interact with intestinal epithelial cells, and increase the synthesis of anti-inflammatory cytokines.(Latif et al., 2024)

Gram-positive, facultative anaerobic, catalase-negative, and non-spore-forming bacilli are known as Lactobacillus species. Lactic acid and acetic acid are two examples of the short-chain aliphatic organic acids that are produced by Lactobacilli. Since the vaginal environment is anaerobic or microaerobic while acetic acid is mostly produced under aerobic conditions, the concentration of acetic acid in the vaginal milieu is very low, ranging from 1-4 mM. On the other hand, anaerobic respiration produces lactic acid, which is thought to reduce the pH in the vaginal canal. Around 110 mM of lactic acid are present in the vaginal environment. It has been shown that lactic acid and low pH suppress C. albicans. The plasma membrane architecture of yeast cells is altered by lactic or acetic acids, which may improve the yeast cell's ability to absorb azoles.(Zangl et al., 2020a) Numerous reproductive tract infections, such as those caused by Neisseria gonorrhoeae, Candida species, and bacteria linked to bacterial vaginosis, have been shown to be inhibited by lactic acid. By directly inhibiting the pro-inflammatory mediators IL-6, IL-8, and TNFα and activating the

interleukin 23 (IL-23)/IL-17 T lymphocyte pathway, lactic acid has immunomodulatory effects.(Wang et al., 2024)

Usually, adhesion to the mucosa is thought to be the first stage of infection.(Zangl et al., 2020a) Cellular endocytosis is triggered when C. albicans attaches itself to vaginal epithelial cells and changes their morphology. Candida spp. adherence, hyphal growth, and proliferation were all reduced when L. crispatus was applied to these infected cells.(Niu et al., 2017) After preincubating Vk2/E6E7 cells with extracellular polysaccharide (EPS) produced by L. crispatus L1, the adherence of C. albicans to these cells was reduced. This decrease was similar to the cell-dependent adhesion decline seen with L. crispatus L1 that had been preincubated. The adherence of C. albicans was not reduced by co-cultivating EPS and C. albicans on Vk2/E6E7 cells, but it was decreased when C. albicans and L. crispatus were co-cultured.(Donnarumma et al., 2014) EPS and C. albicans co-cultivation on Vk2/E6E7 cells did not reduce C. albicans adhesion, but C. albicans and L. crispatus co-cultivation reduced C. albicans adhesion. EPS has the potential to be a revolutionary coating agent. The co-aggregation of Lactobacillus and Candida species is probably the cause of the cell-dependent decrease in adhesion. One characteristic of early biofilm formation is co-aggregation, which involves adhesion receptor interactions between the surfaces of microbial cells. As a result, competition for binding sites may have an impact on Candida's proper adherence to mucosal surfaces.(Jørgensen et al., 2017) The shape of C. albicans is influenced by Lactobacillus species. Development of hyphae was impeded when co-cultured with L. paracasei. The gene expression profile is altered in favor of the yeast form by the interaction between Lactobacillus and C. albicans. Less adherence and biofilm formation are frequently seen in the yeast form of C. albicans. Genes linked to adhesion, the yeast-to-hyphal transition, and biofilm formation exhibit altered expression when Lactobacillus species and Candida interact. For example, C. albicans cells treated to L. paracasei supernatant showed downregulated levels of ALS3, EFG1, and HWP1. ALS3, HWP1, and SAP (secreted aspartate proteases) are among the genes involved in the yeast-hyphae transition that are regulated by Efg1. Additionally, YWP1, a gene associated with the yeast phenotype, was produced in response to interaction with L. paracasei. Furthermore, in C. albicans co-cultured with L. reuteri RC-14 and L. rhamnosus GR-1, PHR1, a pH-responsive gene encoding a glucan remodeling enzyme that promotes hyphal growth in Candida, was downregulated. This suggests that C. albicans is impacted by Lactobacillus species, which promotes its less invasive form and could help prevent fungal overgrowth.(Zangl et al., 2020a)

Research indicates that L. crispatus-dominated vaginal microbiome (VMB) can bolster the integrity of the vaginal mucosa, hence reducing vulnerability to infectious pathogens such as HIV. Lactobacillus-based probiotics have been suggested as an alternate approach to reestablish the vaginal microbiome balance in response to vulvovaginal candidiasis. Additionally utilized as probiotics to reinstate vaginal eubiosis. The mucosal immune system plays a crucial role in defending against infections. Most antigens or pathogenic agents infiltrate the body via the mucosa, which encompasses the epithelial lining of the gastrointestinal, respiratory, and genitourinary tracts.(Dongarrà et al., 2013) Probiotics also improve normal microbiota and enhance mucosal immunity. The application of Lactobacillus spp. to epithelial cells modifies the immunological response. In vaginal epithelial cells, L. crispatus increased IL-2 synthesis and decreased IL-8 responsiveness. Another study found that when L. rhamnosus GG or L. reuteri RC-14 is used to stimulate epithelial cells without any previous interaction with Candida, the release of IL-8 is increased. There was no visible damage or apoptotic activation in the treated cells. For polymorphonuclear leukocytes (PMNs) and other granulocytes, IL-8 acts as a chemoattractant. Leukocytes that are polymorphonuclear are associated with defenses against Candida infections. They also trigger a Th1 reaction. Therefore, by enlisting PMNs to speed up the immune response during an infection, Lactobacillus species' IL-8 production may act as a defense mechanism for the host. Therefore, by enlisting PMNs to speed up the immune response during an infection, Lactobacillus species' IL-8 production may act as a defense mechanism for the host. In addition to reducing the host's inflammatory response, the simultaneous stimulation of epithelial cells with C.

albicans and Lactobacillus supernatants increased the synthesis of IL-8 (from L. reuteri RC-14) and IFNγ-induced protein 10 (IP-10) (from L. rhamnosus GR-1). Probiotics are being studied more and more as an adjuvant treatment.(Matsubara et al., 2016)

This is a narrative-based study due to its explanatory nature; our limitation is a lack of statistical analysis. It can't provide a more comprehensive quantitative picture of the effects of the azole-probiotic combination. In addition, there were variations in probiotics and azoles, making it difficult to generalize the results. The combination of azole and probiotics provides beneficial effects in the treatment of candidiasis and has the potential for future therapeutic approaches, especially in resistant cases. However, further large-scale studies, such as blinded RCTs and systematic reviews/meta-analyses, are needed to statistically confirm the effectiveness and long-term safety.

CONCLUSION

Probiotics not only enhance the therapeutic efficacy of vulvovaginal candidiasis treatment but also contribute to reducing the risk of azole resistance. Furthermore, evidence from previous studies indicates that the combination of azole antifungals and probiotics may lower recurrence rates and significantly alleviate clinical symptoms of vulvovaginal candidiasis, including burning sensation, abnormal discharge, and itching. The combination of azole and probiotics shows promising therapeutic potential in addressing candidiasis.

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