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Probiotics for oral and vulvovaginal candidiasis: A review

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Abstract

Dermatologists commonly prescribe medications such as antibiotics and corticosteroids that can increase the risk for candidiasis. Though conventional antifungals are often effective against candidiasis, they are not without side effects and species of *Candida* are gaining resistance. Probiotics help treat conditions such as post-antibiotic diarrhea and infectious diarrhea, and thus have the potential to help with *Candida* infections, as well. For this reason, we provide an overview of therapies prescribed in dermatology that may increase the risk for candidiasis, and we review the literature on whether probiotics are useful in the treatment and prevention of oral and vulvovaginal candidiasis to help dermatologists treating the condition be better informed about their supplemental use with conventional antifungals.

KEYWORDS
candidiasis, lactobacilli, probiotic

1 | INTRODUCTION

Candida species are commensal yeast of the healthy human oral cavity, gastrointestinal tract, and vagina, but they may also cause superficial infection or invasive, life-threatening disease. Many drugs commonly prescribed by dermatologists, such as antibiotics and corticosteroids, can increase the risk for candidiasis. Though oral and vulvovaginal candidiasis (VVC) can be treated with antifungals, they are not without side effects and species of *Candida* are gaining resistance to conventional therapies (Whaley et al., 2016). It is thus of interest to discuss whether alternative therapies such as probiotics may provide benefit in the management and prevention of *Candida* infections.

According to the International Scientific Association for Probiotics and Prebiotics (ISAPP), probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" (Hill et al., 2014). Examples include *Bifidobacterium adolescentis*, *animalis*, *bifidum*, *breve*, *longum* and *Lactobacillus acidophilus*, *casei*, *fermentum*, *gasseri*, *johnsonii*, *paracasei*, *plantarum*, *rhamnosus*, *salivarus* (Hill et al., 2014). These organisms provide competition for pathogenic microorganisms and prevent their colonization, thus contributing to host defense mechanisms (Hill et al., 2014).

Probiotics have demonstrated benefit in maintaining the health of the digestive tract in conditions such as infectious diarrhea, irritable bowel syndrome, and antibiotic-associated diarrhea, and are being investigated in a variety of other conditions, such as prevention of atopic dermatitis (Ritchie & Romanuk, 2012). The aim of this review is twofold; first, we discuss therapies commonly prescribed in dermatology that may increase the risk for candidiasis; second, we discuss the use of probiotics to prevent and treat oral and vulvovaginal *Candida* infection, so that dermatologists who encounter candidiasis can be better informed of the evidence regarding their supplemental use with conventional antifungals.

2 | THERAPIES THAT MAY PREDISPOSE TO CANDIDIASIS

2.1 | Antibiotics

Antibiotics can predispose to oral and VVC by removing protective bacterial flora, creating an environment that is more conducive to growth of *Candida* (Akpan & Morgan, 2002; Sobel, 2007). Spinillo et al. compared the prevalence of antibiotic use in women with symptomatic VVC and controls. After adjusting for age, marital status, and contraceptive use, they found that the likelihood of developing VVC within 1 month of antibiotic use was increased compared to controls, and that the risk was directly correlated to duration of antibiotic use

but not to the type of antibiotic (Spinillo, Capuzzo, Acciano, De Santolo, & Zara, 1999). However, not all patients taking antibiotics develop candidiasis; factors such as colonization with *Candida* prior to antibiotic use may increase risk of symptomatic VVC after antibiotic use (Pirotta & Garland, 2006).

2.2 | Glucocorticoids

Inhaled steroids, particularly fluticasone, used in therapy for asthma, can increase risk for oral candidiasis by suppressing immune response (Fukushima et al., 2003; Rhen & Cidlowski, 2005). Similarly, systemic glucocorticoids can predispose to VVC (Goncalves et al., 2016; Sobel, 2007); Gonçalves et al. propose that this is not only because of their immunosuppressive effect, but also because of their ability to induce hyperglycemia, which contributes to increased VVC in uncontrolled diabetics (Goncalves et al., 2016).

2.3 | IL-17 blockers

Clinical trials for IL-17 blockers including secukinumab, brodalumab, and ixekizumab have reported candidiasis. These infections are not surprising, as IL-17 participates in the defense against *Candida* (Conti & Gaffen, 2015). The ERASURE/FIXTURE trials for secukinumab reported a higher rate of candidiasis in the secukinumab group compared to the etanercept group and controls (Langley et al., 2014). Similarly, the AMAGINE-2 and AMAGINE-3 trials reported a higher rate of candidiasis in brodalumab groups compared to ustekinumab and control groups, (Lebwohl et al., 2015), and the UNCOVER-2 and UNCOVER-3 trials reported that *Candida* infections were more frequent in patients receiving ixekizumab compared to etanercept and controls (Griffiths et al., 2015).

2.4 | Combined oral contraceptives

Certain oral contraceptives are used to treat acne. Combined oral contraceptives have been associated with increased risk of VVC (Jacob, John, Kalder, & Kostev, 2018) and reproductive tract infections (Egbe, Onwufor, Omoregie, & Enabulele, 2011). However, the evidence is conflicting; some studies have not shown an increased risk (Reed, Gorenflo, Gillespie, Pierson, & Zazove, 2000). These discrepancies can potentially be associated with estrogen content of the COCs. Estrogen can increase glycogen content of the vaginal epithelium, providing nutrition for *Candida* species (Dennerstein & Ellis, 2001), and can stimulate the formation of germ tubes in the transition from yeast to hyphae (Cheng, Yeater, & Hoyer, 2006).

2.5 | Medications that decrease salivary secretions

Medications prescribed in dermatology that may decrease salivary secretions include antihistamines and isotretinoin (Guggenheimer & Moore, 2003). These can increase the risk for oral candidiasis because saliva contains antimicrobials that prevent overgrowth of *Candida* (Akpan & Morgan, 2002).

3 | MECHANISMS OF PROBIOTICS AGAINST *CANDIDA*

In vitro studies of probiotics have demonstrated that they reduce the virulence of *Candida* by inhibiting biofilm formation and may provide additional benefit to antifungals. *L. rhamnosus*, *L. casei*, and *L. acidophilus* significantly reduced levels of *Candida albicans* biofilms at the initial colonization phase and the later maturation phase of biofilm development (Matsubara, Wang, Bandara, Mayer, & Samaranayake, 2016). Between these lactobacilli, there were differences in the density of probiotic necessary to elicit these inhibitory effects, indicating that the action of probiotics on *Candida* is strain-specific (Matsubara et al., 2016). The lactobacilli may be able to inhibit *Candida* growth by competing for nutrients and producing lactic acid and other organic acids that lower the pH. This creates an unsuitable environment, and can lead to upregulation of stress-related genes in *Candida* (Kohler, Assefa, & Reid, 2012). Probiotics have also been shown to downregulate genes involved in synthesis of ergosterol, as well as genes associated with a drug efflux pump involved with fluconazole resistance (Kohler et al., 2012). They thus may improve therapy with conventional antifungals. However, additional in vitro studies that include more strains of probiotics and species of *Candida* are necessary to fully characterize their mechanisms. Furthermore, the therapeutic potential demonstrated by these in vitro studies may not translate to substantive benefit in vivo.

4 | PROBIOTICS AND VVC

The studies of probiotics and VVC (Table 1) have conflicting results, possibly because of differences in probiotic strain, delivery mechanism, and treatment schedules investigated. The benefit of probiotics for VVC depends on whether patients have acute infection, recurrent infection, or are at increased risk for infection.

4.1 | Patients with acute VVC

Multiple studies have demonstrated that probiotics may be beneficial to patients with acute VVC treated with standard antifungals by improving vaginal symptoms. Kovachev et al. compared women with acute VVC receiving only antifungal therapy to women with acute VVC receiving antifungal therapy and vaginal probiotic containing *L. acidophilus*, *L. rhamnosus*, *Streptococcus thermophilus*, and *Lactobacillus delbrueckii* subsp. *bulgaricus* and found that the probiotic group had greater improvement in clinical complaints (Kovachev & Vatcheva-Dobrevska, 2015). Similarly, Carriero et al. found the proportion of asymptomatic patients to be significantly higher in a group receiving *L. plantarum* after fluconazole therapy compared to fluconazole alone, both at 4 weeks and 4 months after antifungal administration (Carriero et al., 2007). De Seta et al. reported a significant increase in resolution of symptoms including vaginal burning and itching in women with acute VVC using *L. plantarum* after antifungal therapy compared to women using antifungal therapy alone (De Seta et al.,

TABLE 1 Studies of probiotics in vulvovaginal candidiasis. The "patients" column shows the number of patients completing the study as well as the characteristics of the patients included

Reference	Probiotic	Patients	Duration of therapy	Study design	Results	Conclusions
Kovachev & Vatcheva-Dobrevska, 2015	*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*	416, acute VVC	10 days	Participants were randomly assigned to antifungal therapy (fluconazole and fenticonazole), or antifungal therapy and vaginal probiotic starting 5 days after, administered 10 times.	Clinical complaints and microbiological evidence of *Candida albicans* improved with administration of probiotics.	Administration of vaginal probiotics can increase effectiveness of antifungal therapy for vulvovaginal candidiasis.
Carriero, Lezzi, Mancini, & Selvaggi, 2007	*Lactobacillus plantarum*	476, acute VVC	3 months	Participants were first treated with fluconazole. They then either had no additional therapy (controls), or used a vaginal probiotic capsule daily for 6 consecutive days at the end of menstruation for 3 months.	The proportion of asymptomatic patients at 4 weeks and at 4 months was significantly higher in the probiotic group compared to controls. At 4 months, the odds of relapse of vulvovaginal candidiasis in the probiotic group were significantly lower than in the control group.	Including probiotic therapy with fluconazole can help with treatment and prevention of short-term recurrence of vulvovaginal candidiasis.
De Seta et al., 2014	*Lactobacillus plantarum*	80, acute VVC	~5 weeks	The control group used daily clotrimazole vaginal cream for 3 days and then used a vaginal lubricant once a day for 6 days, then once a week for 4 weeks. A second group of women used clotrimazole, and then vaginal probiotic instead of lubricant in the same schedule.	Women with probiotics had increased presence of *Lactobacillus* and greater resolution of subjective burning and itching compared to controls. The proportion of women with vaginal pH ≥5 was significantly higher in the control group compared to probiotic group.	Vaginal probiotics can help restore a healthy vaginal environment that may help prevent VVC and alleviate acute symptoms.
Martinez et al., 2009	*Lactobacillus rhamnosus* GR-1, *Lactobacillus reuteri* RC-14	55, acute VVC	4 weeks	All participants were treated for VVC with a single dose of fluconazole. Then participants randomly assigned to either 2 probiotic or 2 placebo	After 4 weeks, the probiotic group had significantly less vaginal discharge, vaginal itching, burning, dyspareunia and/or dysuria. The probiotic group also had less yeast	Probiotics can increase the effectiveness of conventional antifungals in acute VVC.

(Continues)

TABLE 1 (Continued)

Reference	Probiotic	Patients	Duration of therapy	Study design	Results	Conclusions
				capsules daily for 4 weeks.	growth on culture. There was no significant difference in remission of symptoms between probiotic and control groups in patients with recurrent VVC.	
Palacios, Espadaler, Fernandez-Moya, Prieto, & Salas, 2016	*Lactobacillus plantarum*	55, acute VVC	2 months	One cohort received initial clotrimazole therapy, and then vaginal probiotic 3 times per week for 2 months. The other cohort received only clotrimazole. Non-randomized study.	There was a significant increase in vaginal candidiasis recurrence-free survival at 3 months with probiotic use compared to placebo. There was a significant reduction in the number of VVC episodes in the probiotic group but not in placebo group.	Probiotic therapy after clotrimazole for VVC significantly reduces the risk of symptomatic recurrence over 3 months.
Davar et al., 2016	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*	59, acute VVC	10 days	All were initially treated with fluconazole. Then, participants were randomly assigned to either oral probiotic or placebo twice daily for 10 days.	At 6 months, there was a significant difference in the recurrence rate of vulvovaginal candidiasis in the probiotic versus control group.	Probiotics with antifungal therapy can help prevent recurrence of vulvovaginal candidiasis.
Anukam et al., 2009	*Lactobacillus rhamnosus* GR-1, *Lactobacillus reuteri* RC-14	26, Nigerian, acute VVC in patients with recurrent VVC	3 months	After single dose of oral fluconazole, participants randomly assigned to either daily placebo or daily probiotic for 3 months.	Fewer patients receiving probiotic developed VVC after 90 days compared to placebo, but the difference was not significant.	There is evidence that probiotics can help reduce recurrence of vulvovaginal candidiasis.
Witt et al., 2009	*Lactobacillus gasseri*	150, acute VVC in patients with recurrent VVC	6 months	Participants randomly assigned to either classic homeopathy or an induction treatment with itraconazole, twice weekly for 4 weeks. Maintenance regimen for 6 months was either itraconazole once a month or itraconazole	Women in the itraconazole only and in the itraconazole with probiotic group were free of *Candida* in vaginal culture significantly earlier than in the classic homeopathy group. Patients in the	Vaginal lactobacilli did not provide additional benefit to itraconazole therapy in eradication of *Candida* in patients with recurrent vulvovaginal candidiasis.

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TABLE 1 (Continued)

Reference	Probiotic	Patients	Duration of therapy	Study design	Results	Conclusions
				with vaginal probiotic once a month.	homeopathy group had more subjective complaints. Addition of the probiotic had no significant effect on eradication of *Candida* compared to itraconazole alone.	
Pendharkar, Brandsborg, Hammarstrom, Marcotte, & Larsson, 2015	*Lactobacillus rhamnosus*, *Lactobacillus gasseri*	38, with bacterial vaginosis or acute VVC in patients with recurrent VVC	2 periods of 10 days, then weekly for 4 months	Participants received 28 days of fluconazole and 10 days of EcoVag®. Then after first menstruation, used EcoVag® for 10 days and fluconazole weekly for 2 months. Then for 3 months, given fluconazole once every 2 weeks. Finally, after second menstruation, EcoVag® was given weekly for 4 months. Another group of participants received only fluconazole at the same schedule.	The 12-month cure rate, but not the 6-month cure rate, was higher in women receiving fluconazole and EcoVag® compared to fluconazole alone, but the difference was not significant.	The probiotics used can slightly improve the ability of fluconazole to prevent recurrent vulvovaginal candidiasis.
Hilton, Isenberg, Alperstein, France, & Borenstein, 1992	*Lactobacillus acidophilus*	13, recurrent VVC	6 months	Participants randomly assigned to either consume 8 oz of yogurt daily for 6 months, and then refrain from yogurt consumption for 6 months, or vice versa. At 8 months, protocol changed so all participants start without yogurt consumption.	A decrease in vaginal candidiasis and *Candida* colonization over 6 months was seen when patients consumed yogurt containing probiotics compared to no yogurt consumption.	Daily ingestion of yogurt with *Lactobacillus acidophilus* can decrease vaginal *Candida* colonization and infection in women with recurrent vulvovaginal candidiasis.

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TABLE 1 (Continued)

Reference	Probiotic	Patients	Duration of therapy	Study design	Results	Conclusions
Shalev, Battino, Weiner, Colodner, & Keness, 1996	*Lactobacillus acidophilus*	28 (completed 4 months), 7 (completed 6 months), recurrent VVC or bacterial vaginosis	2 months	Participants randomly assigned to either 150 mL yogurt with probiotic daily for 2 months, then refrain from yogurt consumption for 2 months, then 150 mL of pasteurized yogurt daily for 2 months, or in reverse order (pasteurized yogurt, no consumption, yogurt with probiotic).	At 1 month and 2 months, there was no significant difference in positive *Candida* cultures between the two groups. At 6 months, there was no difference between the two groups in candidal vaginitis or colonization.	Compared to pasteurized yogurt, consumption of yogurt with probiotic did not provide added benefit in reducing *Candida* colonization or infection in patients with recurrent vulvovaginal candidiasis.
Vicariotto, Del Piano, Mogna, & Mogna, 2012	*Lactobacillus fermentum* LF10, *Lactobacillus fermentum* LF11, and *Lactobacillus acidophilus* LA02 + arabinogalactan and fructooligosaccharides	30, acute VVC in patients with recurrent VVC	2 months	Participants vaginally administered probiotics once a day for 7 days, then once every 3 days for 3 weeks, and then once per week for 4 weeks. No control/placebo group. in vitro activity against Candida was also assessed.	In vitro, all the probiotic strains inhibited *Candida*. In vivo, there was an 11.5% recurrence rate at 2 months.	Probiotics can be effective in therapy and prevention of vulvovaginal Candida infection.
Murina, Graziottin, Vicariotto, & De Seta, 2014	*Lactobacillus fermentum* LF10, *Lactobacillus acidophilus* LA02 + arabinogalactan and fructooligosaccharides	58, acute VVC in patients with recurrent VVC	~11 weeks	All participants treated with fluconazole initially. Then participants were given vaginal probiotic for 5 days, then weekly for 10 weeks. No placebo group.	Overall, 72.4% of participants did not have symptomatic recurrence of VVC at 7 months.	Probiotics may help decrease recurrence of VVC.
Pirotta et al., 2004	*Lactobacillus rhamnosus and Bifidobacterium longum* or *Lactobacillus rhamnosus, Lactobacillus delbrueckii, Lactobacillus acidophilus, and Streptococcus thermophilus*	235, after oral antibiotics for non-gynecologic infection	10 days	Participants randomly assigned to receive either oral and vaginal probiotic, oral probiotic and vaginal placebo, oral placebo and vaginal probiotic, or oral and vaginal placebo.	The risk of developing vulvovaginitis while taking oral or vaginal probiotic was not significantly reduced.	Oral and vaginal administration of *Lactobacillus* was not effective in preventing post-antibiotic vulvovaginal candidiasis.

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TABLE 1 (Continued)

Reference	Probiotic	Patients	Duration of therapy	Study design	Results	Conclusions
Hu et al., 2013	*Bifidobacterium*, *Lactobacillus*	24, including some with HIV	Two periods of 15 days	There was an initial period of 60 days without probiotic consumption. Then one 3.1 oz yogurt of DanActive™ was consumed daily for 15 days. After 30 days without yogurt consumption, one 4 oz yogurt of YoPlus™ was consumed daily for 15 days.	Compared to periods without yogurt consumption, there was significantly less vaginal fungal colonization when consuming DanActive™ but not when consuming YoPlus™.	Though these results show possible benefits of probiotics, the sample size is too small to draw generalizable conclusions.
Williams, Yu, Tashima, Burgess, & Danvers, 2001	*Lactobacillus acidophilus*	164, HIV+	21 months	Participants randomly assigned to receive either vaginal clotrimazole, probiotic, or placebo weekly.	The time to onset of first episode of vaginal candidiasis was longer in the clotrimazole group and probiotic group compared to placebo, but was only significant in the clotrimazole group. The relative risk of experiencing an episode of vaginal candidiasis was significantly reduced in the clotrimazole group but not the probiotic group compared to placebo.	Clotrimazole was slightly more effective than *Lactobacillus* in preventing vaginal candidiasis in HIV-infected women, but both prophylactic therapies may be effective.

2014), and Martinez et al. reported that women with acute VVC using a probiotic containing *L. rhamnosus* and *Lactobacillus reuteri* after antifungal therapy had significantly less vaginal discharge compared to women receiving antifungals alone (Martinez et al., 2009).

Other studies have demonstrated that probiotics can benefit patients with acute VVC treated with standard antifungals by decreasing recurrence of infection. Palacios et al. found that there was a statistically significant, threefold reduced risk of recurrence of VVC three months after single-dose clotrimazole therapy in women receiving vaginal *L. plantarum* compared to clotrimazole alone (Palacios et al., 2016). Other studies have similarly shown a decreased recurrence rate in patients receiving probiotics after single-dose fluconazole therapy compared to fluconazole alone; this effect was demonstrated at 4 months with *L. plantarum* (Carriero et al., 2007), as well as at 6 months with a combination of *L. acidophilus*, *B. bifidum* and *B. longum* (Davar et al., 2016).

These studies have promising results and together demonstrate that multiple strains and combinations of probiotics can provide additional benefit to antifungals in the treatment and prevention of acute VVC. However, it is difficult to draw generalizable conclusions from them due to small sample sizes and the limited quantity of studies on each probiotic.

4.2 | Patients with recurrent VVC

Recurrent VVC is defined as at least four episodes of acute VVC within the prior 12 months. Overall, studies show that patients with recurrent VVC may not benefit from probiotic therapy. Two studies examined whether probiotic therapy after a single dose of fluconazole decreased recurrence of infection. Although Anukam et al.'s study of Nigerian women with recurrent VVC taking *L. rhamnosus* and *L. reuteri* showed that a greater percentage of women in the probiotic group were free of *Candida* at 90 days compared to placebo, the difference was not statistically significant (Anukam et al., 2009). Similarly, Martinez et al. found therapy with *L. rhamnosus* and *L. reuteri* in women with recurrent VVC provided no significant difference in remission of symptoms compared to placebo after 4 weeks (Martinez et al., 2009).

Furthermore, studies examining whether probiotics provide additional benefit to maintenance antifungal therapy in preventing recurrent VVC have not shown promising results. Witt et al. found that adding *L. gasseri* to maintenance itraconazole therapy provided no additional benefit in achieving a culture-negative status within 12 months compared to itraconazole alone (Witt et al., 2009). Similarly, Pendharkar et al. found that adding a vaginal probiotic containing *L. rhamnosus* and *L. gasseri* to maintenance fluconazole therapy did not significantly affect the 6-month or 12-month cure rate of patients with recurrent VVC (Pendharkar et al., 2015).

Studies demonstrating favorable outcomes from probiotic therapy in patients with recurrent VVC using probiotics are limited. Though one study of women consuming yogurt with *L. acidophilus* found decreased *Candida* colonization and fewer infections than a period without yogurt consumption (Hilton et al., 1992), a different study found no difference in colonization or infection when women consumed pasteurized yogurt compared with yogurt with *L. acidophilus* (Shalev et al., 1996). This disparity can be possibly attributed to small sample sizes, different duration of probiotic yogurt consumption, and varying ability of the oral probiotic to colonize the vagina. Interestingly, two studies that combined probiotics with the prebiotics arabinogalactan and fructooligosaccharides, which are meant to enhance colonization of probiotics, found a recurrence rate of only 11.5% after 2 months (Vicariotto et al., 2012) and 27.6% after 7 months (Murina et al., 2014), but neither study included a control group and both had small sample sizes. Thus, current evidence of the benefit of probiotics in patients with recurrent VVC is lacking and larger, well-controlled studies are necessary to elucidate any potential benefits.

4.3 | Post-antibiotic VVC

Pirotta et al. evaluated the effect of an oral probiotic containing *L. rhamnosus* and *B. longum* and a vaginal probiotic containing *L. rhamnosus*, *L. delbrueckii*, *L. acidophilus* and *S. thermophilus* on VVC in women taking oral antibiotics for non-gynecological reasons. The results showed that the probiotics were ineffective at preventing post-antibiotic VVC (Pirotta et al., 2004). They provide multiple explanations for these results; first, the lactobacilli may not have colonized the vagina effectively; second, the vaginal pH remains normal in candidiasis, so that hydrogen peroxide-producing lactobacilli may not aid in therapy as they do in conditions such as bacterial vaginosis, where the vaginal pH is increased (Pirotta et al., 2004). Additional studies involving patients with post-antibiotic VVC are necessary to further examine the potential preventative benefits of probiotics.

4.4 | Patients with HIV

Although one study by Hu et al. found that HIV-infected women who consumed probiotic yogurt had significantly less vaginal fungal colonization compared to periods without yogurt consumption, it is difficult to draw reliable conclusions from this study given its limited sample size (Hu et al., 2013). In a larger study, Williams et al. compared whether administration of *L. acidophilus* or clotrimazole prevented development of vaginal candidiasis in HIV+ women. Though risk of developing VVC in women taking the probiotic was reduced compared to placebo, the difference was not significant. In contrast, the women taking clotrimazole had a significantly reduced risk of developing VVC compared to placebo (Williams et al., 2001). From the limited evidence available, it seems that probiotics may not provide substantial benefit in HIV+ patients at risk for VVC; however, given that most studies of probiotics and VVC exclude patients with HIV, more studies are necessary in this population to better understand their therapeutic and preventative effects.

5 | PROBIOTICS AND ORAL CANDIDIASIS

Multiple studies have examined whether probiotics affect oral candidiasis (Table 2), particularly in patients at increased risk for infection, such as the elderly. Hatakka et al. investigated whether consumption

TABLE 2 Studies of probiotics in oral candidiasis. The "patients" column shows the number of patients completing the study as well as the characteristics of the patients included

Reference	Probiotic	Patients	Duration of therapy	Study design	Results	Conclusions
Hatakka et al., 2007	*Lactococcus lactis*, *Lactobacillus helveticus*, *Lactobacillus rhamnosus* GG (ATCC 53103), *Lactobacillus rhamnosus* LC705, *Propionibacterium freudenreichii* ssp. *shermanii* JS	192, age 70–100	16 weeks	Participants randomized to consume either 50 g of probiotic cheese or 50 g of control cheese daily for 16 weeks.	The risk of high yeast counts ($\geq 10^4$ cfu/mL) significantly decreased in the probiotic group compared to the control group. The number of participants and the risk of hyposalivation was decreased in the probiotic group.	Probiotic bacteria can reduce hyposalivation and the colonization of oral *Candida* in the elderly.
Kraft-Bodi, Jorgensen, Keller, Kragelund, & Twetman, 2015	*Lactobacillus reuteri* DSM 17938, *Lactobactillus reuteri* ATCC PTA 5289	174, age 60–102	12 weeks	Randomly assigned to receive two lozenges daily of either probiotic or placebo for 12 weeks.	The prevalence of high salivary *Candida* (colony density > 10^3 cfu/mL) was significantly decreased in the probiotic group but not in the placebo group, and there was a statistically significant difference in high *Candida* counts between the two groups.	Probiotic lactobacilli can reduce the prevalence of high counts of salivary *Candida* in the elderly.
Petti, Tarsitani, & D'Arca, 2001	*Lactobacillus bulgaricus*, *Streptococcus thermophilus*	42	8 weeks	In Phase 1, participants did not consume yogurt or casein-free soybean ice cream for 8 weeks. In Phase 2, participants were randomly assigned to consume either 125 g of yogurt or control ice cream twice daily for 8 weeks. In Phase 3, participants did not consume yogurt or ice cream for 2 weeks.	The yogurt-consuming group did not have lower *Candida* counts during Phases 1, 2, or 3 compared to control group.	Yogurt consumption may have an effect on other oral microbes, but did not affect *Candida*.
Ishikawa et al., 2015	*Lactobacillus rhamnosus* HS111, *Lactobacillus acidophilus* HS101, *Bifidobacterium bifidum*	55, with dentures	5 weeks	Participants randomized to one capsule of placebo or probiotic applied to the palatal region of the maxillary denture daily for 5 weeks.	The probability of undetectable *Candida* levels was significantly higher in the probiotic group than in the placebo group. Baseline	Probiotic bacteria can effectively reduce the colonization of oral *Candida* in those wearing dentures and thus may be an effective prophylactic therapy.

(Continues)

TABLE 2 (Continued)

Reference	Probiotic	Patients	Duration of therapy	Study design	Results	Conclusions
					Candida levels did not affect efficacy of probiotics.	
Miyazima, Ishikawa, Mayer, Saad, & Nakamae, 2017	*Lactobacillus acidophilus* NCFM, *Lactobacillus rhamnosus* Lr-32	60, with dentures	8 weeks	Participants were randomly assigned to consume cheese supplemented with either probiotic or control cheese daily for 8 weeks.	After 4 weeks, there was a significant reduction in *Candida* levels for the *L. acidophilus* group only; after 8 weeks, both the *L. acidophilus* and the *L. rhamnosus* groups had significantly reduced counts while the placebo group did not.	Eating cheese with probiotics can decrease oral *Candida* in elderly, denture-wearing patients.
Li et al., 2014	*Bifidobacterium longum*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*	65, with *C. albicans* stomatitis	4 weeks	Participants were randomly assigned to use oral sodium bicarbonate, nystatin, and probiotic lozenge or only sodium bicarbonate and nystatin, 3 times daily for 4 weeks. No placebo given.	Both the probiotic group and control group had a significant reduction in the detection rate of *Candida* after 2 and 4 weeks. There was a significant difference in the detection rate between the probiotic group and control group at 4 weeks. There was no significant difference in visual analogue scores or hyperaemia between the probiotic group and control group at 4 weeks.	Probiotics can decrease *Candida* counts in patients with *Candida*-associated stomatitis treated with nystatin, but may not significantly improve clinical symptoms.
Keller & Kragelund, 2018	*Lactobactillus reuteri* DSM 17938, *Lactobactillus reuteri* ATC PTA 5289	22, with oral lichen planus (OLP)	16 weeks	Participants with symptomatic OLP were initially treated with conventional therapy for OLP or oral candidiasis for 3 weeks, then randomized to use either probiotic or placebo lozenges three times daily for 16 weeks.	No statistically significant difference in *Candida* count or recurrence of oral candidiasis infection between placebo and probiotic groups.	Probiotics did not reduce recurrence of oral candidiasis or *Candida* count in oral lichen planus patients.
Hu et al., 2013	*Bifidobacterium*, *Lactobacillus*	24, including some with HIV	Two periods of 15 days	There was an initial period of 60 days without probiotic consumption. Then one 3.1 oz yogurt of DanActive™ was consumed daily for 15 days. After 30 days without yogurt consumption, one 4 oz yogurt of YoPlus™ was consumed daily for 15 days.	No significant differences in oral *Candida* colonization with yogurt consumption compared to periods without yogurt consumption.	Though these results show possible benefits of probiotics, the sample size is too small to draw generalizable conclusions.

of cheese containing *L. rhamnosus* and *Propionibacterium freudenreichii* in elderly patients aged 70–100 affected salivary yeast counts. The results showed that probiotic consumption significantly reduced the prevalence of high salivary yeast count ($\geq 10^4$ cfu/mL) and hyposalivation (Hatakka et al., 2007). Similarly, Kraft-Bodi found that administration of lozenges containing *L. reuteri* to elderly patients in nursing homes significantly reduced the prevalence of high salivary *Candida* (Kraft-Bodi et al., 2015). In contrast, in a study involving patients aged 20–40 years old, consumption of yogurt with *Lactobacillus bulgaricus* and *S. thermophilus* did not significantly affect salivary *Candida* counts compared to controls (Petti et al., 2001).

Studies of probiotics in patients with dentures who are also at increased risk for candidiasis have likewise shown promising results. Ishikawa et al. found that application of *L. rhamnosus*, *L. acidophilus*, and *B. bifidum* to the palatal region of dentures was associated with a significantly higher probability of undetectable levels of *Candida* from the palatal mucosa, regardless of the baseline *Candida* levels (Ishikawa et al., 2015). Miyazima et al. similarly found reduced levels of oral *Candida* in patients who wore dentures and consumed cheese with either *L. acidophilus* or *L. rhamnosus* compared to controls at 8 weeks. However, the difference was only significant at 4 weeks for *L. acidophilus* consumers (Miyazima et al., 2017). This finding demonstrates how different strains of probiotic can have varying effects on *Candida* colonization.

Though these studies have demonstrated that probiotic therapy in the elderly and denture-wearing populations is advantageous in reducing *Candida* count, probiotics may not provide additional benefit to conventional therapies used in oral *Candida* infections. Li et al. investigated whether probiotic lozenges containing *L. bulgaricus*, *B. longum*, and *S. thermophilus* used with nystatin in patients with *Candida*-associated stomatitis reduced clinical symptoms and *Candida* counts. Both the control group and the probiotic group had a significant decrease in *Candida* detection rate at 4 weeks, and while probiotics had a significantly lower detection rate compared to controls, this difference did not translate into clinical effect; there was no significant difference in visual analogue scale scores or hyperaemia between the two groups at 4 weeks (Li et al., 2014). Similarly, after conventional treatment for oral lichen planus with fluocinolone acetonide gel or oral candidiasis with nystatin, there was no significant difference in oral candidiasis recurrence or need for symptomatic treatment in patients receiving lozenges containing *L. reuteri* compared to controls (Keller & Kragelund, 2018).

These studies have demonstrated how probiotics can reduce the salivary *Candida* count in patients at risk for oral infection, but do not seem to significantly benefit patients already undergoing treatment for infection. Thus, the current evidence indicates that probiotics are more useful in the prevention rather than in treatment of oral candidiasis. However, the quantity of studies is limited and additional research is necessary before generating sound conclusions.

6 | SAFETY OF PROBIOTICS

The majority of evidence has shown that probiotics are safe (Didari, Solki, Mozaffari, Nikfar, & Abdollahi, 2014). However, when discussing their safety with patients, dermatologists should be aware that some adverse effects have been reported, such as fever and gastrointestinal symptoms including abdominal pain, nausea, soft stools, and flatulence (Goldenberg et al., 2017). Systemic infections such as sepsis, endocarditis, fungemia, and bacteremia have also rarely been reported (Doron & Snydman, 2015).

7 | CONCLUSIONS

Given the current evidence, the effect of probiotics on oral and VVC depends not only on the characteristics of the probiotic, such as the strain, mode of administration, and frequency of administration, but also on the characteristics of the patient. Probiotics may be beneficial in specific populations, particularly elderly patients at increased risk for oral candidiasis, and to supplement conventional antifungal therapies in patients with acute VVC. However, larger studies are necessary to confirm their potential benefit, and dermatologists should be cautious in applying the current evidence to the immunocompromised (who are particularly at risk for candidiasis), as most studies excluded these patients. Though few studies reported adverse events and probiotics are generally considered safe, before confidently recommending their use to patients, future studies should investigate the optimal probiotic strain and duration of therapy in specific populations at risk for candidiasis, especially patients on antibiotics and the immunocompromised.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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