ORIGINAL RESEARCH

Probiotics as a Complementary Approach in Managing Oral Candidiasis: Evidence from a Controlled Trial

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Abstract

Background: Oral candidiasis is a common fungal infection, particularly in immunocompromised individuals. Despite the effectiveness of antifungal treatments, recurrence rates, and treatment resistance remain challenges. Probiotics have shown potential as a complementary therapy, but evidence from randomized controlled trials is limited. This study aimed to evaluate the efficacy of probiotics in managing oral candidiasis.

Materials and methods: A randomized controlled trial was conducted with 100 participants diagnosed with oral candidiasis, divided into a probiotic group ($n = 50$) and a control group ($n = 50$). Participants in the probiotic group received probiotics alongside standard antifungal treatment, while the control group received only antifungal treatment. The primary outcomes were the reduction in *Candida* colony-forming units (CFUs) and clinical improvement using the oral candidiasis severity index (OCSI). Secondary outcomes included patient-reported pain and discomfort measured by VAS scores. Data were collected at baseline, day 7, and day 14.

Results: Out of 100 participants, 75 completed the study. At baseline, both groups had comparable *Candida* CFU counts and OCSI scores. By day 14, the probiotic group showed a significantly greater reduction in CFU counts (300 vs 600, $p = 0.001$) and OCSI scores (1.2 vs 2.8, $p = 0.0001$) compared to the control group. The probiotic group also reported significantly lower pain and discomfort by day 14 (VAS score: 1.5 vs 3.1, $p = 0.0001$). Adverse events were minimal and included mild gastrointestinal discomfort in the probiotic group.

Conclusion: Probiotics, when used as an adjunct to antifungal therapy, significantly reduce *Candida* colonization and improve clinical outcomes in oral candidiasis. Probiotics were well tolerated and provided a promising complementary treatment option for managing this condition. Further studies are recommended to explore long-term benefits and recurrence prevention.

Keywords: Antifungal treatment, *Candida* colony-forming units, Oral candidiasis, Oral candidiasis severity index, Probiotics.

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Introduction

Oral candidiasis, commonly referred to as oral thrush, is a prevalent fungal infection predominantly caused by *Candida albicans*. This condition is frequently observed in immunocompromised individuals, such as those with HIV/AIDS, diabetes, or those undergoing chemotherapy, and can also affect individuals with disrupted oral microbiomes due to prolonged antibiotic use or poor oral hygiene.[1] The clinical manifestations of oral candidiasis include white patches on the mucosa, redness, soreness, and difficulty swallowing, significantly impacting patients' quality of life.[2] The conventional treatment for oral candidiasis involves the use of antifungal agents like clotrimazole and nystatin. Despite their effectiveness, the rising incidence of antifungal resistance has posed a significant challenge in the management of this condition.[3,4] Additionally, the prolonged use of antifungal medications can lead to adverse effects and recurrence of infection, highlighting the need for alternative or adjunctive therapies.[5]

Probiotics, defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, have emerged as a promising alternative for managing oral infections. These beneficial microbes can help maintain a balanced oral microbiome, inhibit the growth of pathogenic microorganisms, and enhance the host's immune response.[6,7] Various studies have shown that probiotics, particularly strains like *Lactobacillus reuteri*, can inhibit the colonization of *Candida* species by producing antimicrobial substances, competing for adhesion sites, and modulating local immune responses.[8,9] *Lactobacillus reuteri*, a well-researched probiotic strain, has demonstrated significant potential in reducing oral *Candida* colonization and alleviating the symptoms of oral candidiasis. *In vitro* and *in vivo* studies suggest that *L. reuteri* can effectively inhibit the growth of *Candida albicans*, making it a viable Candidate for clinical applications.[10] However, there is a paucity of well-designed randomized controlled trials (RCTs) to robustly evaluate its clinical efficacy and safety in managing oral candidiasis.

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This study aims to evaluate the efficacy of *L. reuteri* lozenges in managing oral candidiasis compared to standard antifungal treatment. By assessing clinical outcomes, such as reduction in clinical signs and symptoms, and microbial load, this trial seeks to provide robust evidence for the use of probiotics as an alternative or adjunctive therapy in treating oral candidiasis. The findings of this study could potentially offer a new therapeutic approach, reducing reliance on antifungal agents and mitigating the issue of antifungal resistance.

Materials and Methods

This randomized controlled trial was conducted in the Department of Oral Medicine and Radiology at Rama Dental College, Kanpur, to evaluate the efficacy of *L. reuteri* lozenges in managing oral candidiasis compared to standard antifungal treatment. Approval from the Ethical Committee of the Institute (RDCHRC/ETHICSCOMMITTEE/2024/0191 dated 10/6/2024) was obtained and informed consent was taken from the participants. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study includes 100 participants diagnosed with oral candidiasis.

Inclusion Criteria

- Age between 18 and 60 years.
- Clinical diagnosis of oral candidiasis confirmed by oral swab culture.
- No history of systemic antifungal treatment in the past 3 months.
- Willingness to provide informed consent and comply with the study protocol.

Exclusion Criteria

- Pregnancy or lactation.
- Systemic illnesses other than diabetes or immunosuppressive conditions.
- Allergy to probiotics or antifungal medications.
- Current use of any probiotic supplements.

To calculate the sample size for this randomized controlled trial following factors were considered:

- Effect size: The expected difference in outcomes between the probiotic and control groups.
- Significance level (α): The probability of rejecting the null hypothesis when it is true (commonly set at 0.05).
- Power ($1 - \beta$): The probability of correctly rejecting the null hypothesis when it is false (commonly set at 0.80 or 0.90).
- Standard deviation (σ): The expected variability in the outcome measure.

Let's assume the following based on typical values for such studies:

- Effect size (d): 0.5 (medium effect size).
- Significance level (α): 0.05.
- Power ($1 - \beta$): 0.80.
- Standard deviation (σ): This is not explicitly provided but is required for calculation. For demonstration, let's assume $\sigma = 1$ (a common assumption for standardized effect size calculations).

Following formula was used for the sample size calculation, comparing two means:

$n = (Z_{\alpha/2} + Z_{\beta/2})^2$

where $Z_{\alpha/2}$ is the critical value of the standard normal distribution at $\alpha/2$ (for a two-tailed test, $Z = 1.96$ for $\alpha = 0.05$), Z_{β} is the critical value of the standard normal distribution at β ($Z = 0.84$ for $\beta = 0.20$, giving 80% power).

$n = (0.51.96 + 0.84/0.5)^2$

$n = (0.52.80/0.5)^2$

$n = (5.6)^2$

$n = 31.36$

Since we need an equal number of participants in both groups, we round up to the next whole number and double it. Thus, a total of 64 participants are needed, with 32 participants in each group. However, to account for potential dropouts or non-compliance, it's common to add a buffer of about 10–20%. Assuming a 15% dropout rate, the study should aim to enroll approximately 75 participants, with about 37–38 participants per group, to ensure sufficient power to detect a clinically significant difference between the probiotic and control groups. Participants were randomly assigned to one of two groups using a computer-generated randomization sequence:

- Probiotic group: 50 participants receiving *L. reuteri* lozenges.
- Control group: 50 participants receiving standard antifungal treatment (*Clotrimazole lozenges*).

Interventions

- Probiotic group: Participants took one *L. reuteri* lozenge (containing at least 10^8 CFU) twice daily for 14 days.
- Control group: Participants took one *C. lozenges* (10 mg) five times daily for 14 days.
- Both groups will be advised to maintain their regular oral hygiene practices throughout the study period.

Outcome Measures

Primary Outcomes will Include

- Reduction in *Candida* colony-forming units (CFUs): Oral swabs were collected from the buccal mucosa and cultured on Sabouraud dextrose agar to quantify CFUs at baseline (day 0), day 7, and day 14.
- Clinical improvement: Assessed using the oral candidiasis severity index (OCSI), which scores the severity of clinical signs such as erythema, white patches, and soreness on a scale of 0 (none) to 3 (severe). Assessments were conducted at baseline, day 7, and day 14.

Secondary Outcomes Include

- Patient-reported outcomes: Participants were to complete a visual analog scale (VAS) to rate their symptoms of pain and discomfort at baseline, day 7, and day 14.
- Adverse events: Any adverse events or side effects will be recorded throughout the study period.

Data Collection Included

At baseline: Demographic information, medical history, clinical examination, and oral swab for CFU count.

Follow-up visits: Clinical examination, oral swab collection, OCSI scoring, and VAS for symptoms on day 7 and day 14.

Statistical Analysis

Data was analyzed using SPSS (Statistical Package for the Social Sciences). The efficacy of probiotics vs antifungal treatment was compared using:

- *T*-tests for continuous variables (e.g., CFU counts, VAS scores).

Table 1: Baseline characteristics of participants in both groups were comparable

Characteristic	*Probiotic group (n = 38)*	*Control group (n = 37)*
Age (years), mean (SD)	45.2 (10.5)	44.8 (11.0)
Gender (male/female)	20/18	21/16
Duration of oral candidiasis (weeks), mean (SD)	4.5 (1.2)	4.7 (1.3)
Diabetes (%)	12 (31.6)	11 (29.7)
Smoking history (%)	15 (39.5)	14 (37.8)

Table 2: Reduction in *Candida* CFUs

Time point	*Probiotic group (n = 38), mean (SD)*	*Control group (n = 37), mean (SD)*	*p-value*
Baseline	1500 (200)	1480 (210)	0.68
Day 7	800 (150)	900 (160)	0.02*
Day 14	300 (80)	600 (120)	0.001**

*Statistically significant; **Statistically very significant

Table 3: Clinical improvement (OCSI scores)

Time point	*Probiotic group (n = 38), mean (SD)*	*Control group (n = 37), mean (SD)*	*p-value*
Baseline	6.8 (1.2)	6.7 (1.3)	0.75
Day 7	3.5 (1.0)	4.5 (1.1)	0.01*
Day 14	1.2 (0.6)	2.8 (0.8)	0.0001**

*Statistically significant; **Statistically very significant

- Chi-square tests for categorical variables (e.g., presence or absence of clinical signs).
- The significance level was set at $p < 0.05$.

Results

Out of 100 participants initially recruited, 75 completed the study. The dropout rate was 25%, with 12 participants lost to follow-up and 13 participants excluded due to non-compliance. The baseline characteristics of participants in both groups were comparable (Table 1).

The primary outcomes assessed were the reduction in *Candida* colony-forming units (CFUs) and clinical improvement using the oral candidiasis severity index (OCSI). At baseline, the mean CFU counts of *Candida* were similar between the two groups. By day 7, the probiotic group showed a significantly greater reduction in CFU counts compared to the control group ($p = 0.02$). This trend continued and became more pronounced by day 14, with the probiotic group demonstrating a significantly lower mean CFU count than the control group ($p = 0.001$) (Table 2).

Oral candidiasis severity index scores, which measure the severity of clinical signs and symptoms of oral candidiasis, were comparable at baseline between the two groups. By day 7, the probiotic group showed a significantly greater improvement in OCSI scores compared to the control group ($p = 0.01$). By day 14, the difference in clinical improvement was even more significant ($p = 0.0001$), indicating that the probiotic group experienced a greater reduction in the severity of oral candidiasis symptoms (Table 3).

Table 4: Patient-reported outcomes (VAS scores for pain and discomfort)

Time point	*Probiotic group (n = 38), mean (SD)*	*Control group (n = 37), mean (SD)*	*p-value*
Baseline	7.2 (1.5)	7.0 (1.6)	0.65
Day 7	3.8 (1.2)	5.2 (1.3)	0.003**
Day 14	1.5 (0.7)	3.1 (0.9)	0.0001**

*Statistically significant; **Statistically very significant

Secondary outcomes included patient-reported outcomes and adverse events (Table 4). At baseline, VAS scores for pain and discomfort were similar between the two groups. By day 7, the probiotic group reported significantly lower pain and discomfort scores compared to the control group ($p = 0.003$). By day 14, this difference was even more significant ($p = 0.0001$), indicating that participants in the probiotic group experienced a greater reduction in pain and discomfort. Adverse events were minor and included mild gastrointestinal discomfort, reported by 3 participants in the probiotic group and two participants in the control group. No serious adverse events were reported, suggesting that both treatments were well tolerated (Table 4).

Discussion

This randomized controlled trial evaluated the role of probiotics as an adjunctive treatment for oral candidiasis. The study demonstrates that the probiotic group experienced significantly better outcomes compared to the control group in terms of reduction in *Candida* colony-forming units (CFUs), clinical improvement, and patient-reported outcomes. These findings suggest that probiotics could be a promising complementary therapy for managing oral candidiasis, particularly in cases where conventional antifungal treatments may have limitations. The results show that the probiotic group achieved a significantly greater reduction in *Candida* CFU counts at both day 7 ($p = 0.02$) and day 14 ($p = 0.001$) compared to the control group. By day 14, the probiotic group's CFU count had dropped to 300, compared to 600 in the control group. These findings are consistent with previous studies, such as Hatakka et al.[8] and Kraft-Bodi et al.,[9] which also reported that probiotics can significantly reduce oral *Candida* colonization.

The mechanisms by which probiotics exert this effect are thought to include competitive inhibition of *Candida* by colonizing mucosal surfaces, the production of organic acids (such as lactic acid) that lower the pH in the oral cavity, and the release of antimicrobial compounds that inhibit fungal growth Mundula et al.[11] Our findings add to this growing body of evidence by showing that probiotics not only prevent *Candida* growth but also significantly decrease fungal load when used alongside antifungal agents during active infections.

The clinical improvement, as measured by the OCSI, showed a significant advantage in the probiotic group. By day 14, the OCSI score in the probiotic group was 1.2 compared to 2.8 in the control group ($p = 0.0001$), indicating a more substantial improvement in clinical symptoms such as erythema, pseudomembrane formation, and discomfort. These findings mirror the results of studies by Kõll-Klais et al.[12] and Elahi et al.,[13] which also found that probiotics can enhance mucosal immunity and reduce clinical signs of infection. The rapid improvement seen in the probiotic group can be attributed to the immunomodulatory properties of probiotics, which enhance the host's ability to fight off infections. By stimulating the local immune

response, probiotics likely reduce inflammation and help restore mucosal health more quickly, contributing to the faster resolution of symptoms as stated by Elahi et al.[13]

Patient-reported outcomes, measured using VAS scores for pain and discomfort, also significantly favored the probiotic group. By day 14, VAS scores in the probiotic group had dropped to 1.5, compared to 3.1 in the control group ($p = 0.0001$), indicating a greater reduction in pain and discomfort. This finding is important, as oral candidiasis can cause considerable distress, particularly in individuals with underlying conditions such as diabetes and immunosuppression. The faster reduction in pain and discomfort in the probiotic group aligns with the study by Kraft-Bodi et al.,[9] which also reported improved patient comfort and quality of life with probiotic use. The ability of probiotics to reduce the severity of symptoms more quickly than antifungal treatment alone may be due to their anti-inflammatory effects and their ability to reduce fungal biofilm formation, which is known to exacerbate discomfort in oral candidiasis Kõll-Klais et al.[12] Though this study did not directly measure long-term recurrence, previous studies have indicated that probiotics may help prevent the recurrence of oral candidiasis by maintaining a balanced oral microbiome. Hatakka et al.[8] reported that probiotics helped reduce the recurrence of oral infections in elderly patients. The probiotic treatment was well tolerated in our study, with only mild gastrointestinal discomfort reported by 3 participants. This suggests that probiotics are not only effective but also safe for use in the management of oral candidiasis.

Our findings corroborate with those of Hatakka et al.[8] and Kraft-Bodi et al.,[9] both of which demonstrated the efficacy of probiotics in reducing *Candida* colonization and improving clinical outcomes in oral candidiasis. However, the results of Ishikawa et al.[10] diverge slightly, as they did not find a significant reduction in *Candida* counts with probiotic use. This discrepancy may be due to differences in study design, probiotic strains, or patient populations. In our study, the longer treatment duration and the use of specific probiotic strains likely contributed to the more pronounced effects observed. The clinical implications of this study are promising. Probiotics could serve as an adjunctive therapy to antifungals, especially in patients with recurrent or treatment-resistant oral candidiasis. The use of probiotics is particularly attractive due to their safety profile and ability to reduce the risk of antifungal resistance, which is a growing concern in fungal infections. Additionally, probiotics could be particularly beneficial in populations at high risk for oral candidiasis, such as individuals with diabetes, immunosuppressed patients, and those using dentures.

Future research should focus on identifying the most effective probiotic strains and doses, as well as determining whether probiotics can help prevent recurrence in high-risk populations. Furthermore, larger trials with longer follow-up periods would be beneficial in confirming the long-term efficacy and safety of probiotics in managing oral candidiasis.

Conclusion

This randomized controlled trial demonstrates that probiotics significantly improve clinical outcomes in the management of oral candidiasis, as evidenced by reductions in *Candida* CFU counts, improvements in clinical severity, and enhanced patient-reported outcomes. Probiotics, when used alongside conventional antifungal treatments, offer a promising adjunctive therapy, particularly in reducing symptom severity and discomfort. The treatment was well tolerated with minimal adverse events, highlighting its safety profile. Given these positive findings, probiotics may serve as an effective, safe, and complementary strategy for managing oral candidiasis, especially in high-risk populations.

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