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Effect of probiotics on oral *Candida*-a review

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ABSTRACT

Oral candidiasis is a frequently encountered fungal infection of the oral cavity. Its etiology is multifactorial, attributable to the disparity in the microorganisms inhabiting the oral cavity. Probiotics are live microorganisms that can have antagonistic effects on other pathogens. The benefits of probiotics in the management of gastrointestinal disorders are well known. Probiotics have been tried as a newer treatment option for managing oral candidal infections. Therefore, the present review attempts to summarize the significant data available from clinical trials about the efficacy of probiotics on oral candidal infections. A computerized search in PubMed and the Cochrane Library was conducted using the terms Candidosis (OR) Candidiasis (OR) oral *Candida* (AND) probiotics, to identify randomized controlled trials published from 2010 to April 2020. We identified forty-six articles and six of them fulfilled the inclusion criteria for this review. The studies have assessed the role of probiotics in oral *Candida* by measuring the candidal counts in samples from various intraoral sites, the clinical cure rate, or both. The probiotics used in most studies were of *Lactobacillus* species and *Streptococcus salivarius*. This review concludes that probiotics have preventive and curative effects on oral candidal infections, but the efficacy depends on the dosage, duration, and type of the probiotic strains.

Introduction

Oral candidiasis is an opportunistic fungal infection caused by *Candida* species. Under normal circumstances, *Candida* exists in the oral mucous membrane as a beneficial oral flora. When there is an imbalance in the microbial flora of the oral cavity, *Candida* species, most predominantly *Candida albicans* cause infections. Old age, an immunocompromised state, and prolonged consumption of broad-spectrum antibiotics are the predisposing factors. The pseudomembranous form of oral candidiasis is the most common, which presents as a scrapable curdy white patch in the oral mucosa and tongue (1). Live microorganisms that can provide health benefits to the host are called probiotics (2). Several probiotic microorganisms, such as lactic acid bacteria and yeasts, are well known for their therapeutic benefits. Probiotic therapy is the administration of a single or a combination of beneficial strains of microorganisms for managing various diseases such as gastrointestinal disorders and candidal vaginitis (2,3). In the management of oral candidiasis, antifungal drugs are the most commonly preferred line of therapy. However, the administration of antifungal drugs has various limitations because of the emergence of resistant strains to conventional antifungals and the recurrent nature of the disease in affected individuals (4). Probiotics are one of the newer therapeutic options tried in the management of various candidal infections. This article aims to review the available literature to determine the efficacy of probiotics in oral candidal infections.

Methods

A computerized search in PubMed and the Cochrane Library was conducted using the following search terms: (candidosis OR candidiasis OR oral *Candida*) AND (probiotics). Filters that were used in the PubMed database included "Randomized Controlled trails" and "Humans," and in the Cochrane Library, the filter was "Trials". Only the articles published in the English language between January 2010 to April 2020 were included. The inclusion criteria were as follows: 1. Randomized controlled trials to treat or prevent oral candidal infections using probiotics, with or without a placebo. 2. Studies have reported on candidal assessment after the administration of probiotics. 3. Studies on oral candidal infections with no other coexisting oral lesions. The review was performed following the PRISMA guidelines. The database search yielded 46 articles, out of which 22 were selected and screened after the removal of duplicates (Figure 1). Following the screening, 7 articles were assessed for eligibility and after excluding those that did not fulfill the exact aim of our present review, 6 articles were selected.

Characteristics of the included trials

The studies included in our review assessed the *Candida* counts in samples from various intraoral sites, the clinical cure rate, or both. The included studies differed widely concerning the age group, background, nutritional status, ethnicity, systemic factors of the study population, and the type, form, and duration of probiotic administration (Table 1).

Candida colonization in the oral cavity

The human oral cavity serves as a habitat for a wide variety of microorganisms, and interkingdom interactions among those microorganisms play a direct role in oral health. *Candida albicans* and a few other fungi of *Candida* species frequently colonize the oral cavity and participate in various complex microbial reactions like biofilm formation (5). Candidal colonization occurs sequentially by acquisition, adhesion, replication, and establishment of a stable population of yeast forms. The adhesion sites include epithelial surfaces, extracellular matrix proteins, bacterial cell-surface molecules, and dental acrylic. Basic proline-rich proteins and other salivary molecules promote the adherence of *Candida albicans*. Lectin, protein-protein, and hydrophobic interactions aid in the active adhesion of the fungal colonies. They also express alternate modes of adhesion in the oral cavity. They can escape host defense mechanisms and they can adhere to and colonize new environments by penetrating tissues, thereby establishing successful colonization (6).

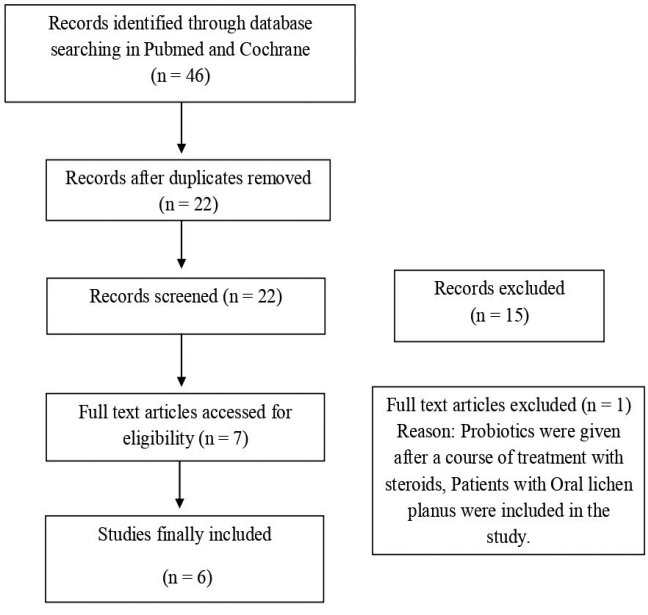

Figure 1. PRISMA flow diagram

Mechanism of action of probiotics on oral *Candida*

Probiotic bacteria adhere to the oral mucosa and compete with *Candida* species for nutrition and adhesion sites. They inhibit *Candida* by the production of various metabolites, stimulate the innate immune response of the host and decrease the production of inflammatory factors (7).

Lactobacillus species, which is the main constituent of most probiotic supplements, is known for its cell surface hydrophobicity and can directly form a mechanical barrier, and prevents candidal adhesion to the epithelium (8). Probiotics increase the levels of salivary immunoglobulin A and promote immunomodulation (9). Reuterin, a hydrogen peroxide-like toxin produced by live strains of *Lactobacillus reuteri*, is known to inhibit oral *Candida* by selective inhibition (10). Probiotic bacteria also produce various organic acids, hydrogen peroxide, bacteriocins, and antifungal peptides, thereby causing inhibition of candidal adherence and colonization in the host tissue (11,12).

Strain specificity of probiotic bacteria

The most widely used probiotic has been the *Lactobacillus* species. According to the evidence from available literature, probiotics containing *Lactobacillus* colonize the oral cavity only at the time of consumption, hence are capable of exerting only a short-term effect. But probiotics must show a long-term effect to prevent candidal colonization for a longer period. *Lactobacillus rhamnosus GG* is known to exist in the oral cavity for an extended period (13). A study by Miyazima et al. (14) found *Lactobacillus acidophilus NCFM* to be superior to *Lactobacillus rhamnosus Lr-32* in reducing the number of candidal colonies in highly infected individuals. On the other hand, experimental studies in infected immune-suppressed mice models have shown *Lactobacillus rhamnosus Lr-32* to be more effective than *Lactobacillus acidophilus NCFM*. It is also more effective than the antifungal agent Nystatin, in reducing the oral colonization of *Candida Albicans* (15). *Lactobacillus reuteri* DSM 17938 and *Lactobacillus reuteri* ATCC PTA 5289 have been used

successfully in frail elderly patients to reduce oral candidal counts (16). *Lactobacillus reuteri* also inhibits various other pathogenic bacteria by affecting their tissue binding ability and inhibiting the release of proinflammatory cytokines (7).

Streptococcus salivarius K12 has a higher tendency to bind with the hyphae form compared to the yeast forms of *Candida* and suppresses the adhesion of *Candida*. They exert an indirect antifungal activity that cannot be related to the anti-microbial activity of the bacteriocin (17).

Li et al. (12) found a combination of probiotics including *Bifidobacterium longum*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* to be effective in patients who were already on topical antifungal therapy (2% Nystatin paste) in reducing *Candida* species. It was also found to decrease the number of Gram-negative bacilli and increase the detection rate for *Staphylococcus epidermidis* in the saliva samples (12). *Staphylococcus epidermidis* inhibits *Staphylococcus aureus, Streptococcus mitis*, and *Streptococcus sanguis*, which exert synergistic properties with *Candida albicans*. Thus, *Staphylococcus epidermidis* interferes indirectly with the candidal growth or their adhesion to the biofilms of the oral mucosa (18,19). Hence, strain specificity is one of the vital factors determining the efficacy of probiotics against oral *Candida*.

Mycological cure

The mycological cure can be assessed by the detection of *Candida* in the culture (Table 2). Hu et al. (20) demonstrated negative microscopy and no growth of *Candida* in culture by administering *Streptococcus salivarius K12* along with topical antifungal therapy with Nystatin (500,000 U) to patients with oral candidiasis, thereby achieving an enhanced mycological cure rate of about 90% compared to the use of antifungals alone. Thus, combined probiotics and conventional antifungals can shorten the course of treatment. Kraft-Bodi et al. (16) reported a major reduction of *Candida* in the saliva and plaque samples of frail elderly patients, up to 51% of the reduction was noted in the probiotic group at the end of treatment. All the studies included in this review have shown significantly reduced *Candida* after the intervention.

Clinical cure

Studies indicate that the severity of denture stomatitis (DS) is directly related to *Candida albicans* in 72% of the patients. The management of DS is complex as it requires identification, correction, and elimination of the local and systemic predisposing factors. Newton has classified DS into three types based on the clinical appearance of the lesion; type 1 comprises a simple, localized inflammatory lesion, type 2 comprises a diffuse, generalized inflammatory lesion on the mucosal contacting the denture, and type 3 is characterized by chronic inflammatory lesion with granulomatous papillary hyperplasia (21). Lee et al. (22) have successfully demonstrated clinical improvement in the severity of DS after intervention with probiotics. In their study group, 11 participants had type 1, 6 had type 2 and one participant had type 3 DS at the beginning of the trial. After a six-month probiotics intervention (T1), only six had type 1, and one had type 2 DS. On the other hand, one participant who had type 3 DS maintained the same severity. Finally, six months after the discontinuation of the intervention (T2), there was no change in the clinical type of DS concerning T1. Thus, a significant improvement in the clinical presentation of DS compared to the pre-intervention and post-intervention was evident, also between pre-intervention and six months after the discontinuation of the probiotics. Li et al. (12) used parameters such as grading of hyperemia using a card with four levels of red colors and pain assessment using a visual analog scale (VAS) to assess the clinical presentation of oral candidiasis among the study participants before, during, and after the intervention. The probiotic group showed significantly decreased VAS scores after two weeks of treatment. But there was no significant difference in the reduction of hyperemia in the probiotic group.

Prophylaxis against denture stomatitis

Oral candidiasis has a chronic course and often recurs in elderly individuals, as they use dentures and have a weak immune status. Therefore, there is a need for therapeutic agents with relatively low toxicity and side effects without compromising their effectiveness against *Candida*. Various systemic conditions, including diabetes, immune deficiencies, xerostomia, and various local factors such as ill-fitting dentures, and poor oral and denture hygiene, predispose to candidal infections (23). Patients using removable dentures are more prone to DS associated with *Candida*. The denture base materials serve as a substrate for the growth and colonization of microorganisms. It has been reported that 11-67% of complete denture wearers suffer from DS (24). Hence, there is a strong need for therapeutic agents that can prevent *Candida* with relatively lesser toxicity. Topical application of a lyophilized capsule containing *Lactobacillus rhamnosus HS111*, *Lactobacillus acidophilus HS101*, and *Bifidobacterium bifidum* over the tissue contacting area of maxillary dentures for 5 weeks showed successful elimination of *Candida* in samples taken from the palatal mucosa (25). Miyazima et al. (14) reported a significant reduction of *Candida* in the mouthwash samples of complete denture wearers who consumed probiotic cheese containing either *Lactobacillus acidophilus NCFM* or *Lactobacillus rhamnosus Lr-32* daily for 8 weeks. Hence, daily consumption of probiotic supplements in any convenient form such as cheese or milk can help in the reduction of the candidal load, thereby providing prophylaxis against oral candidal infections like DS in highly susceptible individuals.

Table 1. Characteristics of the included studies

Study	Probiotic used	Form of intervention	Treatment regimen	Duration of intervention
Li et al. (12)	*Mixture of Bifidobacterium longum, Lactobacillus bulgaricus and Streptococcus thermophilus*	Lozenges	1. Mouth gargling using 2% sodium bicarbonate solution for 30 seconds, 2. Application of 2% Nystatin paste, 10 minutes after mouth gargling, 3. After one hour, four probiotic lozenges were held in mouths (Procedure followed three times/ day).	4 weeks
Ishikawa et al. (25)	*Lactobacillus rhamnosus HS111, Lactobacillus acidophillus HS101, Bifidobacterium bifidum*	Lipophilized capsules	Local application by pouring the capsule content into the palatal region of the previously cleaned maxillary denture (1 capsule/day).	5 weeks
Kraft-Bodi et al. (16)	*Lactobacillus reuteri DSM 17938, Lactobacillus reuteri ATCC PTA 5289*	Lozenges	One lozenge in the morning, One lozenge in the early evening (2 lozenges/day).	12 weeks
Miyazima et al. (14)	*Lactobacillus acidophilus NCFM, Lactobacillus rhamnosus Lr-32*	Supplementation with cheese	20 g of fresh white cheese will be given every 2 weeks (Daily consumption).	8 weeks
Hu et al. (20)	*Streptococcus salivarius K12*	Lozenges	One lozenge of probiotic BID One Nystatin tablet (500,000 U) TID-Topical application.	4 weeks at 1-week interval
Lee et al. (22)	*Lactobacillus rhamnosus SP1*	Supplementation with milk	Oral hygiene training before the start of the study was given, 200 mL of probiotic milk for 5 days a week.	6 months

Table 2. Pre and post-interventional status with regard to the mycological load/cure

Study	Mycological load/cure	
	Before the intervention/baseline	**Post-intervention**
Li et al. (12)	Detection of *Candida* in samples: 100%	Detection of candida in samples: 8.21%
Ishikawa et al. (25)	*Candida* was detected in samples in all 30 participants in the probiotic group.	*Candida* was detected in samples in only 5 participants.
Kraft-Bodi et al. (16)	*Candida* in saliva: 72% *Candida* in plaque: 67%	*Candida* in saliva: 51% *Candida* in plaque: 50%
Miyazima et al. (14)	3.5 $\log_{10}$ CFU/mL (before intervention with *L. acidophilus* NCFM)	2.5 $\log_{10}$ CFU/mL (after intervention with *L. acidophilus* NCFM)
Hu et al. (20)	Mycological cure rate: -	Mycological cure rate: 90.48%
Lee et al. (22)	Viable cells: 1.98e+03 CFU/mL	Viable cells: 1.32e+03 CFU/mL

CFU: Colony forming units, mL: Milliliter

Adverse effects

While most studies have not reported any side effects, Hu et al. (20) reported xerostomia, numbness, burning sensation in the oral cavity, borborygmus and pharyngeal discomfort, light dizziness, and headache in a few participants who received *Streptococcus salivarius K12* with nystatin. However, there is evidence in the literature that the fermentation and enzymatic reactions of *Streptococcus salivarius K12* probiotics do not show harmful effects on humans (26).

There were no reports of major side effects after the intake of probiotic supplements in most studies. In the study by Kraft-Bodi et al. (16), a few participants reported a feeling of intense taste of tablets. Two participants in the probiotic group and three in the placebo group reported gastric complaints within the first week of the intervention, which may not be directly related to the probiotic. Instead, it may also be linked to the chemical composition of the lozenges. Probiotic-supplemented milk and cheese are not recommended for lactose-intolerant individuals.

Advantages of treatment with probiotics

Therapeutic and prophylactic use of probiotics in oral candidal infections can reduce the use of conventional antifungals and their side effects. They also have the added advantage of preventing the development of drug resistance by certain *Candida* species against azoles which are the most commonly used anti-fungal therapies in oral candidiasis.

Conclusion

All the studies included in our review compared the pre-interventional and post-interventional candidal status of the patients and probiotics were found efficient in both prophylaxis and management of oral candidal infections. From the available literature, it is evident that probiotics can be alternative to conventional antifungal therapy in oral candidal infections. It should also be noted that the effect of probiotics depends on the dosage, duration, and type of probiotic strain used. Therefore, it is necessary to select an appropriate probiotic strain for a successful treatment outcome.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.F.A., Concept: M.F.A., S.B., Design: M.F.A., S.B.G., Data Collection or Processing: M.F.A., Analysis or Interpretation: S.B.G., Literature Search: M.F.A., S.B., Writing: M.F.A.

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