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The Role Of Probiotics As Viable Alternative Therapy In Prevention Of Oral Candidiasis – A Systematic Review

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Abstract

Background: Oral candidiasis (OC) is an emerging opportunistic infection spreading at an accelerated rate around the globe, more in part due to the fact that there is currently a worldwide pandemic (Covid-19) which in itself has given rise to a host of other comorbidities like candidiasis. This systematic review aims to establish whether the use of probiotics is helpful in controlling oral candidiasis alongside other the other treatment modalities available.

Methods**:** After a thorough literature search, it was found that 6 studies and 4 randomized clinical trials (RCTs) resulted as eligible for the systematic review. The studies selected included a number of parameters for example; type of study, nature of aim of the study, size of the sample in the study, gender and age of the subjects included in the study, analysis of different variables and the strain of the probiotic bacteria employed.

Result: Both the reviews on the selected studies and the subset of the clinical trials found that the usage of probiotics, in conjunction with the traditionally used treatment modalities, had a marginally positive impact effect on reducing oral Candida spp. numbers.

Conclusion: It can be deduced summarily that probiotics do influence the reduction in Candida counts in the oral cavity. However, this is subjected to more extensive trials and the results need to be taken with a pinch of salt.

Keywords: Candidiasis, lactobacillus, probiotics, treatment

Introduction

Daniel M. Lilly and Rosalie H. Stillwell coined the word "probiotic" in 1965 to describe chemicals generated through one organism that stimulate the growth of another. [1] Antibiotics, immunosuppressive medication, and irradiation, among other treatments, may

produce changes in the composition and have an impact on the gastrointestinal tract (GIT) flora. As a result, introducing beneficial bacterial species to the gastrointestinal (GI) tract could be a very appealing option for re-establishing microbial balance and preventing disease. [2] Prebiotic is a non-digestible food element that benefits the host by activating one bacterium or a group of bacteria with probiotic qualities in the colon. Escherichia, Lactobacillus, Enterococcus, Bacillus, and Streptococcus are some of the most frequent bacteria used in probiotic formulations. Fungal cultures from the genus Saccharomyces were also employed. Probiotics have been shown to help with everything from infantile diarrhoea to necrotizing enterocolitis, antibiotic-associated diarrhoea, relapsing Clostridium difficile colitis, Helicobacter pylori infections, inflammatory bowel disease, cancer, female urino-genital infection, and surgical infections. The lactobacillus rhamnosus strain has been shown to improve gut immunity. It increases the number of cells in the intestinal mucosa that secrete IgA and other immunoglobulins. It also causes interferons to be released locally. It increases antigen uptake in Peyer's patches by facilitating antigen transport to underlying lymphoid cells. Because probiotics are live bacteria, they have the potential to cause illness in the host.

Probiotics, as a term, was first proposed in 1908 by Eli Metchnikoff, co-recipient of the Nobel prize for physioslogy/medicine in the year 1908 (along with Paul Ehrlich) for his pioneering work in the field of immunology who claimed that Bulgarian peasants' long lives were due to their ingestion of fermented milk products. Lilly and Stillwell used the word "probiotic" in 1965 to describe chemicals secreted by one organism that aid in the growth of another. [3] Microbial preparations or components of microbial cells that have a favourable influence on health and well-being, as defined by Marteau et al. in 2002. [3]

Humans coexist with a great number of microorganisms on their skin, in their mouths, and in their gastrointestinal tracts. The GI tract, which has almost 400 square metres of surface area, contains the highest concentration of commensal microbes. The interactions between the intestinal microbiota and the host during development culminate in the establishment of a unique and distinct intestinal immune system. The difficulty for this host's mucosal immune system is to distinguish between infections and harmless species while boosting protective immunity without inducing an excessive inflammatory response that could compromise the well-being of the individual.

A predominantly fungal infection, oral candidiasis is caused by Candida albicans, and is accepted to be the most prevalent oral mucosal infectious illness. C. albicans is detected in 20 to 75 percent of the general population. Oral candidiasis affects 15 to 71 percent of denture wearers and 80 percent to 95 percent of HIV-positive people, according to studies. Antifungal medications such as nystatin, fluconazole, or miconazole are commonly used to treat oral candidiasis. The therapeutic applicability of antifungal medicines can be limited due to adverse effects and side effects, such as candida resistance to antifungal agents and gastrointestinal discomfort, including nausea, vomiting, and diarrhoea. As a result, new prophylactic and therapeutic techniques for oral candidiasis need to be investigated.

Candida is a tiny, thin-walled, spherical yeast with a diameter of approximately 4-6 um that reproduces through budding. In tissue, this genus' organisms take three forms: blastospores, pseudohyphae, and hyphae. Candida thrives on simple media, and lysis centrifugation improves its recovery from blood. Biochemical testing (now with automated machines) or special agar are used to identify the species. There are around 150 species of Candida, but only a few of them cause disease in humans. Human pathogens include C. albicans, C. quilliermondii, C. krusei, C. parapsilosis, C. tropicalis, C. kefyr, C. lusitaniae, C. dubliniensis, C. glabrata, and C. auris. [2-6]

Probiotics have been shown to help with vulvovaginal candidiasis, dermatophytosis, gastrointestinal infections, hypertension, and colorectal cancer in prior findings. Probiotics are known to restore the balance of the microbial population and the immune system by modulating innate and acquired immunity and producing antioxidants and bacteriocidal enzymes. Meanwhile, probiotics have been suggested as a possible treatment for oral disorders such periodontal disease, dental

caries, halitosis, and oral candidiasis. In the elderly and denture wearers, probiotics outperformed the placebo and blank control in preventing and curing oral candidiasis. Although probiotics showed promise in treating oral candidiasis, additional evidence is needed to support their efficacy in comparison to traditional antifungal medications. Furthermore, data on the safety of probiotics is currently lacking, necessitating additional research. [7,8]

Probiotics have been shown in recent years to aid in the management of the oral microbiota. Lactobacillus rhamnosus and Lactobacillus reuteri have been found in studies to lower oral Candida levels. Probiotics' projected effects in the treatment of oral candidiasis, however, are mixed. Furthermore, there is a scarcity of information on the safety of probiotics. So, the goal of this review is to use a systematic evaluation to analyse the effectiveness and safety of probiotics in the prophylaxis and treatment of oral candidiasis. A daily dose of five billion colony forming units (5x109 CFU/day) has been recommended for at least five days to provide adequate health benefits. [4-9]

Materials and methods

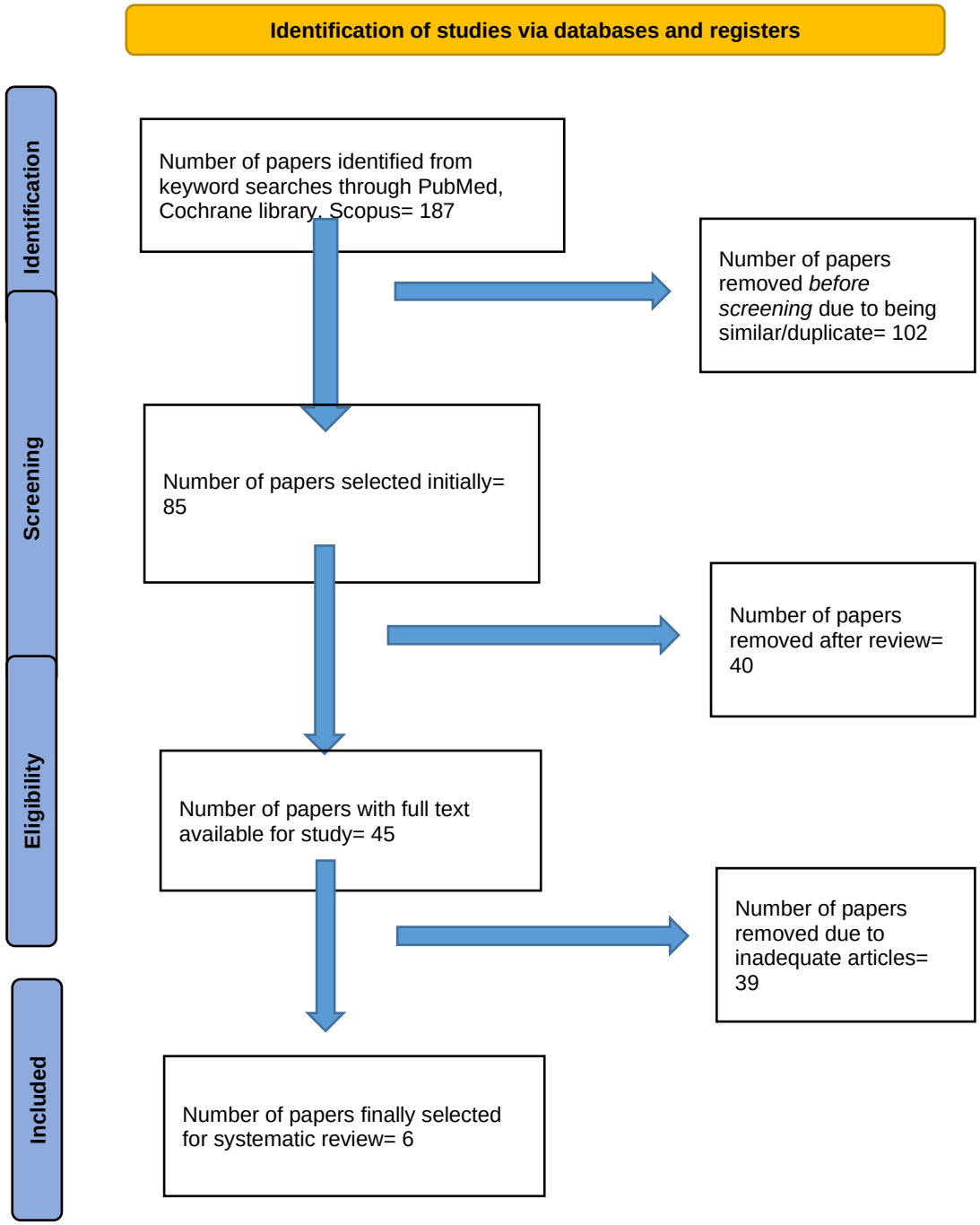
Using the following search keywords- probiotics, oral candidiasis, Candidiasis spp., Candidiasis treatment, Lactobacillus, a detailed search of the articles published was conducted in PubMed, Cochrane library, Scopus, and other individual journal sources, focusing on the applications, literature, and current treatment modalities with respect to probiotic treatment and prophylaxis in the case of oral candidiasis. There were no limitations on language, follow-up time, or participant characteristics (age, race, or gender).

There was a total of 187 documents discovered after the extensive search. Following that, 102 publications that were similar/duplicate articles were eliminated, which resultantly made 85 separate papers available at first. The abstracts and titles of submissions were then reviewed, and a further 79 papers were eliminated. Finally, 6 papers that completely met the inclusion and exclusion criteria were chosen, which included study articles and randomised control trials.

Only those studies that met certain criteria, such as papers that reflected the use of probiotics for treatment purposes in the context of oral candidiasis infection, were chosen. Shortlisted studies also included topics in which probiotics were employed alone or in combination with other treatment modalities in the study, as well as papers that were exclusively published in English.

Papers focusing on the use of probiotics in the treatment of candidiasis in locations other than the oral cavity (such as vulvovaginal candidiasis, acute/chronic mucocutaneous candidiasis, or patients with highly invasive Candida infections due to haematogenous seeding) were not chosen. This study also excluded patients who had persistent mucocutaneous candidiasis and endocrine problems (the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy-APECED syndrome).

Figure 1: Representation of selection of articles for systematic review



Results:

Lactobacillus species	Bifidobacterium species	Saccharomyces species	Streptococcus species	Others
L. acidophilus	B. bifidum	S. thermophiles	S. boulardii	Bacillus cereus
L.casei (rhamnosus)	B. breve	S. salivarius		Escherichia coli
L. fermentum	B. lactis			Enterococcus
L. gasseri				

L. johnsonii L. lactis L. paracasei L. plantarum L. reuteri L. salivarius L. bulgaricus	B. longum B. infantis B. adolescentis			Propionibacterium fraudenrichii

Table 1: List of microorganisms currently being used as probiotics

Fungal infections are very widespread, particularly in developing/near developed countries. [5] Candida spp. infections are linked to a number of risk factors, including the use of dentures, malnutrition, endocrine abnormalities, smoking, and chronic diseases like diabetes, HIV infection, and cancer. Antifungal medicines are the most common anti-OC treatment, however varied clinical forms of OCs and the growing number of Candida spp. multi-resistance phenotypes pose significant public health problems. As a result, developing alternative therapeutic or complementary treatments to avoid the formation of fungal resistance appears to be important. Probiotics have been shown in numerous trials to be an effective alternative treatment for Candida spp. infections. [6]

Table 2: Details of the studies and randomized control trials included in the systematic review

Details of authors of the study	Details of the subjects undergoing the study	Duration of the study	Treatment modality/modalities employed	Results obtained
MK Keller, C Kragelund et al	22 patients with recurrent oral candidiasis	16 weeks, followed up for a further 36 weeks	Lozenges containing Lactobacilli reuteri or placebo dissolved intra-orally	Probiotic intervention did not reduce recurrent oral candidiasis or Candida count
Agda Lima dos Santos et al	111 individuals with oral candidiasis	20 days	Yakult LB (Lactobacillus casei and Bifidobacterium breve, 2 x 107 to 109 and 5 x 107 to 109 CFU/mL)	Reduction in Candida CFU/mL counts was observed after probiotics use
E. Kraft-Bodi et al	215 older adults (ranging from 60 to 102 years)	12 weeks	1 lozenge containing 2 strains of the probiotic bacterium Lactobacillus reuteri or placebo twice daily (morning and evening)	Slight reduction in the prevalence of high oral Candida counts in frail elderly residents
Ishikawa, Mayer et al	59 denture wearers harboring Candida spp. in the oral cavity	5 weeks	Capsule containing lyophilized Lactobacillus rhamnosus, Lactobacillus acidophillus, and Bifidobacterium bifidum	Reduction in the colonization of the oral cavity with Candida in denture wearers
Radhika Doppalapudi, et al	86 patients	Oral rinse samples incubated on Sabouraud's Dextrose Agar with Chloramphenicol at 37°C for 48 h	Single sachet contained at least 1.25 billion live cells of a blend of four probiotic strains: Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium longum, and Saccharomyces boulardii	Probiotic bacteria were effective in reducing oral Candida spp
Hatakka et al	276 elderly people	16 weeks	50 g of either probiotic or control cheese	No significant changes observed in the oral candida levels

(CFU/ml- Colony forming unit/millilitre)

The microorganisms used in probiotic preparations are generally recognised as safe (GRAS), meaning they are resistant to bile, hydrochloric acid, and pancreatic juice, have anti-carcinogenic activity, and stimulate the immune system. They should also have reduced intestinal permeability, produce lactic acid, and be able to survive both acidic and alkaline conditions in the stomach and duodenum. Fermented milks, cheeses, fruit juices, wine, and sausages are examples of foods that contain mostly lactic acid bacteria for human consumption. Probiotics are made up of single and mixed cultures of living microorganisms.

Furthermore, they are simple to use, and as a result, patients often embrace these goods. The current research presents a review of the literature on this topic as well as a quantitative analysis that integrates the findings of multiple independent investigations of various designs. The medication had an equivocal effect on reducing oral Candida spp. counts, according to both the evaluations of the selected papers and the subset of RCTs.

Discussion:

The heterogeneity among research was significant, as expected, because studies of various designs were merged, focusing on different populations, using different treatments and doses, and being affected by various types and levels of bias. The sensitivity analysis revealed that some of the observed variation may be related to differences in treatment effect when employed in various populations. It was discovered, for example, that the effect on denture wearers was greater than the effect on non-denture wearers. The findings on denture users were based on a single RCT and should be treated with caution, but they do reveal a real difference. The direct application of probiotic items on the denture surface may have caused the greater reduction in the number of Candida spp. colonies in these patients. [7] This theory supports the assumption that probiotics have a reduced effect because of the low frequency of use, number of probiotic cells, and delivery technique, all of which influence the length of time probiotics stay in the oral cavity. In this regard, developing a mucoadhesive drug delivery method that allows for longer retention at the site of action should improve the therapeutic effect. [8] The comparisons of the numerous studies in our analysis also appear to support the relevance of the number of doses per day. If we concentrate on non-denture wearers, Li et al. found a bigger benefit when the patients were given three doses each day instead of one or two. [9] In one of the investigations, three dosages were given as well, although the results were based on a very limited number of individuals due to recruitment issues. [10]

A secondary source of variability was the possibility that different microbial probiotic strains might have varying impacts on Candida spp. count decrease. [11] Matsubara and colleagues discovered that treating mice with Lactobacillus rhamnosus (Lr-32) [12] was more efficient than treating animals with Lactobacillus acidophilus at reducing Candida spp. colonisation levels in a mouse model. Unfortunately, because the number of papers we found in the literature was insufficient to create a network of comparisons involving numerous treatments, we assumed that all treatments had the same effect, which was clearly a strong assumption. As a result of the findings, we can conclude that probiotics protect against Candida spp. infection and, more specifically, colonisation. As previously stated, anti-Candida capabilities can be explained in a variety of ways, by means of co-aggregation, oral pH modification [13], and H_2O_2 generation, the release of large volumes of lactic acid, and the full blockage of fungal biofilms. [14-15] These beneficial effects, however, are largely dependent on the route of administration, dosage, and probiotic strains employed. Furthermore, no papers on prebiotics or synbiotics were found to be eligible for our analysis. To uncover novel antifungal effects, more research into the impact of these products on oral candidiasis is needed. In fact, some studies have shown that combining probiotics with other treatment options can be quite beneficial in treating diseases. [16-17]

In terms of safety, stomach discomfort and foul taste were reported as adverse effects of probiotics in the in vivo trials included in this comprehensive review. In both the clinical trials and the animal investigations, no serious adverse events were reported. However, a 2011 analysis from an organisation stated that while existing clinical trials do not show an elevated risk, this does not guarantee the safety of probiotics in intervention research. [18] Systemic infections, harmful metabolic activities, excessive immunological stimulation in sensitive people, and gene transfer were all theoretically plausible negative effects of probiotics. [19] For example, after receiving Bifidobacterium breve for 12 days, a neonate with an umbilical bulge developed sepsis. [20] On the contrary, based on the bulk of data from clinical trials, animal research, and in vitro investigations, a 2015 study concluded that probiotics are typically safe for most populations. [21] Another trial separated 80 rotavirus-infected infants aged 3 months to 3 years into placebo and treatment groups. The

treatment group that received commercial Bifidobacterium sachets experienced no side effects during or after treatment. [22] Furthermore, Lactobacillus and Enterococcus bacteria have long been utilised as food additives. [23] The widespread consumption of beverages containing probiotics such as Lactobacillus and Bifidobacterium has been shown to reduce the occurrence of oral candidiasis in healthy people. [24] As a result, the reports are incompatible. As a result, more study is needed to confirm the safety of probiotics and to assess adverse occurrences in healthy persons and patients.

There were a number of constraints that were faced with regards to this investigation. To begin with, the number of studies included in the analysis was limited, especially when we concentrated on RCTs. Furthermore, some of the research were highly likely to be biased. Furthermore, in order to provide an overview of the literature, no strict exclusion criteria were used, resulting in greater variation among research. For the same reason, we had to make approximations in order to derive a single comparable effect measure from the results provided in the original studies; this could have skewed the systematic review.

Conclusion

It would seem, by analysing the literature and studies available, that introducing beneficial bacterial species into the oral and gastrointestinal system may be a viable option for re-establishing microbial balance and ameliorating the existing treatment modalities in the case of oral candidiasis. It must be mentioned though that the danger and morbidity of sepsis caused by probiotic bacteria should be evaluated against the risk of sepsis caused by more pathogenic bacteria and the morbidity of diseases treated with probiotic bacteria. Future placebo-controlled research with validated results is also needed to determine the genuine health advantages of probiotics. In this case, careful selection of the probiotic agent, standardisation of the given dose, and comprehensive information of its therapeutic effects are critical.

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