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Original Article

Mechanisms of action of *Lactobacillus* spp. in the treatment of oral candidiasis

Mecanismos de ação de *Lactobacillus* spp. no tratamento de candidíase oral

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Abstract

Candida albicans is often associated with oral candidiasis, and drug-resistance profiles have contributed to an increase in morbidity and mortality. It is known that *Lactobacillus* spp. acts by competing for adhesion to the epithelium, absorption of nutrients and modulation of the human microbiota. Therefore, they are important to assist in the host's microbiological balance and reduce the growth of *Candida* spp. Until now, there have been no reports in the literature of reviews correlating to the use of *Lactobacillus* spp. in the treatment of oral candidiasis. Thus, this review aims to highlight the mechanisms of action of *Lactobacillus* spp. and methods that can be used in the treatment of oral candidiasis. This is a study carried out through the databases PubMed Central and Scientific Electronic Library Online, using the following keywords: Oral Candidiasis and *Lactobacillus*. Original articles about oral candidiasis were included, with both *in vitro* and *in vivo* analyses, and published from 2012 to 2022. *Lactobacillus rhamnosus* was the most common microorganism used in the experiments against *Candida*, acting mainly in the reduction of biofilm, filamentation, and competing for adhesion sites of *Candida* spp. Among *in vivo* studies, most researchers used immunosuppressed mouse modelsof *Candida* infection. The studies showed that *Lactobacillus* has a great potential as a probiotic, acting mainly in the prevention and treatment of mucosal diseases. Thus, the use of *Lactobacillus* may be a good strategy for the treatment of oral candidiasis.

Keywords: oral candidiasis, probiotics, *Lactobacillus*, *Candida*.

Resumo

Candida albicans está frequentemente associada à candidíase oral e os perfis de resistência aos medicamentos têm contribuído para o aumento da morbidade e mortalidade. Sabe-se que *Lactobacillus* spp. atuam competindo pela adesão ao epitélio, absorção de nutrientes e modulam a microbiota humana. Portanto, são importantes para auxiliar no equilíbrio microbiológico do hospedeiro e reduzir o crescimento de *Candida* spp. Até o momento não há relatos na literatura de revisões correlacionando o uso de *Lactobacillus* spp. no tratamento da candidíase oral. Assim, esta revisão tem como objetivo destacar os mecanismos de ação de *Lactobacillus* spp. e métodos que podem ser utilizados no tratamento da candidíase oral. Trata-se de um estudo realizado a partir da busca em bases como: *PubMed Central* e *Scientific Electronic Library Online*, utilizando as seguintes palavras-chave: "Oral Candidiasis" e "*Lactobacillus*". Foram incluídos artigos originais sobre candidíase oral, com análises *in vitro* e *in vivo*, publicados de 2012 a 2022. *Lactobacillus rhamnosus* foi o microrganismo mais utilizado nos experimentos contra Candida, atuando principalmente na redução de biofilme, filamentação e competindo por sítios de adesão de *Candida* spp. Entre os estudos *in vivo*, a maioria dos pesquisadores utilizou modelos de camundongos imunossuprimidos para infecção por Candida. Os estudos mostraram que os Lactobacillus possuem grande potencial como probiótico, atuando principalmente na prevenção e tratamento de doenças da mucosa. Assim, o uso de Lactobacillus pode ser uma boa estratégia para o tratamento da candidíase oral.

Palavras-chave: candidíase oral, probióticos, *Lactobacillus*, *Candida*.

1. Introduction

The microbiota that colonizes the skin and mucous membranes surfaces are essential to prevent the invasion and colonization of pathogens and protect and defend the organism. The oral cavity comprises a complex microbiota of bacteria, archaea, fungi, viruses, and protozoa. Although fungi are present in lower numbers, *Candida* spp. is a common and opportunistic pathogen and one of the leading causes of human infections. Worldwide, about 700,000 cases are reported (Sardi et al., 2013; Hillman et al., 2017; Bongomin et al., 2017).

Due to the AIDS (Acquired Immunodeficiency Syndrome) epidemic in the 1980s, interest in oral infections increased,

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primarily because of the prevalence of oral candidiasis as an opportunistic infection in seropositive individuals (Lewis and Williams, 2017). Imbalances in the oral microbiota favor the proliferation of *Candida* spp., which leads to oral candidiasis. This pathology can affect all types of patients. However, it is more common in immunocompromised patients, such as those infected with HIV, hepatitis, cancer, or prolonged antimicrobial therapy, and can be fatal if disseminated (Černáková and Rodrigues, 2020; Gheorghe et al., 2021).

Oral candidiasis is a disease whose inflammation of the mucosa can occur under different clinical manifestations, either in the form of acute pseudomembranous candidiasis, acute and chronic erythematous candidiasis, or as chronic hyperplastic candidiasis (Quindós et al., 2019; Williams and Lewis, 2011).

Despite studies describing an increase in the prevalence of oral candidiasis, mainly affecting immunocompromised patients and the elderly, these mycoses remain neglected, with few epidemiological surveillance and insufficient progress in diagnostic and therapeutic methods (Justiz Vaillant and Qurie, 2023; Bessa et al., 2021).

In Brazil, systemic mycoses are not on the national list of notifiable diseases and are not in the routine of epidemiological surveillance. Therefore, there is a lack of epidemiological data on the occurrence, magnitude, and transcendence of infections caused by *Candida* (Brasil, 2021).

According to the Centers for Disease Control and Prevention (CDC), in 2019, there were 34,800 hospitalizations and 1,700 deaths due to *Candida* spp. drug-resistance. Of these, 323 cases were related to multidrug-resistant *Candida auris* (CDC, 2019). Thus, fungal infections are a significant problem for public health (Brown et al., 2012).

Of the 200 species that make up the genus *Candida*, about 20 are recognized as causing infections (Turner and Butler, 2014; Macêdo et al., 2009). *Candida albicans* is often associated with oral candidiasis, considered the primary agent of mucosal and systemic infections, in addition to being related to about 70% of infections caused by fungi in the world (Morad et al., 2018). Non-*albicans species* associated with oral candidiasis include *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei* (Mushi et al., 2016). *C. glabrata* and *C. tropicalis* are related to high rates of morbidity and mortality (Macêdo et al., 2009; Richardson and Lass-Flörl, 2008).

C. albicans can have different morphologies, including yeast, pseudohyphae and hypha (Saghrouni et al., 2013). Infection occurs due to several virulence factors, which make fungal colonization successful (Deorukhkar and Roushani, 2017). The yeast should settle in the oral cavity for the disease to establish itself, and this adhesion mechanism is a determining factor for fungal colonization. Furthermore, as host defense factors, salivary flow and swallowing should not completely remove the fungal cells attached to mucosal surfaces (Vila et al., 2020).

Conventional antifungals are used for treatment. However, due to the increase in resistant *Candida* strains, the effectiveness of these drugs becomes impaired. Thus, searching for new therapies is relevant (Muñoz et al., 2020). Treatment depends on early diagnosis and identification of candidiasis forms, risk factors and the use of suitable antifungal drugs (Garcia-Cuesta et al., 2014).

Currently, four classes of antifungals against *Candida* are available: polyenes, azoles, echinocandins and 5-flucytosine, a fluorinated cytosine analogue (Bhattacharya et al., 2020). However, drug resistance profiles among pathogenic fungi have increased and contributed to mortality (Muñoz et al., 2020; Ravikumar et al., 2015).

In 2016, the *Infectious Diseases Society of America* (IDSA) published updated guidelines on treating oral candidiasis (Pappas et al., 2016). One tablet of miconazole 50 mg should be used once a day for seven to fourteen days for mild illness. Alternatively, nystatin may be used four times a day for seven to fourteen days. Oral Fluconazole during this same period should be used in cases of moderate-to-severe oral candidiasis. Despite being widely used for a long time, Fluconazole has still considered a good choice due to its excellent bioavailability, low toxicity, and few adverse effects (Pappas et al., 2016; Quindós et al., 2019). It is important to note that some *Candida* species are intrinsically resistant to antifungal agents, and Fluconazole's widespread use in prophylaxis has contributed to increasing cases of resistance (Diniz-Neto et al., 2024; Sardi et al., 2013). Furthermore, *C. albicans* can form biofilms and secrete hydrolytic enzymes that are considered virulence factors (Nicholls et al., 2011).

Thus, it is necessary to develop therapeutic alternatives associated with the use of new antifungal drugs, probiotics and even peptides with antifungal activities (Marcos-Arias et al., 2011). Probiotics are live microorganisms beneficial to the health of their host. The International Scientific Association of Probiotics and Prebiotics (ISAPP) defines products that can be classified as probiotics and prebiotics, and these include medicines, formulas and supplements that benefit human health. The most commonly used strains include *Bifidobacterium* spp., *Lactobacillus* spp. and *Saccharomyces* spp. These probiotics compete for adherence to the epithelium, uptake of nutrients, and modulate the microbiota to modify the microbiological balance of the host and reduce the growth of pathogens, such as *Candida* spp. (Amara and Shibl, 2015; Hill et al., 2014; Rossoni et al., 2018). In addition, *Lactobacillus* species secrete products that modulate the expression of *C. albicans genes* and inhibit biofilm formation (James et al., 2016).

Research with *Lactobacillus* spp. demonstrate that these bacteria reduce the growth of *Candida*, inhibit the formation of biofilms, and act on the immune response, stimulating the release of cytokines by macrophages and the expression of pattern recognition receptors in response to *C. albicans*, which may improve symptoms and invasive infections (Matsubara et al., 2016, 2017). In addition, in the cultivation of *Candida* with *L. rhamnosus*, a reduction in the production of proteinase, hemolysis, hyphae and biofilms was observed (Oliveira et al., 2016).

Therefore, it is believed that advances in the use of probiotics in the prevention and treatment of oral candidiasis are an attractive alternative to restoring the microbiota between the bacterial and fungal communities in the oral cavity (Doppalapudi et al., 2020). Thus, our review aims to highlight the mechanisms of action of

Lactobacillus spp. and methods used *in vitro* and *in vivo* that can be used in the treatment of oral candidiasis.

2. Material and Methods

This is a narrative bibliographic review carried out through the following databases: PubMed Central (PMC) and Scielo (*Scientific Electronic Library Online*) with the keywords used: Oral Candidiasis AND *Lactobacillus*. Original articles were included, which had *in vitro* and *in vivo* analyses focused on oral candidiasis, in English, published between 2012 and 2022. Articles that did not meet the inclusion criteria were excluded.

During the review, 11 articles focused on oral candidiasis were selected, with analyses performed *in vitro* and *in vivo*. However, before discussing the effects of *Lactobacillus* directly on oral candidiasis, we chose to mention the mechanisms of action of *Lactobacillus* spp. against *Candida* spp.

2.1. Mechanisms of action of Lactobacillus spp. against Candida spp.

Recently, a new classification was adopted in the list of prokaryotes with *Standing in Nomenclature* (LPSN). In this update, *Lactobacillus spp.* became part of the genus *Lactiplantibacillus*, which includes *Lactobacillus plantarum*, *Lactobacillus paraplantarum* and *Lactobacillus pentosus*. *Lactobacillus casei*, considered to be of the genus *Lacticaseibacillus*, includes *Lactobacillus paracasei*, and *Lactobacillus rhamnosus*. The group of *Lactobacillus reuteri* was called *Limosilactobacillus*, with the species *Lactobacillus reuteri* and *Lactobacillus vaginalis*. *Lactobacillus delbrueckii* remained in the genus *Lactobacillus* with the species *Lactobacillus acidophilus*, *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus jensenii*, *Lactobacillus johnsonii*, and the subspecies *Lactobacillus delbrueckii*, such as *Lactobacillus delbrueckii* ssp. bulgaricus and *L. delbrueckii* ssp. (Zheng et al., 2020; ICSP, 2022).

Bacterial and fungal species can occupy the same places on the mucous membranes. However, *Lactobacillus* may present activities against *Candida*, preventing fungal infections (Vazquez-Munoz et al., 2022). *Lactobacillus* spp. are facultative anaerobic, Gram-positive, and catalase-negative microorganisms that can form spores. Their peculiar characteristic is lactic acid production as a product of anaerobic fermentation (Zangl et al., 2020). This acid is commonly reported as a metabolite that inhibits the growth of *C. albicans* (Ballou et al., 2016). In addition, they present several mechanisms of action, whether in competition for receptors, secretion of metabolic products, or stimulation of the innate and adaptive immune response (Mundula et al., 2019).

Probiotics as adjuvants in therapies are conducive to preventing and reducing symptoms, keeping the microbiota in balance, and improving the immune system, mainly due to their mechanisms that act by helping in mucosal barriers, being antagonistic to pathogens, inhibiting adhesion and invasion of microorganisms, stimulating the immune system, and even the regulation of the central nervous system (Stavropoulou and Bezirtzoglou, 2020).

A recent study demonstrated several antifungal activities of *Lactobacillus*, in which this genus restricts the progression of chronic periodontitis by inhibiting the secretion of Th17 lymphocytes, which are responsible for the increased production of cytokines that cause an inflammatory process by altering periodontal tissues (Kaźmierczyk-Winciorek et al., 2021).

De Gregorio et al. (2020) showed that *L. crispatus* BC1 biosurfactants could induce changes in cell morphology, contributing to the inhibition of *Candida* adhesion to epithelial cells. Thus, the specific action of probiotics against *Candida* spp. is related to decreased fungal adhesion through coaggregation, biofilm formation, competition for nutrients, and the production of organic acids and antimicrobial substances, such as bacteriocins, acetic acid, biosurfactants, hydrocarbons and hydrogen peroxide (Matsubara et al., 2016; Parolin et al., 2021; Borges et al., 2014; Kovachev, 2018).

2.2. In vitro assays using Lactobacillus spp. against Candida spp. in studies focused on oral candidiasis

Table 1 lists different *in vitro* tests demonstrating Lactobacillus's performance against *Candida* spp. The species used were *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. rhamnosus*, *Lactobacillus fermentum*, *L. reuteri*, *L. gasseri*, *Lactobacillus helveticus*, *L. casei*. We observed that *L. rhamnosus* was the most commonly used in experiments against *Candida*. It is worth mentioning that this species is highly genetically characterized (Segers and Lebeer, 2014).

Several studies report the antifungal potential of *L. rhamnosus*, mainly through the reduction of biofilm, filament and adhesion of *C. albicans* (Allonsius et al., 2017, 2019; Stivala et al., 2021; Ribeiro et al., 2017; Ribeiro et al., 2020). Song and Lee (2017), when testing the action of the probiotics *L. rhamnosus* GG (ATCC 53103) and *L. casei* (ATCC 334) on the production of biofilm and hyphae in the resin prosthesis, found that the probiotic association reduced the production of blastoconidia and hyphae of *C. albicans* without modifying the prosthesis structure. It is known that the transition in yeast-hyphae morphology is paramount for the pathogenicity of *Candida* species (Witchley et al., 2019).

According to Mailander-Sánchez et al. (2017), the antifungal property of *L. rhamnosus* GG is mediated by adhesion blocking and nutrient depletion mechanisms. Using oral epithelial cells (Reconstructed Human Oral Epithelium - RHOE), the authors observed that *C. albicans* in contact with RHOEs stimulates the production of lactate dehydrogenase (LDH) and lysis of epithelial cells. However, when the cells were pre-incubated with the probiotic, there was a reduction in *C. albicans* and also in the release of LDH, with attenuation of evasion mechanisms and hyphae production.

Lactobacillus spp. modulate the proliferation of pathogens through the production of antimicrobial metabolic by-products, such as biosurfactants (BSs) and bacteriocins (Zheng et al., 2020; Borges et al., 2014). BSs produced by *Lactobacillus* are reported to have potential effects on *Candida* adhesion and biofilm formation. An *in vitro* model of adhesion and biofilm formation using

Table 1. *In vitro* assays using *Lactobacillus* spp. against *Candida* spp. in studies focused on oral candidiasis.

***Lactobacillus* species**	**Concentration**	***Candida* species**	**Concentration**	**Main Assays**	**Main Effects**	**References**
L. acidophilus, *L. plantarum*	10^2 to 10^{10} CFU/mL	*C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. kefyr and C. krusei*	1.5×10^3 to 10^6 CFU/mL	Co-aggregation; Agar overlay interference; MIC.	Both *L. acidophilus* and *L. plantarum* inhibited the growth of most of the oral Candida species, isolated from HIV/AIDS patients.	Salari and Almani (2020)
L. paracasei 28.4	10^6 to 10^9 cells/mL	*C. albicans* (ATCC 18804), *C. albicans* 60, *C. albicans* 14	10^6 to 10^7 cells/mL	Agar overlay interference; Biofilm; Effect of formulation on hyphae production.	The probiotic-gellan gum formulations provide a released of *L. paracasei* cells of 24 h; showed inhibitory, anti-biofilm and anti-hyphae activity.	Ribeiro et al. (2020)
L. acidophilus (ATCC 4356), *L. casei* (ATCC 334), *L. rhamnosus* GG (ATCC 53103)	$1x10^7$ cells/mL	*C. albicans* (ATCC 10231)	$1x10^6$ cells/mL	Disk diffusion susceptibility test; Biofilm; MIC.	*L. casei* and *L. rhamnosus* GG exhibited stronger antifungal activity against blastoconidia and biofilm of C. albicans, as well as inhibited formation of *Candida* biofilm on denture surface.	Song and Lee (2017)
L. paracasei (1.1, 3.1, 4.2, 6.2, 7.5, 8.4, 10.5, 11.6, 15.8, 16.4, 17.1, 20.3, 21.4, 23.4, 24.1, 25.4, 26.1, 27.1, 28.4, 37.1, 39.2), *L. rhamnosus* (5.2, 13.1, 19.3, 19.9, 36.4), *L. fermentum* (14.5, 20.4, 31.4)	10^7 cells/mL Supernatant	*C. albicans* ATCC 18804, *C. albicans* CA60 and CA230S	10^7 cells mL^{-1}	Antibacterial activities in planktonic cultures; Biofilm; *C. albicans* gene expression by RT-PCR.	*L. rhamnosus* 5.2, *L. fermentum* 20.4 and *L. paracasei* 28.4 exhibited the most significant inhibitory activity against *C. albicans* (ATCC 18804). The three strains of *lactobacillus down*-regulated expression of *C. albicans* biofilm specific genes (*ALS3*, *HWP1*, *CPH1* and *EFG1*)	Rossoni et al. (2018)

Table 1. Continued...

***Lactobacillus* species**	**Concentration**	***Candida* species**	**Concentration**	**Main Assays**	**Main Effects**	**References**
L. reuteri (DSM 17938 and ATCC PTA 5289)	10^3 to 10^9 CFU/mL	*C. albicans* (CBS 562 NT and CCUG 46390),	0.2 at 500 nm	Co-aggregation;	Both *L. reuteri* strains showed co-aggregation abilities with the yeasts. The lactobacilli almost completely inhibited the growth of *C. albicans* and *C. parapsilosis*, but did not affect *C. krusei*.	Jorgensen et al. (2017)
	supernatant	*C. dubliniensis* (41_3 ZZMK and CCUG 48722),		Agar overlay interference test;	The pH measurements suggested that *C. krusei* can resist the acids produced by the lactobacilli.	
		C. glabrata (CBS 863 and CCUG 63819),		pH effect; H_2O_2 production by the lactobacilli.		
		C. krusei (RV 491 and CCUG 56126),				
		C. parapsilosis (26 PBS and CCUG 56136),				
		C. tropicalis (DSM 7524 and CCUG 47037).				
L. rhamnosus GG	OD_{600} of 0.669	*C. albicans* (SC 5314)	$5x10^6$ /mL	Cell culture and generation of three-dimensional mucosal models; Infection of RHOEs and TR146 cell monolayers; Epithelial cell damage; ELISA, Adhesion and Invasion assays; Quantification of RNA-Seq; DNA sequencing.	*L. rhamnosus* protects oral epithelia against *C. albicans* infection by preventing fungal adhesion, invasion and damage in model of oral candidiasis. Transcriptional profiling using RNA-Seq indicated dramatic metabolic reprogramming of *C. albicans*.	Mailander-Sánchez et al. (2017)

Table 1. Continued...

***Lactobacillus* species**	**Concentration**	***Candida* species**	**Concentration**	**Main Assays**	**Main Effects**	**References**
Lactobacillus gasseri	Cell-free Supernatants	*C. tropicalis*	OD_{600} 0.1 or OD_{600} 0.01	Biofilm;	The lactobacilli supernatants reduced the biofilm formation of all non-*Candida species*.	Tan et al. (2018)
L. rhamnosus		*C. krusei*		Cell viability;	Confocal laser scanning microscopy and scanning electron microscopy confirmed that lactobacilli supernatants inhibited the mixed biofilms and damaged the cells.	
		C. parapsilosis		Scanning electron microscopy.		
L. plantarum SD5870	$5x10^6$	*C. albicans* TIMM 1768	$1x10^6$ to $1x10^7$ UFC	Biofilm, *Candida* gene analysis (qPCR)	Combinations of live probiotics or their supernatants reduced biofilm formation of *C. albicans*.	James et al. (2016)
L. helveticus CBS N116411	Supernatants				Supernatants significantly reduced the expression of several *C. albicans* genes critical to the yeast-hyphae transition, biofilm formation, tissue invasion and cellular damage.	

pre-incubation of *Lactobacillus* species in BSs-sensitized microplates showed that these interfered *with C. albicans* biofilm formation (Itapary et al., 2019).

Ribeiro et al. (2017) reported that *L. rhamnosus* down-regulates genes related to filament and adhesion (*als3* and *hwp1*) and transcription (*bcr1* and *cph1*) of *C. albicans*. When *Lactobacillus* supernatant was used, *Candida* metabolism was reduced by about 61%. The same occurred with *L. rhamnosus* supernatant, which reduced fungal biomass and metabolic activity of single and mixed cultures of *Candida*. On *C. tropicalis*, the reduction was 66.84%. For *C. krusei*, 70.56%, and *C. parapsilosis*, 41.33%. In mixed cultures of these *Candida* species on silicone, there was a decrease of 67.16% by *L. rhamnosus* (Tan et al., 2018).

Rossoni et al. (2018) also evaluated the effect of *L. rhamnosus*, *L. fermentum*, and *L. paracasei* supernatants against *C. albicans*. The strains *L. paracasei* 30.1, 37.1, and 39.2 and *L. rhamnosus* 36.4 had no inhibitory effects on *C. albicans* ATCC 18804. On the other hand, it is essential to highlight that not all *Lactobacillus* spp. are beneficial and protective (Kalia et al., 2020). The isolates that showed the highest antifungal activity against *C. albicans* ATCC 18804 were *L. rhamnosus* 5.2, *L. fermentum* 20.4, *and L. paracasei* 28.4. Although the three strains reduced the expression of the *als3*, *hwp1*, *cph1* and *efg1 genes* of *C. albicans*, *L. paracasei* showed a better reduction of *C. albicans* cells and gene expression (Rossoni et al., 2017).

Recently, it was found that *L. paracasei* 28.4 also interferes with the growth of *C. auris* (Rossoni et al., 2020), which is quite interesting, given that *C. auris* is an emerging multidrug-resistant pathogen that causes systemic infections (Jeffery-Smith et al., 2017).

Ribeiro et al. (2020) developed formulations with gellan gum containing *L. paracasei* 28.4 to improve the availability of the probiotic in the oral cavity. The tested formulations were able to inhibit *Candida* spp. biofilms, decreasing the total biomass and preventing the formation of hyphae.

A study on the genomic analysis of *L. fermentum* ATCC 23271 detected genes related to proteins with the ability to tolerate digestive enzymes, bile salts, acid pH, oxidative stress, and the production of lactic acid and host cell adhesion molecules (Santos et al., 2021). In addition, Carmo et al. (2016) observed that *L. fermentum* ATCC 23271 produces biofilm, co-aggregates and binds to mucin, interacting effectively against *C. albicans*.

L. acidophilus can co-aggregate with *Candida* species, with a high rate of coaggregation with *C. krusei* and *C. glabrata* being reported. Supernatants from *L. acidophilus* and *L. plantarum* have an inhibitory effect on the growth of *C. krusei*, *C. parapsilosis* and *C. kefyr* compared to the antifungal Fluconazole (Salari and Almani, 2020).

Supernatants from *L. acidophilus* 8MR7 and *L. paracasei* subspecies *paracasei* 10MR8 have been shown to inhibit *Candida spp.* biofilms (Kivanç and Er, 2020). *L. acidophilus* reduces the growth of *C. albicans* and decreases the production of hyphae (Vilela et al., 2015).

The supernatant of *L. plantarum SD5870 and L. helveticus* CBS N116411N considerably reduced the *C. albican's* adhesion to polyurethane. When the probiotic cells were combined, there was a greater capacity to destroy pre-formed biofilms and decrease the expression of *als3*, *efg1*, *hwp1* and *sap5* genes, related to adhesion, invasion and defenses of *C. albicans* (James et al., 2016).

Studies by Zeng et al. (2022) corroborate the data presented, since *L. plantarum* 14917 inhibited the growth of *C. albicans* under planktonic conditions, as well as the formation of biofilm. *L. plantarum* strains 8014 and 14917 eliminated cariogenic biofilm formation. When the supernatant of *L. plantarum* 14917 was tested, there was antibacterial and antifungal activity against *C. albicans*, but the supernatant of *L. plantarum* 8014 had bacteriostatic and fungistatic effects.

Parolin et al. (2021) found that *L. plantarum* was a strong biofilm producer, as was *L. gasseri*, and provided broad activity against *Candida* when applied in planktonic media, particularly when exposed to *C. lusitaniae* SO22 and *C. parapsilosis* SO27. *L. gasseri* has also been mentioned as a biofilm inhibitor in mixed cultures of *Candida* species (Tan et al., 2018).

Jorgensen et al. (2017) analyzing the *in vitro* efficacy of *L. reuteri* DSM 17938 and ATCC PTA 5289 against clinical isolates of *C. albicans* CBS 562 NT, *C. dubliniensis* 41_3 ZZMK, *C. glabrata* CBS 863, *C. krusei* (*Issatchenkia orientalis*) RV 491, *C. parapsilosis* 26 PBS and *C. tropicalis* DSM 7524, and reference isolates of *C. albicans* CCUG 46390, *C. dubliniensis* CCUG 48722, *C. glabrata* CCUG 63819, *C. krusei* CCUG 56126, *C. parapsilosis* CCUG 56136 and *C. tropicalis* CCUG 47037, found that *L. reuteri* (DSM 17938) exhibited greater coaggregation with *C. krusei* and had inhibition of *Candida* strains, except for the two strains of *C. krusei*. A lower inhibition of *C. tropicalis* by *L. reuteri* (DSM 17938) was observed at a concentration of 10^9 CFU/mL, while *C. glabrata* was inhibited at the highest concentration.

2.3. In vivo assays using Lactobacillus spp. against Candida spp. in studies focused on oral candidiasis

Most models use immunosuppressed mice for infection by *Candida* spp. (Table 2). Ito et al. (2021) used mice infected with *C. albicans* GDH18 to treat *L. rhamnosus* L8020. The probiotic was effective as the treated group had smaller lesions on their tongues when compared to the control group, administered only in water. The probiotic reduced the expression of Dectin-2 and CCL2 and decreased TLR2 and CXCL1/KC levels.

On the other hand, Leão et al. (2018) used *L. rhamnosus* ATCC 7469 in their oral candidiasis model by infecting Wistar rats with *C. albicans*. In the study, probiotics were administered for seven and 21 days to different groups of animals. Ingestion of *L. rhamnosus* ATCC 7469 for seven days did not significantly influence the CFU count. Meanwhile, *C. albicans* was not detected in most infected animals that received the probiotic for 21 days.

In the study by Ribeiro et al. (2020) when administering *L. paracasei* 28.4 in Swiss mice in a 1% probiotic formulation, observed an inhibition of the growth of *C. albicans* when compared to the control group, preventing the appearance of lesions caused by the candidiasis and inflammation.

Matsubara et al. (2012) used a model of oral candidiasis in DBA/2 mice. It was found that *L. acidophilus* and *L. rhamnosus* inhibited yeasts in the oral mucosa. Compared with the control group containing nystatin, it was observed

Table 2. *In vivo* tests using *Lactobacillus* spp. against *Candida* spp. in studies focused on Oral Candidiasis.

***Lactobacillus* species**	**Concentration**	***Candida* species**	**Concentration**	**Main Essay**	**Main Effects**	**Reference**
L. rhamnosus (ATCC 7469)	10^6 cells/mL	*C. albicans*	10^9 cells/mL	Oral candidiasis model in Wistar-immunosuppressed male mice (11-12 weeks old); Histological evaluation Cytokines quantification.	Groups that consumed probiotics had lower histological and inflammatory infiltrates when compared to the group candidiasis with no probiotic intake.	Leão et al. (2018)
L. paracasei 28.4	10^6 to 10^8 cells/mL	*C. albicans*	10^8 cells/mL	Oral candidiasis model in Swiss male mice	The 1% probiotic formulation inhibited the growth of *C. albicans*, prevented the development of candidiasis lesions and suppressed the inflammatory process.	Song and Lee (2017)
L. acidophilus NCFM *L. rhamnosus* Lr-32	10^9 cells/mL	*C. albicans* ATCC 90028	10^8 cells/mL	Oral candidiasis model in DBA/2-immunossuppressed mice (6-8 weeks old)	Probiotics reduced the *C. albicans* colonization significantly on the oral mucosa in comparison with the untreated animal group. In the group treated with *L. rhamnosus*, the reduction in yeast colonization was significantly higher compared with that of the group receiving nystatin.	Matsubara et al. (2012)
L. rhamnosus L8020	10^6 cells/mL	*C. albicans* GDH18	109	Oral candidiasis model in ICR-immunosuppressed female mice (6 weeks old); Histological evaluation; RT-PCR (expression of receptors and chemokines)	Oral consumption of *L. rhamnosus* L8020 by *C. albicans* infected mice abolished the pseudomembranous region of the mouse tongue; it also significantly reduced the expression levels of Dectin-2 and CCL2, and tended to reduce the expression levels of TLR2 and CXCL1/KC, after infection with *C. albicans* GDH18.	Ito et al. (2021)

that the drug did not cause a significant reduction in *C. albicans*, as observed with the group where lactobacilli were administered. Once again, the study points to the importance of new therapeutic methods aimed at oral candidiasis.

Several species of *Lactobacillus* have probiotic activities that promote intestinal, vaginal and oral health (Mahasneh and Mahasneh, 2017; Vicariotto et al., 2014). However, when focused on oral health, there are few reports in the literature, even though there is evidence that *Lactobacillus* can decrease the growth of *Candida* in the human oral cavity (Ishikawa et al., 2015).

The development of probiotic formulations that maintain the viability of the microorganisms and are effective for the consumer is another challenge related to the lack of studies (Fenster et al., 2019). For Chugh and Kamal-Eldin (2020), a probiotic formulation to be considered therapeutic should be in the range of 10^8 to 10^9 CFU/g, so that bioavailability, when ingested, is in the range of 10^6 to 10^7 CFU/g. It is noticeable that cell viability is necessary and that several mechanisms help maintain the viability of probiotic formulations. Cell inactivation mechanisms are one of the prerequisites (Coutinho et al., 2010).

Gelatin is widely used as a delivery method for probiotics. Gellan gum is a natural polysaccharide commonly used as a food additive and can potentially be manipulated by the pharmaceutical industry to encapsulate *Lactobacillus* (Coutinho et al., 2010; Ribeiro et al., 2020). However, since the viability of microorganisms is maintained for a short time during their storage, another way to maintain cell viability is to reduce the amount of water available through freezing procedures to allow drying and prolongation of cell viability (Broeckx et al., 2017; Govender et al., 2014). On the other hand, there are complications with liquid formulations since patients do not accept these formulations well due to storage criteria for microbial viability (Vorländer et al., 2020).

Thus, we find that there is a demand to create new mechanisms that protect probiotics, thus improving their shelf life. The application of these microorganisms and their antimicrobial products must be well-validated to have space on the market and not have toxic effects. For this, studying the interactions between microorganisms and the host is crucial.

3. Conclusion

Different fungal genera, such as *Candida*, *Pneumocystis* and *Cryptococcus*, cause morbidity and mortality worldwide. In this context, fungal diseases are advancing, mainly due to their disregard by organ-competent bodies. Therefore, the description of the prevalence of oral candidiasis, its clinical manifestations, and its treatment is of great importance for preserving health, especially when resistance strains to conventional drugs are involved. Thus, it is necessary to search for new therapeutic alternatives for treating oral candidiasis and new probiotic strains and describe their mechanisms of action through *in vitro* and *in vivo* studies.

The search for new probiotic strains and mechanisms of action are of great importance. It is known that probiotics are part of the population's daily life and that their benefits are due to the recovery of homeostasis by reducing pathogens, regulating the immune system, and even preventing infections. Therefore, it is expected that new probiotic strains will be able to reduce *Candida* infection in the oral cavity, as well as the production of its virulence factors, in addition to controlling the inflammatory process resulting from the infection process.

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