Referência

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Pro & *Postbiotics* play a role in disruptive relationships between yeast and bacteria

Pré & Pós-biótico desempenham um papel nas relações disruptivas entre leveduras e bactérias

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ABSTRACT

Antimicrobial resistance is an inevitable evolutionary event. Pathogenic strains of *Candida* spp. have been increasing in several cases, so candidiasis has become a serious public health problem. Alternative therapeutic approaches are gaining "space" and attention in the treatment of fungal diseases. This study is a systematic review, using the identification, selection, inclusion, and exclusion criteria of the PRISMA method. Works were selected and separated into 5 tables. The *Lactobacillus* spp. causing opposite effects against several pathogenic microorganisms, being considered one of the probiotics that play essential functions of immunomodulation in the intestinal mucosa, with beneficial effects, restores and promotes the maintenance of vaginal microbiota. It is clear from the data investigated that the use of *Lactobacillus* may be an alternative therapeutic approach for the treatment or control of the spread of *Candida* species responsible for candidiasis.

Keywords: *Candida*; *Lactobacillus*; Probiotics; Prebiotics;

RESUMO

A resistência a antimicrobianos é um evento evolutivo inevitável. Linhagens de *Candida* spp. patogênicas vêm aumentando em número de casos, de modo que a candidíase se tornou grave problema de saúde pública. Abordagens terapêuticas alternativas vêm conquistando “espaços” e atenção no tratamento de doenças fúngicas. O presente estudo trata-se de uma revisão sistemática, em que foram utilizados os critérios de identificação, seleção, inclusão e exclusão do método PRISMA. Foram selecionados trabalhos e separados em 5 quadros. Os *Lactobacillus* spp. vem ganhando cada vez mais atenção por causar efeitos opostos contra diversos micro-organismos patogênicos, sendo considerados um dos micro-organismos probióticos que mais atuam em funções essenciais de imunomodulação na mucosa intestinal, com efeitos benéficos, restaura e promove a manutenção microbiota vaginal. É notório pelos dados investigados que o uso de *Lactobacillus* pode ser uma abordagem terapêutica alternativa para o tratamento ou controle da disseminação de espécies de *Candida* responsáveis pela candidíase.

Palavras-chave: *Candida*; *Lactobacillus*; Probiótico; Prebiótico

INTRODUCTION

In nature, there are ecological relationships between living things called harmonic and disharmonic. Competition for nutrients and space is the ‘’kick’’ that led to the premise postulated by Herbert Spencer and later explored by Charles Darwin: survival of the fittest, or the concept relating to competition for dominance (Schluter, 2001). Such “competition” occurs in all ecological niches, whether in a macro-ecosystem (oceans and forests, for example) or micro-ecosystem (microbiota of the skin, gut, for example).

Antimicrobial resistance is a prime example of the above; it is an inevitable evolutionary event. However, it can be controlled and dosed temporally. Fungi and bacteria exposed to antimicrobial agents, suffer selective pressure in the environment where these drugs are employed, and the more they are exposed, the more resistant strains emerge due to genetic changes that favor survival and colonization (Bottery et al., 2021; Davies & Davies, 2010)

Being that drug-resistant infections already cause at least 700,000 deaths worldwide annually, including 230,000 deaths from multidrug-resistant tuberculosis. In a more alarming scenario, if no action is taken, about 10 million deaths per year worldwide by 2050, such that 2,4 million people could die in high-income countries between 2015 and 2050 (Interagency Coordination Group on Antimicrobial Resistance, 2019).

Taxonomically and morphologically, *Candida* spp. is a genus of commensal yeast fungus belonging to the family *Saccharomycetaceae*, responsible for the pathology called candidiasis (Rodríguez-Cerdeira et al., 2020). There is a new nomenclature for *Candida glabrata*, *Nakaseomyces glabrata*, however, we will continue to use the old nomenclature as it is still rarely applied in the literature (Gómez-Gaviria et al., 2022). Some species belonging to the human microbiota, colonize the mucosal surfaces of different tissues, such as the skin, urogenital system, oral cavity, respiratory system, and gastrointestinal tract (Mundula et al., 2019)

According to studies, most *Candida* species are considered opportunistic and depending on the conditions they encounter, they are able to change from commensal (harmless form) to an infectious form (Mundula et al., 2019; Quindos et al., 2019). These opportunistic species are divided into two groups, first group with higher incidences of infections is called the *C. albicans* complex and the second group with lower incidence is called *Candida*-non-*albicans* (*C.glabrata, C.tropicalis, C.krusei,* among others) (Rodríguez-Cerdeira et al., 2020).

Pathogenic *Candida* spp. strains have been increasing in a number of cases, so that candidiasis has become a serious public health problem, particularly among women of childbearing age (Paniágua et al., 2021) and immunocompromised people, due to the high level of mortality and resistance to antifungal drugs (Hellstein & Marek, 2019).

It is estimated, that 70% to 75% of women have had or will have at least once vulvovaginal candidiasis (VVC) in their lifetime (Xie et al., 2017) and that 8 to 10% of women are susceptible to this disease (Pericolini et al., 2017). Epidemiological data report that approximately 138 million women annually are comed with VVC (Yano et al., 2019).

Alternative therapeutic approaches are gaining space and attention in the treatment of fungal diseases. There is an evident growth in research investigating the role of probiotics and their beneficial effects in the treatment of fungal diseases. According to the WHO (World Health Organization), probiotics are: “microorganisms that, when administered in adequate amounts, confer a health benefit to the host” (Buggio et al., 2019; De Gregorio et al., 2020), an example of a microorganism convenient for human organisms, are *Lactobacillus.*

Lactobacillus spp. are commensal, facultative anaerobic, gram-positive, non-spore-forming bacteria (Rocha-Ramírez et al., 2017), which inhabit the human organism, and hava been gaining increasing attention for causing opposing effects against several pathogenic microorganisms(Chew et al., 2015), being considered one of the probiotic microorganisms that act most in essential functions of immunomodulation in the intestinal mucosa, with beneficial effects (Zangl et al., 2020), restores and promotes the maintenance vaginal microbiota (Buggio et al., 2019).

Another alternative method is the use of probiotics such as sodium butyrate (NaBut) which is a short-chain fatty acid produced by fermenting bacteria (example: *Clostridium butyricum*) in the large intestine and has the ability to modulate the immune system of intestinal mucosae, as it facilitates macrophage polarization (Ji et al., 2016). NaBut acts as an inhibitor of histone deacetylases, having a role in epigenetic modulation (Brandão et al., 2015; Oliveira, 2012). The result of the application of these modulators, decreased the growth of pathogenic yeasts, such as *C.albicans* (Nguyen et al., 2011).

METHODOLOGY

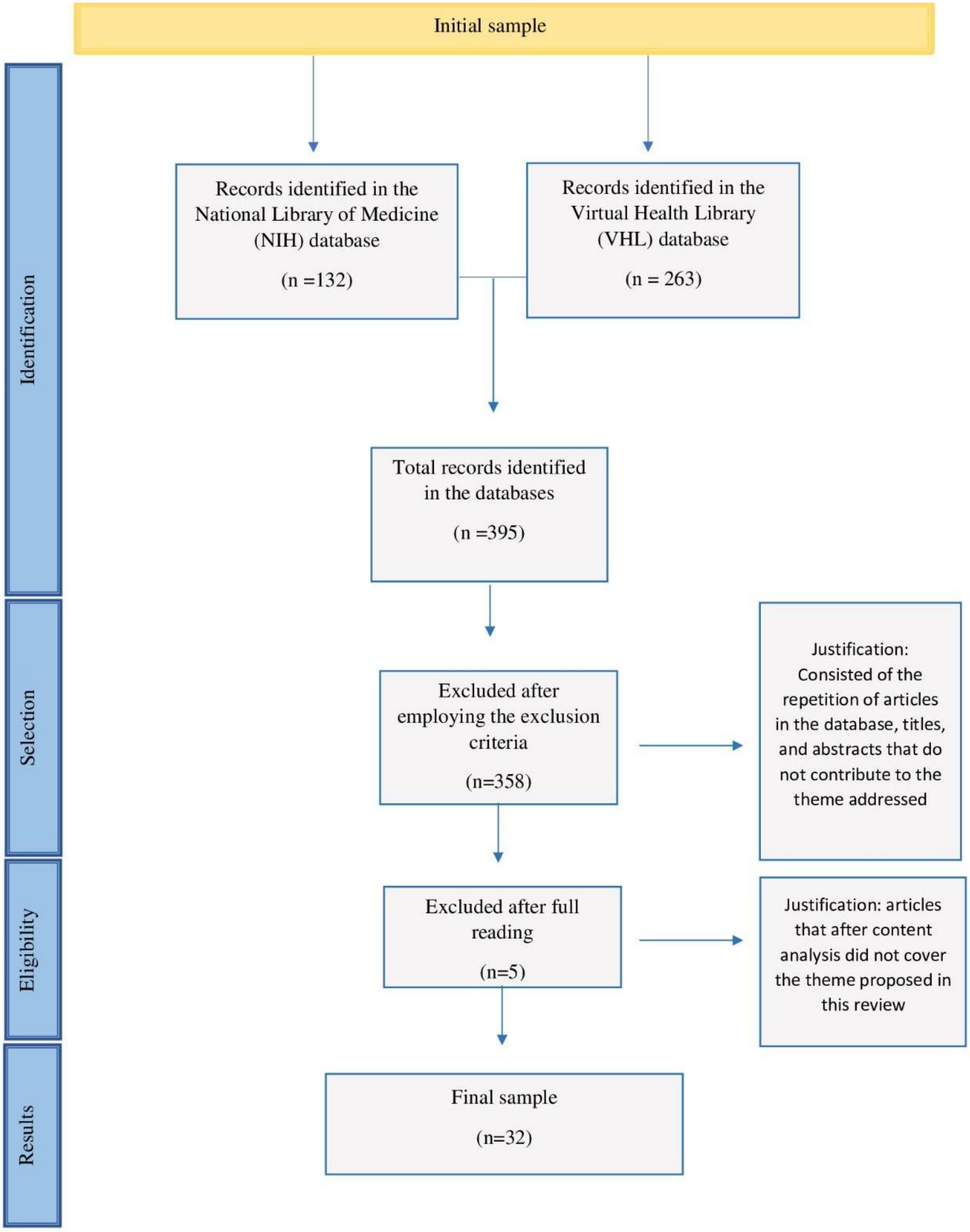
This study is an integrative literature review. The literature survey occurred in the second half of 2021, with a structured search conducted in PubMed- National Library of Medicine and Virtual Health Library (VHL) databases without language restrictions and selecting articles published in the last 22 years. The following descriptors were obtained from the search in Health Sciences Descriptors (DeCS): "*Lactobacillus* spp and *Candida* spp", *"Lactobacillus* spp and *Probiotics", "Candida* spp and Virulence Factors" and "*Candida glabrata* or *Candida albicans* and *Lactobacillus", "*Sodium Butyrate *and Candida glabrata* as well as the and or connectors.

The process of selection of articles for content analysis was based on the identification, selection, inclusion and exclusion criteria of the PRISMA method (Main Items for Reporting Systematic Reviews and Meta-Analyses); (Galvão et al., 2015; Sampaio & Mancini, 2007). The criteria for the selection of articles considered in this study met the following inclusion criteria: articles that have relevance to study that report the microbicidal activity of *Lactobacillus* extract in the presence of *Candida* and effect of pure supernatant or *Lactobacillus* compared to the use of antibiotics. The exclusion criteria were a repetition of articles in the database, titles and abstracts that did not contribute to the theme addressed, and articles that after content analysis did not cover the theme proposed in this review.

RESULT

Initially, articles were found, of which, after analysis used inclusion and exclusion criteria, 32 papers were selected (Figure 1) that covered the study proposal. For a better understanding, the results were separated into 5 tables, with the first table referring to the review on *Candida* spp. *C.glabrata*, the second and third table results in the analysis of works regarding virulence factor (table 2) and fluconazole resistance (table 3), and finally, the last tables 4 and 5 regarding *Lactobacillus* spp. (table 4) and Sodium Butyrate (table 5) the use of supernatant against *Candida* spp. in addition, the study by Mundula et al, 2019, was included in the tables related to *Candida* spp. and *Lactobacillus* spp. whereas the study by Pristov e Ghannoum, 2019, was included in the table related to *Candida* spp., Virulence Factors, and Fluconazole Resistance, and the study by Rodrigues et al., 2017, was included in the table related to Virulence Factors and Fluconazole Resistance. In the construction of the tables, they were separated into topics: Title belonging to the article, Author/Year, Objective, and the Results of the Articles.

Figure 1: Flowchart of the selection steps for review articles.



Source: Torquati and Araújo (2023)

Table 1: *Candida* spp.

Title	Author/ Year	Objectives
Therapeutic tools for oral candidiasis: Current and new antifungal drugs	(Quindos et al., 2019)	The present study conducts a literature review on the therapeutic tools available against oral candidiasis and their usefulness in each clinical situation.
Effect of Probiotics on Oral Candidiasis: A Systematic Review and Meta-Analysis	(Mundula et al., 2019)	This study systematically reviews the effects of the oral intake of probiotics, prebiotics, and synbiotics on *Candida* spp. counts (colony-forming units (CFU)/mL) in oral and palatal samples.
Pathogenesis and Clinical Relevance of *Candida* Biofilms in Vulvovaginal Candidiasis	(Rodríguez-Cerdeira et al., 2020)	Discuss the main characteristics of the female vulvovaginal mucosa and the mechanisms employed by *Candida* spp. to colonize the host. In addition, the different types of biofilms formed by *Candida* spp., their impact on clinical practice, and the development of new agents against them will also be reviewed in depth.
Resistance of *Candida* to azoles and echinocandins worldwide	(Pristov & Ghannoum, 2019)	Here, we discuss the mechanisms that *Candida albicans, Candida dubliniensis, Candida glabrata, Candida parapsilosis, Candida tropicalis* and *Candida auris* are implementing to increase resistance to azoles and echinocandins, and how they are affecting clinical, or hospital, settings worldwide.
Non-albicans *Candida* Infection: An Emerging Threat	(Deorukhkar et al., 2014)	Investigated the prevalence of non-albicans *Candida* spp. among *Candida* isolates from various clinical specimens and analysed their virulence factors and antifungal susceptibility profile. A total of 523 *Candida* spp. were isolated from various clinical specimens. Non-*albicans Candida* species were the predominant pathogens isolated.

Adhesins in *Candida glabrata*	(Timmermans et al., 2018)	We will update our current knowledge about *C. glabrata* adhesion and its importance in virulence.
Candidiasis: Red and White Manifestations in the Oral Cavity	(Hellstein & Marek, 2019)	This review will concentrate on intraoral, pharyngeal and perioral manifestations and treatment. A history of the origins associated with candidiasis will be introduced.
Vaginitis: Diagnosis and Treatment	(Paladine & Desai, 2018)	Was not informed
Candidiasis (vulvovaginal)	(Martin Lopez, 2015)	The systematic review, aims to answer the following clinical questions: What are the effects of drug treatments for acute vulvovaginal candidiasis in symptomatic non-pregnant women? What are the effects of alternative or complementary treatments for acute vulvovaginal candidiasis in symptomatic non-pregnant women? What are the effects of treating asymptomatic non-pregnant women with a positive swab for candidiasis?
Oral Candidiasis: A Disease of Opportunity	(Vila et al., 2020)	Review the virulence factors that cause oral candidiasis.

Source: Own author (2023)

Table 2: Virulence factor - Biofilm formation

Title	**Author/Year**	**Objectives**
Prevalence, antifungal susceptibility, and virulence determinants of oral yeast species isolated from immunodeficient patients in Northeastern Brazil	(Cavalcante et al., 2020)	Investigate the prevalence, virulence determinants, and antifungal susceptibility of yeast colonizing the mucosa of immunocompromised patients in Northeastern Brazil.
Resistance of *Candida* to azoles and echinocandins worldwide	(Pristov & Ghannoum, 2019)	We discuss the mechanisms that *Candida albicans, Candida dubliniensis, Candida glabrata, Candida parapsilosis, Candida tropicalis,* and *Candida auris* are implementing to increase resistance to azoles

		and echinocandins, and how they are affecting clinical, or hospital, settings worldwide.
Candida glabrata Biofilms: How Far Have We Come?	(Rodrigues et al., 2017)	In this article, the knowledge available on *C. glabrata*'s resistance will be highlighted, with a special focus on biofilms, as well as new therapeutic alternatives to control them.
Candida albicans biofilm growth and dispersal: contributions to pathogenesis	(Wall et al., 2019)	Provide a summary of some of these major contributions, with emphasis on some of the most recent work on this topic.

Source: Own author (2023)

Table 3: Fluconazole resistance

Title	Author/Year	Objectives
Candida glabrata Biofilms: How Far Have We Come?	(Rodrigues et al., 2017)	In this article, the knowledge available on *C. glabrata*'s resistance will be highlighted, with a special focus on biofilms, as well as new therapeutic alternatives to control them.
Azoles de antes y ahora: una revisión	(Nocua-Báez et al., 2020)	Review the history, pharmacological characteristics, and clinical trials that demonstrate its clinical efficacy in different clinical settings.
Candida glabrata Transcription Factor Rpn4 Mediates Fluconazole Resistance through Regulation of Ergosterol Biosynthesis and Plasma Membrane Permeability	(Pais et al., 2020)	Shows that the *C. glabrata* transcription factor (TF) CgRpn4 is a determinant of azole drug resistance.
Resistance of *Candida* to azoles and echinocandins worldwide	(Pristov & Ghannoum, 2019)	We discuss the mechanisms that *Candida albicans, Candida dubliniensis, Candida glabrata, Candida parapsilosis, Candida tropicalis* and *Candida auris* are implementing to increase resistance to azoles and echinocandins, and how they are affecting clinical, or hospital, settings worldwide

Transcriptional responses of *Candida glabrata* biofilm cells to fluconazole are modulated by the carbon source	(Alves et al., 2020)	Whole-transcriptome analysis of *C. glabrata* biofilm cells exposed to different environmental conditions and constraints in order to identify the molecular pathways involved in fluconazole resistance and understand how acidic pH niches, associated with the presence of acetic acid, are able to modulate these responses.

Source: Own author (2023)

Table 4: *Lactobacillus* spp.

Title	**Author/Year**	**Objectives**
Biosurfactant from vaginal Lactobacillus crispatus BC1 as a promising agent to interfere with *Candida* adhesion	(De Gregorio et al., 2020)	Characterize the biosurfactant (BS) isolated from a vaginal *Lactobacillus crispatus* strain, *L. crispatus* BC1, and to investigate its safety and antiadhesive/antimicrobial activity against *Candida* spp., employing in vitro and in vivo assays.
Probiotics and vaginal microecology: fact or fancy?	(Buggio et al., 2019).	Check whether probiotics benefit pregnant and non-pregnant women, and whether the magnitude of the effect justifies the expense.
Probiotic *Lactobacillus* Strains Stimulate the Inflammatory Response and Activate Human Macrophages	(Rocha-Ramírez et al., 2017)	Analyzed the mechanism by which four different strains of probiotics affected innate immunity, such as regulation of ROS, cytokines, phagocytosis, bactericidal activity, signaling by NF-*κ*B pp65, and TLR2 activation.
Probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 exhibit strong antifungal effects against vulvovaginal candidiasis-causing *Candida glabrata* isolates	(Chew et al., 2015)	Investigate the probiotic effects of the *Lact. rhamnosus* GR-1 and *Lact. reuteri* RC-14 strains against vaginal isolates of the emerging NCAC species *C. glabrata*.
The role of *Lactobacillus* species in the control of	(Zangl et al., 2020)	Focus on the molecules and mechanisms behind the putative interactions between *Lactobacillus* and *Candida* spp.

Candida via biotrophic interactions		
Competition of *Candida glabrata* against *Lactobacillus* is Hog1 dependent	(Beyer et al., 2018).	Investigated the potential role of the high osmolarity glycerol response (HOG) MAP Kinase pathway for *C. glabrata* virulence. The *C. glabrata* MAP kinase CgHog1 becomes activated by a variety of environmental stress conditions such as osmotic stress, low pH, and carboxylic acids and subsequently accumulates in the nucleus.
Effect of Probiotics on Oral Candidiasis: A Systematic Review and Meta-Analysis	(Mundula et al., 2019)	This study systematically reviews the effects of the oral intake of probiotics, prebiotics, and synbiotics on *Candida* spp. counts (colony-forming units (CFU)/mL) in oral and palatal samples
Diversity of vaginal microbiome and metabolome during genital infections	(Ceccarani et al., 2019)	We describe and compare the changes that occur in the vaginal microbiome and metabolome during common genital infections.
Recurrent Vulvovaginal Candidiasis: a Dynamic Interkingdom Biofilm Disease of *Candida* and *Lactobacillus*	(McKloud et al., 2021)	This study aimed to assess a panel of clinical samples from healthy women and those with RVVC to investigate the influence of *Candida*, the vaginal microbiome, and how their interaction influences disease pathology.
Antifungal effects of *Lactobacillus acidophilus* and *Lactobacillus plantarum* against different oral *Candida* species isolated from HIV/ AIDS patients: an in vitro study	(Salari & Ghasemi Nejad Almani, 2020)	The antifungal effects of both cells and cell-free supernatants (CFSs) of *L. acidophilus* and *L. plantarum* were investigated against different oral *Candida* species by co-aggregation, agar overlay interference and broth microdilution assays, respectively.
Vaginal Lactobacillus Impair *Candida* Dimorp hic Switching and Biofilm Formation	(Parolin et al., 2022)	Investigate the interrelation between mode of growth and functionality, supernatants were collected from *Lactobacillus* planktonic cultures and, for the first time, from adherent ones, and were evaluated

		towards *Candida* dimorphic switching and biofilm.
A small molecule produced by *Lactobacillus* species blocks *Candida albicans* filamentation by inhibiting a DYRK1-family kinase	(MacAlpine et al., 2021)	This work identifies a natural product secreted by *Lactobacillus* under standard laboratory culture conditions that inhibits the yeast-to-hyphae transition and biofilm formation in *C. albicans*.
Vulvovaginal candidiasis and current perspectives: new risk factors and laboratory diagnosis by using MALDI TOF for identifying species in primary infection and recurrence	(Pereira et al., 2021)	The study aimed to identify the etiologic agent of infections as accurately as possible, characterizing new RFs associated with infection and evaluating recurrence with laboratory diagnosis.
Lactobacillus acidophilus, L. plantarum, L. rhamnosus, and *L. reuteri* Cell-Free Supernatants Inhibit *Candida parapsilosis* Pathogenic Potential upon Infection of Vaginal Epithelial Cells Monolayer and in a Transwell Coculture System In Vitro	(Spaggiari et al., 2022)	Four different *Lactobacillus* spp., already employed as probiotics, can also exert a postbiotic-like activity; metabolic compounds released from such lactobacilli have been tested by using an *in vitro* model of the vaginal epithelium.

Source: Own author (2023)

Table 5: Sodium butyrate

Title	Author/Year	Objectives
Lactobacillus acidophilus and *Clostridium butyricum* ameliorate colitis in murine by strengthening the gut barrier function and decreasing inflammatory factors	(Wang et al., 2018)	The study focused on the evaluation of the anti-inflammatory activities of *Lactobacillus acidophilus* CGMCC 7282 and *Clostridium butyricum* CGMCC 7281.
Histone deacetylases inhibitors effects on *Cryptococcus neoformans* major virulence phenotypes	(Brandão et al., 2015)	The effect of NaBut and TSA on the expression of *C. neoformans* major virulence phenotypes and on the survival rate of an animal model infected with drugs-treated yeasts.
Histone Deacetylase Inhibitors Enhance *Candida albicans* Sensitivity to Azoles and Related Antifungals: Correlation with Reduction in CDR and ERG Upregulation	(Smith & Edlind, 2002)	The effects of HDA inhibitors on *C. albicans* in vitro growth, heat sensitivity and germ tube formation.

Source: Own author (2023)

DISCUSSION

Candida spp.

According to epidemiological data, *Candida albicans* is considered the fourth leading pathogen responsible for systemic infections in hospitals and the most prevalent in mucocutaneous infections, with 90% of invasive infections being the responsibility of opportunistic *Candida* species (Deorukhkar et al., 2014; Pristov & Ghannoum, 2019).

In their research, Timmermans et al., (2018) noted that among the most "terrorizing" *Candida* species, *C. glabrata* species is considered the second most commonly isolated in blood system infections in immunocompromised patients, and the most common species with respect to antifungal resistance in hospitals. It is observed that, *C. glabrata* presents greater plasticity regarding the capacity of resistance to antifungal treatments, particularly fluconazole, a drug used worldwide in the treatment of *Candida* spp. infections, but that *C. glabrata* is intrinsically resistant. This yeast species has variations in the fungal wall, as well as a set of virulence factors that ensure the success of infection in humans.

Studies point out that, systemic candidiasis is an infection that has prevalence in patients with deficiency in immune mechanisms, such as patients with HIV and Systemic Lupus Erythematosus, patients undergoing chemotherapy or radiotherapy treatments, intensive care unit (ICU) patients, and diabetic patients (Hellstein & Marek, 2019; Quindos et al., 2019)

Research has observed that, *C. glabrata* accounts for 10% to 15% of VVC cases, the characteristic symptoms of this infection is inflammation of the vagina (vaginitis), with swelling, erythema, vulvar itching, abnormal discharge, vulvar burning, pain, and irritation (Martin Lopez, 2015; Paladine & Desai, 2018)

In addition, about 30% to 75% of healthy adult individuals afflict *Candida* species in the oral cavity (Hellstein & Marek, 2019; Pristov & Ghannoum, 2019). The main characteristic feature of oral candidiasis are white patches (form of "toads") on the mucosa of the mouth, tongue and throat. The lesions are classified into acute (pseudomembranous and erythematous) and chronic (hyperplastic) lesions. Most individuals have no symptoms and the infection is usually acute. However, in immunocompromised patients, oral candidiasis may develop into a chronic lesion and promote systemic infections due to the vulnerable immune system of the patient (Quindos et al., 2019; Vila et al., 2020).

Virulence factor- Biofilm formation

According to Cavalcante et al., (2020), *Candida* can present different virulence factors among them high adhesion capacity, polymorphism, toxin production, ability to produce hydrolytic enzymes, and biofilm formation is considered one of the most important factors.

Biofilms are a microbial structure, highly organized, with various cell division sequences, embedded in an extracellular matrix, forming a three-dimensional structure on biological or artificial surfaces (Pristov & Ghannoum, 2019; Rodrigues et al., 2017)

Studies have observed that, the *Candida* species most associated in biofilm formation is *C.albicans*, however *C.glabrata* demonstrates a prominent role in hospital settings for its ability to form multiple layers of compact biofilms with carbohydrates, proteins, ergosterol in its matrix, and to the high prevalence of clinical findings in immunocompromised patients and patients in ICU or with catheters (Rodrigues et al., 2017; Wall et al., 2019)

Fluconazole Resistance

The function of fluconazole is to act on the cytochrome P450 biosynthetic pathway of the lipid component (ergosterol) of the fungus. The drug inhibits the catalytic enzyme 14α-cholesterol-desmethylase (which is dependent on cytochrome p-450), resulting in a plasma membrane with defects in structure and function, inhibiting nutrient transport and signaling, between yeast cells (Nocua-Báez et al., 2020; Rodrigues et al., 2017)

Research indicates that the resistance of *C.glabrata* to fluconazole is associated with small mutations in its gene, by continuous pressure of the drug and is linked to several mechanisms, such as the induction of efflux pumps, encoded by the ABC or MDR transporter genes. These genes belong to the superfamily of key facilitators that lead to a decrease in the concentration of the drug in the yeast cytoplasm. In addition, the drug has a decreased affinity, disabling the drug from binding on the yeast membrane (Pais et al., 2020; Pristov & Ghannoum, 2019; Rodrigues et al., 2017).

In their study Alves et al., (2020) demonstrates that biofilm-forming *C.glabrata* yeasts still survive under high concentrations of fluconazole and that biofilm formation is dependent on modulation by the carbon source and pH available in the host organism.

***Lactobacillus* spp.**

In their research Beyer et al., (2018), observed that the species of *Lactobacillus,* such as: *L. rhamnosus , L. gasseri , L. paracasei , L. fermentum , L. casei e L. crispatus* is responsible for modulating the host immune response by summoning an increased number of phagocytic cells, propagating the release of pro-inflammatory cytokines. In addition, these bacteria, influenced in pathogen-host interactions, act as anti-adhesive and antibiofilm agents (De Gregorio et al., 2020), inhibiting biofilm formation by *Candida* species (Mundula et al., 2019).

Lactobacillus species produce in high amounts, lactic acid, acetic acid and hydrogen peroxide (Ceccarani et al., 2019), keeping the pH acidic around 4.5 or less (Buggio et al., 2019). Studies have analyzed that, lactic acid production by *Lactobacillus* species can maintain healthy vaginal microbiota by regulating gene expression of *C.albicans* and the ability to reduce fungal compounds in biofilm formation, with *L rhamnosus* showing the greatest inhibition effect on biofilm formation. Another study showed that both *L.acidophilus* and *L.plantarum* have antimicrobial actions, inhibiting the growth of *Candida* strains isolated from immunocompromised patients (Salari & Ghasemi Nejad Almani, 2020) Another study, found that *L.crispatus, L.gasseri, L.vaginalis* and *L.plantarum* inhibited biofilm formation and dimorphic

Candida shedding as well. with *L.crispatus* showing higher antibiofilm activity compared to other species (Parolin et al., 2022).

Compounds produced by *Lactobacillus,* blocks one of the main virulence factors of *C.albicans*, according to the study of MacAlpine et al., (2021), demonstrated that the filtered supernatant of *L.rhamnosus* blocked the transition of *C.albicans* from yeast to filament. Other probiotic bacteria were tested and, *L.reuteri* also showed an anti-filamentation effect, resulting in a blockage in the resulting in blockage in morphogenesis of hyphae, in this same study, they analyzed some compounds that were produced by *Lactobacillus* such as lactic acid, however, it was realized that compound 1-ABC was sufficient to block the filamentation of *C.albicans* where the inhibition of filamentation happens by the binding of compound 1-ABC on yak1 of the fungus (a kinase of the DYRK1 family), furthermore, the study showed that, the structure of 1-ethoxycarbony1-B-carboline blocks the biofilm formation of *C.albicans.*

In another study, the potential of the supernatant of *L.acidophilus, L.plantaru, L.rhamnosus* and *L.reuteri* against the main virulence factors of *C.parapsilosis* was observed. The results demonstrated that viability of the organic acids produced by *Lactobacillus* are only partially responsible for inhibiting fungal growth even if they do not prevent the production of pseudohyphae (Spaggiari et al., 2022).

Sodium butyrate

In one study, it was evaluated that *Clostridium butyricum* (NaBut producing bacteria) with the combination with *Lactobacillus acidophilus* potentiated the anti-inflammatory activity of NaBut. They demonstrated that the pairing of the two bacteria exhibited effects capable of decreased mortality, change in gut microbiota alteration, and a greater anti-inflammatory effect compared to in vitro isolates (Wang et al., 2018).

In the study by Brandão et al., (2015), it was observed that NaBut affected the growth of *Cryptococcus neoformans* yeast, as well as reduced the virulence phenotypes of this fungus. In addition, another study demonstrated the effects of NaBut on *C. albicans*, showed effects on growth, heat sensitivity, germ tube formation. In addition, it showed that NaBut in a specific amount increased the effect of fluconazole for a few hours (Smith & Edlind, 2002).

CONCLUSION

The number of cases of candidiasis is increasing and conventional treatments are not having the expected effect. *C. glabrata*, for example, is intrinsically resistant to fluconazole, and high doses of the drug may be toxic to the human organism. Thus, new therapeutic approaches are emerging and are needed to assist or even replace protocols in clinical use. Thus, this review shows that the use of *Lactobacillus* may be a promising therapeutic approach, since they are microorganisms present in human and animal microbiota, which naturally produce molecules that control or inhibit growth of pathogenic *Candida* spp refractory to conventional treatments. In addition, in vitro and in vivo tests need to be performed to evidence the therapeutic effect of the compounds produced by *Lactobacillus.*

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