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PROBIOTICS AS ANTIFUNGAL AGENTS: AN ANTI-*Candida* REVIEW

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Abstract

In recent years, microbial infections have become increasingly difficult to treat. Classical treatments, which involve the use of antibiotics in various pharmaceutical compounds with antimicrobial activity, shows the problems difficult to be solved. For this purpose, researchers are looking for a solution and therefore possible alternative treatments to treat microbial infections. Favorable results are obtained from the use of probiotics, a lot of in vitro and in vivo studies demonstrating the ability of certain probiotics, in particular lactic acid bacteria, to inhibit the growth of pathogenic microorganisms. Probiotics are a class of bacteria similar to those existing in specific human microflora, with beneficial role on human health. Real problems came from endemic fungal infections of humans who, in their favorable conditions, proliferate and lead to the appearance of serious diseases. An example and also a cause of many diseases is the genus Candida. The review presents the main findings related to the response of different Candida species to in vitro and in vivo treatments with different probiotics.

Key words*: Candida sp., candidiasis, probiotics.*

INTRODUCTION

Human microbiota is complex and includes both commensal microorganisms, and pathogenic or facultative pathogenic microorganisms. *Candida* species is an example of microorganisms present in human microbiota which, in terms of balance of microflora of the human individual, it doesn't pose any health problems. However, in cases of proliferation, the genus *Candida* can produce some mucous infections, such as oral or vaginal infections, but also spread infections throughout the body, called candidemia. The main trigger of candidiasis is *Candida albicans* (Silva M. P. et al., 2016), followed by *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and *Candida krusei*, representing over 90% of cases of invasive infections caused by the genus *Candida* (Sardi J. C. O. et al., 2013; Pappas P. G. et al., 2015). According to the CDC (Centers for Diseases Control and Prevention) and the National Health Care Safety Network, genus *Candida* is in the fifth place in the above hospital-acquired and in fourth place in the case of bloodstream infections (Yapar N., 2014). However, a high percentage of 36.5% was reported in community-acquired candidemia, within North America (USA and Latin America) percentage rising to 68.8% of reported cases of candidemia and in Europe the percentage it was 22.4% (Pfaller M. A., 2011). According to the clinical data of the 2019 patients with candidemia between July 1, 2004 and March 5, 2008 from Prospective Antifungal Therapy (PATH) Alliance database, presented in 2009 by Horn D. L. et al, the main organism in the incidence of candidemia is *Candida albicans*, with a rate of 45.6%. After 12 weeks of monitoring, 711 of the 2019 patients died (35.2%), 704 were alive (34.9%), while in the case of the 604 patients monitoring was lost. The highest mortality was in the case of *Candida krusei* infections (52.9%), and lowest in the case of *Candida parapsilosis* (23.7%). Other more recent sources indicate a mortality of up to 50% in the case of systemic *Candida* infections acquired in U. S. A. hospitals (Silva M. P. et al., 2016) or, according to the European Society of Anesthesia (ESA) Intensive scientific subcommittee, up to 70% (Pamela Oleary R.-A. et al., 2017). Classic treatments and most used as well in treatment of candidiasis are antifungal medicines, such as type of azoles fluconazole or ketoconazole, the type, such as echinocandins micafungin, caspofungin or type polyenes, like amphotericin B or nucleoside analogues, such as type flucytosine (Spampinato C. et Leonardi D., 2013). But in

recent years, genus *Candida* acquires resistance to antifungal therapy, resulting in a real problem for treating different types of candidiasis (Sanguinetti M. et al., 2015). For this reason, it is absolute necessity to search and develop alternative therapies for the treatment of candidiasis. **Probiotics** are part of the new trends in world medicine, and their successful use as alternative treatments would be a real gain in human battle with microorganisms, in this case the most dangerous species of *Candida*.

In 2001, probiotics have been defined by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) as "live Microorganisms Which When Administered in Adequate trace confer a health benefit on the host", definition accepted and adopted almost completely globally (Hill C. et al., 2014). There are numerous studies in the literature describing the benefits, not few in number, of probiotics on human health. Of these, should be mentioned the following: treatment of infections caused by microorganisms or viruses, combating diarrhea caused by antibiotic treatment, alleviating inflammatory chronic bowel disease, decreased risk of developing allergies, restoring the balance of intestinal microflora, strengthening the immune system, decreased cancer risk colon (Saad N. et al., 2013) or their use in treatments against other cancers (Chen K. et Khismatullin D.B., 2014). Moreover, they can increase nutrient uptake and due to their antimicrobial properties indirectly decrease the need to administer antibiotics (X.-H. Guo et al., 2010; Angmo K. et al., 2016). Another remarkable effect is that probiotics lower the serum cholesterol (X.-H. Guo et al., 2010; C.-F. Guo et al., 2015; Lee N.-K. et al., 2015; Angmo K. et al., 2016), and their use in the treatment of diabetes, is also important (G. Giraffa, 2012; Chen P. et al., 2014; Lee N.-K. et al., 2015). Microorganisms used as probiotics are worthily mentioned *Lactobacillus* sp., *Bifidobacterium* sp., *Bacillus* sp., *Saccharomyces* sp. (Silva M.P. et al., 2016) and genetically modified bacteria which naturally are facultative pathogen or pathogen, for example *Escherichia coli* (Silva M.P. et al., 2016; Hwang I.Y. et al., 2017).

In the presented context the use of probiotics in fighting candidiasis may be aviable solution in current medical conditions.

DATA COLLECTION

Online research was conducted using PubMed, ScienceDirect, Cochrane, and Embase data. Also, were included several studies published in InTech and Hindawi databases. *In vitro* and *in vivo* tests were generally selected, as well as some reviews published between 2009 and 2017, in which promising results of probiotics were presented in the treatment of various types of candidiasis.

The words or clusters of keywords that were searched for in this research were: "Candida genus", "Candida species", "candidiasis", "candidemia", " oral candidiasis", "vaginal candidiasis", "invasive candidiasis", "esophageal candidiasis", "cutaneous candidiasis", "probiotic and candidiasis", "probiotic anti-Candida", "candidiasis treatment", "candida treatment", "*Lactobacillus Candida*", "*Bifidobacterium Candida*", "*Bacillus Candida*", "clinical trial candidiasis", "*in vivo* candidiasis", "*in vitro* candidiasis".

DATA FINDINGS

The collected data has approached both *in vivo* and *in vitro* studies related to main *Candida* species to different probiotic groups (Table1).

(1) *In vitro studies and possible mechanisms by which probiotics act against Candida*

The first step in studying the properties and effects of probiotics against various types of candidiasis is the analysis of the data from *in vitro* tests, which can analyze both the mechanisms of probiotics acting against the *Candida* genus, but also the actual effect of some probiotic strains against *Candida* strains.

Some **active probiotic compounds**, such as capric acid of *Saccharomyces boulardii*, may reduce filamentous growth and biofilm formation or *Candida albicans* adhesion (Murzyn A. et al., 2010). The effect on *Candida* filamentous growth, biofilm formation and adhesion to the cellular substrate and the immune response of *C. albicans* to the production of cytokines has been studied; promising results were obtained using *L. rhamnosus*, *L. reuteri* and *L. crispatus*

(Martinez R. C. R. et al., 2009; Rizzo A. et al., 2013). There are reported cases in which strains of *L. casei* and *L. rhamnosus* can produce antifungal peptides as a viable alternative to the prevention and treatment of *Candida* stomatitis (Song Y.-G. and Lee S.H., 2017). They are not excluded from use for prevention or against *Candida* infections neither combinations of probiotics with prebiotics such as arabinose, xylose and xylitol. Combinations of *Lactobacillus species* with prebiotics had an inhibitory effect on the growth of *Candida albicans* and *Porphyromonas gingivalis*, but also on the production of insoluble glucan by *Streptococcus mutans* (Kojima Y. et al., 2015).

Decreasing pH by producing lactic acid by the *Lactobacillus* genus can also inhibit the growth of the *Candida* species (Köhler GA etal., 2012; Chew SY et al., 2015), while the production of H_2O_2 could inhibit *C. albicans* (Köhler GA et al., 2012), but not *C. glabrata* (Chew SY et al., 2015). The inhibitory effect on *Candida sp*. by lowering the pH by the accumulation of organic acids such as lactic or acetic, secreted by lactic species in the gastrointestinal tract was also evidenced by Shokryazdan P. and collaborators in 2014.

The effectiveness of the *Lactobacillus* genus against *Candida* was also analyzed by the action of a filtered culture, LAB supernatant, demonstrating the anti-*Candida* activity of *L. acidophilus* (Vilela S. F. et al., 2015). Seneviratne C.J. and al. succeeded in 2016 fractionation and purification of the cell-free LAB supernatant. Of the 41 fractions, 8 completely inhibited the growth of *Candida albicans* after a 24 h incubation, 4 of the 8 inclusive after 48 h, and 2 fractions had a total inhibitory effect after 72 h of incubation.

In a study published in 2010, Hasslöf et al. have studied the antifungal activity of 8 strains of *Lactobacillus* (*L. plantarum* 299v, *L. plantarum* 931, *L. rhamnosus* GG ATCC 53103, *L. rhamnosus* LB21, *L. reuteri* PTA 5289, *L. reuteri* ATCC 55730, *L. acidophilus* La5 and *L. paracasei*) against 2 *Candida albicans* reference strains (ATCC 28366 and ATCC 10231) and 3 clinically isolated strains (*C. albicans* 1957, *C. albicans* 3339 and *C. albicans* GDM8). The test included 4 probiotic concentrations (10^9, 10^7, 10^5 and 10^3 CFU / ml) and overlay interference tests. Depending on the concentration, most of *Lactobacillus* strains inhibited the growth of *Candida* strains. Antimicrobial activity can also be enhanced by enriching cell cultures of probiotics with some minerals. If the use of supernatant probiotics such as *L. plantarum* and *L. johnsonii* does not influence the growth of *C. albicans*, the enrichment of supernatants with selenium nanoparticles strongly inhibits the growth of *C. albicans* cells (Kheradmand E. et al., 2014).

Studies published in 2014 (Coman MM et al., Verdenelli MC et al., Jiang Q. et al.) have analyzed the inhibition of *Candida* strains growth (*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*) on culture media or vaginal epithelial cells. The lactic species included in the research were *L. rhamnosus*, *L. paracasei*, *L. brevis*, *L. casei*, *L. plantarum* or *L. fermentum*. All lactobacilli strains have had the ability to inhibit all *Candida* strains but to varying degrees. A very strong inhibition effect was obtained by combination of two strains, *L. rhamnosus* IMC 501 and *L. paracasei* IMC 502, called SYNBIO®.

The inhibitory action of probiotics against *Candida albicans* may also be due to the proliferation of probiotics by nutrient depletion in the culture medium (Ujaoney S. et al., 2014). There have also been reports of non-probiotic bacteria without direct fungicidal activity (*Streptococcus salivarius*) inhibiting *Candida* substrate adhesion (Ishijima S.A. et al., 2012).

(2) *In vivo studies on animals*

The general way in which both the human body and the animal respond to *Candida* infections is the immune system. Improving the immune response to infections caused by *C. albicans* has been successfully obtained following treatments with probiotics in animals. The *L. casei* diet of malnourished mice resulted in the proliferation of pro-inflammatory cytokines, the activation of phagocytic cells, and the increase in IL-10 levels that could help prevent damage caused by the inflammatory response to *Candida* infections (Villena J. et al., 2011).

Stimulation of the immune system with probiotics had promising results from the data of two recent studies in which *Galleria mellonella* was treated with *L. rhamnosus* (Ribeiro F. de C. et al., 2016) and *L. paracasei* (Rossoni R.D. et al., 2017).

Table 1. **Reported probiotics with anti- *Candida* effects**

Pathogen	Probiotic (Genera/Species)	Reference
Candida albicans	***Lactobacillus* sp.** *L. rhamnosus, L. paracasei, L. plantarum , L. acidophilus, L. reuteri, L. casei, L. brevis, L. bulgaricus, L. johnsonii, L. animalis, L. salivarius, L. murinus, L. fermentum, L. gasseri, L. crispatus, L. delbrueckii* ssp. *bulgaricus*	Coman M.M. et al., 2014; Hasslöf P. et al., 2010; Kheradmand E. et al., 2014; Köhler G.A. et al., 2012; Kojima Y. et al., 2015; Kovachev S.M. & Vatcheva-Dobrevska R.S., 2014; Kumar S. et al., 2013; Jiang Q. et al., 2014; Martinez R.C.R et al., 2009; Matsubara V.H. et al., 2012; Mendonça F.H.B.P. et al., 2012; Ribeiro F.de C. et al., 2016; Rizzo A. et al., 2013; Romeo M. J. et al., 2011; Rossoni R.D. et al., 2017; Roy A. et al., 2014; Song Y.-G. & Lee S.-H., 2016; Ujaoney S. et al., 2014; Verdenelli M.C. et al., 2014; Vicariotto F. et al., 2012; Vilela S.F. et al., 2015; Villena J. et al., 2011;
	***Streptococcus* sp.** *S. salivarius, S. thermophiles*	Kovachev S.M. & Vatcheva-Dobrevska R.S., 2014; Ujaoney S. et al., 2014; Song Y.-G. and Lee S.-H., 2016; Ishijima S.A. et al., 2012
	***Bifidobacterium* sp.** *B. longum, B. bifidum, B. breve, B.lactis, B. infantis*	Kumar S. et al., 2013; Mendonça F.H.B.P. et al., 2012; Roy A. et al., 2014; Song Y.-G. &bLee S.-H., 2016; Ujaoney S. et al., 2014;
	***Saccharomyces* sp.** *S.boulardi, S.thermophilus*	Murzyn A. et al., 2010; Kumar S. et al., 2013
	***Bacillus* sp.** *B. coagulans*	Ujaoney S. et al., 2014
Candida glabrata	***Lactobacillus* sp.** *L. rhamnosus; L. reuteri, L. paracasei, L. fermentum, L. plantarum, L. casei, L. brevis, L. bulgaricus, L. acidophilus*	Chew S.Y. et al., 2015; Coman M.M. et al., 2014; Jiang Q. et al., 2014; Mendonça F.H.B.P. et al., 2012; Roy A. et al., 2014; Verdenelli M.C. et al., 2014; Vicariotto F. et al., 2012;
	***Bifidobacterium* sp.** *B. breve, B. longum, B. bifidum, B. lactis*	Mendonça F.H.B.P. et al., 2012;Roy A. et al., 2014
Candida krusei	***Lactobacillus* sp.** *L. rhamnosus, L paracasei, L. casei, L. reuteri, L. brevis, L. casei, L. reuteri, L. brevis, L.bulgaricus, L. acidophilus, L. fermentum, L. plantarum*	Coman M.M. et al., 2014; Jiang Q. et al., 2014; Mendonça F.H.B.P. et al., 2012; Roy A. et al., 2014; Verdenelli M.C. et al., 2014; Vicariotto F. et al., 2012;
	***Bifidobacterium* sp.** *B. breve, B. bifidum, B. longum, B. lactis*	Mendonça F.H.B.P. et al., 2012; Roy A. et al., 2014
Candida parapsilosis	***Lactobacillus* sp.** *L. rhamnosus, L. paracasei, L.casei, L.reuteri, L. plantarum, L. acidophilus, L. fermentum*	Romeo M. J. et al., 2011; Coman M.M. et al., 2014; Mendonça F.H.B.P. et al., 2012; Roy A. et al., 2014; Verdenelli M.C. et al., 2014; Vicariotto F. et al., 2012;
	***Bifidobacterium* sp.** *B. breve, B. longum, B. bifidum, B. lactis*	Mendonça F.H.B.P. et al., 2012; Roy A. et al., 2014
Candida tropicalis	***Lactobacillus* sp.** *L. rhamnosus, L paracasei. L. acidophilus, L. casei, L. plantarum, L. fermentum*	Kumar S. et al., 2013; Coman M.M. et al., 2014; Mendonça F.H.B.P. et al., 2012; Verdenelli M.C. et al., 2014
	***Bifidobacterium* sp.** *B. longum, B. bifidum, B. breve*	Kumar S. et al., 2013; Mendonça F.H.B.P. et al., 2012
	***Saccharomyces* sp.** *S. boulardi, S. thermophilus*	Kumar S. et al., 2013
Candida kefyr	*Lactobacillus casei,*	Mendonça F.H.B.P. et al., 2012
Candida lipolytica	*Bifidobacterium breve*	Mendonça F.H.B.P. et al., 2012
Candida guillermondii	***Lactobacillus* sp.** *L. casei, L. rhamnosus, L. reuteri*	Mendonça F.H.B.P. et al., 2012; Romeo M. J. et al., 2011
	Bifidobacterium breve	Mendonça F.H.B.P. et al., 2012

In both cases, treatment with lactobacilli resulted in a significant increase in hemocytes and, implicitly, in a much stronger immune response against *C. albicans*.

The efficacy of probiotics was also analyzed in relation to classical treatments against oral candidiasis.

In 2012, Matsubara VH and colleagues tested two strains of lactobacilli (*L. acidophilus* and *L. rhamnosus*) and nystatin, a widely used drug for treating oral candidiasis, to reduce *C. albicans* infection in the oral mucosa. In this case, the subjects were groups of mice infected with *C. albicans* on which nystatin treatment

did not have the expected effect, but the use of probiotics, particularly *L. rhamnosus*, significantly reduced colonization of *C. albicans*. In the treatment of oral candidiasis, probiotics that are not fungicidal, but still prevent the adhesion of *Candida* to the substrate can also be used. In a study published in 2012, Ishijima S.A. and coworkers, working on mice, concluded that *Streptococcus salivarius*, although not having antifungal properties, can be used to treat oral candidiasis because of its properties to compete with *Candida albicans* for oral mucosal adhesion.

(3) *Human clinical trials*

Due to the major problems in recent years of treating human patients against candidiasis, the efficacy of probiotics as alternative treatments is impetuously needed to be proven in clinical trials.

A major and extremely common problem, especially of the elderly, is **oral candidiasis**. There are numerous clinical studies in which probiotics have been tested in treating this candidiasis. A simple way to prevent or treat oral candidiasis could be to consume food containing probiotics. The products of a dairy company have been tested several times. In the case of the product containing only *Lactobacillus casei* Shirota, there were no obvious reductions in *Candida* colonization at the oral level after a 28 days daily consumption (Sutula J. et al., 2012; Sutula J. et al., 2013). However, in the variant of *Bifidobacterium breve* and *Lactobacillus casei*, reductions in the presence of various *Candida* strains at the buccal level were reported. In 2009, a study by Dos Santos A. L. and collaborators was published in which 111 people were tested. The results concluded that daily consumption, over a 20-day period, significantly reduces the *Candida* population. Consumption-friendly results of this product were reconfirmed in 2012 with the onset of a clinical trial by Mendonça F. and colleagues.

If treating candida with food enriched with probiotics does not always have the expected results, formulating probiotics in the form of tablets, capsules or even paste and administering them for a while may yield optimal results. Applying a paste containing *Lactobacillus bulgaricus*, *Bifidobacterium longum* and *Streptococcus thermophilus* at the buccal level 3 times a day for 4 weeks can significantly reduce the population of various types of *Candida* in the elderly (Li D. et al., 2014). Similar results were obtained by daily administration of capsules containing *L. rhamnosus*, *L. acidophilus* and *B. bifidum* for 5 weeks (Ishikawa KH et al., 2014) or by treatment with tablets containing *L. reuteri* strains (Kraft- Bodi E. et al., 2015).

Urogenital candidiasis is also very common, especially among women. Treating them with classical agents, such as fluconazole, is still the primary way to treat vaginal candidiasis. However, supplementing classical treatment with probiotics (*Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Streptococcus thermophilus*) can reduce, besides *Candida* species, the symptoms associated with this type of candidiasis, such as vaginal discharge, burning vaginal feeling, dyspareunia or dysuria (Martinez R.C.R. et al., 2009), or even to reduce the negative local changes caused by *Candida*-enhanced population on vaginal fluorine, vaginal tissue changes and pH (Kovachev S.M. and Vatcheva-Dobrevska R.S., 2015).

Also, consumption of yogurt enriched with *Bifido bacterium* and *Lactobacillus* strains can reduce colonization of the urogenital tract in HIV-infected individuals (Hu H. et al., 2013). The effects of vaginal candidiasis and its relapse can be drastically reduced by treatment with products of latobacillus (*L. acidophilus* and *L. fermentum*) and prebiotics (arabinogalactan and fructooligosaccharides). After 28 days, the symptoms associated with candidiasis disappeared in 86.6% of patients, and 11.5% of patients were recurrent in the following month (Vicariotto F. et al., 2012).

In cases of **gastrointestinal candidiasis**, there are numerous deficiencies in treating them due to some factors present in these cases: the presence of diseases such as ulcerative colitis or Crohn's disease or the need to treat infants or very young children. In case of treatment for newborns or children, milk products enriched with probiotics or other probiotic preparations as a powder may be used. These preparations contain strains of *L. reuteri*, *L. rhamnosus*, *L.*

acidophilus, *S. boulardii*, *S. thermophilus*, *B. longum*, *B. bifidum*, *B. lactis*, and prebiotics (fructooligosaccharides) which, after administration, reduce the *Candida* populations, even in cases of candidemia (Romeo MG et al., 2011, Demirel G. et al., 2013, Kumar S. et al., 2013, Roy A. et al., 2014). The administration of probiotics together with a prebiotic complex can improve the health of patients diagnosed with Crohn's disease by improving the immune system (Steed H. et al., 2010). In the case of remission or moderate ulcerative colitis, after the administration of probiotics and prebiotics, the improvement of the patient's health status was revealed, a major role in the improvement of the immune system being due to the growth of microflora of lactobacilli and bifidobacteria and the increase of IL- 10 (Miele E. et al., 2009; Fujimori S. et al., 2009; Hegazy S. K. and El-Bedewy M. M., 2010; Tursi A. et al., 2010; Wildt S. et al., 2011; D'Incà R. et al., 2011; Ishikawa H. et al., 2011; Oliva S. et al., 2012).

CONCLUSION AND FUTURE PERSPECTIVES

Data from clinical trials, from animal studies or from *in vitro* studies indicates that the probiotics can be used with favorable outcomes in treating different types of candidiasis. Of course, it is still necessary to test the efficacy of probiotics in the treatment of candidiasis on different age groups or different states of severity of the disease. It is necessary to understand the mechanisms whereby probiotics work, the long-term effects of their administration and sought solutions for optimal treatment, fast and without adverse effects.

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