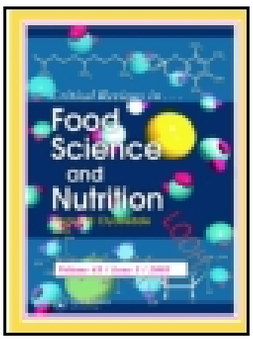

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: José Carlos Andrade, Sunil Kumar, Awanish Kumar, Lucia Černáková & Célia F. Rodrigues (2021): Application of probiotics in candidiasis management, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1926905

To link to this article: https://doi.org/10.1080/10408398.2021.1926905

Published online: 22 May 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1926905

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REVIEW

Application of probiotics in candidiasis management

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ABSTRACT

Candidiasis (e.g., oral, gastrointestinal, vaginal, urinary tract, systemic) is a worldwide growing problem, since antifungal resistance and immunosuppression states are rising. To address this problem, very few drugs are available for the treatment of *Candida* spp. infections. Therefore, novel therapeutic strategies are urgently required. Probiotics have been proposed for the prevention and treatment of bacterial infections due to their safety record and efficacy, however, little is still known about their potential role regarding fungal infections. The purpose of this review is to present an updated summary of the evidence of the antifungal effects of probiotics along with a discussion of their potential use as an alternative/complementary therapy against *Candida* spp. infections. Thus, we performed a literature search using appropriate keywords ("Probiotic + Candida", "Candidiasis treatment", and "Probiotic + candidiasis") to retrieve relevant studies (both preclinical and clinical) with special emphasis on the works published in the last 5 years. An increasing amount of evidence has shown the potential usefulness of probiotics in the management of oral and vulvovaginal candidiasis in recent years. Among other results, we found that, as for bacterial infections, *Lactobacillus*, *Bifidobacterium,* and *Saccharomyces* are the most studied and effective genus for this purpose. However, in other areas, particularly in skincandidiasis, studies are low or lacking. Thus, further investigation is necessary including in vitro and in vivo studies to establish the usefulness of probiotics in the management of candidiasis.

KEYWORDS

Candida spp; candidiasis; antifungal resistance; probiotics; *Lactobacillus*; *Bifidobacterium*; infection

Introduction

Candida is the main fungal pathogen, causing infections in humans (candidiasis). Several *Candida* spp. are commensals usually found in the skin, oral cavity, and the gastrointestinal, uro-genital, and respiratory tracts of healthy humans (Mundula et al. 2019; Sardi et al. 2013). However, under certain circumstances, they can cause superficial (skin or mucosal) and even life-threatening systemic infections (Sardi et al. 2013; Ribeiro et al. 2020). Candidiasis are mainly caused by *Candida albicans*, but other species such as *Candida glabrata, Candida parapsilosis, Candida tropicalis*, and *Candida krusei* are also often implicated (Mundula et al. 2019; Sardi et al. 2013). In the last decades, the incidence of human fungal infections has increased significantly probably due to the increase in some immune-related chronic illnesses (e.g., diabetes, cancer, AIDS) and the widespread use of some drugs, such as antibiotics, chemotherapy, and immunosuppressants (Mundula et al. 2019; Lass-Flörl 2009). Though pharmacological treatments are available for candidiasis, however, its side effects can not be ignored and hence the species of *Candida* are gaining resistance to conventional therapies (Whaley et al. 2017). In fact, according to the World Health Organization (WHO), *Candida* spp. infection is a significant concern for human health in vulnerable populations due to the emergence of new resistance mechanisms in the microorganisms which appears to be more frequent among non-albicans species (WHO 2014). Therefore, it is extremely important to seek and develop new prophylactic and complementary strategies. The use of probiotics may be one of the methods to achieve these purposes (Matsubara et al. 2016; Rodrigues et al., 2018).

Currently, the most widely accepted definition of probiotics is "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host." Such definition was recommended by the International Scientific Association for Probiotics and Prebiotics (Hill et al. 2014) which maintained an earlier probiotics definition given by the Food and Agriculture Organization of the United Nations and WHO (2001) with only minor grammatical adjustments. The most used probiotics belong to the *Lactobacillus* or *Bifidobacterium* genera but selected species of other genera such as *Bacillus, Streptococcus, or Saccharomyces* are being increasingly used (Machado et al.

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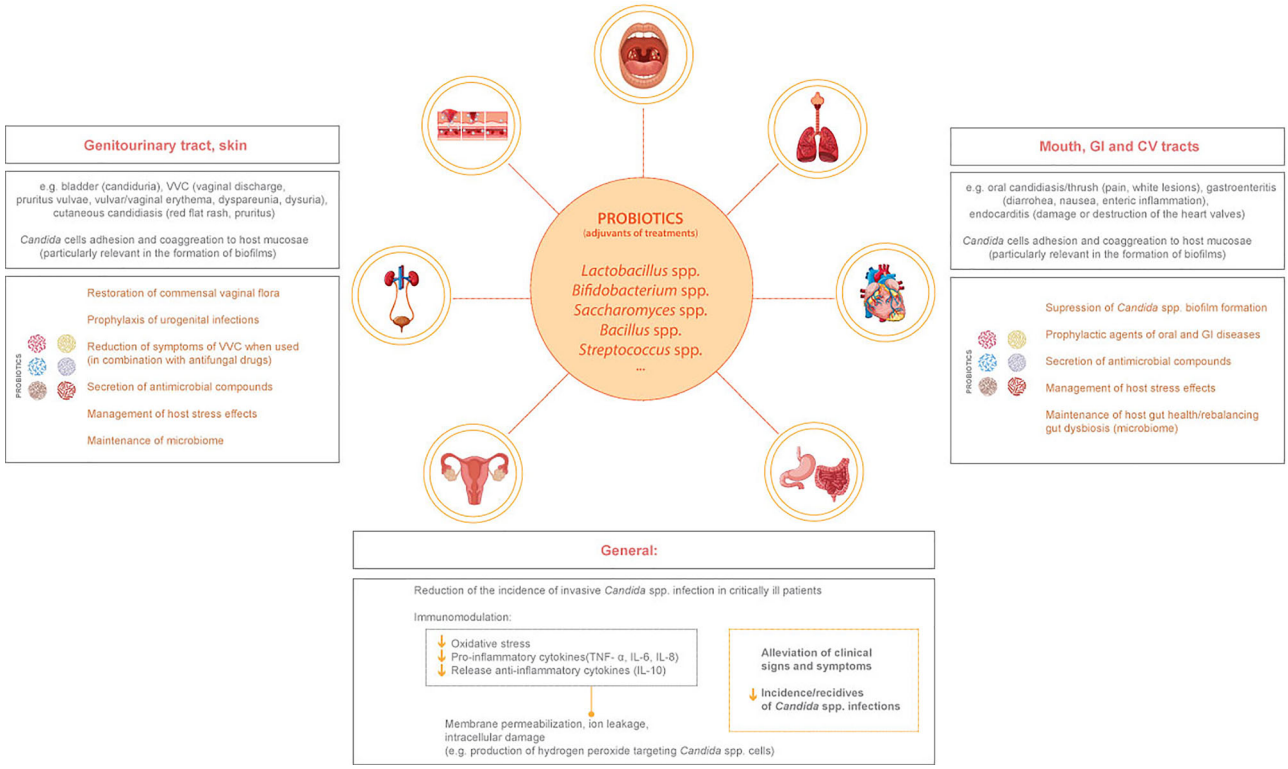

Figure 1. Main probiotics used as adjuvant for the treatment of several types of candidiasis, their antimicrobial activity and final outcomes.

2020). In the last decades, the use of probiotics as a way to prevent and treat a variety of human gastrointestinal and extraintestinal disorders has achieved higher importance among clinicians and researchers (Salehi et al. 2021; Stavropoulou and Bezirtzoglou 2020; Emre et al. 2020; Tamtaji et al. 2020). More specifically, probiotics have been shown to suppress *Candida* spp. growth and biofilm development in vitro. Furthermore, some clinical trials have shown the beneficial effects of probiotics in reducing oral, vaginal, and enteric colonization by *Candida* spp.; alleviation of clinical signs and symptoms; and, in some cases, reducing the incidence of invasive fungal infection in the critically ill patient (Mundula et al. 2019; Sardi et al. 2013; Ribeiro et al. 2013). Antifungal action mechanism of probiotic includes the following: (i) inhibition of adhesion sites; (ii) inhibition of adhesion by coaggregation; (iii) secretion of antimicrobial molecules; (iv) host immune system modulation; v) management of the effects of stress – link between the mental health, the gut, and skin health (gut–skin brain axis); and vi) maintenance of gut health rebalancing gut dysbiosis (Ribeiro et al. 2020; Gagliardi et al. 2018; Silverberg and Silverberg 2014; Azad, et al. 2018; Bernini et al. 2018; Cosseau et al. 2008) (Figure 1). In this review, an updated summary of in vitro, in vivo, and clinical evidence of the antifungal effects of probiotics has been presented. For that, a structured search of bibliographic databases for peer-reviewed research literature (e.g., PubMed, WOS) with the words "Probiotic + Candida", "Candidiasis treatment", and "Probiotic + candidiasis" was performed with an emphasis on works published in the last five years. Additionally, their potential use as an alternative/complementary therapy against several *Candida* spp. infections have also been discussed.

Fighting *Candida* spp. infections: Using probiotics for a possible mission

Oral candidiasis

As mentioned before, *Candida* spp. are present in the human oral cavity as harmless commensals. However, they become opportunistic pathogens in immunologically weak and immunocompromised patients. These oral infections [oral candidiasis (OC)] are mainly caused by *C. albicans* and can affect the oropharynx and/or the esophagus (Vila et al. 2020). The development of OC is associated with different predisposing factors, including the use of dental prostheses, topical corticosteroid therapy, salivary dysfunction, advanced age, nutritional deficiencies, prolonged administration of broad-spectrum antibiotics, and immunosuppression associated with antineoplastic treatments, hematological diseases, or AIDS (Patil et al. 2015; Vila et al. 2020). Oral candidiasis can cause chronic pain or discomfort upon mastication, limiting nutritional intake and, if the infection spreads through the bloodstream or upper gastrointestinal tract in immune-compromised patients, it can lead to significant morbidity and mortality (Ai et al. 2017; Patil et al. 2015). Up till now, antifungal agents such as nystatin, fluconazole, or miconazole, have proven to be effective in preventing mucosal and invasive fungal infections (Hu, Zhou, et al. 2019; Ai et al. 2017). However, antifungal drugs have marked side effects, such as hepatic and renal toxicity and gastrointestinal discomfort, including nausea, vomiting, and diarrhea (Ribeiro et al. 2020; Lass-Flörl, 2009). Furthermore, the emergence of drug-resistant strains may also limit the clinical application of antifungals (Sardi et al. 2013; Vila et al. 2020).

Table 1. Selected studies and probiotics used in oral candidiasis.

Probiotic	Biological effects	In vitro/in vivo/clinical study	Reference(s)
Lactobacillus plantarum SD5870, *Lactobacillus helveticus CBS* N116411 and *Streptococcus salivarius* DSM 14685	Decreased *C. albicans* biofilm formation	In vitro	(James et al. 2016)
Lactobacillus rhamnosus LR32, *Lactobacillus acidophilus* NCFM, and *Lactobacillus casei* L324m	Inhibition of early stages of *C. albicans* biofilm development	In vitro	(Matsubara et al. 2016)
Lactobacillus reuteri DSM 17938 and ATCC PTA 5289	Almost complete inhibition of the growth of *C. albicans* and *C. parapsilosis* but did not affect *C. krusei.*	In vitro	(Jørgensen et al. 2017)
Lactobacillus paracasei 28.4, *Lactobacillus rhamnosus* 5.2, and *Lactobacillus fermentum* 20.4	Co-incubation resulted in deterrence of biofilm development and retardation of hyphal formation	In vitro	(Rossoni et al. 2018)
Streptococcus salivarius K12	Inhibition of mycelial growth and adherence to plastic of C. albicans. Oral treatment significantly protected the mice from severe candidiasis	In vitro/ In vivo	(Ishijima et al. 2012)
Bacillus subtilis R0179	Significant inhibitory effect on the growth of *C. albicans* and *C. parapsilosis*	In vitro	(Zhao et al. 2016)
Pediococcus acidilactici PTCC 1602	Growth inibition of several *Candida* species and the germ tube and biofilm formation in a dose-dependent manner	In vitro	(Zareshahrabadi 2020)
Saccharomyces cerevisiae CNCM I-3856	Administration of probiotics in the oral cavity of C57BL/6J mice resulted in a protective effect against oropharyngeal candidiasis	In vivo	(Roselletti et al. 2019)
Lactobacillus paracasei 28.4	Reduction in vitro hyphae formation of C. *albicans* and prevents the filamentation in *Caenorhabditis elegans*	In vitro/ In vivo	(de Barros et al. 2018)
Lactobacillus paracasei 28.4	Modulate the immune system of *Galleria mellonella* and protect against candidiasis	In vivo	(Rossoni et al. 2017)
Lactobacillus rhamnosus ATCC 7469	Lower *Candida* counts on immunosuppressed mice.	In vivo	(Leão et al. 2018)
Lactobacillus rhamnosus GG (ATCC 53103), *Lactobacillus rhamnosus* LC705, *Propionibacterium freudenreichii* subsp. *shermanii* JS	Probiotic intervention reduced the risk of high yeast counts in saliva by 75%	RCT	(Hatakka et al. 2007)
Lactobacillus rhamnosus HS111, *Lactobacillus acidophillus* HS101, and *Bifidobacterium bifidum*	Significant reduction of *Candida* infection after probiotic administration in denture wearers	RCT	(Ishikawa et al. 2015)
Lactobacillus reuteri DSM 17938 and ATCC PTA 5289	Significant reduction of *Candida* cells in saliva and plaque after probiotic administration in frail elderly	RCT	(Kraft-Bodi et al. 2015)
Lactobacillus acidophilus NCFM or *Lactobacillus rhamnosus* Lr-32	Daily consumption of cheese supplemented with probiotics reduce the colonization of *Candida* in denture wearers	RCT	(Miyazima et al. 2017)
Lactobacillus rhamnosus SP 1	Regular consumption of milk supplemented with probiotics along with the establishment of a protocol of oral/ prosthetic hygiene reduced the severity of denture stomatitis in institutionalized elders who wore removable prostheses	RCT	(Lee et al. 2019)
Streptococcus salivarius K12	In combination with nystatin, the probiotic enhanced mycological cure and shortening the treatment course	RCT	(Hu et al. 2019)

RCT, randomized controlled trial.

In this context, probiotics have been studied as an alternative approach for the control of OC. Several pre-clinical and clinical studies have investigated whether probiotics affect OC. Table 1 illustrates the variety and the extent of bacterial strains used to evaluate the anti-*Candida* activity of probiotic bacteria in the last few years. Jørgensen et al. (2020) screened the antifungal activity of 14 *Lactobacillus* strains, of oral and vaginal origin, against *C. albicans* and non-albicans species (from culture collection and clinical isolates) using the agar overlay growth inhibition assay. Two oral isolates, *Lactobacillus rhamnosus* DSM 32992 and *Lactobacillus rhamnosus* DSM 32991, were the most active. The various *Candida* spp. differed in susceptibility; the growth of the clinical and control strains of *C. parapsilosis* was highly inhibited, while the two *C. krusei* strains presented no growth inhibition or only slight growth inhibition. However, it should be mentioned that compared to *C. albicans*, *C. parapsilosis* and *C. krusei* have a testimonial role in the etiology of OC. In another in vitro study (Rossoni et al. 2018), thirty *Lactobacillus* strains isolated from caries-free subjects were evaluated for their antifungal activity against *C. albicans* (one reference and two clinical strains). Three isolates, *Lactobacillus paracasei* 28.4, *L. rhamnosus* 5.2, and *L. fermentum* 20.4, exhibited the most significant inhibitory activity against *C. albicans*. Co-incubation between these microorganisms resulted in the avoidance of biofilm development and retardation of hyphal formation. These effects also occurred when only the culture supernatant of

Lactobacillus strains was added to the *C. albicans* biofilms, suggesting that these strains may produce acids or other metabolites capable of inhibiting *C. albicans* growth. The inhibition of biofilm development was also characterized by the downregulated expression of *C. albicans* biofilm-specific genes (*ALS3*, *HWP1*, *EFG1*, and *CPH1*). Earlier, Matsubara et al. (2016) have also shown that probiotic lactobacilli cells, namely *Lactobacillus rhamnosus* LR32, inhibit the early stages of *C. albicans* biofilm development by reducing their growth, cell adhesion, and filamentation. The cell supernatants of *L. rhamnosus* also reduced *Candida* spp. biofilms formation in the early stages but had no significant effect on the mature biofilm. James et al. (2016) evaluated the combinations of *Lactobacillus plantarum* SD5870, *Lactobacillus helveticus* CBS N116411, and *Streptococcus salivarius* DSM 14685. They have demonstrated that the co-incubation with probiotic supernatants or live probiotics under hyphae-inducing conditions decreased *C. albicans* biofilm formation and size in all treatment groups. Furthermore, the combined supernatants showed a significant reduction in the expression of several *C. albicans* genes involved in the yeast–hyphae transition, biofilm formation, tissue invasion, and cellular damage. Thus, the combination of *L. plantarum* SD5870, *L. helveticus* CBS N116411, and *S. salivarius* DSM 14685 may be effective at both preventing the formation of and removing *C. albicans* pre-formed biofilms. The use of cell supernatants or postbiotics may be of interest as the application of live probiotic cells in immunocompromised patients may be risky due to the possibility of bacteremia (Salminen et al. 2006). The term "postbiotics" indicates products resulting from the metabolic activity of alive bacteria capable of providing health benefits to the host. Thus, postbiotics can comprise many different constituents including metabolites, short-chain fatty acids, microbial cell fractions, proteins, polysaccharides, cell lysates, peptidoglycan derived peptides, and pili-type structures (Wegh et al. 2019). Cell-free supernatants of *Lactobacillus gasseri* and *L. rhamnosus* (undisclosed strains) showed in vitro inhibition and disruption activity on single and mixed-species biofilm of non-*albicans Candida* species (clinical isolates), including *C. tropicalis, C. krusei*, and *C. parapsilosis* (Tan et al. 2018). In another study, the antifungal effects of cells and postbiotics of *Lactobacillus acidophilus* and *L. plantarum* (undisclosed strains) on different *Candida* spp. isolated from the oral cavity of HIV/AIDS patients were investigated and compared to fluconazole (Salari and Ghasemi Nejad Almani 2020). These clinical species involved *C. albicans, C. parapsilosis, C. glabrata, C. kefyr*, and *C. krusei*. Both *L. acidophilus* and *L. plantarum,* at cell concentrations 10^{10} to 10^{2} CFU/mL, were able to inhibit the growth of most of the oral *Candida* spp., except for *C. albicans*, and to some *C. krusei* strains. *Candida albicans* and *C. parapsilosis* displayed the highest and least susceptibility to the postbiotics of the two *Lactobacillus*, respectively. It is noteworthy that the fungicidal effects of the postbiotics were higher than fluconazole for the five different *Candida* spp. Rossoni et al. (2020) investigated the postbiotic activity of *L. paracasei* 28.4 against *C. auris*, an emerging pathogen with considerable resistance to antifungal agents. Both live cells and their postbiotic elements (crude extract and a fraction) showed antifungal activity against planktonic cells, biofilms, and persister cells of *C. auris*. Moreover, the postbiotic also protected *Galleria mellonella* (an invertebrate infection model) infected with *C. auris* and enhanced its cellular and humoral immune response indicating a dual function in modulating the host immune response. Unfortunately, the exact molecules responsible for the postbiotic activities were not identified. Some *lactobacilli* are known to produce a range of antifungal metabolites including organic acids (acetic, propionic, lactic, 3-phenyllactic), hydrogen peroxide, reuterin and cyclic peptides (Sadiq et al. 2019).

Besides lactobacilli, other potential probiotic species have been shown to be effective against *Candida* spp. Zhao et al. (2016) screened four commercial probiotic products (for inhibitory activity against *Candida* spp.). *Bacillus subtilis* R0179 was found to have a significant antifungal effect on *C. albicans* and *C. parapsilosis* but not for *C. krusei*. The production of Iturin A (a cyclic lipopeptides antibiotic) by *B. subtilis* R0179 was detected which may be the main antifungal mechanism against *Candida* spp. The lactic acid bacteria, *Pediococcus acidilactici* PTCC, 1602 has also demonstrated to exert significant anti-*Candida* activity both in vitro and in vivo assays (Zareshahrabadi 2020). This strain inhibited the growth (assessed by the broth microdilution method) of several *Candida* spp. including some clinical azole-resistant isolates of *C. albicans*. Inhibition of biofilm and germ tube formation by *C. albicans* (CBS 5982) was also observed. Moreover, feeding live *P. acidilactici* to mice infected with *C. albicans* orally protected them against OC. The clearance of *C. albicans* from the oral cavity of BALB/c mice fed with *P. acidilactici* increased significantly which was in line with the in vitro results. The nonpathogenic commensal oral probiotic, *S. salivarius* K12, showed in vitro inhibition of mycelial growth of *C. albicans* and its adherence to the plastic Petri dish (Ishijima et al. 2012). *Streptococcus salivarius* K12 was not directly fungicidal but appeared to inhibit *Candida* spp. adhesion to the substratum by preferentially binding to hyphae rather than yeast. The potential of *S. salivarius* was further demonstrated in a murine OC model. Oral treatment with *S. salivarius* K12 significantly protected the mice from severe candidiasis. Other studies have identified several probiotic yeasts, namely *Saccharomyces cerevisiae (Sac. cerevisiae)* var. *boulardii*, that effectively inhibit virulence of *Candida* spp. (Kunyeit et al. 2020) but essentially applied to the gastrointestinal tract (see also section Gastrointestinal tract candidiasis). Recently, the effectiveness of *Sac. cerevisiae* CNCM I-3856 (live and inactivated cells) against oropharyngeal candidiasis (OPC) was demonstrated in a mouse model (Roselletti et al. 2019). *Sac. cerevisiae* CNCM I-3856 was able to significantly decrease the local fungal burden generally observed in OPC in the oral cavity, the esophagus, and the stomach, thus preventing the translocation of *C. albicans* to the small intestine. The inactivated yeast showed an inferior protective effect as compared to the live probiotic yeast. However, it should be noted that that use of *Sac. cerevisiae* should be cautious,

specially in immunodeficient patients, as it may cause fungemia (Roy et al. 2017; Martin et al. 2017; Appel-da-Silva et al. 2017).

A number of clinical studies have also been performed over the past years in order to evaluate the antifungal activity of probiotics in humans (Table 1). Elderly individuals are particularly susceptible to OC as they frequently wear a prosthesis (dentures) and produce less saliva (Ai et al. 2017). A recent meta-analysis of randomized trials assessing the effects of probiotic preparations on oral OC in the elderly concluded that probiotics have a preventing effect. This study only included three articles (Hatakka et al. 2007; Ishikawa et al. 2015; Kraft-Bodi et al. 2015) reporting double-blind randomized placebo-controlled studies rather than a large number of uncontrolled studies, in order to improve the validity of the analysis. Similar findings were also obtained in other meta-analysis (Mundula et al. 2019; Hu, Zhou, et al. 2019) which also concluded that probiotics intake may have a beneficial effect on OC particularly in the elderly and denture wearers. Another group prone to suffer from OC is patients with Sjogren's syndrome (SS), an autoimmune chronic disease. A double- blinded, placebo- controlled, randomized trial demonstrated that probiotic capsules containing *Bifidobacterium bifidum, L. bulgaricus, L. acidophilus,* and *Streptococcus thermophilus*, significantly reduced *Candida* spp. loads in patients with SS (Kamal et al. 2020). However, this study was considered to have not enough power to detect differences that may have existed as it was small and of short duration (Brignardello-Petersen 2020).

Probiotics can be administered in various forms, such as mouth rinses, toothpastes, lozenges, capsules, or foods. Amižić et al. (2017) evaluated the in vitro antimicrobial capacity of two probiotic toothpastes, one containing *L. paracasei* and the other *L. acidophilus*, comparing to a toothpaste without probiotic, and in a combination with two different mouth rinses (one containing essential oils and the other containing hexetidine). Their results showed that the probiotic toothpastes had a clear, better inhibitory effect than the toothpaste without probiotics in the case of *C. albicans* (and *S. salivarius*). In all cases, probiotic toothpaste had a stronger inhibition capacity than mouth rinses and may contribute to the prevention of oral infectious diseases. In a randomized clinical trial conducted on 60 subjects aged between 6 and 14 years, for a period of 9 months, Mishra et al. (2017) showed that a probiotic rinse was equally effective as 0.2% chlorhexidine digluconate rinse in reducing *C. albicans* cells after one week of intervention. The probiotic rinse used consisted of a commercial probiotic tablet (ProBiora3), containing in *S. oralis* KJ3sm, *S. uberis* KJ2sm, and the spontaneous lactic acid-deficient variant of *S. rattus* JH145, (Zahradnik et al. 2009) mixed with bottled or filtered water. Regular consumption of cheese supplemented with probiotics has also been shown to reduce *Candida* loads (Miyazima et al. 2017). In this study conducted on sixty denture wearers harboring oral *Candida*, daily consumption for 8 weeks, of cheese supplemented with *L. acidophilus* NCFM or *L. rhamnosus* Lr-32, consumed daily for 8 weeks was shown to reduce *Candida* colonization suggesting its potential in reducing the risk of OC in this highly susceptible population. In another study, realized with 36 elders presenting denture stomatitis and who carried removable prostheses, regular consumption of milk supplemented with *L. rhamnosus* SP1 resulted in a significant decrease in the prevalence and clinical severity of *Candida*-associated denture stomatitis. However, to effectively control oral infections, it is necessary to use formulations targeted for local administration (Kraft-Bodi et al. 2015). In the case of probiotics, this can pose several challenges since the amount delivered and viability of probiotics is crucial for their effectiveness (Machado et al. 2020). Ribeiro et al. (2020) developed gellan gum formulations containing *L. paracasei* 28.4, for local application in the oral cavity. Probiotic-gellan gum formulations were stable for 7 days when stored at room temperature or 4 °C. Long-term storage of probiotic-loaded gellan gum was achieved when *L. paracasei* 28.4 was lyophilized. Moreover, the pretreatment with the probiotic-gellan gum formulation preparation resulted in a significant reduction of *C. albicans* in the oral cavity of mice. More recently, Elvan et al. developed a lozenge using microencapsulated *Lactiplantibacillus pentosus* NRRL-B227 (formerly *Lactobacillus pentosus*), a strain that showed in vitro inhibitory activity against *S. mutans* and *C. albicans* (Elvan et al. 2021). Microencapsulation of this strain within whey protein concentrate-pullulan emulsion matrix significantly protected cell viability, only 0.11 log CFU/g decrease was found in the lozenge formulation stored at 4 °C at the end of three months. Thus, microencapsulation was regarded as a good preservation method to keep *L. pentosus* stable during the shelf life.

Gastrointestinal, urinary tract, and vaginal candidiasis

Several events can induce *Candida* spp. overgrowth in gastrointestinal, urinary tract, and vagina. Although *Candida* spp. overgrowth is not always a synonym of candidiasis, this increase in yeasts, can lead to candidiasis, demanding appropriate treatments. Among them, bowel mucosa atrophy and gut flora deregulation, broad-spectrum antibiotic therapies, immunodepression, antacid use, diarrhea, radiotherapy, chemotherapy, surgical trauma, bowel preparations, and complete parenteral feeding, can induce microbiota deregulation, favoring overgrowth of *Candida* spp. and eventual invasion of these systems (Charlet et al. 2018; Kirchner et al. 2019; Rodrigues et al. 2019).

Gastrointestinal tract candidiasis

Candida albicans is the major human gastrointestinal (GI) commensal yeast, but other *Candida* spp. have also been implicated in GI infections. Indeed, high quantities of *Candida* spp. are produced inside the peritoneum when a GI perforation happens in a colonized stomach. Recurrent GI surgery, bowel inflammation, and radiotherapy are key risk factors for GI candidiasis (Martínez-Jiménez et al. 2015; Dupont et al. 2002; Bassetti et al. 2013). The use of

probiotics as adjuvants for the treatment of GI candidiasis has become more usual. Dyachenko et al. (2019) revealed significant quantitative and qualitative fluctuations of intestinal microbiota in patients with chronic infections. Indeed, dysbiotic changes led to a reduction in the number of *Lactobacillus* spp., *Bifidobacterium* spp., *Escherichia coli* (with normal enzymatic properties), and a rise in the number of *Staphylococcus aureus, Clostridium* spp., *Candida* spp. After using probiotics, the number of *Staphylococcus aureus, Staphylococcus saprophyticus, Staphylococcus epidermidis, C. albicans,* and *Clostridium perfringens* (*Cl. perfringens*) decreased and restored the variety of microbial landscape, indicating progress in the qualitative and quantitative composition of the microbiota (Dyachenko et al. 2019).

It is known that gut fungi may positively or negatively influence the course of *Clostridium difficile (Cl. difficile)* infection. Panpetch and colleagues (2019) have shown that *C. albicans* administration increased the severity of the *Cl. difficile* infection in vivo model. Also, *C. albicans* lysate with *Cl. difficile* increased IL-8 production from HT-29 and Caco-2 human intestinal epithelial cell-lines. After the administration of *Bifidobacterium* spp., the disease severity decreased (Panpetch et al. 2019). The work reveals that studying the fungal mycobiome in patients with *Cl. difficile* is necessary and may be a novel source of therapeutic targets. Alterations in gut fungi may also be involved in inflammatory bowel diseases (IBD). Lam et al. (2019) reported growth in fungal load, mostly of *Candida* spp. and *Malassezia* spp., in the feces and mucosa of Crohn's disease patients, and an inferior fungal diversity in the feces of ulcerative colitis patients. Besides, they noticed that a diet high in carbohydrates increased the total abundance of *Candida* spp., whereas a protein-rich diet had the opposite effect. The supplementation with *Saccharomycopsis fibuligera*, *S. boulardii*, and *S. cerevisiae* strain CNCM I-3856 strain showed therapeutic effects in IBD, indicating that a modulation of the fungal microbiota is a potential therapeutic approach for IBD (Lam et al. 2019). De Sire et al. indicate that the IBD patients can also show a decrease in *Faecalibacterium prausnitzii*, an increase of *Proteonbacteria* and *C. albicans*, Basidiomycota/Ascomycota ratio over *Sac. cerevisiae* and of the Caudovirales over Microviridae. These authors also reveal that an indirect (antibiotics, probiotics) and direct (fecal microbiota transplantation) modulation of gut microbiota has an appropriate clinical implication in IBD management (De Sire et al. 2018). Another important report evaluated the protective effect of *Lactobacillus* spp. against *Candida* spp. infection of the GI tract. Maekawa and colleagues assessed the inhibitory effects of *L. pentosus* S-PT84 (a heat-killed preparation of *L. pentosus*) and JCM1558^{T}, *L. gasseri* JCM1131^{T}, and *L. casei* JCM1134^{T}, on mycelial growth of *C. albicans*. The in vitro results indicated that *L. pentosus* S-PT84 directly adhered to *Candida* spp. and had the strongest growth-inhibitory activity among the tested *Lactobacillus* strains. In a murine model, it was shown that the oral administration of *L. pentosus* S-PT84 may be effective in preventing GI candidiasis (diminishing coverage of stomach lesions by patchy whitish plaques and suppressing the vascular permeability observed in *C. albicans*-infected stomach) but also in inhibiting gastric inflammation induced by the infection (Maekawa et al. 2016). Hayama et al. reported the in vivo and in vitro effect of *L. pentosus* S-PT84 on the growth of *C. albicans*, for a potential application on oral and gastric candidiasis. The work signpost that the mycelial growth was inhibited by S-PT84 and appeared to bind to the hyphae. After in vivo (murine model) oral administration (three times), the number of viable *Candida* cells in the stomach was reduced significantly on day 2. The findings propose S-PT84 as a potential food ingredient supporting the treatment of *Candida* spp. infection in the GI tract (Hayama et al. 2014).

Several studies have put in evidence the potential role of probiotics in the prevention of *Candida* colonization and invasive candidiasis in children. Roy et al. (2014) demonstrated that supplementation with a mix of probiotics (*L. acidophilus*, *Bifidobacterium longum*, *B. bifidum*, and *B. lactis*) in preterm infants and neonates (112 subjects gestational age of not more than 37 weeks and birth weight of not more than 2500 g) significantly reduced the time of hospitalization in the probiotic group ($P = 0.002$). Results revealed reduced enteral yeast colonization, reduce invasive fungal sepsis and the earlier establishment of full enteral feeds in the probiotics group. Kumar et al. (2013) estimated the efficacy of probiotics in the prevention of *Candida* spp. colonization in a Pediatric Intensive Care Unit. Children (150 subjects, 3 months to 12 years old on broad spectrum antibiotics for at least 48 hours) received one sachet twice a day of either probiotics – *L. acidophillus, L. rhamnosum, B. longum, B. bifidum, Sac. boulardi, S. thermophilus*, fructo-oligosaccharides – or placebo (lactose) for 7 days and followed until completion of 14 days study period or death of the patient. In the probiotic group, there was a relative decrease in *Candida* spp. colonization on day 7 (34.5%) and 14 (37.2%), contrary to the placebo group. Finally, it was concluded that probiotic supplementation might be a potential approach to lower GI *Candida* spp. colonization in critically ill children receiving broad-spectrum antibiotics (Kumar et al. 2013). Oncel et al. compared the efficacy of *L. reuteri* (oral administrated) versus nystatin to inhibit fungal colonization and invasive candidiasis in very low birth weight infants (300 preterm infants with gestational age of not more than 32 weeks and birth weight of not more than 1500 g). Results indicated that GI (and skin) colonization rates were not significantly altered among the groups. Nonetheless, sepsis, feeding intolerance, and duration of hospitalization were expressively inferior in the probiotics group than in the antifungal group, which led to the conclusion that prophylactic *L. reuteri* supplementation is as efficient as the antifungal drug, and more successful in dropping the incidence of proven sepsis furthermore to its satisfactory effect on feeding intolerance (Oncel et al. 2015).

Notwithstanding, it should be noted that a routine use of probiotics cannot be sustained on the basis of current scientific evidence, and that, although seldom, probiotics may cause bacteremia/fungemia, and sepsis in

Table 2. Main studies and probiotics used in gastrointestinal candidiasis.

Probiotic/Study	Biological effect	In vitro/in vivo/clinical study	Reference(s)
Probiotic preparations	Decrease in the number of *S. aureus, S. saprophyticus, S. epidermidis, C. albicans,* and *Cl. perfringens* and restoration of the variety of microbial landscape	RTC	(Dyachenko et al. 2019)
Bifidobacterium spp.	Decreased the disease severity of *Cl. difficile–C. albicans* infection	In vitro/in vivo	(Panpetch et al. 2019)
Saccharomycopsis fibuligera, Saccharomyces boulardii and *Saccharomyces cerevisiae* CNCM I-3856	Positive therapeutic effects in IBD	Literature search	(Lam et al. 2019)
Lactobacillus pentosus S-PT84 (a heat-killed preparation of *Lactobacillus pentosus*)	*Lactobacillus pentosus* S-PT84 adhesion to *Candida* spp., high growth-inhibitory activity. It may be effective in preventing GI candidiasis, and inhibiting gastric inflammation induced by *C. albicans* infection	In vitro/in vivo	(Hayama et al. 2014)
Lactobacillus pentosus S-PT84	Inhibition of *C. albicans* mycelial growth, and appears to bind to the hyphae. The number of viable *Candida* cells in the stomach reduces significantly	In vitro/in vivo	(Hayama et al. 2014)
Lactobacillus spp. – *Lactobacillus casei* subsp. *rhamnosus*, *Lactobacillus reuteri* – alone or in combination with *Bifidobacterium* spp.	Prevention of late-onset sepsis and GIT colonization by *Candida* spp. in preterm very low birth weight infants (in PICU)	RTC	(Singhi and Kumar 2016)
Lactobacillus reuteri (versus nystatin)	*Lactobacillus reuteri* is efficient as the nystatin, and more successful in dropping the incidence of proven sepsis furthermore to its satisfactory effect on feeding intolerance, in very low birth weight infants	PRCS	(Oncel et al. 2015)
Lactobacillus rhamnosus IMC 501 and *Lactobacillus paracasei* IMC 502 and their combination (SYNBIO®; 1:1)	Microbicidal effect in Gram-positive, nine Gram-negative bacteria strains, *Candida* strains; The time of hospitalization was significantly lowered	In vitro	(Coman et al. 2014)
Lactobacillus acidophillus, Lactobacillus rhamnosum, Bifidobacterium longum, Bifidobacterium bifidum, Saccharomyces boulardi, Saccharomyces thermophilus (and fructo-oligosaccharides)	Lowered GI *Candida* colonization in critically ill children receiving broad spectrum antibiotics	RTC	(Kumar, Bansal, et al. 2013)

IBD, inflammatory bowel disease; PICU, Pediatric Intensive Care Unit; PRCS, prospective, randomized comparative study; RTC, randomized controlled trial.

immunocompromised critically ill children (Singhi and Kumar 2016). Table 2 summarizes the most relevant works in this area.

Urinary tract and vulvovaginal candidiasis

Annually, one billion women worldwide are infected by urogenital tract infections (UGTI) (MacPhee et al. 2010). Sexually transmitted diseases, bacterial vaginosis, aerobic vaginitis, vulvovaginal candidiasis (VVC), and UGTI (Larsson and Forsum 2005; Zhou et al. 2009; Donders et al. 2009). Female UGTIs are the outcome of urogenital environment imbalances induced by multiple exogenous or endogenous elements, which affect indigenous vaginal microbiota, and commonly result in a decline of defensive lactobacilli (Ravel et al. 2011). Conventional treatments may generate adverse outcomes, drug-resistant development, and recurrence of the infections. An effective solution suggested for the prevention and treatment of UGTI is the use of probiotics (e.g., lactobacilli) (Barrons and Tassone 2008; Martín et al. 2008). Indeed, the growth of antimicrobial resistance events and the small pipeline of new drugs has contributed to the hypothesis that the treatment for UGTIs may be improved by probiotics. This therapy allows the restoration of ecological harmony in the urogenital tract, as well as the restitution of women's sexual and reproductive health (Kadam et al. 2019; Salehi et al. 2021).

Notably, several trials have shown improved treatment with antibiotic therapy for bacterial vaginosis and VVC, plus one-month oral probiotic use (Anukam et al. 2006; Martinez et al. 2009; Anukam et al. 2009). The dynamics have not yet been entirely explained, although there has been some insight into how this could occur. For example, in the case of metronidazole joint therapy, lactobacilli have been shown to function in the presence of antimicrobial agents (Anukam and Reid 2008). The treatment of bacterial vaginosis and regeneration of a "natural" vaginal microbiota may be due to this effect, as orally administered lactobacilli pass through the intestine and rise into the vagina, probably decreasing the seeding of pathogens from the rectum to the vagina (Reid et al. 2003).

In fact, the rationalization to use urogenital probiotics is focused on the assumption that pathogens (fungi and bacteria) can be counteracted by replenishing natural microbiota, contributing to a return to the lactobacilli-dominated environment seen in healthy women. This administration also prevents inflammation noticed in urinary tract infections (UTI) and VVC. In UTI, pathogens originate from the vaginal cavity and rise into the bladder, becoming a chronic source of reinfection in some cases. In VVC, yeasts do not naturally displace lactobacilli, so antifungal therapy is

required before probiotics can be successful. *Candida albicans* is a major agent that causes the most prevalent vaginal infection worldwide known as vulvovaginal candidiasis. *Candida* spp. infections damage the epithelial cell of the vagina by switching from its yeast to mycelial form (Pericolini et al. 2017). Experiments using in vitro cell culture demonstrated that *L. reuteri* RC-14, either alone or paired with *L. rhamnosus* GR-1 reduced the cell-recoverable yeast population and raised IL-8 levels of antimicrobial cytokine, in VVC (Martinez et al. 2009). This immunomodulatory effect agrees with a post-administration genomic array study of the vagina of *L. rhamnosus* GR-1 (Kirjavainen et al. 2008). To unravel these pathways, further studies are required. Tomás et al. indicated the inhibition of some causal agents of UGTI: *Streptococcus agalactiae* (a pathogen that causes infections by vertical transmission from mother to fetus and neonate), *E. coli*, *S. saprophyticus*, *Klebsiela pneumoniae*, and *Enteroccoccus* sp., which is a remarkable characteristic of some of the potentially probiotic vaginal lactobacilli (Tomás et al. 2011). However, none of the strains studied were able to inhibit *C. albicans*. In agreement, Osset et al. described the ability of lactobacilli to inhibit the growth of *C. albicans* strains in liquid but not in solid culture media (Osset et al. 2001). Recent epidemiological studies have also suggested that the colonization of vaginal lactobacilli would not be able to afford protection against VVC (Anukam et al. 2006; Yeganegi et al. 2009). *Sac. cerevisiae* showed to inhibit the adherence of *C. albicans* to epithelial cells by suppressing its major virulence factors and checking the switching capacity from yeast to mycelial form (Pericolini et al. 2017). Another work also reported that *Sac. cerevisiae* significantly influences the expression of enzyme aspartyl proteinases (SAPs), hyphae-associated proteins Hwp1, and Ece1 that are virulence factors of *C. albicans* found on the vaginal cavity. A study was done by Kovachev and Vatcheva-Dobrevska (2014) involved 436 women having VVC, randomly assigned to two treatment groups. The first group (207 patients) received fluconazole (150 mg) and a single vaginal globule of fenticonazole (600 mg) on the same day. The second group (209 patients) followed the same treatment schedule; however, some vaginal probiotics containing *L. acidophilus*, *L. rhamnosus*, *L. delbrueckii* subsp. *bulgaricus*, and *S. thermophilus*, were also administered beginning the fifth day after azole treatment. The use of probiotics increased therapy efficacy as well as prevent relapse for treatment *C. albicans* vaginal infections (Kovachev and Vatcheva-Dobrevska 2014). In another work, 5×10^9 CFU/capsule of *L. plantarum* P17630 was orally given to women with a recurrent VVC history throughout 3 treatment cycles (15 days/cycle) separated by 15-day washout intervals. Probiotic intake significantly improved lactobacilli colonization on vaginal epithelial cells and successfully prevented VVC episodes (Vladareanu et al. 2018). Er et al. have isolated *L. acidophilus*, *L. crispatus*, *L. fermentum*, *L. paracasei* subsp. *paracasei*, *L. pentosus*, and *L. plantarum* and checked anticandidal activity (Er et al. 2019). Probiotics exhibited in vitro antifungal activity against *C. albicans* and other *Candida* spp. isolated from the vagina (Er et al. 2019). Saduakhasova et al. isolated seven species of lactobacilli – *L. fermentum*, *L. salivarius*, L. *gasseri, L. crispatus, L. jensenii, L. plantarum, L. delbrueskii. L. fermentum, L. salivarius, L. gasseri*, and *L. jensenii* – from the vaginal epithelium of healthy women in reproductive age (Saduakhasova et al. 2014). Importantly, the authors revealed that these species have high antagonistic activity against *C. albicans* (Saduakhasova et al. 2014). Another relevant report demonstrated that LF5, LF09, LF10, and LF11 strains of *L. fermentum* significantly inhibit the development of acute VVC and other vaginal infections caused by *Candida* spp. (Deidda et al. 2016). Parolin and colleagues revealed that several *Lactobacillus* strains (*L. crispatus* B1-BC8, *L. gasseri* BC9-BC14, and *L. vaginalis* BC15-BC17) isolated from vaginal swabs of healthy premenopausal women, showed, in vitro, a fungistatic as well as fungicidal activities against *C. albicans*, *C. glabrata*, *Candida lusitaniae*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis* (Parolin et al. 2015). Finally, the oral intake of *L. acidophilus* GLA-14 and *L. rhamnosus* HN001 and a lactoferrin complex for a short time (i.e., 15 days), led to vaginal colonization by the lactobacilli which was correlated with the restoration of normal Nugent score (values 0–3) and an improvement of symptoms of abnormal vaginal microbiota including itching and discharge (Russo et al. 2018). Table 3 summarizes these and other main studies in this area.

Other candidiasis

Skin candidiasis

The constitution of the microbiome is not consensual, but it is recognized that the dermal microbial community is universal between healthy individuals (Bay et al. 2020). Differences in microbial community can be found in both healthy skin and in the skin with diseases, injuries (e.g., cuts that allow the entrance of microorganisms), or immunity state (Paetzold et al. 2019; Byrd, Belkaid, and Segre 2018; Church et al. 2006; Krüger et al. 2019). For instance, in bruises or cuts, microorganisms can reach the bloodstream through transfer from wounds followed by physiological changes (Krüger et al. 2019). *Candida* spp. is not the typical natural occupant of the skin. Still, and as seen, *C. albicans* can be found on mucosal surfaces (e.g., vagina, urogenital tract, or oral cavity) (da Silva Dantas et al. 2016; Zangl et al. 2020), and *C. parapsilosis* can be found on the hypothenar palm, volar forearm or other dry sites (Byrd, Belkaid, and Segre 2018). Probiotics are known to be able to inhibit the growth of harmful microorganisms in the gut microbiome (Rao and Samak 2013), locally and at far-reaching sites of the body, such as the skin (Salem et al. 2018).

Cutaneous candidiasis is an opportunistic infection that arises, in most cases, from endogenous, saprophytic candidal blastospores. This skin infection can be either acute or chronic in nature and most often occurs in warm, moist, creased areas such as the armpits and groin (Watts, Wagner, and Sohnle 2009). The presence of some *Candida* spp., especially *C. albicans*, on the cutaneous surface is normally harmless and part of the natural mycobiome, but can

Table 3. Main studies and probiotics used in urinary and vaginal candidiasis.

Probiotic/Study	Biological effect	In vitro/in vivo/clinical study	Reference(s)
Saccharomyces cerevisiae	Beneficial therapeutic effects on vaginal mucosal infections	In vitro	(Pericolini et al. 2017; Gabrielli et al. 2018)
Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus delbrueckii subsp. *bulgaricus* and *Streptococcus thermophilus*	Increase therapy efficacy and prevention of relapse of *Candida albicans* vaginal infections	Case study	(Kovachev and Vatcheva-Dobrevska 2014)
Lactobacillus plantarum (P17630)	Recolonization of vaginal epithelial cells and prevention of VVC	RTC	(Vladareanu et al. 2018)
Lactobacillus acidophilus, Lactobacillus crispatus, Lactobacillus fermentum, Lactobacillus paracesei subsp. *paracesei, Lactobacillus pentosus,* and *Lactobacillus plantarum*	Antifungal activity against *Candida albicans, Candida glabrata,* and *Candida tropicalis* strains isolated from the vagina	In vitro	(Er et al. 2019)
Lactobacillus fermentum, Lactobacillus salivarius, Lactobacillus gasseri, Lactobacillus crispatus, Lactobacillus jensenii, Lactobacillus plantarum, Lactobacillus delbrueskii, Lactobacillus fermentum, Lactobacillus salivarius, Lactobacillus gasseri, and *Lactobacillus jensenii*	High antagonistic activity against *Candida albicans*	In vitro and in vivo	(Saduakhasova et al. 2014)
Lactobacillus fermentum strains LF5, LF09, LF10, and LF11	Significantly inhibit the development of acute VVC and other vaginal *Candida* spp. infections	In vitro	(Deidda et al. 2016)
Lactobacillus crispatus B1-BC8, *Lactobacillus gasseri* BC9-BC14 and *Lactobacillus vaginalis* BC15-BC17	Fungistatic and fungicidal activities against *C. albicans, C. glabrata, C. lusitaniae, C. krusei, C. parapsilosis,* and *C. tropicalis*	In vitro	(Parolin et al. 2015)
Mixture of lactobacilli and lactoferrin	Prophylaxis of VVC	In vitro	(Russo et al. 2018)
Lactobacillus acidophilus ATCC 4356	Inhibitory effect on the biofilm formation and *Candida albicans* filamentation	In vitro and in vivo	(Vilela et al. 2015)
Bifidobacterium longum, Bifidobacterium bifidum, Lactobacillus acidophillus, Lactobacillus rhamnosum, Saccharomyces boulardii, and *Streptococcus thermophilus*	Reduction of the prevalence of candidemia and candiduria in the PICU	Case study	(Kumar, Singhi, et al. 2013)
Combination of *Lactobacillus fermentum* LF10 and *Lactobacillus. acidophilus* LA02	Decrease in VVC symptoms and recurrence of VVC	In vivo	(Vicariotto et al. 2012)
Lactobacillus rhamnosus GR-1, *Lactobacillus reuteri* RC-14	No significant impact on VVC treatment, but decrease in recurrence of VVC	In vivo	(Anukam et al. 2009)
Lactobacillus fermentum LF-10 (DSM 19187), *Lactobacillus acidophilus* LA02 (DSM 21717)	Decrease in recurrence of VVC	In vivo	(Murina et al. 2014)

RTC, randomized controlled trial.

promote invasion of the tissues (Raz-Pasteur et al. 2011). Even though the skin defense mechanisms are very efficient (Kühbacher et al. 2017), the advantage of this yeast is the ability to form hyphae (Watts et al. 2009). Hence, occasionally, cutaneous candidiasis may be caused by other species of this genus, including *C. parapsilosis, C. tropicalis,* or *C. glabrata*, but these are more uncommon (Watts et al. 2009). *Candida spp* are also the common cause of diaper rash in infants. This dermatitis occurs in diaper-covered areas and if the dermatological problem continues more than three days, candidiasis uses to be the secondary infection (Mohamadi et al. 2014). Additionally, *Candida* spp. skin infections are also particularly common in obese people or patients with diabetes (Dhandha 2020).

As explained, probiotics are considered to be effective for the health of the host mainly when consumed in appropriate amounts (Fuchs-Tarlovsky et al. 2016). Undeniable beneficial effect on the skin (e.g., acne, eczema, atopic dermatitis, diaper dermatitis) is taken after oral administration of certain probiotics species/strains (e.g., *L. bulgaricus* and *S. thermophilus, L. acidophilus* and *L. delbrueckii* sp. *bulgaricus* and/or *B. bifidum*), as they can modulate the harmony of endogenous microbiota and its metabolic activity (Kim et al. 2010; Jung et al. 2013; Wu et al. 2012; Yeşilova et al. 2012; Prakoeswa et al. 2017; Cabana et al. 2017; Dang et al. 2013; Cuello-Garcia et al. 2015). As an example, a study showed a positive effect of probiotics utilization during pregnancy and lactation when children's eczema (which can be related to *Candida* spp. infection) was reduced (Bustamante et al. 2019). Similar results were obtained beforehand (Mansfield et al. 2014). Nonetheless, very recently Yu et al. indicate that few clinical trials evaluate the effectiveness of probiotics for the prevention and treatment of dermatologic diseases (except atopic dermatitis) (Yu et al. 2020).

Techniques to alter the skin microbial population have proven to be a new insight into the therapeutic strategy for

Table 4. Main studies and probiotics used in several types of candidiasis.

Probiotic/Study	Biological effect	In vitro/in vivo/clinical study	Reference(s)
Saccharomyces cerevisiae var. *boulardii*	Inhibition of the virulence of *C. tropicalis, C. glabrata, C. parapsilosis, Candida krusei* and *Candida auris*	In vitro and in vivo	(Kunyeit et al. 2020)
Bifidobacterium animalis subsp. *lactis* Bb12 and *Lactobacillus rhamnosus* strain GG	Improvement of *C. albicans*-related psychiatric symptoms	Patient recruitment and clinical trial	(Severance et al. 2017)
Lactobacillus acidophilus ATCC 4356	Inhibitory effect on biofilm formation and *C. albicans* filamentation	In vitro and in vivo	(Vilela et al. 2015)
Lactobacillus casei subsp. *rhamnosus*	Prevention of enteric colonization by *Candida* spp.	RTC in the newborn baby	(Manzoni et al. 2006)
Saccharomyces boulardii	Prevention of invasive fungal infection in premature infants	RTC in the newborn baby	(Demirel et al. 2013)
Lactobacillus rhamnosus GG	Support in candidemia treatment	Case report	(Meini et al. 2015)
Lactobacillus crispatus, Lactobacillus jensenii and *Lactobacillus gasseri*	Protection in endocarditis	In vitro	(Martínet al. 2008)

RCT, randomized controlled trial.

skin diseases such as psoriasis or acne vulgaris (Paetzold et al. 2019). Currently, research of probiotics for skin treatment is focused mainly on oral administration and ingestion, and topical application remains largely unexplored (Bustamante et al. 2019; Lee et al. 2019). Nonetheless, in truth, topical probiotics have been used for skincare and treatment since the early 20th century (Lee et al. 2019). The application of probiotics directly to the skin should positively influence the local microbiome, preventing the growth of other present pathogens (Rao et al. 2013). Certainly, the ability of ingested probiotics to alter distant microbial residents suggests that topical probiotics may also have an important dermatological role (Kumaret al. 2014). Moreover, as one of the most common reasons for local candidiasis incidence is antibiotic therapy followed by disbalance in the microbiota, probiotic strains can be administrated not only as a treatment but also as prevention indeed (Mailänder-Sánchez et al. 2011). However, there are still very low clinical trials focused on consumption or topical application of probiotics against skin infections caused by *Candida* spp., a low number of reports suggested a positive contribution for cutaneous homeostasis and regulation of the skin immune system (Gueniche et al. 2009). Furthermore, probiotics have also been said as an interesting approach for the inhibition of growth of harmful microorganisms and support wound healing in burn (Nole et al. 2014), and for patients with mental health issues, such as anxiety and depression, which occur frequently alongside chronic skin conditions such as acne (Silverberg and Silverberg 2014). Thus, it is reasonable to assume that further investigation and experiments involving testing large groups of the population are necessary for confirmation beneficial use of probiotics in dermatology practice, namely skin candidiasis (Table 4).

Invasive candidiasis

Candidemia is the most common indication of invasive candidiasis. As shown several probiotics have a role in preventing *Candida* colonization and thus, ultimately may prevent invasive candidiasis. For example in section Gastrointestinal tract candidiasis, several randomized control trial studies which have addressed the positive role of probiotics to prevent the colonization of *Candida* spp. and invasive fungal sepsis in children (Roy et al. 2014; Kumar et al 2013;Oncel et al. 2015) were referred.

A life-threatening inflammation in the inner lining of heart chambers is known as endocarditis. It is usually caused by the infection of bacteria, fungi, and some other infectious agents, which damage the heart wall and destroys heart valves. Endocarditis can be caused by *C. albicans*, with a substantial rise in morbidity and mortality, especially in hospitals. Martín et al. speculate that common vaginal probiotics – *L. crispatus, L. jensenii and L. gasseri* – may protect from endocarditis (Martín et al. 2008). The authors assumed that as these microorganisms regenerate and protect the vaginal ecosystem, they could also eliminate the heart infection while treating them (Martín et al. 2008).

Intra-abdominal candidiasis

In cultures of samples from intra-abdominal sites, the clinical importance of *Candida* spp. is controversial, as mixed bacterial infections are common and thus the settings in which antifungal treatment is useful are not conclusively established (Bassetti et al. 2015; Rex 2006). Clearly, in many patients with intra-abdominal infections, *Candida* spp. leads to bad performance (Montravers et al. 2006). As colonization is a crucial step for the development of intra-abdominal candidiasis (IAC) (Bassetti et al. 2013; Montravers et al. 2015; Bassetti et al. 2015), it is considered that any approach that seeks to reduce the growth of *Candida* spp. within the intestinal flora is therefore important (Montravers et al. 2013). The administration of probiotics may serve as an important instrument for preventing fungal colonization, by competing with pathogenic microorganisms and indirectly by improving the role of the intestinal membrane (see also section Gastrointestinal tract candidiasis). Moreover, laboratory trials have shown that probiotics stimulate the innate immune response to *C. albicans*-induced systemic infections, probably due to the capacity of probiotics to trigger immune response improvements, promoting the development of cytokines, secretion of immunoglobulin-A, and phagocytosis (Villena et al. 2011). Unfortunately, no clear experimental evidence to date has seen either the avoidance of IAC

through the application of probiotics or the impact of the effects of probiotics on invasive candidiasis.

Conclusion and future perspectives

As is evident from many recent studies, probiotics have a promising role in the prevention and treatment of *Candida spp*. infections, in oral, urinary tract, and vaginal environments. The genera with the most positive applications are *Lactobacillus* and *Bifidobacterium*, but there have been other probiotics showing good anti-*Candida* activity, such as *Saccharomyces* strains. On the other hand, the evidence available and accessible published data is still low, particularly in candidiasis located in the skin and central nervous system. For instance, most studies focus on the oral probiotic route, and, of those employing topical probiotics, rare involve skin commensals. Although the use of probiotics generally considered safe, their use in severely debilitated or immunosuppressed persons must be cautious due to the risk of probiotics-sepsis. In this case the use of postbiotics may be useful as it does not comprise living cells.

Hence, additional studies and research data is required to clarify relevant questions, such as the efficacy of a single versus a mix of probiotics species or strains, determination of the most successful probiotic strains, use of postbiotics, duration of the treatments, optimum dosage regimens, risk-benefit potential for the prevention of *Candida* spp. infection, and effectiveness of cost.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

S.K. and A.K. Authors thank the Shri Ramswaroop Memorial University, Barabanki (UP), India, and National Institute of Technology, Raipur (CG), India, for continuous support and assistance during the work and scientific writing. L.C. thanks the Slovak Research and Development Agency under contract no. APVV-15-0347 and the grant of VEGA 1/0537/19 from the Ministry of Education, Science, Research, and the Sport of the Slovak Republic. C.F.R. would like to acknowledge the UID/EQU/00511/2020 Project—Laboratory of Process Engineering, Environment, Biotechnology and Energy (LEPABE), financed by national funds through FCT/MCTES (PIDDAC).

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