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Probiotics as an alternative antimicrobial therapy: Current reality and future directions

Diego Romário Silva[a], Janaína de Cássia Orlandi Sardi[b], Nayla de Souza Pitangui[c], Sindy Magri Roque[e], Andréa Cristina Barbosa da Silva[f], Pedro Luiz Rosalen[a,d,*]

[a] Department of Physiological Sciences, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, SP, Brazil
[b] Faculty of Pharmaceutical Sciences, Food and Nutrition, Federal University of Mato Grosso do Sul, Campo Grande,MS, Brazil
[c] Department of Cellular and Molecular Biology and Pathogenic Bioagents, Ribeirão Preto Medical School, University of São Paulo (USP), Ribeirão Preto, SP, Brazil
[d] Biological Sciences Graduate Program, Federal University of Alfenas, MG, Brazil
[e] Faculty of Pharmaceutical Science, State University of Campinas, Campinas, SP, Brazil
[f] Department of Pharmacy, Center of Biological and Health Sciences, State University of Paraíba, Campina Grande, PB, Brazil

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ABSTRACT

Probiotics are defined as microorganisms that live in symbiosis with the human host. When ingested in adequate quantities, probiotics may modulate biological functions, with health benefits. Different biological properties have been reported for probiotics, including antimicrobial activity. However, there are few studies investigating the use of probiotics as candidates for alternative antimicrobial therapy or as a source of new antibiotics. Thus, in this review we provide a general approach to the current situation of probiotic antimicrobial research and point out future directions in the field. Despite the promising benefits of probiotics on intestinal health, there remains no consensus or standardization on the development of delivery systems and on the application of probiotic formulations for antimicrobial therapy. Thus, further bioguided studies and clinical trials are needed to address the existing gaps in the knowledge. Future research should focus on the isolation, doses, clinical efficacy, safety and mechanisms of action of probiotics in humans.

1. Introdution

Immediately after birth, the human body is colonized by different microorganisms, such as archaea, bacteria, fungi, viruses and micro-eukaryotes (Aagaard et al., 2014). Over time, colonization occurs so intensely that the human microbiome of an adult individual contains more bacterial cells than human cells (Sender, Fuchs, & Milo, 2016). Different types of microorganisms can cause disease in humans and some of which have a high fatality rate (Peterson et al., 2009). For many years, scientific research has focused on understanding pathogenic bacteria and finding ways to preventing and treating human diseases. Conversely, some bacterial species may bring benefits to the host through a symbiotic relationship. These microorganisms are generally named probiotics (Fijan, 2014).

Probiotics are living microorganisms that provide health benefits when ingested in adequate amounts (FAO/WHO, 2001). Most probiotic bacteria are Gram-positive, and their main functions are related to modulation and maintenance of the intestinal tract health (*e.g.*, *Lactobacillus* and *Bifidobacterium*) (Marco, Pavan, & Kleerebezem, 2006).

The probiotics that colonize the human host are most numerous in the intestines. The commensal intestinal microbiome contributes to increased resistance against infections, host immune system differentiation, and synthesis of nutrients (Ubeda & Pamer, 2012).

There is evidence that probiotics may act in the treatment and prevention of infectious diseases (Yang et al., 2019). Currently, infectious diseases are commonly managed with the administration of antibiotics. However, an irrational use of antibiotics may cause consequences at the patient level, such as drug-specific adverse effects, and at the public health level, such as selection of multidrug-resistant bacteria (Yang et al., 2019). Thus, the search for new alternatives in antimicrobial therapy is much needed, with a special interest in natural product-based therapies (Silva et al., 2019).

Clinical trials have shown that probiotics are effective against a wide range of pathological conditions, such as constipation, diarrhea, polycystic ovary syndrome, ulcerative colitis, stress and anxiety,

* Corresponding author at: Department of Physiological Sciences, Piracicaba Dental School, State University of Campinas, Av. Limeira, 901 – Areião, Piracicaba, SP CEP: 13414-018, Brazil.
E-mail address: rosalen@fop.unicamp.br (P.L. Rosalen).

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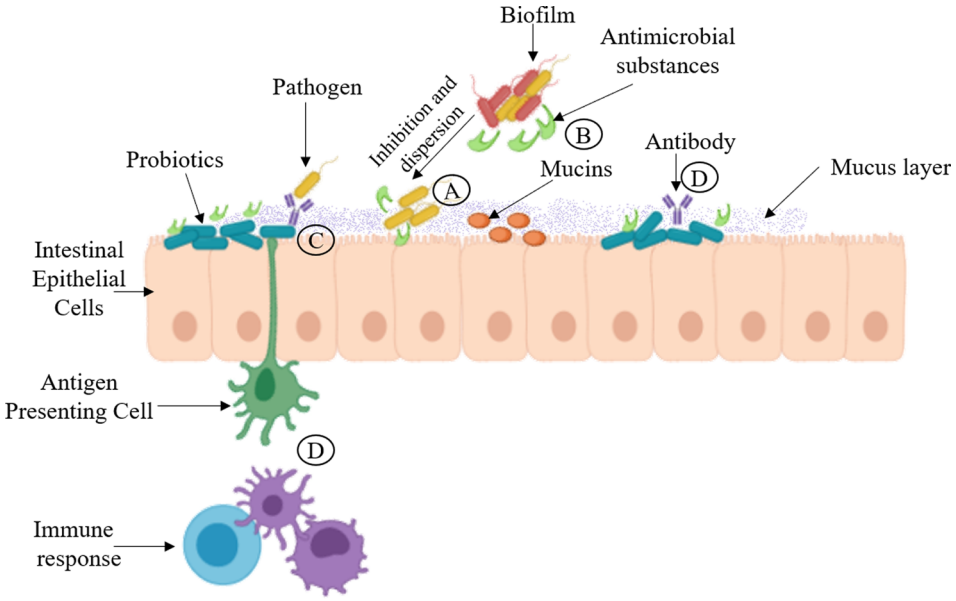

Fig. 1. Mechanisms of action of probiotics. (A) Competitive exclusion of pathogenic microorganisms. (B) Production of antimicrobial substances. (C) Increased adhesion to the intestinal mucosa and improvement of the epithelial barrier. (D) Stimulation of the immune system.

inflammatory bowel disease, breast cancer and diabetes (Kechagia et al., 2013).

Despite the proven biological properties of probiotics, such as antimicrobial activity, research in this area is still incipient and needs further discussion. Thus, this review provides a general approach to the current situation of probiotic antimicrobial research and points out future directions in the field.

2. Probiotics

Ancient civilizations, such as Greeks and Romans, developed recipes for fermented milk, and the Bible mentions sour milk a few times. Thus, the beneficial effects of lactic acid fermentation on human health have been long discussed (Hosono, 1992).

Probiotics are living microorganisms (yeast or bacteria) that provide beneficial effects while colonizing the host. Lactic acid bacteria species (*Lactococcus, Lactobacillus, Streptococcus* and *Enterococcus*) and *Bifidobacterium* (Doron & Snydman, 2015; Prado & de Lindner, 2015; Soccol et al., 2015) are among the best-known probiotics. These microorganisms have characteristics that give them the ability to withstand adverse conditions in the host organism, such as enzymatic action and acidity. They can colonize the host and contribute to health by regulating the microbiome and performing biological functions (de Melo Pereira et al., 2018).

There is mounting evidence on the biological efficacy of probiotics; however, the indication of these microorganisms for clinical use should be seen with caution (de Melo Pereira et al., 2018). In 2002, the United Nations Food and Agriculture Organization/World Health Organization (FAO/WHO) published the "Guidelines for the Evaluation of Probiotics in Food." These guidelines established safety and efficacy standards for probiotics, systematizing their discovery and selection (Araya et al., 2002). Thus, the FAO/WHO guidelines suggest different criteria that should be evaluated for the selection of probiotics, namely: resistance to unfavorable conditions in the human body, ability to adhere to epithelial tissues, antimicrobial activity, and safety for use (de Melo Pereira et al., 2018). The safety of a probiotic strain is defined by its origin and lack of association with pathogenic cultures, in addition to its antibiotic resistance profile (Markowiak Slizewska, 2017a,b).

Lactobacillus is considered the oldest documented probiotic. It is a genus with Gram-positive bacteria of the LAB group. These rod-shaped bacteria comprise about 183 known species and are commonly applied in different industrial food processes (König & Fröhlich, 2009).

The main biological mechanisms of action of probiotics include increased epithelial barrier, increased adhesion to the intestinal mucosa and inhibition of microbial adhesion and competitive exclusion of pathogenic microorganisms, production of antimicrobial substances and immune system modulation (Bermudez-Brito et al., 2012). Fig. 1 shows a schematic representation of how these mechanisms occur in the intestinal mucosa.

Microorganisms of the LAB group produce lactic acid from different carbon sources, such as simple carbohydrates (Carr, Chill, & Maida, 2002). In addition, they eliminate secondary metabolites (*e.g.*, bacteriocins, exopolysaccharides and enzymes) that inhibit the growth of other microorganisms. These factors are related to the different antimicrobial mechanisms of action of probiotics (Leroy & De Vuyst, 2004, de Melo Pereira et al., 2018). These mechanisms are well understood in improving bowel function, as shown in Fig. 1. However, the literature is still incipient regarding the potential of probiotics for alternative antimicrobial therapy against infectious diseases.

3. Methods for determining the antimicrobial activity of probiotics against other microorganisms

There are different *in vitro* methods for determining the antimicrobial activity of a substance. In the case of probiotics, it is possible to determine a direct antagonism between a probiotic culture and that of a pathogenic strain or to determine the antimicrobial activity of a probiotic extract (planktonic cells) (Fijan, 2016). When the purpose of the analysis is merely to discover the antagonism of one microorganism in relation to another, then microbial antagonism assays on solid media are most appropriate (Tagg, Dajani, & Wannmaker, 1976; Balouiri, Sadiki, & Ibnsouda, 2016). This approach involves the detection of growth inhibition of an indicator strain caused by the test culture. In this section, we make a critical analysis of the main methods currently available for *in vitro* evaluation of the antimicrobial activity of probiotics.

The Agar Spot Test was described by several authors (Tagg et al., 1976; Tharmaraj & Shah, 2009; Choi & Chang, 2015; Macaluso et al., 2016), with several modifications over time. We describe here the variation of this method that is mostly indicated to determine the antimicrobial activity of probiotics. There are two variations of this method that are commonly used, namely: simultaneous (or direct) and

deferred antagonism. In the direct assay, the test and indicator cultures are grown simultaneously, and the demonstration of antagonism depends on the release of a diffusible inhibitor at the beginning of the test culture growth (Tagg et al., 1976). In deferred antagonism, the probiotic microorganism under test is grown on agar media for a certain period and then inactivated; next, an overlap of the indicator strain is placed on the surface of the on the molten agar. This method is considered more sensitive and allows an independent variation of time and incubation conditions of test and indicator cultures (Tagg et al., 1976). After incubation, the antimicrobial activity is expressed either as inhibition zone (mm) or as arbitrary units (AU/mL).

The Agar Well Diffusion assay can be used to determine the antagonistic effects of cell-free supernatants. Different nutrients, selective or differential media, are prepared. The plates are inoculated with the indicator microorganism. Subsequently, 6-mm or 7-mm wells are prepared in each plate. The supernatant of the probiotic microorganism is centrifuged and diluted in aliquots at different concentrations and then pipetted into the wells. After incubation, the antimicrobial activity is expressed as an inhibition zone or as arbitrary units (AU/mL) (Tagg et al., 1976; Parente, Brienza, Moles, & Ricciardi, 1995). We do not recommend using the disk diffusion method for this purpose because of standardization issues due to variations between the viscosity of the test substance and the physical differences of the discs (Hoelzer et al., 2011; Balouiri et al., 2016).

A study tested 104 strains of *Lactobacillus acidophilus* to compare broth microdilution, disc diffusion and Etest methods in determining the antimicrobial activity of probiotics. Except for some specific agent-related effects, there was a good agreement between Minimum Inhibitory Concentration (MIC) values in the broth microdilution method and the Etest. Another study demonstrated a higher capacity of cell-free supernatants of *Lactobacillus plantarum* strains against pathogenic bacteria in liquid medium than on agar plates (Mayrhofer et al., 2008). However, given the importance of obtaining a MIC value for determining possible dosages in *in vivo* tests (Turnidge, 1990; Mouton et al., 2018), we recoomend the broth microdilution method when the objective of the analysis is to screen biomolecules for their potential antimicrobial drug.

Microdilution is one of the simplest and most reproducible methods for antimicrobial susceptibility screening. The procedure involves the preparation of 1:2 dilutions of the antimicrobial agent (cell-free supernatant), (*e.g.*, 32, 64, 138, 256, 512 μg/m) in a liquid growth medium dispensed into a 96-well microplate. Subsequently, each well is inoculated with a standard inoculum of the pathogenic strain (0.5 McFarland) and the plate is incubated after mixing under conditions appropriate for each microorganism. The broth microdilution method provides the MIC value, which is the lowest concentration of the antimicrobial agent that completely inhibits microbial growth (Balouiri et al., 2016). For details on broth microdilution testing and its specific conditions for each microorganism, we suggest consulting the Clinical Laboratory Standards Institute (CLSI) guidelines.

The antimicrobial activity proven by agar susceptibility or broth microdilution methods unfortunately does not characterize a probiotic microorganism as promising, as there are other factors to consider. In the microbiological viewpoint, an extremely important factor is the ability of microorganisms to develop as biofilms (Flemming et al., 2016). Bacterial biofilms are formed by communities embedded in a self-produced matrix of extracellular polymeric substances. Organized as a biofilm, microorganisms exhibit different living conditions than when in planktonic growth. Biofilms also serve as a physical barrier and exhibit a genotype that provides increased virulence, which makes them up to 1000 times more resistant to antimicrobials than planktonic bacteria (Donlan & Costerton, 2002; Marsh, 2004; Flemming et al., 2016).

A standardized assay to assess the activity of antibiofilm agents has not been established yet. However, there are different methods available for studying biofilms as well as for evaluating the antibiofilm activity of a substance. Several approaches have been standardized for this purpose, such as modified Robbins device, Calgary biofilm device, disk reactor, Centers for Disease Control (CDC) biofilm reactor, perfused biofilm fermenter, and bladder model (Kırmusaoğlu, 2019). The analysis of biofilms involves many techniques ranging from older established methods – such as counting of bacterial colonies – to more modern techniques – such as fluorescent labeling of biofilms in combination with mathematical predictive modeling, such as COMSTAT (Wilson et al., 2017). The studies screening for the antibiofilm activity of probiotics are even more limited than those testing planktonic cultures. However, some studies have evaluated this biological activity of probiotics by different methods and with different ways of analyzing the results (Missaoui, Saidane, Mzoughi, & Minervini, 2019; Manna, Ghosh, & Mandal, 2019; Hager et al., 2019; Mahdhi et al., 2018; Abdelhamid, Esaam, & Hazaa, 2018; Aarti et al., 2018; Cui, Yan et al., 2018; Cui, Shi et al., 2018). There is no consensus on what the most cost-effective method is to determine the antibiofilm activity of probiotic microorganisms.

Another challenge for the alternative antimicrobial therapy or any other therapy is that *in vitro* results can be reproducible in *in vivo* models and, subsequently, in the human body. *In vivo* testing should be very well designed to avoid bias. To establish the efficacy of the probiotic product, randomized, double-blind, placebo-controlled clinical trials should be performed (Fijan, 2016). To determine if a probiotic can prevent or treat a specific pathogen infection, two types of study can be performed: a preventive study (clinical study to check if exposure to that pathogen is prevented after probiotic use) or an interventional study (prior exposure to the pathogen and subsequent treatment with the probiotic or its supernatant) (Fijan, 2016). In many cases, animal model results are not reproducible in humans. To prevent this problem, it is possible to use alternative methods, such as 3D cell cultures and human tissues.

Although clinical trials in humans are considered mandatory for establishing the health benefits of probiotics, a few strains that showed positive results have been employed after legal authorities were convinced about these health claims. This may dramatically impact the validity of workflows currently used to characterize probiotics (Papadimitriou et al., 2015). Thus, in order to optimize and standardize the selection and use of probiotics for antimicrobial therapy, we recommend conducting research in the form of a bioguided study. Bioguided studies aim to monitor the biological activity of interest, increasing the chances of isolating a compound with high biological potential; this type of study has been indicated for the discovery and establishment of new therapies (Pieters & Vlietinck, 2005; Porte et al., 2014). Fig. 2 summarizes our proposed bioguided study for monitoring the antimicrobial properties of probiotic microorganisms.

4. Antimicrobial activity of probiotics against human pathogens

According to the United Nations Food and Agriculture Organization and the World Health Organization, probiotics are living microorganisms that confer a benefit to the health of the host when administered in adequate amounts (FAO/WHO, 2019).

Currently, the main probiotic microorganisms used by humans are *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum, L. acidophilus, L. casei, L. casei Shirota, L. paracasei, L. reuteri, L. johnsonii, L. plantarum e L. rhamnosus L. reuteri, L. rhamnosus, L. paracasei, Bifidobacterium bifidum, B. infantis, B. lactis, Saccharomyces bourlardii,* and *Propionibacterium freudenreichii* (Morais & Jacob, 2006; Lesbros-Pantoflickova, Corthesy-Theulaz, & Blum, 2007; Reddy & Narendera, 2010; Sikorska & Smoragiewicz, 2013; Markowiak Slizewska, 2017a,b).

In recent years, several studies have revealed benefits in the administration of probiotics, ranging from direct inhibition of pathogenic microorganisms to improvements in host immune system functions (Sajedinejad et al., 2017; Lopes, Moreira et al., 2017; Rossoni et al., 2017; Markowiak Slizewska, 2017a,b; Goderska, Agudo Pena, &

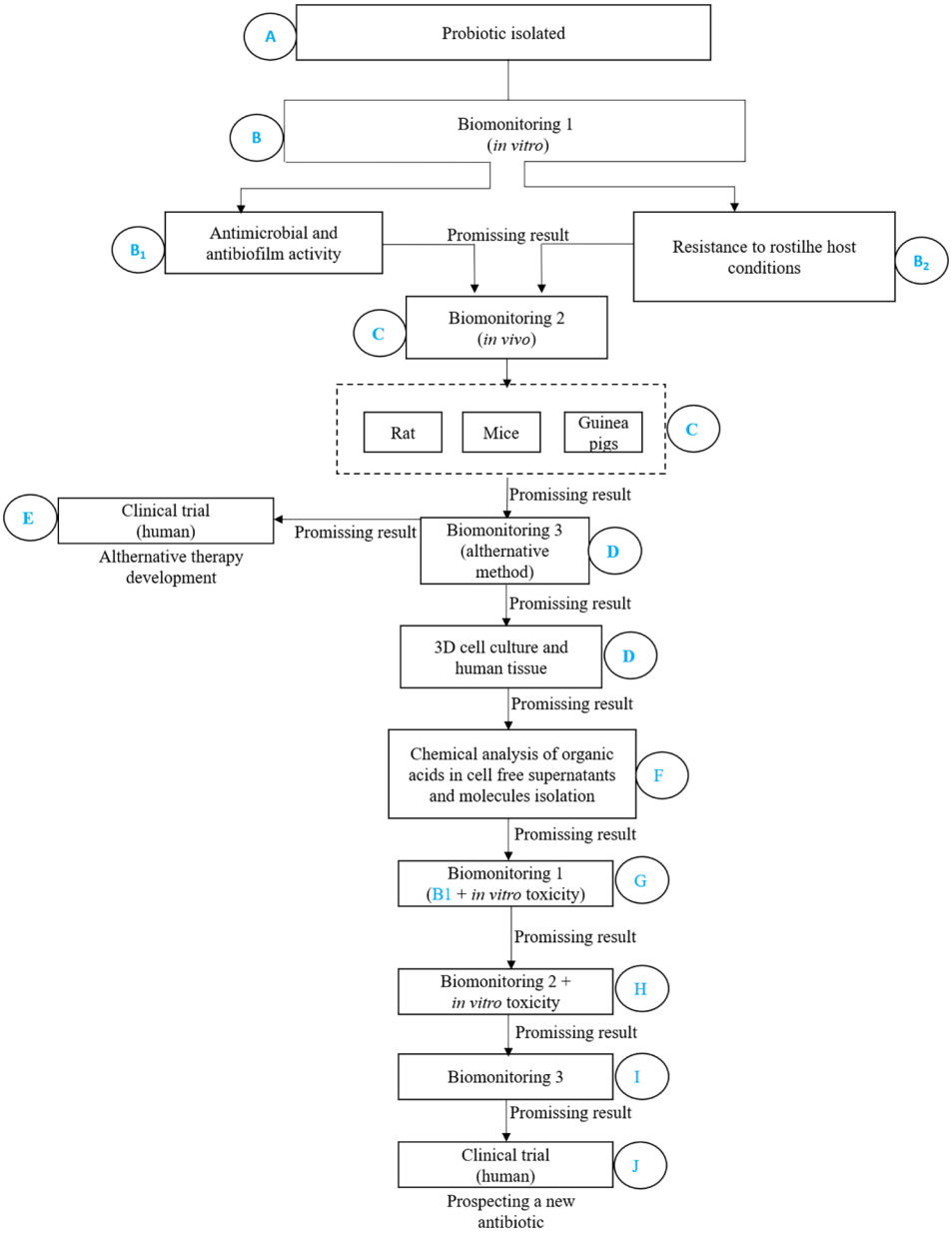

Fig. 2. Proposed bioguided study for monitoring the antimicrobial activity of probiotic microorganisms. (A) Probiotic microorganism isolated from any source. (B) Biomonitoring (B1- determination of *in vitro* antimicrobial activity and B2 - probiotic resistance to hostile conditions. Upon confirming promising results in Biomonitoring 1, start Biomonitoring 2 (C), which is the *in vivo* analysis of antimicrobial properties. After obtaining promising results in an animal model, move forward to Biomonitoring 3 (D) to evaluate biological properties and safety in alternative models of 3D cell cultures and human tissues. At this point, two approaches are possible, namely: clinical trials in humans (E) to determine an alternative antimicrobial therapy, or the analysis and isolation of probiotic-derived molecules (F) to develop a new antibiotic (monodrug). After detection of supernatant components of the antibiotics and their isolation, these molecules should again pass through the three biomonitoring phases (F, G, H and I) added of toxicity assays. Finally, the most promising molecule is submitted to human clinical testing for the development of the new antibiotic.

Table 1
Most studied probiotic microorganisms with antimicrobial activity. Adapted from (Marco et al., 2006; Lesbros-Pantoflickova et al., 2007; Reddy & Narendera, 2010; Sikorska & Smoragiewicz, 2013; Ouwehand et al., 2016; Markowiak Slizewska, 2017a,b; Wong et al., 2019).

Lactobacillus	*Bifidobacterium*	Other bacteria
L. acidophilus	*B. bifidum*	*Saccharomyces bourlardii*
L. amylovorus	*B. infantis*	*Propionibacterium freudenreichii*
L. casei	*B. lactis*	*Enterococcus faecalis*
L. crispatus	*B. adolescentis*	*Enterococcus faecium*
L. plantarum	*B. animalis subsp. lactis*	*Lactococcus lactis*
L. casei Shirota	*B. longum R0175*	*Leuconstoc mesenteroides*
L. paracasei	*B. breve*	*Pediococcus acidilacticiei*
L. rhamnosus		*Sporolactobacillus inulinus*
L. reuteri		*Streptococcus thermophilus*
L. johnssonii		*Escherichia coli*
L. helveticus R0052		*Saccharomyces cerevisiae var. boulardi*
L. fermentum		*Bacillus coagulans*

Alarcon, 2018; Moraes, Costa, Segundo, & Peruzzo, 2019). Table 1 shows the main probiotic microorganisms with antimicrobial effects. The use of probiotics has intensified, but the vast majority of studies relate them to intestinal health (Underwood, 2019).

The use of probiotic microorganisms is intended to support the health of the host. The literature shows a large number of studies using probiotics, but most of them explain only how probiotics can maintain the intestinal health of the host. The mechanisms of action of probiotics are various, such as the production of inhibitory substances, such as bacteriocins and hydrogen peroxide, which inhibit Gram negative and Gram positive pathogenic bacteria; blockage of adhesion sites; competition for nutrients; among others (Kanmani et al., 2013; Neal-McKinney et al., 2012; Sikorska & Smoragiewicz, 2013; Markowiak Slizewska, 2017a,b; Moraes, Costa, Segundo, & Peruzzo, 2019). Probiotics participate in immune response modulation in several ways, namely: by increasing nonspecific phagocytic activity through macrophage activation (Jain et al., 2008) and altering the release of pro and anti-inflammatory cytokines (Dong, Rowland, & Yaqoob, 2012; Zhao et al., 2012; Ganguli et al., 2013; Plaza-Díaz et al., 2017).

Several probiotic species are widely used in research (Villena et al.,

Table 2
In vivo and *ex vivo* studies reporting the antimicrobial activity of probiotics.

Probiotic	Objective	Conclusion	Reference
Lactobacillus casei	*In vivo* study, comparing the therapeutic effectiveness of the probiotic *L. casei* alone and together with antiprotozoal drugs against giardiasis in a murine model.	Oral administration of the probiotic *L. casei* associated with albendazole reduced Giardia infection, as evidenced by the normal recovered intestinal morphology.	Shukla et al., 2013
Lactobacillus rhamnosus HS111, *Lactobacillus acidophillus* HS101 and *Bifidobacterium bifidum*	Randomized double-blind study with 59 denture wearers who had *Candida* spp. in the oral cavity	Decrease in *Candida* spp. in individuals who used the probiotic formulation.	Ishikawa et al., 2015
Bifidobacterium animalis subsp. *Lactis*	Randomized controlled trial with 51 patients using yogurt for four weeks supplemented with *B. animalis* for periodontal health	The use of yogurt supplemented with *B. animalis* can have a positive effect against the accumulation of bacterial plaque and gingival inflammatory parameters.	Eren, Laleman, Yalnizoglu, Kuru, & Teughels, 2017
Lactobacillus salivarius	Randomized double-blind study with development of an experimental mouthwash for the treatment of periodontitis.	The results suggest that the mouthwash containing probiotics was healthy for daily use as an alternative to maintain dental and periodontal health.	Sajedinejad et al., 2017
Lactobacilus paracasei	*In vivo* study. *Lactobacilus paracasei* was used to treat *Candida albicans* infection in *Galleria mellonella* larvae. The number of hemocytes and gene expression of antifungal peptides were further assessed.	*L. paracasei* was able to modulate the immune system of *G. mellonella* and protect against candidiasis.	Rossoni et al., 2017
Lactobacillus reuteri DSM 17938	Use of *L. reunteri* to ameliorate inflammation in an *ex vivo* skin model, and *in vitro* antimicrobial activity against skin pathogens.	The probiotic decreased the inflammatory process and presented antimicrobial action against *S. aureus, S. pyogenes, Cutibacterium acnes,* and *P. aeruginosa.*	Khmaladze et al., 2019

2016; Yang et al., 2014; Yun, Oh, & Griffiths, 2014). Among these benefits are antimutagenic (Yu & Li, 2016; So, Wan, & El-Nezami, 2017), anticarcinogenic (Wollowski, Rechkemmer, & Pool-Zobel, 2001; Casas-Solís et al., 2019; Devaraj et al., 2019) and antidiarrheal properties (Liu et al., 2017; Devaraj et al., 2019), immune system stimulation (Casas-Solís et al., 2019), prevention of atopic dermatitis (Rather et al., 2016; Huang et al., 2017; Lise, Mayer, & Silveira, 2018) and reduced blood cholesterol (Shimizu et al., 2015; Nath et al., 2018).

Thus, the use of probiotics has been considered a promising strategy for the prevention and control of various infectious diseases Tahmourespour, Salehi, Kermanshahi, & Eslami, 2011; Ishikawa et al., 2015; Matsubara et al., 2016; Eren, Laleman, Yalnizoglu, Kuru, & Teughels, 2017; Sajedinejad et al., 2017; Lopes et al., 2017; Rossoni et al., 2017; Goderska, Agudo Pena, & Alarcon, 2018; Moraes, Costa, Segundo, & Peruzzo, 2019). Table 2 shows *in vivo/ex vivo* studies that validated the antimicrobial activity of probiotics.

There are a multitude of probiotic formulations that are supposed to benefit human health, including immunostimulatory effects or interbacterial competition between beneficial and pathogenic bacteria (Piewngam et al., 2019). In this context, the use of probiotics has been considered a promising strategy for the prevention and control of various infectious diseases.

A study performed by (Lahtinen et al., 2007) showed that three of 38 *Bifidobacterium* strains were able to inhibit the growth of *Staphylococcus aureus*, which is commonly found in systemic and peri-implant infections. Lazarenko (2012) investigated the antibacterial activity of several probiotic *Lactobacilli* strains. The authors reported that *Bifidobacterium bifidum* (*B. bifidum*) was mostly effective against *S. aureus* in an intravaginal infection model in mice, with a significant reduction in the number of *S. aureus* cells from vaginal smears. *B. bifidum* showed the best anti-staphylococcal activity when compared to other probiotic strains of different genera.

Piewngam et al. (2018) identified an inverse correlation between human colonization with *Bacillus* species and *S. aureus*. The authors further discovered a primary mechanism by which *Bacillus* species can kill *S. aureus* through the inhibition of quorum sensing. Fengycins are a specific classes of lipopeptides secreted by *Bacillus* species – identified by chromatography and mass spectrometry – that also present antifungal activity (Chung & Raffatellu, 2019). Lee et al. (2019) studied the probiotic *Pediococcus acidilactici* HW01 against *Pseudomonas aeruginosa* (*P. aeruginosa*) and observed decreased motility of *P. aeruginosa* as well as decreased production of pyocyanin, decreased production of proteases and rhamnolipid, and decreased biofilm formation on the surface of stainless steel. Another study conducted by Moraes, Costa, Segundo, and Peruzzo (2019) showed that *Lactobacillus brevis* and *Bifidobacterium bifidum* were effective against *S. aureus* biofilms grown on titanium discs. The results showed reduction of *S. aureus* growth on titanium discs when both probiotics were used, but the greatest inhibitory effect on biofilm formation was observed for *L. brevis* strains.

Other study performed by Sikorska and Smoragiewicz (2013) demonstrated that the probiotics *Lactobacillus reuteri, L. rhamnosus* GG, *Propionibacterium freudenreichii, P. acnes, L. paracasei, L. casei, L. plantarum, L. bulgarocus,* and *L. fermentus* inhibited methicillin-resistant *S. aureus* (MRSA) biofilm formation, possibly by competition and production of acids and/or bacteriocin inhibitors.

A review performed by Goderska et al. (2018) showed that *Helicobacter pylori* (*H. pylori*) has been regarded as a difficult-to-treat infection mainly because of acquired resistance to commonly used antibiotics. There is a growing interest in using probiotics in combination with antibiotic regimens to eradicate *H. pylori*. Probiotics have been proven to be useful in the treatment of several intestinal diseases such as diarrhea, in addition to the benefits of probiotic bacteria to the intestines; some beneficial effects on the stomach have also been reported, including anti-*Helicobacter pylori* activity (Aiba et al., 2017). The benefits of probiotic therapy in *H. pylori* cases are decreased microbial load and improved host tolerability. Several studies have shown favorable effects of different probiotics against *H. pylori* by strengthening the mucosal barrier, while promoting competition for adhesion and immunomodulation.

Klebsiella pneumoniae (*K. pneumoniae*) is a multi-resistant opportunistic pathogen able to colonize the human gut, with a high ability to form biofilm. In a study conducted by Lagrafeuille et al. (2018), the anti-biofilm activity of 140 species of *Lactobacillus* (supernatant cultures) was evaluated against *K. pneumoniae*. Of this total, the supernatant of 13 strains significantly impaired biofilm formation, including that of *Lactobacillus plantarum* (*L. plantarum*) CIRM653 – which was also able to disrupt *K. pneumoniae* preformed biofilms. The association of *K. pneumoniae* with *L. plantarum* CIRM653 showed reduced three-dimensional structures associated with a decrease in *K. pneumoniae* biomass. Research has shown that *L. plantarum* CIRM653 supernatant induced transcriptional modifications of *K. pneumoniae* biofilm-related genes, including down-regulation of quorum detection-related lsr operons and

overexpression of the type 3 pili structure genes. Another *in vivo* study by Vieira et al. (2016) demonstrated that *Bifidobacterium longum* 5 can reduce *K. pneumoniae* infection in mice. This probiotic protected mice from *K. pnemoniae* lung infection, specifically by inducing secretion of pro-inflammatory cytokines and neutrophil recruitment, and decreasing bacterial load in the lung, thereby reducing lethality rates by 50%.

Recent studies by Xu et al. (2020) suggested that patients affected by COVID 19 should use probiotics to avoid secondary infections. Some patients with COVID-19 had intestinal microbial dysbiosis. The nutritional and gastrointestinal functions must be assessed in all patients. Nutritional support and application of probiotics are suggested to regulate the balance of the intestinal microbiota and reduce the risk of secondary infection due to bacterial translocation.

Annual mortality rates from infectious diarrhea are about 2.2 million. Children are more vulnerable to severe gastroenteritis, and group A rotavirus is the main cause of the disease. Studies by Gonzalez-Ochoa et al. (2017) demonstrated that the association of probiotics, such as *Bifidobacterium* and *Lactobacillus* species, in combination with prebiotics, showed an improved anti-rotavirus response by reducing infectiousness and increasing rotavirus-specific anti-IgA levels. In addition, these probiotics have been linked to a shorter duration and severity of diarrhea due to rotavirus infection, not only preventing the infectious process, but also contributing to a lower incidence of re-infections.

Evidence indicates that the pathogenic potential of *Candida* spp. also depends on their ability to produce biofilms on abiotic and biotic surfaces (Ribeiro et al., 2019). Nyanzi et al. (2014) investigated the anti-*Candida* activity of the crude extract of 13 different *Lactobacillus* strains. The authors found MIC values ranging from 1.25 to 10 mg/mL. Wannun et al. (2016) studied the antimicrobial activity of supernatant cultures of *L. paracasei* and identified a protein with a molecular weight of approximately 25.000 Da, which showed antimicrobial activity against Gram-positive, Gram-negative bacteria and yeast in *in vitro* microdilution tests.

Orsi et al. (2014) verified that the crude filtrate supernatants from *L. acidophilus* ATCC 314, *L. rhamnosus* ATCC 7469, *L. plantarum* ATCC 8014 and *L. reuteri* ATCC 55730 were able to affect both *Candida albicans* (*C. albicans*) hyphae formation and preformed and mature biofilm development. The inhibitory effects were *Lactobacilli* strain-dependent. *L. plantarum, L. acidophilus* and *L. reuteri* impaired biofilm formation and only *L. plantarum* and *L. reuteri* disrupted biofilm cells. Recent studies have also confirmed that *Lactobacillus* spp. can reduce *C. albicans* hyphae formation (Ribeiro et al., 2017; Santos et al., 2019) by releasing antimicrobial compounds.

Chew et al. (2015) used *L. rhamnosus* GR-1 and *L. reuteri* RC-14 to treat *Candida glabrata* (*C. glabrata*). Biofilm formation was evaluated by scanning electron microscopy (SEM) and genes related to biofilm formation were also analyzed. The SEM analysis revealed disrupted mixed biofilm cultures of *C. glabrata* and probiotic *lactobacilli*. In addition, the biofilm-related *C. glabrata* genes EPA6 and YAK1 were downregulated in response to the probiotic *lactobacilli* challenges.

Rossoni et al. (2017) evaluated the protective action of probiotics against *C. albicans* infection. Exposure to a dose of *L. paracasei* 28.4 activated the immune system of *Galleria mellonella* larvae, which may allow the larvae to modulate *C. albicans* infection. These results show that probiotics can affect the immune response of larvae. Other study performed by Rossoni et al. (2018) evaluated the inhibitory effects of probiotic microorganisms on three *C. albicans* strains. Thirty lactobacilli strains were isolated and tested for their antimicrobial activity against *C. albicans* biofilms *in vitro*. *L. paracasei* 28.4, *L. rhamnosus* 5.2 and *L. fermentum* 20.4 isolates exhibited the most significant inhibitory activity against *C. albicans*, disrupting biofilm development and retarding hyphal formation. qPCR analysis showed that the ALS3, HWP1, EFG1 and CPH1 genes were downregulated after treatment with the probiotic microorganisms. *L. paracasei* 28.4, *L. rhamnosus* 5.2 and *L. fermentum* 20.4 demonstrated antifungal activity through inhibition of *C. albicans* biofilms.

Liao et al. (2019) analyzed the effects of *L. casei* administration for vaginal candidiasis in an experimental model of *C. albicans*-infected mice. For the prophylactic test, the animals were submitted to vaginal inoculation of *L. casei* for 7 days. Next, the animals were infected with *C. albicans* into the vaginal cavity, and two days after the infection, all mice were euthanized, and the number of CFU/mL was determined. In the therapeutic assays, the animals were infected with *C. albicans*, and after 2 days, they received *L. casei* for five days. Next, the number of CFU/mL in the vaginal samples were determined. The results showed that prophylactic administration of *L. casei* was able to improve the immunity of vaginal mucosa, increasing the production of IL-17 during the infection. IL-23 levels were lower than those in the control group, showing that *L. casei* also had anti-inflammatory properties. Regarding to the therapeutic group, *L. casei* reduced the fungal vaginal burden after a 5-day treatment.

Krzyściak et al. (2017) studied *L. salivarius* as a possible probiotic candidate against mixed biofilm cultures of *C. albicans* and *Streptococcus mutans* (*S. mutans*), since this microbial association has been implicated in the progression of early childhood caries. The probiotic treatment reduced the biofilm mass and the number of *S. mutans* and *C. albicans* cells. Moreover, *C. albicans* cells treated with *L. salivarius* had their ability to form hyphae or germ tubes significantly impacted.

Poor skin conditions can affect the patient's quality of life because of discomfort. Human skin is composed of numerous fungi and bacteria that live in symbiosis (Mottin & Suyenaga, 2018). Acne and Atopic Dermatitis (AD) are chronic skin conditions which require long periods of treatment and maintenance. Studies have shown that the use of probiotics in these cases has shown good results without adverse effects. *In vitro* studies have shown the capacity of probiotics, such as *Streptococcus salivarius* and *Enterococcus faecalis*, to directly inhibit *P. acnes* growth through the production of antibacterial proteins (bacteriocins) and immunomodulatory effects. Probiotics have been shown to have direct benefits (by inhibiting *P. acnes*) and indirect benefits (by decreasing the inflammatory response) (Kober et al., 2015; Bowe et al., 2006).

In a clinical study using *Lactobacillus plantarum* (*L. plantarum*) extract, Muizzuddin et al. (2012) observed a reduction in mild acne lesions, with amelioration of erythema and skin barrier reconstruction.

A study performed by Oh et al. (2006) reported an inhibitory effect of a bacteriocin produced by *Lactococcus* sp. HY 499 against *S. epidermidis*, *S. aureus* and *P. acnes*, in a patch test. The authors suggested the use of this bacteriocin produced by *Lactococcus* sp. HY 449 as an antimicrobial agent in cosmetic formulations. A lack of normal microbial skin diversity combined with an abundance of staphylococcal species in patients with atopic dermatitis further leads to disruption of skin-barrier homeostasis (Knackstedt, Knackstedt, & Gatherwright, 2020). The absence of allergic reactions and irritation consists of a great advantage for the use of probiotics compared to current treatments (Powers et al., 2015). The inhibitory effects on *P acnes*, *S. epidermidis* and *S. aureus* are relevant, as the same probiotic can be potentially used to treat different skin conditions.

Studies indicate that individuals with atopic dermatitis have an abundance of *Staphylococcus aureus*, when compared with individuals without the disease. Such an imbalance may be related to the breakdown of the skin barrier (D'Auria et al., 2016), which results in an ineffective protection from allergens and microorganisms.

A group of researchers led by Kawahara (Kawahara, Hanzawa, & Sugiyama, 2018) evaluated the topical application of homogenized *Lactobacillus reuteri* in water and showed that there was significant suppression in the development of atopic skin lesions induced by mites and other pathogens.

In another study, Rosignoli et al. (2018) tested whether the topical application of *Lactobacillus johnsonii* could inhibit *S. aureus* adhesion to the skin and increase innate skin immunity. The authors demonstrated that application of this suspension reduced *S. aureus* adhesion by up to

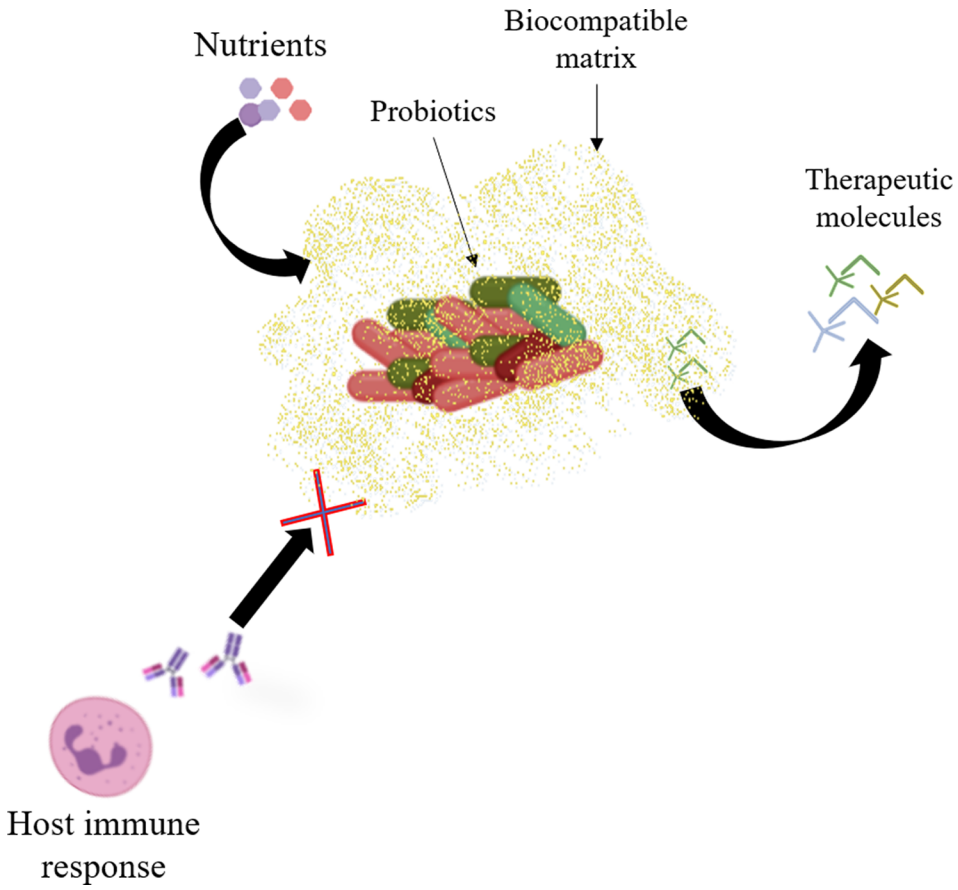

Fig. 3. Schematic representation of the encapsulation of probiotic microorganisms using a biocompatible matrix for delivery of therapeutic substances to the site of action.

74% and modulated endogenous expression of antimicrobial peptides (AMPs).

A study conducted by Navarro Lopes et al. (2018) determined the effectiveness of a mixture of oral probiotics. The authors showed a significant decrease in the SCORAD index [Scoring of Atopic Dermatitis (SCORAD) index] in the experimental group when compared to the control. In addition, they demonstrated that the probiotic mixture reduced the use of topical steroids in individuals with moderate atopic dermatitis (AD). This study corroborates the data found by Huang et al. (2017), who demonstrated that a mixture of *Lactobacillus fermentuns* and *Lactobacillus salivaris* reduced the SCORAD scores in individuals aged 1 to 18 years.

As for atopic dermatitis and seborrheic dermatitis, topical probiotics have demonstrated the ability to increase skin ceramides, improve erythema, flaking and itching and reduced *S. aureus* microbial load. However, studies have used different probiotics, vehicles and dosage and investigated several parameters. The most used probiotics were *S. thermophiles, V. filiformis, S. hominis, S. epidermidies* and *L. johnsonii* (Di Marzio et al., 2003; Blanchet-Réthoré et al., 2017; Knackstedt et al., 2020).

Thus far, several studies have evaluated the action of probiotics against fungal and bacterial. Although the results are quite surprising, the exact molecular mechanisms by which probiotics can inhibit pathogenic strains remain largely unknown and speculative. Thus, for future studies, new approaches should be developed to improve probiotic research. Even though probiotics are considered safe, additional studies are needed to improve the exact composition and routes of administration.

5. Probiotic encapsulation for delivery to the action site

The benefits of probiotics to human health are unequivocal. However, for these beneficial bacteria to exercise their biological activities effectively, the number of viable organisms must be greater than or equal to 10^7 CFU/mL or gram of product in use (Rossier-Miranda et al., 2010; Serna-Cock & Vallejo-Castillo, 2013). In addition, the survival of probiotic microorganisms can be affected by different factors (*e.g.*, pH, temperature, peroxide production etc.), which makes delivering viable cells to the place where they should exercise their action a challenging task. Thus, the study and investment in technologies for probiotic encapsulation is much needed (Gbassi & Vandamme, 2012).

Drug encapsulation technologies have been studied over time and shown significant benefits, such as increased therapeutic efficacy and reduced dose-dependent toxicity (Singh, Hemant, Ram, & Shivakumar, 2010). To date, nanotechnology provides different viable nanocarrier options for preserving and delivering drugs, such as liposomes, micelles, carbon nanotubes and dendrimers (Kumari, Singla, Guliani, & Yadav, 2014).

In addition to drugs, living cells (*e.g.*, probiotic microorganisms) can also be encapsulated. Common nanocarriers used for drug delivery may not serve for cell encapsulation. Instead, a biocompatible matrix should be employed to encapsulate and immobilize viable cells protecting them from a hostile environment, such as chemical and physical stress and the host's immune response (Orive, Santos, Pedraz, & Hernández, 2013). The biocompatible matrix should act as a semipermeable membrane, allowing bi-directional transport of nutrients (Griffith & Naughton, 2002, Gurruchaga et al., 2015). Thus, the cells can remain viable and produce therapeutic substances that will be delivered more than once to the site of action by permeating through the polymer matrix (Fig. 3).

The effectiveness of cell encapsulation depends on the matrix polymers, which can be obtained from natural sources (polysaccharides, polypeptides and polynucleotides) or manufactured. Different biocompatible materials have been used to immobilize cells in a matrix, such as hyaluronic acid, fibrin, agarose and collagen (Vrana et al., 2009). Table 3 shows a selection of recent studies that carried out the encapsulation of probiotic microorganisms in order to assess their antimicrobial potential. Alginate was considered the most studied and appropriate biomaterial due to its biocompatibility and ease of handling (Vrana et al., 2009). It has been shown that alginate can pass through stomach acids without any degradation, with the spheres formed by this gel reaching the intestine satisfactorily (Rayment et al., 2009). Probiotic encapsulation with alginate was compared to the formation of a "beneficial" biofilm by these bacteria (Li et al., 2018).

Although probiotics have been extensively studied in recent decades, their biological activity remains little explored (Fig. 4). In addition, the number of probiotic encapsulation studies is well below the total number of studies on encapsulation systems. Fig. 4 shows the number of published articles reporting encapsulation systems (red line) as compared to antimicrobial activity of probiotics (green line) and other biological activities of probiotics (blue line).

Encapsulation of probiotic microorganisms to treat infectious conditions other than intestinal infections may open new avenues for alternative antimicrobial therapies as well as adjuvant and/or synergistic approaches with conventional antibiotic therapy.

6. Probiotics-conventional drugs synergism for antimicrobial therapy

While the antimicrobial drugs currently used in clinical practice are effective, they have a high cost, side effects and therapeutic resistance (Graham & Fischbach, 2010; Vítor & Vale, 2011). For this reason, the combination between probiotic microorganisms and conventional drugs has been considered. The advantages of this synergism include: (*i*) faster healing; (*ii*) half dose of conventional drug needed; (*iii*) reduction of side effects caused by classical therapy; and (*iv*) increasing eradication rates of some microbial infections (Wolvers et al., 2010; Kosgey et al., 2019).

Lesbros-Pantoflickova, Corthesy-Theulaz, and Blum (2007) reviewed nine studies addressing the benefits of co-administration of probiotics with antibiotics for the treatment of *H. pylori* infections, particularly in the prevention of side effects and improvement of eradication rates. Probiotics administered together with standard therapy (two antibiotics and a proton pump inhibitor) for *H. pylori* infection achieved an eradication rate of 81%, as compared to 71% of conventional therapy alone. Consistent with this, the probiotics-conventional drugs synergism promoted reduction in *H. pylori* therapy-associated side effects (23% *vs* 47%, synergism *vs* conventional therapy alone) (Lesbros-Pantoflickova et al., 2007).

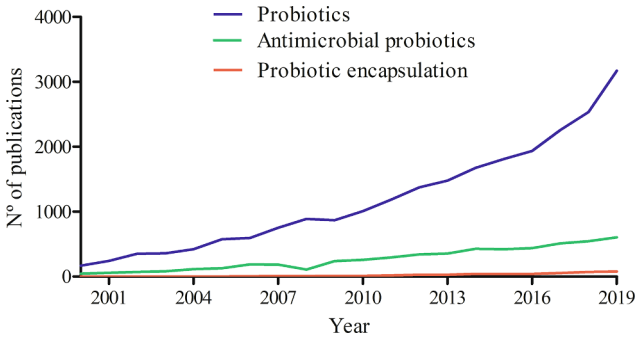

Fig. 4. Global production of probiotic research in the last 20 years (2000–2020). Data obtained from bibliographic searches in Pubmed using general descriptors (Probiotics, antimicrobial probiotics and probiotic encapsulation) and the Boolean operator "NOT" to limit the total number of productions with probiotics that did not address their antimicrobial activity.

As shown in Table 4, some studies have validated the beneficial effect of synergism between probiotics and conventional therapies for the treatment of fungal and bacterial infections. A report by Russo et al. (2018) evaluated the effectiveness of an oral formulation containing probiotics with lactoferrin glycoprotein as an adjuvant therapy to topical clotrimazole for vulvovaginal candidiasis (VVC) episodes. Key findings showed that the investigated probiotics (*Lactobacillus acidophilus* GLA- 14 and *Lactobacillus rhamnosus* HN001) and the lactoferrin mixture administered simultaneously with the antifungal drug (clotrimazole) was able to reduce the symptoms and recurrence of VVC. The authors highlighted the administration of probiotics and lactoferrin after conventional therapy with topical clotrimazole as a potential maintenance treatment that reduced candidiasis relapse at a 3- and 6-month follow-up. Similarly, Martinez et al. (2009) evaluated whether lactobacilli improved the efficacy of fluconazole in patients with VVC. The results evidenced the importance of adjuvant treatment with probiotics (*L. rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14) that were added to a single dose of 150 mg fluconazole during a 4-week therapy for VVC. The effectiveness of the combination between probiotics and an antifungal drug was validated based on the rate of culture-free women (38.5%) as compared to that of women who received only fluconazole (10.3%). Evidence shows that probiotics represent an alternative and effective approach for the treatment of VVC, in view of

Table 3
Recent studies that carried out the encapsulation of probiotic microorganisms to assess their antimicrobial potential.

Probiotic microorganism	Material	Results	Reference
Bifidobacterium animalis subsp. *Lactis* Bb12 (probiotic 1) and a combination of *Streptococcus thermophilus* (TH-4®), *Lactobacillus paracasei* 431® and Bb-12 (probiotic 2)	Poly(vinyl alcohol)	Probiotic 1 showed an encapsulation efficiency of 84.07% and 85.73% before and after 1 week, respectively. Probitic 2 showed 90.09% and 93.59% encapsulation efficiency before and after 1 week, respectively .	Akbar et al., 2018
Pediocucus acidilactici, Lactobacillus reuteri and *Lactobacillus salivarius*	Alginate with inulin	The bacterial protection against acidity was increased by the addition of inulin. Samples with 5% w/v inulin were the most effective in protecting the probiotics against bile salts.	Atia et al., 2016
Two *Lactobacillus plantarum* strains ando ne *Lactobacillus paraplantarum* strain isolated from pig's stool.	Gum arabic (30%) and gelatine (15%), Alginate	The three isolates had a survival rate greater than 80% in lyophilized and microsphere forms.	Cui, Yan et al., 2018; Cui, Shi et al., 2018
Lactobacillus acidophilus	Ovalbumin matrix with glyceryl monostereate	*L. acidophilus* probiotic was protected from the bactericidal effects of amoxicillin in the double formulation.	Govender et al., 2016
Lactobacillus curvatus CRL705, CRL1532 e CRL1533 and *Lactobacillus sakei* CRL1613	Calcium alginate solution and skim milk	Alginate encapsulation improved gastrointestinal tolerance. Henc, these strains should be considered as potential probiotic candidate against intestinal pathogenic bacteria.	Castellano et al., 2018
Lactobacillus plantarum ST-III	Sodium alginate	The correlation analysis showed that the viability of encapsulated bacteria after exposure to gastric sulcus and bile salts was positively correlated with the mechanical strength of the microspheres.	Qu et al., 2016.

Table 4
Synergism between probiotics and conventional antibiotic therapies.

Author (ref.)	Probiotic	Conventional therapy	No. of patients	Clinical condition	Synergism impact
Sheu et al. (2002)	*Lactobacillus* + *Bifidobacterium* containing yogurt	Amoxicillin + clarithromycin + lansoprazole	160	*Helicobacter pylori* gastritis	Improved eradication rates and reduced therapy-associated side effects
Martinez et al. (2009)	*Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14	Fluconazole	55	Vulvovaginal candidiasis	Increased treatment effectiveness (according to culture method)
Russo, Superti, Karadja, and De Seta (2018)	*Lactobacillus acidophilus* GLA-14 and *Lactobacillus rhamnosus* HN001	Clotrimazole	48	Vulvovaginal candidiasis	Reduced symptoms and relapse
Ikram et al. (2019)	*Lactobacillus reuteri*	Scaling and root planing	30	Chronic periodontitis	Improved clinical periodontal outcomes and ameliorated periodontal inflammation

their ability to resist *Candida* spp. and maintain or recover the normal vaginal microbiota (Matsubara et al., 2016). Additionally, the co-aggregation between lactobacilli and *Candida* spp. prevents the binding of yeast cells to receptors on the vaginal epithelium, thereby blocking an important virulence factor of *Candida* species – host-yeast adhesion (Reid et al., 2003; Reid & Hammond, 2005).

Some studies have investigated the synergistic effect of probiotics with conventional antifungal drugs for the treatment of *Candida* spp. infections. However, the potential of probiotics as an adjuvant to conventional antifungal therapy for other highly prevalent invasive fungal infections remains to be determined in future research.

The administration of beneficial microrganisms in the form of probiotics as an adjuvant treatment has been also a valuable approach for the therapy of chronic periodontitis (CP). Ikram et al. (2019) reported an evaluation and comparison of the clinical efficacy of administration of probiotics containing *L. reuteri* as an adjuvant to scaling and root planing (SRP) for the treatment of CP. Research findings demonstrated that the adjunctive use of *L. reuteri* was effective in resolving inflammation and improving periodontal outcomes through improvement of the clinical periodontal parameters, including plaque index, bleeding on probing, periodontal pocket depth, and clinical attachment level gain.

Collectively, it is possible to affirm that the use of probiotics are presently being investigated as an adjuvant innovative treatment to current antimicrobial agents, but these novel therapeutic strategies remain to be further tested and validated.

7. Final considerations

The human body is the target of several pathogenic microorganisms, such as *S. aureus,* MRSA*, P. aeruginosa* and *C. albicans*. This review provided unequivocal evidence on the antimicrobial activity of probiotics against clinically relevant pathogens. Nonetheless, while some molecules have been considered responsible for the antimicrobial activity of probiotics (*e.g.*, biosurfactants, hydrogen peroxide, lactic acid, acetic acid and bacteriocins), further studies should characterizate new molecules and elucidate their inhibitory mechanisms against pathogenic fungal and bacterial strains. Probiotic research needs to be bioguided during the whole process until they enter the clinical phase. Currently, there is no consensus or standardization for the clinical use of probiotics as an antimicrobial therapy, and the definition of dosage, mechanism of action and clinical efficacy remain to be determine. Lastly, the use of nanotechnologies to encapsulate molecules from probiotic extacts should be encouraged for the development of more effective therapeutic approaches.

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Ethical statement

The authors declare that this is a literature review work. Thus, it does not imply human or animal experimentation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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