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Research review paper

How to select a probiotic? A review and update of methods and criteria

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ABSTRACT

International competition within the dairy market and increasing public awareness about the importance of functional food consumption are providing new challenges for innovation in the probiotic sector. In this context, countless references are currently dedicated to the selection and characterization of new species and more specific strains of probiotic bacteria. In general, these studies adopt basic selection criteria established by the World Health Organization (WHO), including host-associated stress resistance, epithelium adhesion ability, and antimicrobial activity. These aspects are applied to ensure that the candidate probiotic could withstand the stressful conditions of the human digestive system and exert functional proprieties. However, it cannot be assumed that these novel microbial strains are capable of offering several biological benefits attributed to probiotics. Additionally, safety-associated selection criteria, such as plasmid-associated antibiotic resistance spreading and enterotoxin production, are often neglected. This article reviews the recent developments in the processes, strategies, and methods, such as anticarcinogenic, antidepression, antianxiety, antiobesity, antidiabetic, immunostimulatory, and cholesterol-lowering assessments, to select probiotic strains with the ultimate objective of assisting future probiotic microbe evaluation studies.

1. Introduction

Probiotics are defined as viable microorganisms (bacteria or yeasts) that, when ingested in an appropriate concentration, exert various beneficial effects on the host. Among the known probiotic microorganisms, species of lactic acid bacteria (LAB) (e.g., *Lactococcus*, *Lactobacillus*, *Streptococcus*, and *Enterococcus*) and *Bifidobacterium* have a long history of safe use (Doron and Snydman, 2015; Prado et al., 2015; Soccol et al., 2015). These microbial groups possess the ability to withstand unfavourable conditions of the human body (e.g., salivary enzymes, low pH, and pancreatic juice), colonize gut epithelial cells, and contribute to the health of the host environment regulating microbes and exerting biological functions (Liong et al., 2015; Marchesi et al., 2016; Zoumpopoulou et al., 2017).

Although diverse functional LAB have been applied in commercial probiotic fermented foods worldwide, the market for biofunctional products is continuously in need of the implementation and diversification of the available products. For this purpose, a growing number of scientific studies has involved the selection of new strains with different and specific functional properties. New microbial groups (e.g., yeast and *Bacillus*) and more specific LAB strains are constantly being identified. These new microbes are usually isolated from humans due to being considered a safe isolation source of microorganisms for product development. However, novel isolation sources are currently being used, such as dairy products, fruits, grains, and waste (El-Mabrok et al., 2012; Fiorda et al., 2017; García-Hernández et al., 2016; Plessas et al., 2017; Prado et al., 2015; Prado et al., 2008; Siddiqee et al., 2012; Sornplang and Piyadeatsoontorn, 2016; Zendo, 2013).

Due to the probiotic range of target functions and technological applications, the selection and evaluation of new probiotic candidates

Abbreviations: BAI, Beck anxiety inventory; BDI, Beck depression inventory; BSH, Bile salt hydrolase; EFSA, European food safety authority; ELISA, Enzyme-linked immunosorbent assay; FAO, Food and Agriculture Organization of the United Nations; FDA, United States Food and Drug Administration; GIT, Gastrointestinal tract; GRAS, Generally recognized as safe; HAM-A, Hamilton anxiety rating scale; HOMA-IR, Homeostatic model assessment for insulin resistance; LAB, Lactic acid bacteria; LSM, LAB susceptibility medium; MATH, Microbial adhesion to hydrocarbons; MIC, Minimum inhibitory concentration; NHPR, Natural Health Products Regulations of the Canadian; PBS, Phosphate buffer solution; PCR, Polymerase chain reaction; qPCR, Real-time quantitative PCR; rep-PCR, Repetitive element palindromic PCR; PFGE, Pulsed-field gel electrophoresis; PROSAFE, Biosafety evaluation of probiotic lactic acid bacteria used for human consumption; QPS, Qualified presumption of safety; RAPD, Random amplified polymorphic DNA; RCT, Randomized clinical trial; WHO, World health organization

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require a comprehensive approach featuring multiple steps. Prior to 2002, there was no international regulation to affirm the efficacy and safety of probiotic microorganisms. Thus, the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) published the "Guidelines for Evaluation of Probiotics in Food," which established safety and effectiveness standards for probiotics (Araya et al., 2002). In this guideline are suggested several criteria for the selection of probiotics, including resistance to unfavorable conditions that the human body imposes, epithelium adhesion ability, antimicrobial activity, and safety assessment.

Accumulated evidence demonstrating the relationship of microorganisms with aspects integral to the health and well-being of humans has generated new strategies for the selection of probiotics. These include methods to evaluate the biological properties of probiotics such as anticarcinogenic, antidepression, anti-obesity, anti-diabetic, and cholesterol-lowering activities, as well as safety aspects relative to virulence, toxicity, and transferable antibiotic resistance. In this review, we provide a comprehensive theoretical guide for selecting probiotic microbes to assist researchers in choosing methods and criteria.

2. Probiotic microorganisms

Probiotic agents are defined as microorganisms that exhibit various beneficial effects on the host's health after ingestion and include LAB, *Bifidobacterium*, *Bacillus*, and yeast. Among these, *Lactobacillus*, under the LAB group, was the earliest discovered probiotic (Fig. 1). This genus of rod-shaped or rod-like-shaped gram-positive bacteria comprises 183 recognized species, applied in several industrial processes as those used to produce preservatives, acidulants, and food flavorings, in drug and cosmetic manufacture, and in the manufacture of biodegradable polylactic acid polymers (König and Fröhlich, 2009). *Lactobacillus*, including *L. acidophilus*, *L. fermentum*, *L. plantarum*, *L. casei*, *L. paracasei*, *L. reuteri*, *L. rhamnosus, L. satsumensis,* and *L. johnsonii*, is the dominant LAB group in animal and human gastrointestinal and digestive systems, possessing

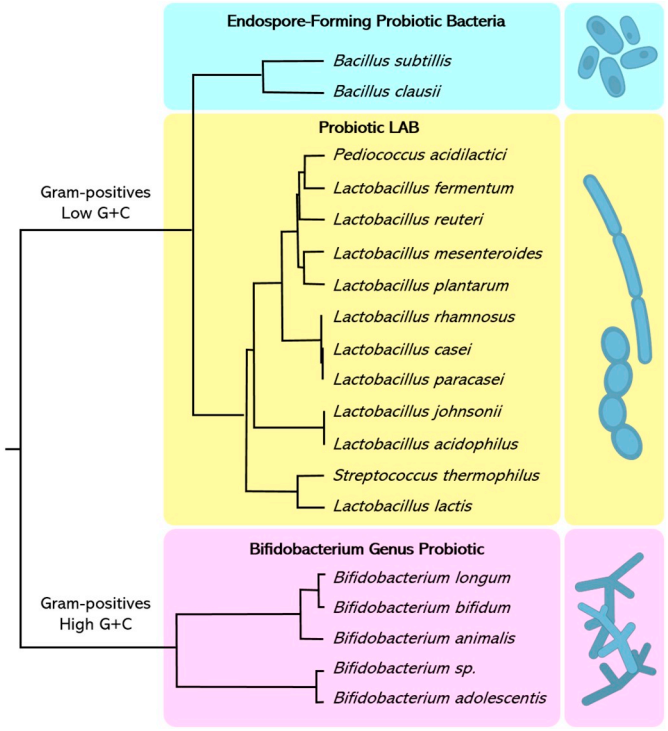

Fig. 1. Neighbor-joining tree showing the phylogenetic relationship of the different probiotic bacterial groups through16S rRNA gene sequences retrieved from GenBank database. Sequences were aligned with ClustalW and the phylogenetic tree was constructed using MEGA 4 program.

proven action in the maintenance and recovery of health. Other LAB genera with proven probiotic action include *Streptococcus*, *Lactococcus*, *Enterococcus*, *Pediococcus*, and *Leuconostoc* (Wood and Holzapfel, 1995). Metabolically, LAB are known to produce high amounts of lactic acid and other metabolites from a diverse source of carbon, including glucose, fructose, lactose, and galactose. From glucose metabolism, LAB are classified as homofermentative, which produce exclusively lactic acid through the Embden-Meyerhof-Parnas pathway, or heterofermentative, which, in addition to lactic acid, produces several other metabolites, including ethanol, acetic acid, and carbon dioxide via the pentose monophosphate pathway (Carr et al., 2002). LAB can also produce secondary metabolites, including bacteriocins, exopolysaccharides, and enzymes, which are used to increase the quality and shelf life of fermented foods (Leroy and De Vuyst, 2004).

The Frenchman Henry Tissier first isolated *Bifidobacterium* in the late 19th century. It was inserted into the actinomycetes order mainly due to the high DNA content of guanine and cytosine, which ranges from 42 to 67% (Fig. 1). These microbes are heterofermentative, nonmotile, catalase-negative, and anaerobic bacteria, with the ability to metabolize glucose, galactose, lactose, and fructose (Russell et al., 2011).). Presently, the genus *Bifidobacterium* includes 30 species, where 10 are from humans (tooth decay, stool, and vagina), 17 from animals, two from residual waters, and one from fermented milk (Picard et al., 2005; Russell et al., 2011). *B. adolescentis*, *B. animalis*, *B. bifidum*, *B. breve*, and *B. longum* have been reported for their diverse probiotic effects and are widely used in yogurts, milk, cheese, and other dairy products (Picard et al., 2005; Russell et al., 2011).

Bacillus species (e.g., *B. clausii* and *B. subtilis*) are also used as a probiotic in the food and pharmaceutical industry (Liu et al., 2018; Ripert et al., 2016). The main feature of this gram-positive, aerobic bacteria group is the formation of endospores (Cutting, 2011) that permit viability maintenance for long shelf periods. However, some species (e.g., *Bacillus anthracis*, *B. cereus*, *B. thuringiensis*, *B. pseudomycoides*, and *B. weihenstephanesis*) are known to produce enterotoxins representing a safety concern (Hong et al., 2008; Sorokulova et al., 2008).

The yeasts constitute a large and heterogeneous group of eukaryotic microorganisms that are widespread in natural environments, including the GIT of humans, plants, airborne particles, and food products (Foligné et al., 2010). The high content of proteins, vitamin B, traces minerals, and various immune-stimulant compounds (proteases, β-glucans, and mannan oligosaccharides) has increased the interest in the use of yeasts as a probiotic (Arévalo-Villena et al., 2018; Fadda et al., 2017; García-Hernández et al., 2012; Gil-Rodríguez et al., 2015). Yeasts also have the advantages of nonsusceptibility to antibiotics and good tolerance for industrial processing conditions (i.e., lyophilization and high temperatures) (Abdel-Rahman et al., 2013; Fleet, 2011; Morgunov et al., 2013; Thorat and Joshi, 2011). *Saccharomyces boulardii*, according to The European Food Safety Authority (EFSA), has a Qualified Presumption of Safety (QPS) status and is mostly used and studied probiotic (Hudson et al., 2016). However, several other potential probiotic yeasts (*Kluyveromyces, Pichia, Rhodotorula, Schizosaccharomyces* and *Candida*) are constantly being identified (Banjara et al., 2015; Lane and Morrissey, 2010; Tokuhiro et al., 2008).

3. Probiotic selection

The selection of probiotic microorganisms requires a systematic approach using a strategy similar to that shown in Fig. 2. In most cases, the large number of isolated strains leads to the need to use a "step-by-step approach", consisting of a sequence of tests to progressively reduce the number of probiotic candidates. At the end of this procedure, the strains that present the highest number of functional properties and, concomitantly, without any negative traits, are selected.

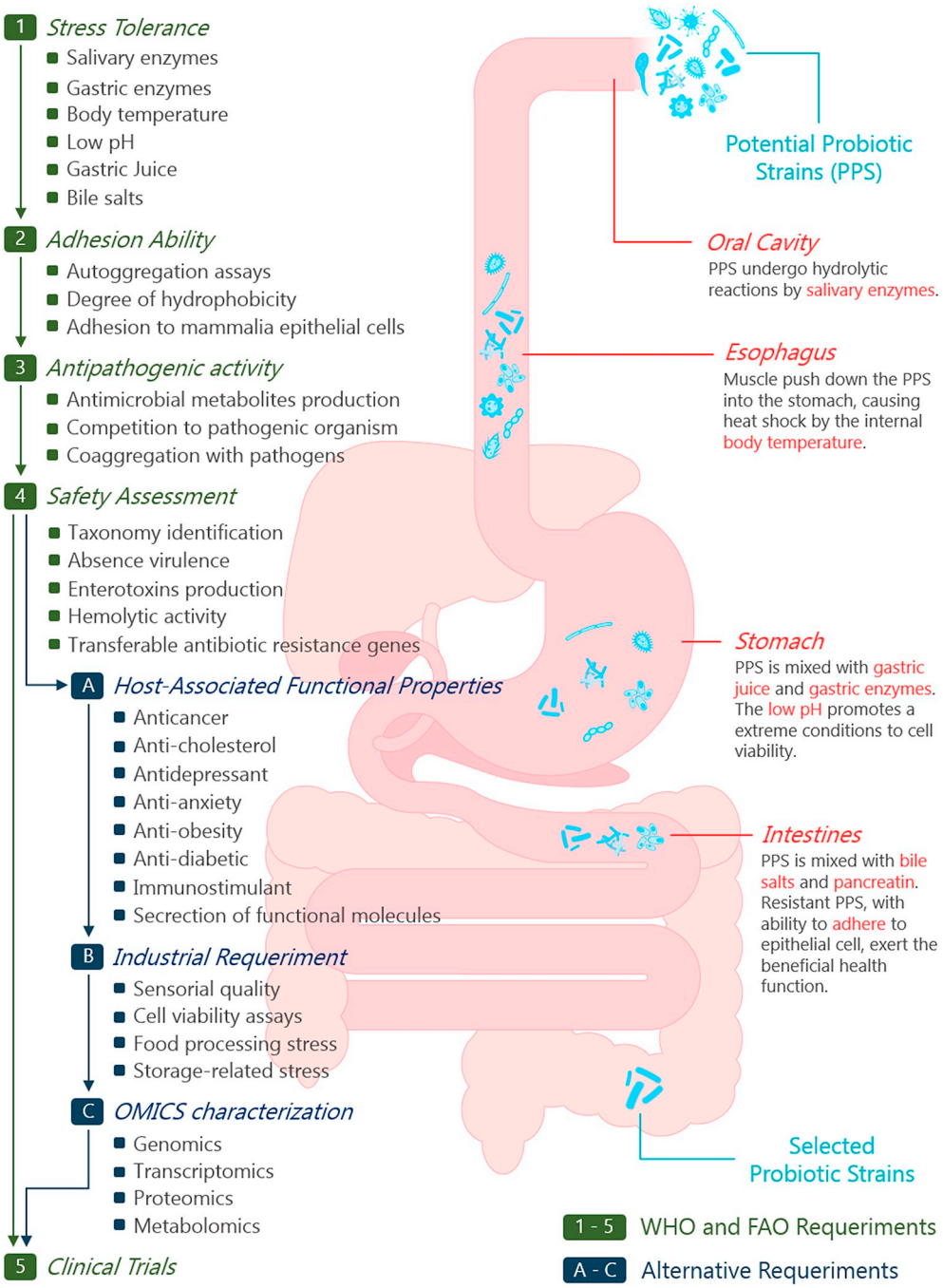

Fig. 2. Screening approaches used for characterization of probiotic strains according to WHO/FAO and studies of (Chang et al., 2010; Divya et al., 2012; Fiorda et al., 2016; Luna and Foster, 2015; Maragkoudakis et al., 2006; Ooi and Liong, 2010; Persichetti et al., 2014; Prescott and Björkstén, 2007; Vidhyasagar and Jeevaratnam, 2013)

3.1. Stress tolerance ability

First, the candidate strains are evaluated to cope with the stress conditions that the human body imposes (Fig. 2). At the time of administration, the probiotic should be resistant to the enzymes present in the oral cavity, such as amylase and lysozyme. Although gram-positive bacteria are generally sensitive to lysozyme, some LAB are more resistant than other gram-positive bacteria, being able to be part of the resident microbiome of the oral cavity of humans (Fuller, 1992; Gilliland, 1979; Koll-Klais et al., 2005). After ingestion, probiotic cells face antimicrobial factors in the stomach (low pH, gastric juice, and pepsin) and intestines (pancreatin and bile salts), as well as mild heat shock caused by the internal body temperature (Fig. 2). The probiotic must have acid and bile tolerance or exclusion mechanisms to survive in the gut. In addition, intracellular accumulation of trehalose is one of the best-known responses associated with the thermotolerance of probiotic microorganisms (Martins et al., 2008). Gastrointestinal resistance varies according to species—for example, *Lactobacillus* are broadly resistant, whereas *Bifidobacteria* are extremely sensitive to low pH, exhibiting low or no survival rates at pH 2 and pH 3 (Fontana et al., 2013; Sanz, 2007; Takahashi et al., 2004). Thus, tolerance to inhibitory conditions generally excludes a considerable number of isolated microorganisms. From 29 *Lactobacillus* strains that Maragkoudakis et al. (2006) evaluated, only six could survive one hour at pH 1, and eight strains could

Table 1
Criteria used for the selection of probiotic bacteria isolated from different sources.

Isolated strains	Source	Host Stress-Resistant	Adhesion Ability	Antimicrobial Properties	Safety Assessment	Antibiotic Resistance	Enzymes-Producing Ability	Host-Associated Functional	Industrial Relevant	Clinical Trials	ReferenceS
Bacillus amyloliquefaciens	Soy sauce	+	+	+	+	+	+	−	−	−	Lee et al. (2017)
Bifidobacterium breve	Faces of infants	+	+	+	+	+	+	+	−	−	Muñoz-Quezada et al. (2013)
Enterococcus spp.	Dry-fermented sausage	+	−	+	−	−	+	−	+	−	Papamanoli et al. (2003)
E. casseliflavus	Sheep milk	+	+	+	−	+	−	−	−	−	Acurcio et al. (2014)
E. durans	Sheep milk	+	+	+	−	+	−	−	−	−	Acurcio et al. (2014)
E. faecium	Sheep milk	+	+	+	−	+	−	−	−	−	Acurcio et al. (2014)
	Intestine of chickens	+	−	+	+	+	+	−	+	−	Shin et al. (2008)
FructoBacillus fructosus	Opuntia ficus-indica fruits	+	+	+	+	−	+	−	+	−	Verón et al. (2017)
Lactobacillus spp.	Dry-fermented sausage	+	−	+	−	−	+	−	+	−	Papamanoli et al. (2003)
L. pentosus	Tarkhineh	+	−	+	+	−	−	−	−	−	Vasiee et al. (2014)
L. brevis	Sow milk	+	+	+	+	+	−	−	−	−	Martín et al. (2009)
	Tarkhineh	+	−	+	+	−	−	−	−	−	Vasiee et al. (2014)
	Quinoa and amaranth seeds	+	+	+	+	+	−	−	+	+	Vera-Pingitore et al. (2016)
L. casei	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
	Quinoa and amaranth seeds	+	+	+	+	+	−	−	+	+	Vera-Pingitore et al. (2016)
L. coryniformis	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
L. curvatus	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
L. delbrueckii	Human milk	+	+	+	−	−	−	−	+	−	Serrano-Niño et al. (2016)
L. diolivorans	Tarkhineh	+	−	+	+	−	−	−	−	−	Vasiee et al. (2014)
L. fermentum	Human milk	+	+	+	−	−	−	−	+	−	Serrano-Niño et al. (2016)
	Human stomach	+	−	+	+	−	−	−	−	−	Ryan et al. (2008)
	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
	Tarkhineh	+	−	+	+	−	−	−	−	−	Vasiee et al. (2014)
	Traditional Dairy Products	+	+	+	+	−	−	−	−	−	Bao et al. (2010)
L. gasseri	Human stomach	+	−	+	+	−	−	−	−	−	Ryan et al. (2008)
L. helveticus	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
L. kandleri	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
L. kefira-faciens	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
L. lactis	Camel milk	+	+	+	+	+	−	+	+	−	Abushelaibi et al. (2017)
L. paracasei	Feta cheese	+	−	−	+	+	−	−	+	−	Plessas et al. (2017)
	Faces of infants	+	+	+	+	+	+	+	−	−	Muñoz-Quezada et al. (2013)
	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
	Kefir grains	+	+	+	+	+	−	−	−	−	Leite et al. (2015)
L. paraplantarum	Sow milk	+	+	+	+	+	−	−	−	−	Martín et al. (2009)
	Olives	+	+	+	+	−	−	−	+	−	Bautista-Gallego et al. (2013)
L. pentosus	Camel milk	+	−	+	−	−	−	−	−	−	Yateem et al. (2008)
	Olives	+	+	+	+	−	−	−	+	−	Bautista-Gallego et al. (2013)

(*continued on next page*)

Table 1 (*continued*)

Isolated strains	Source	Host Stress-Resistant	Adhesion Ability	Antimicrobial Properties	Safety Assessment	Antibiotic Resistance	Enzymes-Producing Ability	Host-Associated Functional	Industrial Relevant	Clinical Trials	ReferenceS
L. plantarum	Camel milk	+	−	+	−	−	−	−	−	−	Yateem et al. (2008)
	Italian and Argentinean cheeses	+	+	+	+	+	+	+	+	−	Zago et al. (2011)
	Fermented Koumiss	+	−	+	+	−	−	−	+	−	Wu et al. (2009)
	Sow milk	+	+	+	+	+	−	−	−	−	Martín et al. (2009)
	Cocoa	+	+	+	+	−	−	−	−	−	Ramos et al. (2013)
	Tarkhineh	+	−	+	+	−	−	−	−	−	Vasiee et al. (2014)
	Opuntia ficus-indica fruits	+	+	+	+	−	+	−	+	−	Verón et al. (2017)
	Quinoa and amaranth seeds	+	+	+	+	+	−	−	+	+	Vera-Pingitore et al. (2016)
	Kimchi	+	+	−	+	+	+	−	+	−	Lee et al. (2016)
	Olives	+	+	+	+	−	−	−	+	−	Bautista-Gallego et al. (2013)
	Camel milk	+	+	+	+	+	−	+	+	−	Abushelaibi et al. (2017)
L. reuteri	Human stomach	+	−	+	+	−	−	−	−	−	Ryan et al. (2008)
	Sow milk	+	+	+	+	+	−	−	−	−	Martín et al. (2009)
	Quinoa and amaranth seeds	+	+	+	+	+	−	−	+	+	Vera-Pingitore et al. (2016)
L. rhamnosus	Faces of infants	+	+	+	+	+	+	+	−	−	Muñoz-Quezada et al. (2013)
L. sakei	Quinoa and amaranth seeds	+	+	+	+	+	−	−	+	+	Vera-Pingitore et al. (2016)
L. salivarius	Human stomach	+	−	+	+	−	−	−	−	−	Ryan et al. (2008)
	Sow milk	+	+	+	+	+	−	−	−	−	Martín et al. (2009)
L. vaginalis	Human stomach	+	−	+	+	−	−	−	−	−	Ryan et al. (2008)
Lactococcus lactis	Camel milk	+	−	+	−	−	−	−	−	−	Yateem et al. (2008)
Leuconostoc sp.	Dry-fermented sausage	+	−	+	−	−	+	−	+	−	Papamanoli et al. (2003)
L. lactis	Quinoa and amaranth seeds	+	+	+	+	+	−	−	+	+	Vera-Pingitore et al. (2016)
L. mesenteroides	Human milk	+	+	+	−	−	−	−	+	−	Serrano-Niño et al. (2016)
	Kimchi	+	+	−	+	+	+	−	+	−	Lee et al. (2016)
Pediococcus sp.	Dry-fermented sausage	+	−	+	−	−	+	−	+	−	Papamanoli et al. (2003)
P. pentosaceus	Intestine of chickens	+	−	+	+	+	+	−	+	−	Shin et al. (2008)
	Quinoa and amaranth seeds	+	+	+	+	+	−	−	+	+	Vera-Pingitore et al. (2016)
Weissella paramesenteroides	Sow milk	+	+	+	+	+	−	−	−	−	Martín et al. (2009)
W. viridescens	Dry-fermented sausage	+	−	+	−	−	+	−	+	−	Papamanoli et al. (2003)

[a] Only cell surface hydrophobicity tests.
[b] Weak adhesion to Caco-2 cells.

not survive with pepsin solution at pH 2. A similar result was also reported in Lim et al. (2004), where from 100 bacterial strains, including *Streptococcus*, *Lactobacillus*, and *Bifidobacterium*, only 51 could survive at pH 2.5. In summary, pH ranging from 2 to 5 and bile salt concentrations from 0.3 to 2% are considered critical for the selection of probiotic microorganisms (Ogunremi et al., 2015; Psani and Kotzekidou, 2006). These resistance properties can be tested by cultivating the strain of interest at a different pH with the presence of enzymes, such as pepsin, lysozyme and amylase, phenol, NaCl, Oxgall, porcine gastric juice, pancreatic, and taurodeoxycholic acid. Resistance to these compounds is measured by the colony count or absorbance at different time intervals (Divya et al., 2012; Lin et al., 2007; Maragkoudakis et al., 2006; Martín et al., 2005).

3.2. Adhesion ability

The next step is to evaluate whether the potential probiotic candidates can colonize the GIT epithelial cells. Microbial adhesion to epithelial cells is a complex contact process involving two membranes (i.e., microbial and human cells) that depend on the chemical and physiochemical composition of the probiotic strain cell surface. This behavior depends on the balance of electrostatic and Van der Waals interactions on the target surface, but studies have suggested that bacterial extracellular components and the surrounding composition can influence adhesion (Boonaert and Rouxhet, 2000; Duary et al., 2011). Adhesion of microbes to epithelial cells is related to both the autoaggregation capacity and hydrophobic properties of the cell surface. Microbial cell autoaggregation ability ensures that the probiotic reaches a high cell density in the gut contributing to the adhesion mechanism, while cell surface hydrophobicity allows an improved interaction between microbe and human epithelial cells. Autoaggregation can be achieved through a simple method where the absorbance of a strain suspension with phosphate-buffered saline (PBS) is measured at various time intervals (Kos et al., 2003; Ogunremi et al., 2015; Tuo et al., 2013). Cell surface hydrophobicity can be measured through MATH (Chelliah et al., 2016; Collado et al., 2008; Del Re et al., 2000; Duary et al., 2011; Wang and Han, 2007). The method consists of mixing water, a hydrocarbon, and a strain suspension. The two phase solutions are mixed, and the hydrophobicity of the strain is measured via absorbance at 600 nm. It is a simple test that does not require any special equipment, and the cells can be readily observed in a microscope at 100× (Rosenberg, 2006). Direct adhesion capacity to mammalian epithelial cells, such as Caco-2, HT-29, fetal I-407, is another way to assess the property of microbial adhesion (Dicks and Botes, 2010; Fontana et al., 2013; Leite et al., 2015; Ramos et al., 2013).

3.3. Anti-pathogenic activity

Once adhered to the gut, probiotics produce extracellular antimicrobial components through the conversion of carbohydrates, proteins, and other minor compounds into important substances that can kill pathogenic bacteria, such as organic acids, enzymes, hydrogen peroxide, bacteriocins, and low-molecular-mass peptides. Other mechanisms of probiotic antagonism include competition for nutrients, coaggregating with pathogens, and immune system stimulation (Lebeer et al., 2008). These antagonist activities vary according to microbial strains (Martín et al., 2009; Vera-Pingitore et al., 2016; Verón et al., 2017). Antimicrobial metabolite production can be evaluated in agar plates through the inhibition zone assay (Cueva et al., 2010; Divya et al., 2012), whereas competition activity can be measured by inhibition of pathogen adhesion to cell lines due probiotic adhesion (Inturri et al., 2016). Coaggregation is another antagonistic probiotic activity that provides pathogen agglomeration with probiotic cells and facilitates its elimination through feces; this property can be evaluated by tests of the coaggregation of probiotic with different pathogens, including *E. coli*, *S. aureus*, *Candida* spp., *Listeria monocytogenes,* and *Salmonella choleraesuis* (Soleimani et al., 2010; Vidhyasagar and Jeevaratnam, 2013).

3.4. Safety assessment

The risk of infection when introducing live microbes to the diet should be assessed, and the conclusion that “probiotics are safe” must not be fully considered (Culligan et al., 2009). Some initiatives by the European community (The European Union Novel Food regulation, QPS, and PROSAFE), United States (FDA and WHO), and Canada (Health Canada: NHPR) have been dedicated to establishing criteria for the safety assessment of probiotics for human use. Common recommendations include records of isolation history, taxonomic identification, and absence of virulence, infectivity, toxicity and transferable antibiotic resistance genes (Sanders et al., 2010).

Most of the probiotics available on the market today were isolated from healthy humans to increase probiotic compatibility with and survival in the GIT (Rivera-Espinoza and Gallardo-Navarro, 2010). A range of new sources is, however, currently being used to isolate of novel probiotic strains (Table 1). In general, the identification of these new probiotic bacteria strains is performed as early as possible in the screening process. This guarantees prior knowledge of bacteria concerning the pathogenicity potential (Yadav and Shukla, 2017). The species level identification is reached by a combination of biochemical (growth in different carbon sources as well as Gram, catalase, nitrate reductase, and urease tests) and genotypic (sequencing of the 16s rRNA gene) methods. The NHPR highlights the importance of strain level identification for the safety establishment of probiotic in human health (Coeuret et al., 2004). Both biochemical and rRNA gene analyses are not adequate (i.e., there is insufficient variation) to compare probiotic bacteria at the strain level, but DNA fingerprinting approaches, including Repetitive element palindromic PCR (rep-PCR), Random Amplified Polymorphic DNA (RAPD), and pulsed-field gel electrophoresis (PFGE), can be used to achieve this aim. For additional details concerning methods and identification criteria, the readers are directed to review the works of Bagheripoor-Fallah et al. (2015), Ben Amor et al. (2007); Temmerman et al. (2004).

For most studies (see some reported in Table 1), enterotoxin production and/or hemolytic activity was the only tests used for the safety assessment of probiotic bacteria. The presence of other properties, including D(-)-lactate production, bile salt deconjugation, and virulence factors (e.g., gelatinase, hemolysin, or DNAse activities), must, however, be considered to meet the standards of international authorities. These factors can be assessed by gene virulence/toxicity detection through PCR, cytotoxicity assays, and *in vivo* studies (Guinebretière et al., 2002; Phelps and Mckillip, 2002; Rowan et al., 2003; Sorokulova et al., 2008).

In 2007, the EFSA first introduced antimicrobial resistance as a safety concern associated with probiotic consumption (Barlow et al., 2007). This was supported due to evidence of horizontal gene transfer from beneficial bacteria to pathogenic bacteria in the gut of the host (Gueimonde et al., 2013). Consequently, in 2012, the QPS program included this criterion for the GRAS status of probiotics (Sanders et al., 2010). Since then, multiple independent studies have evaluated the presence of genes associated with antibiotic resistance in probiotics, given the risk of the genetic transmission among different bacteria (Klein, 2011; Nawaz et al., 2011; Schjørring and Krogfelt, 2011; Sharma et al., 2014; Toomey et al., 2010; Wang et al., 2014).

Susceptibility to antibiotics can be measured by several methods, including agar disk diffusion and agar overlay diffusion, E-test, agar dilution or broth dilution. E-test and dilution methods are based on the minimum inhibitory concentration (MIC) assay, which determines the minimum necessary concentration of an antimicrobial to inhibit microorganism growth, while diffusion tests use antibiotic discs with inhibitory concentrations in agar plates (Ashraf and Shah, 2011; Gullberg et al., 2011; Mathur and Singh, 2005). More recently, LSM was

suggested as a more appropriate tool for the determination of MIC for LAB (Klare et al., 2007, 2005). The use of LSM minimizes growth the problems of LAB in conventional media as well as antagonistic effects between some antimicrobials and growth medium component.

Although phenotypic screening can be considered a "true" measure, it can have low reproducibility among laboratories (Nawaz et al., 2011). Thus, PCR became the gold standard to detect the presence of resistance genes in probiotic bacteria because of its high sensitivity and convenience (Fluit et al., 2001). In the PCR assay, DNA isolated from resistant strains are amplified with primers specific for the respective antibiotic resistance gene, and expected amplicons are analyzed by gel electrophoresis. The PCR products can also be sequenced for confirmation of the amplified sequences (Kastner et al., 2006). On average, 23,317 antibiotic genes effective against at least 249 known antibiotics have been established to date (Hu et al., 2013; Imperial and Ibana, 2016). These sequences can be used to design specific primers to detect antibiotic-resistant genes in probiotic strains (Flórez et al., 2016; Flórez and Mayo, 2017; Giovanetti et al., 2003; Klein et al., 2000; Pillai et al., 2012; Rojo-Bezares et al., 2006; Shevtsov et al., 2011; Whiley et al., 2007). In the supplemental material, we compiled an extensive list of specific primers designed to detect antibiotic resistance genes in probiotic bacteria (Table S1).

Antibiotic resistance of probiotics is considered a safety issue when the risk of gene transfers is present (Gueimonde et al., 2013). When resistance is intrinsic—i.e., acquired as a result of a chromosomal mutation—probiotic bacteria do not constitute a safety concern itself because the antibiotic resistance is only passed onto the next generation via the organism's genetic material; in this case, the resistant probiotic strains can be used concomitantly or after antibiotic treatment to restore the gut microbiota (Galopin et al., 2009; Gueimonde et al., 2013; Hammad and Shimamoto, 2010). It is the ability of probiotics to conduct horizontal gene transfer by mobile elements (e.g., plasmids, conjugative transposons, integrons, and bacteriophages) that hurries the development of antibiotic-resistant strains. Thus, a crucial aspect in studying antibiotic resistance in probiotic bacteria is to separate intrinsic resistance from acquired resistance (Sanders et al., 2010). Gene transfer can be analyzed by filter mating experiments, where the probiotic with a detected antibiotic resistance gene is cultured with recipient cells (not possessing the gene); the transfer ratio to the recipient cell can be then analyzed by phenotypic and molecular methods (Nawaz et al., 2011). More recently, whole-genome sequencing analysis has emerged as a cost-effective approach to test the antibiotic resistance of probiotic bacteria. This approach has demonstrated that certain probiotic bacteria strains (e.g., *Lactobacillus helveticus* MTCC 5463 and *Lactobacillus plantarum* JDM1) carry a range of different genes related to antibiotic resistance. However, in general, there is no threat of the transfer of these genes to host gut commensals because the genes are not plasmid encoded, a phenomenon that does not represent a safety concern (Senan et al., 2015; Zhang et al., 2009).

4. Host-associated functional criteria selection

4.1. Anti-cancer activity

The methods previously described in this review are generally performed in all scientific studies involving the selection of probiotic microbes. These studies, in general, follow the criteria established by the WHO—i.e., host-associated stress resistance, epithelium adhesion ability, antimicrobial activity, and safety assessment. However, several health benefits associated with the consumption of probiotics can be included to select improved strains (Fig. 2).

Probiotic strains can exert anticarcinogenic effects by multiple mechanisms, including (i) the production of compounds with anticarcinogenic activity, (ii) the binding and degradation of potential mutagens, (iii) the reduction of the activity of enzymes involved in carcinogen formation, (iv) the reduction of genotoxic immunosuppressive and nephrotoxic mycotoxins, (v) the inhibition of tumor cell proliferation, and (vi) the induction of the apoptosis in cancer cells (Commane et al., 2005; Ewaschuk et al., 2006; Kumar et al., 2013). Antitumor capacity is, however, highly dependent on the microbial specie or strain studied (dos Reis et al., 2017; Kumar et al., 2010). Thus, various strategies have been used to select probiotics with antitumor ability. It can be assessed the ability of probiotic candidates to inactivate colon enzymes (β-glucosidase, β-glucuronidase, nitrate reductase, azoredutase and 7-α- dehydroxylase) that convert pre-carcinogens into active carcinogens such as ammonia, cresols, phenols, and N-nitroso compounds (Kumar et al., 2013). Additionally, probiotic strains can be selected due to the ability to inhibit the growth of pathogenic bacteria (*Clostridium, Bacteroides, Eubacterium*, and *Escherichia coli*) that exhibit high activity of these enzymes responsible for the synthesis of carcinogenic compounds (Tjalsma et al., 2012).

Probiotic strains can also be screened by the ability to synthesize compounds with direct anticarcinogenic activity, including short-chain fatty acids and conjugated linoleic acid. These compounds are involved in the control of the machinery regulating apoptosis and cellular differentiation within the gut (dos Reis et al., 2017). The high production of conjugated linoleic acid by probiotic strains of *L. bulgaricus* and *S. thermophilus* have been associated with the reduction of viability and induction of apoptosis in HT-29 and Caco-2 cells (Ewaschuk et al., 2006). The anticarcinogenic action can also occur through physical binding between the carcinogenic compounds and peptidoglycan present in the cell walls of some probiotic microorganisms. *In vivo* studies demonstrate that these carcinogenic compounds can be eliminated together with the bacteria through feces (Burns and Rowland, 2004; dos Reis et al., 2017). The binding capacity can be evaluated by culturing potential probiotics in synthetic medium containing mutagens, such as nitrites, ammonia, mycotoxins and secondary bile salts and evaluating the adsorption of these compounds from the medium. Finally, the tumor antiproliferative activity of probiotic can be *in vitro* evaluated with carcinoma cell lines and anti-mutagenicity assays (Maggiora et al., 2004). The cell models adopted include cervical, HeLa, gastric, MCF-7 breast, AGS, colon, and HT-29 (Biffi et al., 1997; Hirayama and Rafter, 2000; Kumar et al., 2010; Nouri et al., 2016; Sekine et al., 1995).

4.2. Anti-cholesterol activity

Recent discoveries have linked probiotics with the prevention of heart disease by lowering the cholesterol serum levels (Ooi and Liong, 2010). Probiotics act to decrease the solubility of cholesterol and, consequently, reduce its uptake from the gut (Nguyen et al., 2007). The selection of lowering-cholesterol strains can be performed by *in vitro* tests, using cholesterol-phosphatidylcholine micelles, MRS broth supplied with cholesterol, or water-soluble cholesterol (polyoxyethylene cholesteryl sebacate). These media are treated with probiotic suspension and the residual amount of cholesterol can be measured using the o-phthalaldehyde method (Pereira and Gibson, 2002).

The cholesterol-lowering effect of probiotics is also attributed to an enzymatic deconjugation of bile acids in the human gut. BSH enzymes produced by probiotics convert conjugated bile salts into deconjugated bile salts, the latter being more easily released by the human organism through feces (Nguyen et al., 2007). Cholesterol, a precursor of bile acids, is most often converted into bile salts to replace those lost through feces leading to a reduction in serum cholesterol (Kumar et al., 2012). BSH activity of candidate probiotics can be evaluated by the well-established agar plate assay or by PCR using specific primers based on conserved regions of BSH enzymes (Dashkevicz and Feighner, 1989; Nguyen et al., 2007).

In vivo studies conducted to select lowering-cholesterol strains can also be performed by detecting cholesterol in such samples as blood, urine, and stool following the ingestion of the probiotic (Costabile et al., 2017; Ding et al., 2017; Kumar et al., 2012; Liong and Shah, 2006; Ouwehand et al., 2002; Wang et al., 2014). In addition, molecular

biology techniques can be used to detect the expression of cholesterol metabolism-related genes in the mouse liver of rats with hypercholesteremia that ingested probiotics (Damodharan et al., 2016).

4.3. Anti-depression and anti-anxiety

Probiotic administration has been associated with the reversal of symptoms of depression and anxiety. The first evidence for this hypothesis was postulated by Tannock and Savage (1974), who showed that stressed mice drastically reduce their populations of *Lactobacilli*. Thereafter, several studies have been devoted to elucidate the function of probiotics in brain function (Dinan and Cryan, 2013). The possibility exists that treatment with probiotics may elicit its beneficial effect on mood by the enhancing immune system or central concentrations of serotonin (Luna and Foster, 2015). The selection of probiotics with potential antidepressant action can be initially performed in rat models by measuring behaviors in the forced swim test, followed by evaluation of immune (e.g., plasma cytokines measurement) and neuroendocrine and central monoaminergic activities (e.g., analysis of monoamine, such as serotonin, noradrenaline and dopamine, in the brain, as well as serotonin-precursor, tryptophan in the plasma) (Desbonnet et al., 2008). Probiotic strains with great potential can be further investigated in clinical studies. The influence of probiotics on anxiety and depression can be seen through the lowering of symptoms according to the scales of the BAI, HAM-A, and BDI in patients supplemented with probiotics. Stress hormones (e.g., adrenocorticotropic and cortisol) are also dosed from the serum, urine, and saliva. Lower levels of these hormones compared with placebos are indicators of the influence of probiotics on anxiety and depression (Collins et al., 2012; Desbonnet et al., 2008; Dinan and Cryan, 2013; Foster and McVey Neufeld, 2013; Luna and Foster, 2015; Pirbaglou et al., 2016; Tillisch et al., 2013). Akkasheh et al. (2016) demonstrated that an eight-week probiotic cocktail intake by patients with depressive disorder beneficially affected BDI and other attributes related to control of emotion and sensation. Similarly, Rao et al. (2009) treated patients who that had chronic fatigue syndrome with the *Lactobacillus casei* strain Shirota and observed a significant reduction on the BAI among those taking the probiotic *vs* controls.

4.4. Anti-obesity and anti-diabetic activities

Probiotics can suppress body weight gain and insulin resistance by modulating gut flora composition and stimulating the formation of gut hormones, such as glucagon-like peptide-1 and gastric inhibitory polypeptide (Kerry et al., 2018; Zhang et al., 2016). The extraction of energy from the diet is another convincing strategy (Erejuwa et al., 2014). *In vivo* studies of certain probiotic strains, such as *L. acidophilus* La5, *L. casei* DN001, *L. gasseri* SBT2055 *L. paracasei* F19, and *B. lactis* Bb12, have shown their potential to prevent type-2 diabetes and weight gain (Brahe et al., 2015; Ejtahed et al., 2011; Kadooka et al., 2013; Kadooka et al., 2010). However, there is heterogeneity in these studies, mainly concerning probiotic dosage and species used (Sáez-Lara et al., 2016).

The selection of probiotics with anti-obesity and anti-diabetic activities can be initiated by different *in vitro* screening criteria, including the abilities to breakdown lipopolysaccharides, modulate the production of cytokines by peripheral blood mononuclear cells, and inhibit mast cell activation (Alokail et al., 2013; Niers et al., 2005). The selected probiotics can be further analyzed in animal studies and clinical trials of patients with diabetes or obesity. Blood samples of probiotic-treated patients and placebo groups can be compared by different biochemical parameters, including glucose, insulin, triglycerides, C-peptide, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, alanine, and hemoglobin levels, and insulin resistance by the lowering of Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values (Aller et al., 2011; Alokail et al., 2013; Brahe et al., 2015; Ejtahed et al., 2012, 2011; Hu et al., 2017). Additionally, the effects on the reduction of the body mass index, waist, abdominal visceral fat area and hip circumference can be evaluated (Kadooka et al., 2010; Sáez-Lara et al., 2016).

4.5. Immunostimulatory activity

Immunostimulatory effects of probiotic occur by enhancing secretory immunoglobulins, phagocytosis of pathogens and/or cytokine production (Rocha-Ramírez et al., 2017; Wold, 2001). These mechanisms are supported by *in vitro* studies and were proven *in vivo* in both animals and, to a limited extent, in humans (Aziz and Bonavida, 2016). The probiotic-induced immune suppression can be evaluated from the production of IgA- and IgM-secreting cells, including IFN-γ, IL-1, TNF-α, IL-10, IL-12, IL-18, and TGF-β (Lammers et al., 2003). The production of some of these components can be measured by ELISA or qPCR. Thus, depending on the objective and target of the product, strains that can induce a certain immune response can be selected (Borruel, 2003; Delcenserie et al., 2008; Dicks and Botes, 2010; Prescott and Björkstén, 2007).

4.6. Functional molecule secretion

Probiotics have cell components and secrete functional molecules, including antioxidants, enzymes, short-chain fatty acids, peptides, essential vitamins, and minerals, which confer a health benefit on the host. The antioxidant compounds produced by probiotics include superoxide dismutase, glutathione dismutase, ascorbic acid, melatonin, and glutathione. These molecules protect the human body against high levels of oxygen radicals that cause damage to lipids, proteins, and DNA (Schieber and Chandel, 2014). Probiotics with antioxidant proprieties can be selected through DPPH, ABTS and Orac assays, which can detect and measure antioxidant production and activity (Amaretti et al., 2013; Nyanzi et al., 2015; Persichetti et al., 2014; Sah et al., 2014). These standard procedures can be applied to measure the antioxidant properties of probiotic metabolites grown in synthetic media or *in vivo* studies through the modulation of endogenous oxidative markers in the mouse brain (Divyashri et al., 2015). Direct human DNA protection can also be detected via molecular biology techniques. Fiorda et al. (2016) tested the DNA protection capacity of kefir-based probiotic beverages against supercoiled DNA. The method consisted of treating plasmid DNA, consisting of circular supercoiled DNA, open circular, and linear forms, with H_2O_2 and a probiotic. The results demonstrated that, when treated with a probiotic, the three structures of the plasmid DNA remained more stable than the control (i.e., plasmid DNA without the addition of probiotic solution). Chang et al. (2010) performed another technique that tested the DNA protection capacity of microbial strains isolated from kimchi, a Korean fermented food, using the comet assay. This technique, also known as single-cell gel electrophoresis, is used to analyze and quantify DNA damage in individual cells. The authors observed that selected LAB strains could protect the DNA against tumor initiation and DNA damage with an immunostimulation characteristic.

Probiotics have been reported to produce and/or secrete B-group vitamin (biotin, folates, riboflavin, nicotinic acid, pyridoxine, thiamine, pantothenic acid, and cobalamin) and vitamin K (Leblanc et al., 2011). The extent of vitamin production mostly depended on the strain, because, instead, probiotic cells can require it for growth (Rossi et al., 2011). The selection of probiotic-producing vitamins could be useful in preventing clinical and subclinical vitamin deficiencies (Leblanc et al., 2011). Probiotics can also be selected for their ability to produce bioactive enzymes (Parvez et al., 2006). Lipases contribute to the improvement of the digestion of lipids to form short-chain fatty acids. The higher concentration of short-chain fatty acids assists in maintaining an appropriate pH in the lumen of the colon, which is crucial for the expression of many bacterial enzymes on foreign compounds and metabolism of carcinogens in the intestine. Amylase promotes the hydrolysis of polysaccharides facilitating the breakdown of starch and glycogen,

Table 2
Criteria used for the selection of probiotic yeasts isolated from different sources

Isolated strains	Source	Host Stress-Resistant	Adhesion Ability	Antimicrobial Properties	Safety Assessment	Antibiotic Resistance	Enzymes-Producing Ability	Host-Associated Functional	Industrial Relevant	Clinical Trials	References
Candida diddensiae	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
C. lusitaniae	Pineapple	+	+[a]	+	−	+	−	−	+	−	Amorim et al. (2018)
C. naeodendra	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
C. oleophila	Portuguese brined olives	+	−	−	−	−	−	+	+	−	Silva et al. (2011)
C. vini	Distillery	+	+[a]	−	−	−	−	−	−	−	Fernandez-Pacheco et al. (2018)
	Culture collection	+	−	−	−	−	−	−	−	−	Arévalo-Villena et al. (2018)
Citeromyces matrinensis	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
Cystofilobasidium bisporidii	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
C. bisporidii	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
Geotrichum sp.	Raw milk	+	+	−	−	−	−	+	−	−	Chen et al. (2010)
Hanseniaspora osmophila	Fermented vegetables	+	+[a]	−	−	−	−	−	−	−	Fernandez-Pacheco et al. (2018)
Issatchenkia occidentalis	Kefir grains	+	+	−	+	−	−	−	−	−	Diosma et al. (2014)
I. orientalis	Fermented cereal	+	+[a]	−	−	−	+	+	−	−	Ogunremi et al. (2015)
Kluyveromyces lactis	Cheese	+	+	+	+	−	−	−	−	−	Fadda et al. (2017)
K. marxianus	Kefir grains	+	+	−	+	−	−	−	−	−	Diosma et al. (2014)
	Kefir grains	+	+	−	−	−	−	+	−	−	Cho et al. (2018)
	Cheese	+	+	+	+	−	−	−	−	−	Fadda et al. (2017))
K. thermotolerans	Winery	+	+[a]	−	−	−	−	−	−	−	Fernandez−Pacheco et al. (2018)
Metschnikowia pulcherrima	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
Meyerozyma caribbica	Pineapple	+	+[a]	+	−	+	−	−	+	−	Amorim et al. (2018)
Pichia anomala	Distillery	+	+[a]	−	−	−	−	−	−	−	Fernandez-Pacheco et al. (2018)
P. fermentans	Raw milk	+	+	−	−	−	−	+	−	−	Chen et al. (2010)
P. guilliermondii	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
P. kluyveri	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
P. kudriavzevii	Winery	+	+[a]	−	−	−	−	−	−	−	Fernandez-Pacheco et al. (2018)
	Fermented cereal	+	+	−	−	−	−	−	−	−	Greppi et al. (2017)
	Raw milk	+	+	−	−	−	−	+	−	−	Chen et al. (2010)
	Fermented cereal	+	+[a]	−	−	−	+	+	−	−	Ogunremi et al. (2015)
P. manshurica	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
P. membranifaciens	Distillery	+	+[a]	−	−	−	−	−	−	−	Fernandez−Pacheco et al. (2018)
	Portuguese brined olives	+	−	−	−	−	−	+	+	−	Silva et al. (2011)
Rhodotorula glutinis	Olive fermentation	+	−[b]	−	+	−	+	−	+	−	Bonatsou et al. (2018)
R. mucilaginosa	Olive fermentation	+	−	−	+	−	+	−	+	−	Bonatsou et al. (2018)
Saccharomyces cerevisiae	Kefir grains	+	+	−	+	−	−	−	−	−	Diosma et al. (2014)
	Winery	+	−	−	−	−	−	−	−	−	Arévalo−Villena et al. (2018)
	Sourdough	+	+	+	−	+	+	−	+	−	Perricone et al. (2014)
	Culture collection	+	+[a]	+	−	+	−	−	−	−	Arévalo-Villena et al. (2018)
S. unisporus	Kefir grains	+	+	−	+	−	−	−	−	−	Diosma et al. (2014)
Schizosaccharomyces pombe	Grape must	+	−	+	−	−	−	+	−	−	Gil-Rodríguez et al. (2015)
Wickerhamomyces anomalus	Fermented excreta of broilers	+	+[a]	+	−	−	−	−	−	−	García-Hernández et al. (2012)

(*continued on next page*)

Table 2 (*continued*)

Isolated strains	Source	Host Stress-Resistant	Adhesion Ability	Antimicrobial Properties	Safety Assessment	Antibiotic Resistance	Enzymes-Producing Ability	Host-Associated Functional	Industrial Relevant	Clinical Trials	References
Yarrowia lipolytica	Raw milk	+	+	–	–	–	–	+	–	–	Chen et al. (2010)
Zygoascus hellenicus	Olive fermentation	+	–	–	+	–	+	–	+	–	Bonatsou et al. (2018)
Zygosaccharomyces rouxii	Winery	+	+[a]	–	–	–	–	–	–	–	Fernandez-Pacheco et al. (2018)

[a] Only cell surface hydrophobicity tests.
[b] Weak adhesion to Caco-2 cells.

whereas proteases catalyze the breakdown of proteins (Bairagi et al., 2002). On the other hand, some enzymes (e.g., lecithinase, gelatinase, and DNase) are related to virulence traits, and their activities should be assessed to exclude potential harmful probiotic candidates. DNase evades the innate immune response in the host by degrading neutrophil extracellular traps and hydrolyzes human DNA interrupting protein synthesis (Thomas et al., 2014). Gelatinase lecithinase, and hyaluronidase act by facilitating the invasion of tissues (Van Reenen and Dicks, 2011).

Probiotic-producing enzymes can be evaluated by cultivating candidate strains in culture media supplemented with precursors (e.g., carboxymethlycellulose, starch, peptone-gelatin, and tributyrin for the activity of cellulases, amylase, protease, and lipase respectively) and quantifying target-enzymes via spectrophotometry (Bairagi et al., 2002; Dipanjan Dutta, 2015; Suzer et al., 2008). In addition, the quantification of gene-encoding enzymes can be accomplished by qPCR (Bessler et al., 2003; Vázquez et al., 2017).

5. Probiotic yeast selection

The criteria adopted by the most studies for the selection of yeasts are essentially those established for bacteria—i.e., the ability to survive during the passage through the human GIT, tolerance to low pH and bile salts, epithelial adhesion capacity, and control of the growth of pathogenic microorganisms. Based on these criteria, a significant number of potential probiotic yeasts, including *Saccharomyces, Rhodotorula, Pichia, Candida, Meyerozyma, Yarrowia, Torulaspora, Debaryomyces*, and *Kluyveromyces*, have been isolated from different sources (Table 2). Nevertheless, presently, *Saccharomyces boulardii* is the only yeast preparation formally recognized and commercialized as probiotic for humans (Arévalo-Villena et al., 2018; Fadda et al., 2017). The literature review presented in Table 2 shows that many studies use adherence to hydrocarbons (i.e., yeast cell surface hydrophobicity) to evaluate yeast intestinal adhesion ability; 30–40% is a suggested hydrophobicity value for yeast interact with mucus. Some studies have demonstrated, however, that many potential probiotic yeast strains show a hydrophilic characteristic after 1 h of treatment, possessing only a transient adhesion capacity (Fernandez-Pacheco et al., 2018; Kumura et al., 2004). This hypothesis is corroborated by studies that indicate the low proportion of yeasts (less than 0.1% of the intestinal gut residue) in the human GIT (Auchtung et al., 2018). Additionally, a good correlation between hydrophobicity and *in vivo* intestinal adhesion was not always found (Bonatsou et al., 2018). The low adhesion capacity and lack of clinical studies may justify the nonrecognition of many yeast strains as probiotic. It should be mentioned, however, that during yeast passage through the GIT, their cells experience fast self-aggregation (30 minutes, on average) and may rapidly adhere to the mucosa before being expelled (Fernandez-Pacheco et al., 2018). Additionally, a single yeast cell needs a larger space to adhere to the surface of an intestinal cell than bacteria (Kumura et al., 2004). These characteristics can be considered an advance for yeasts in the rapid elimination of pathogenic bacteria causing infectious diarrhea, through space competition mechanism and/or yeast-bacterial conglomerate formation. These hypotheses require evidence through clinical trials.

A few studies have evaluated the therapeutic potential of yeasts, including anti-inflammatory properties, stimulation of the immune system, and cholesterol assimilation (Table 1). The predictability for the *in vivo* situation is, however, scarce and essentially dedicated to the strain *S. boulardii.* Additionally, often neglected, the capacity of some yeasts to invade epithelial human cells through yeast hyphal growth, as well as other safety aspects (virulence, infectivity, and toxicity), should be carefully evaluated before using, or even considering, yeasts as probiotics.

6. Clinical trials

After *in vitro* and animal studies, probiotics must be subjected to clinical trials for the validation of safety and efficiency. Placebo-controlled randomized clinical trials (RCTs) are the gold standard to evaluate probiotics (Tamayo, 2008). Several RCT studies have supported evidence of the relationships between the use of probiotics and health and safety outcomes (Gaskins et al., 2008; Llopis et al., 2009; Miele et al., 2009; Miller et al., 2017; Saggioro, 2004; Szajewska and Mrukowicz, 2001). In the RCTs, probiotic administration can be performed via oral, rectal, or vaginal routes (Arribas et al., 2009; Czaja et al., 2007; Sleator and Hill, 2007). The trials should be designed using sound scientific principles, such as determination of the target population for the study, control group, and sample size. The studies can be conducted using a single dose or multiple doses, the latter being preferred to evaluate the dose dependence and the dose-response relationship (Gou et al., 2014; Shane et al., 2010). The level of probiotic adherence in the human intestine can be assessed by different methods, such as directly observed therapy, measurement of probiotic in the stool, and an electronic medication monitor (Osterberg and Blaschke, 2005). Safety-related aspects (hematology, clinical chemistry, and immune parameters) and clinical observations and self-reporting should be considered during the trial design stage (Shane et al., 2010). Finally, regulatory considerations should be carefully addressed to meet the regulatory requirements established by international authorities. Regulatory issues relevant to probiotics have been reviewed elsewhere (Pineiro and Stanton, 2007; Sanders et al., 2005).

7. Industrial requirements and technological properties

Probiotic preparations are to be considered medical or pharmaceutical products when aspects related to health, such as the diagnosis of a disease, therapy, prevention, or relief, are claimed (de Simone, 2018). Thus far, EFSA has rejected all health claims made for probiotics, classifying them as food supplements or dietary supplements (de Simone, 2018; Sanders et al., 2016). In this sense, the selected probiotic should not have adverse effects on the taste or aroma of the product or increase the acidity over the shelf life (Champagne et al., 2005; Goodarzi, 2016; Senaka Ranadheera et al., 2012). Additionally, the probiotic must survive food-processing stressors, such as fermentation, harvesting, freeze-drying, and variations in temperature, pH, and oxidative and osmotic stress during storage. Finally, from a safety perspective, it is crucial that probiotic cells are genetically stable to avoid developing pathogenicity or the loss of productivity.

For probiotic effectiveness, populations of 10^6 to 10^8 CFU/g by the time of consumption are required (Minelli and Benini, 2008). The population ratio can be affected by bacteriophages, which infect probiotic cells, thus causing cellular lysis (Garneau and Moineau, 2011; Leroy and De Vuyst, 2004). The selection of bacteriophage-resistant probiotic strains can be performed via classic methods, such as plaque assays or acidification monitoring, or via more sophisticated tools, such as qPCR, biosensors, and flow cytometry (Garneau and Moineau, 2011; Lucchini et al., 2000). In addition, some products can show modifications during their shelf lives, such as postacidification, thus resulting in the loss of probiotic viability. The presence of oxygen during some processes and storage can also affect cells' viability (Antunes et al., 2005; Pereira et al., 2016). The control of viable cells can be performed via microbiological methods, such as plating in a classical cultivation medium or qPCR using propidium monoazide dye (Davis, 2014; Radulović et al., 2012).

8. Concluding remarks and future prospects

Traditionally, probiotics have been selected based on stress-resistance phenotypes that guarantee their survival through the GIT and subsequent persistence in the gut. The main criteria used in the most studies are those that the WHO has recommended, such as host-associated stress resistance, epithelium adhesion ability, and antimicrobial activity. Using these characteristics, a wide diversity of microbial species claimed to be probiotic are currently being isolated from human and unconventional sources. However, biological properties responsible for the health-promoting effects, including anticarcinogenic, antidepression, antioxidant, and cholesterol-lowering properties, have been in the background for many studies. Additionally, safety characteristics for antimicrobial resistance, harmful metabolite production, and virulence determinants should be addressed prior to the *in vivo* use of new probiotics, which are often neglected.

Recent technological advances in high-throughput techniques—i.e., genomic, transcriptomic, proteomic, and metabolomic—have enabled the development of predictive models for the accurate selection of probiotics. First, extensive genome sequencing programs have revealed a great gene-content diversification within one bacterial species (Stefanovic et al., 2017). Probiotic strains carry genes related to acid and bile salt stresses, adhesion capacity, and antimicrobial substance secretion that are not found in domesticated, industrial LAB strains (Bull et al., 2014; Gibbons and Rinker, 2015). The presence of these genes can be used as solid scientific evidence in searching probiotics that possess the genetic arsenal required to adapt to the gut milieu, especially with the emerging cost reduction of high-throughput sequencing analyses. Accordingly, transcriptome, proteome, and metabolome profiling can be used to evaluate the expression of these genes under different host-related conditions (Fig. 3). For instance, proteins to cope with the toxic effects of the gut environments are differentially expressed in probiotic strains. Some defense mechanisms found in probiotics include the overproduction of proteins involved in energy metabolism, translation, general stress responses, lipid metabolism,

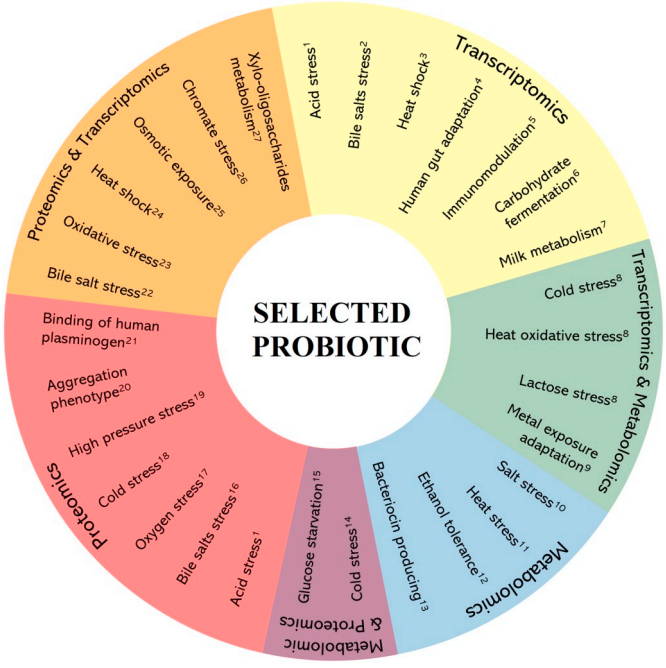

Fig. 3. Schematic representation summarizing how different omics platforms can provided in-depth information about the mechanism of action of probiotic bacteria, according to [1]Koponen et al. (2012); [2]Ruiz et al. (2012); [3]Rezzonico et al. (2007); [4]Marco et al. (2010); [5]van Baarlen et al. (2009); [6]Barrangou et al. (2006); [7]Turroni et al. (2011); [8]Jozefczuk et al. (2010); [9]Tremaroli et al. (2009); [10]Kol et al. (2010); [11]Ye et al. (2012); [12]Zhu et al. (2015); [13]Riboulet-Bisson et al. (2012); [14]Alreshidi et al. (2015); [15]Liebeke et al. (2011); [17]Hamon et al. (2011); [18]Xiao et al. (2011); [19]Budde et al. (2006); [20]Hörmann et al. (2006); [21]Siciliano et al. (2008); [22]Candela et al. (2007); [23]Alcántara and Zúñiga (2012); [24]Mostertz et al. (2004); [25]Suzuki et al. (2006); [26]Chen and Wilson (2007); [27]Brown et al. (2006).

exopolysaccharide synthesis, and oxidation-reduction reactions (Wu et al., 2009b). The proteome and transcriptome also provide a unique framework to identify posttranslational modifications that affect protein functionality and that are not detected by other omics techniques (Koponen et al., 2012; Ruiz et al., 2016).

Safety assessment of probiotics can greatly be improved using mechanistic omics tools. Safety-related genes, including antibiotic resistance and harmful metabolites production, have been reported in certain probiotic strains (Senan et al., 2015; Zhang et al., 2009). However, in general, there are no toxin- or hemolysin-encoding genes, and safety-associated genes are rarely transferable. Additionally, genomics has revealed only a theoretical risk level because gene expression is considered to be dependent on the environmental conditions. Thus, genomic data must be confirmed by *in vitro* studies and human clinical trials for correct probiotic selection. The assays and steps reported in this review are extremely useful support for upcoming starter culture selection and validation research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biotechadv.2018.09.003.

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