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Metabolism and physiology of Lactobacilli: a review

Amanda Rafaela Carneiro de Mesquita[a*], Lucas Pacheco da Mota Silveira[b], Iranildo José da Cruz Filho[c], Valmir Felix de Lima[d], Vladimir da Mota Silveira Filho[e], Ana Albertina Araujo[f], Tacilene Luzia da Silva[g], Klewdma de Freitas Araújo[h], Luciana da Silva Macedo[i]

[a] Universidade Federal Rural de Pernambuco, Departamento de Tecnologia Rural, Laboratório de Processamento e Análises de Alimentos, Rua Manoel de Medeiros, SN, Dois Irmãos, Recife, Pernambuco, Brasil. CEP: 52171-900. E-mail: arcmesquita@gmail.com.

[b] Laboratórios BBraun S/A, Av. Gov. Miguel Arraes de Alencar, 1380, Pontes dos Carvalhos, Cabo de Santo Agostinho, Pernambuco, Brasil. CEP: 54580-875. E-mail: lucaspms@yahoo.com.br.

[c] Universidade Federal de Pernambuco-UFPE, Departamento de Antibióticos, Laboratório de Processos Fermentativos, Av. dos Economistas, SN, Recife, Pernambuco, Brasil. CEP: 52.171-011. E-mail: iranildoj@gmail.com.

[d] Universidade de Pernambuco-UPE, Departamento de Engenharia Química, Laboratório de Cromatografia Instrumental, Av. dos Economistas, SN, Recife, Pernambuco, Brasil. CEP: 52.171-011. E-mail: atrazina@gmail.com.

[e] UPE, Campus Garanhuns, Departamento de Biologia, Rua Cap. Pedro Rodrigues, 105, São José, Garanhuns, Pernambuco, Brasil. CEP: 55295-110. E-mail: vladfilho@hotmail.com.

[f] Laboratório de Saúde Pública do Recife, Rua Major Codeceira, 194, Santo Amaro, Recife, Pernambuco, Brasil. CEP: 50100070. E-mail: anaaaraujo@gmail.com.

[g] Instituto de Medicina Integral Professor Fernando Figueira, Diretoria de Pesquisa, Rua dos Coelhos, 300 - Boa Vista, Recife, Pernambuco, Brasil. CEP: 50070-550. E-mail: tacy-19@hotmail.com.

[h] UFPE, Hospital das Clínicas, Av. Professor Moraes Rego, 1235, Cidade Universitária, Recife, Pernambuco, Brasil. CEP: 50670-901. E-mail: k2arj@hotmail.com.

[i] Hospital Militar de Área do Recife, Laboratório de Análises Clínicas, Rua do Hospício, 563, Boa Vista, Recife, Pernambuco, Brasil. CEP: 50030-230. E-mail: lumacedo2002@hotmail.com.

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ABSTRACT

Probiotics are living microorganisms that are consumed in adequate concentrations and provide beneficial effects to human health. The genus Lactobacillus is the most studied and widely used in commercial products. The mechanism of action of these microorganisms includes the competitive exclusion of pathogens from specific sites of adhesion or nutrients, reduction of pH by the production of organic acids, synthesis of vitamins and enzymes, the release of antimicrobial substances, immunomodulation and digestion of complex carbohydrates undigested by the host. All these mechanisms are used by probiotic microorganisms to maintain intestinal balance and prevent various intestinal conditions such as diarrhea, ulcerative colitis, Crohn's disease and cancer. The objective of this work was to review the metabolism and physiological characteristics of lactobacilli for a better understanding of the benefits that these bacteria promote in the host. The articles selected for the elaboration of this review were articles indexed by the databases: Pubmed, Lillacs and Scielo. Due to the beneficial effects mentioned above, probiotic microorganisms have been essential in the food and pharmaceutical industries. Also, currently, the demand for healthy and functional foods has grown substantially. There are still uncertainties, and disagreements about the biochemical metabolism of lactobacilli, but many genomic and proteomic studies are being performed. Knowledge of these molecular mechanisms may contribute to the development of probiotic lineages and products with greater health benefits.

Keywords: Probiotics, lactobacilli, metabolism.

Introduction

Different definitions of probiotics have been previously published (Sanders, 2003; Coppola & Turnes, 2004). However, the internationally accepted concept is that they are living microorganisms that are administered in adequate quantities conferring health benefits to the host (FAO/WHO, 2002).

The mechanism of action of probiotics includes the competitive exclusion of pathogens for specific sites of adhesion or nutrients, reducing pH through the production of organic acids, the release of antimicrobial substances (hydrogen peroxide and bacteriocins) and immunomodulation (Hickson, 2011; Preidis et al., 2011; Singh et al., 2013).

A previous study reported the immunomodulatory effect of *Zymomonas mobilis*, a probiotic bacterium, in the treatment of sepsis induced by cecal ligation and puncture (CLP) on the survival of mice. It was evidenced that this protective effect was due to increased recruitment of leukocytes and neutrophils to the initial focus of infection (Campos et al., 2013). Additional examples of probiotic microorganisms are species of *Lactobacillus, Lactococcus, Bifidobacterium* and *Pediococcus* (Sieber et al., 2004; O'Shea et al., 2012). However, species belonging to the genus *Lactobacillus* are the most studied and widely used in commercial products (Baugher & Klaenhammer, 2011; Ashraf & Shah, 2014).

The genus *Lactobacillus* belongs to the phylum Firmicutes, class Bacilli, order Lactobacillales and family Lactobacillaceae. Currently, there are more than 150 species of *Lactobacillus* described in the literature, and this is the most abundant genus of the order Lactobacillales (Felis & Delagio, 2007; Drissi et al., 2016).

Members of the genus *Lactobacillus* are Gram-positive, immobile, non-spore producing, most facultative anaerobic, acid-tolerant, and negative catalase bacteria. The genus *Lactobacillus* is characterized by the low G + C content (guanine and cytosine - 33 to 52%) in the genome. They are carbohydrate fermenting microorganisms, and lactic acid is the major final product of this metabolism (Cai et al., 2012; Herbel et al., 2013).

This group of microorganisms is found in different environments, such as in natural niches like plants, soil, and vegetables; oral cavity, skin, gastrointestinal and urogenital tracts of animals and humans. It can also be isolated from beverages and foods such as wine, milk, kefir, meat, fruit, vegetables, cereals and dairy products, mainly in yogurts and cheeses (Pál et al., 2012; Herbel et al., 2013; Barrangou et al., 2012).

Carbohydrates metabolism

Lactobacilli have a large number of enzymes involved in the metabolism of several carbohydrates, and can be classified according to the assimilation of hexoses (glucose, mannose, galactose, fructose) and pentose (arabinose and xylose), as well as other types of carbohydrates (El Kaoutari et al., 2013; Drissi et al., 2016).

According to the final fermentation product, lactobacilli are divided into two groups: homofermentative and heterofermentative, the latter being subdivided into facultative and obligate. Homofermentative lactobacilli are classified exclusively as obligate because they always carry out glycolysis and produce only lactic acid (>85%) by the Embden-Meyerhof-Parnas (EMP) glycolytic pathway from the assimilation of hexoses, which are transported by membrane proteins called permeases, ABC (ATP Binding Cassette) transporters and phosphoenolpyruvate : carbohydrate phosphotransferase (PEP:PTS). This metabolism is characterized by the breakdown of 1,6-diphosphate fructose into two trioses phosphates, which are converted into lactate (Pessione, 2012; Salvetti et al., 2012; Abdel-Rahman et al., 2013).

Other hexoses, in addition to glucose, such as mannose, fructose, and galactose, enter the EMP pathway after different stages of isomerization and phosphorylation to glucose-6-phosphate or fructose-6-phosphate (Von Wright & Axelsson, 2012). However, the use of these other hexoses will only occur after glucose depletion, in which maltose will be hydrolyzed by α-glycosidase (Gänzle et al., 2007).

For galactose, two pathways differ in the way the carbohydrate enters the cell: Tagatose-6-phosphate and Leloir, which will depend on the protein carrier membranes present in each species. In the first pathway, galactose is transported by the PEP: PTS system and enters the cell in the form of galactose-6-phosphate. In the second route, galactose is transported directly into the cell, without any change by a specific permease (Von Wright &Axelsson, 2012; Pessione, 2012).

Lactobacilli belonging to the obligate heterofermentative group can produce lactic acid, acetic acid, ethanol and CO_2 by fermentation of hexoses and produce lactic acid, acetic acid, ethanol by the fermentation of pentose using the phosphogluconate and phosphoketolase pathway. This group does not possess the enzyme fructose-1,6-diphosphatase aldolase, which is the key enzyme of glycolytic metabolism. However, they

have the phosphoketolase enzyme present only in the pentose pathway (Abdel-Rahman et al., 2013).

Species belonging to the facultative heterofermentative group may vary between homo and heterofermentative metabolism, depending on the availability of carbohydrates. It can ferment hexose through the glycolytic pathways or use the pentose phosphate pathway to assimilate pentose because this group has both enzymes: fructose-1,6-diphosphate aldolase and phosphoketolase. However, in the fermentation of pentoses, there is no CO_2 production (Von Wright & Axelsson, 2012; Sutula et al., 2012; Drissi et al., 2016).

Disaccharides metabolism

Of all the disaccharides used by lactobacilli, lactose is the most studied because of its presence in milk, a major source of lactic acid bacteria (Widyastuti al., 2014; Francl et al., 2012).

Lactose can enter the cell by two forms: a specific permease (more common in lactobacilli) or as lactose phosphate, through the lactose specific PEP:PTS transporters, in some cases both systems can coexist. Once transported by a permease, lactose is cleaved into glucose and galactose by a β-galactosidase in the bacterial cytoplasm. Galactose is metabolized via Leloir pathway, whereas glucose enters glycolysis (via EMP). In the PEP: PTS system, another enzyme called phospho-beta-galactosidase is required to hydrolyze lactose-6-phosphate to glucose and galactose-6-phosphate. Glucose is catabolized by the glycolytic pathway, and galactose-6-phosphate enters the Tagatose-6-phosphate pathway (Francl et al., 2012).

Oligosaccharides metabolism

Oligosaccharides are carbohydrates formed by the union of 2 to 10 monosaccharides, whose metabolism is essential for the adaptation of lactobacilli to a particular environment, especially in the intestines of humans and animals (Barrangou et al., 2003; Gänzle & Follador, 2012).

Among these carbohydrates, fructooligosaccharide (FOS) is the most extensively studied. FOS are fructose polymers, whose structure can be represented by GFn or Fn (G: glucose units; F: fructose units; n: number of fructosyl units). They are used commercially in food products and nutritional supplements, they vary in length according to their degree of polymerization and may originate inulin, levan and oligofructose (Barrangou et al., 2003; Saulnier et al., 2007).

These sugars are resistant to digestion in the stomach and small intestine and are only digested in the colon where they are selectively fermented by bacteria, such as *Lactobacillus* spp. Moreover *Bifidobacterium* spp. (Caetano et al., 2016).

Although FOS can stimulate the growth of probiotic bacteria and beneficially modulate the intestinal microbiota balance, *in vivo* and *in vitro*, knowledge about the molecular mechanism of FOS in the metabolism of these microorganisms is still limited (Goh et al., 2006; Saulnier et al., 2007; Chen et al., 2015).

Some researchers have demonstrated that FOS is transferred to the bacterial cell through an ATP-binding cassette transporter (ABC transporter) and hydrolyzed in the cytoplasm by the enzyme β-fructofuranosidase, responsible for cleaving the β (2→1) linkage between glucose and fructose molecules, generating free fructose and glucose-6-phosphate. After this step, fructose is phosphorylated to fructose-6-phosphate and enters the EMP glycolytic pathway, as well as glucose-6-phosphate (Altermann et al., 2005; Klaenhammer et al., 2005).

However, other authors believe that FOS transport through the bacterial cell occurs through PTS (phosphotransferase system) (Goh et al., 2006, 2007; Chen et al., 2015). In the cytoplasm, FOS is hydrolyzed to fructose and glucose-6-phosphate by the action of the enzyme β-fructofuranosidase. Subsequently, fructose is phosphorylated to fructose-6-phosphate and follows the EMP pathway, and glucose-6-phosphate follows the pentose phosphate pathway (Chen et al., 2015).

Solute Transport Systems

Lactic acid bacteria utilize a diverse set of carriers to import sugars for intracellular processing. These carriers are classified into three main classes: the major facilitator superfamily (MFS) transporters, ABC transporters, and PEP: PTS system (Cockburn & Koropatikin, 2016).

MFS are permeases that transport substrates such as organic and inorganic ions, nucleosides, amino acids, small peptides, and lipids. MFS members are made up of: facilitators, symporters, and antiporters. Facilitators catalyze the diffusion of substrates through the membrane through a concentration gradient. Symporters and antiporters use the energy released or the translocation of a substrate to transport ions (H^+ or Na^+) in the same direction (symport) or the opposite direction (antiport) to the concentration gradient (Yan, 2015).

ABC transporters catalyze the transport and phosphorylation of sugars. They have an extracellular protein that recognizes a specific sugar, maintaining the carrier specificity, and then

promotes the hydrolysis of ATP to import the carbohydrate (Cockburn & Koropatikin, 2016).

The PEP: PTS system acts in the transport of sugars and their derivatives (alcohol sugars, disaccharides, glucuronic acid, among other carbon sources), through the membrane with simultaneous phosphorylation. The PTS consists of cytoplasmic components: enzyme I (EI) and histidine-phosphorylatable protein (HPr); and membrane components: enzyme II (EII), composed of three subunits: IIA, IIB, IIC and sometimes IID. Several PTS systems can share the two first cascade proteins (EI and HPr). However, the EIIBC and EIIA enzymes are sugar-specific (Francl et al., 2012; Deutscher et al., 2014).

Phosphoenolpyruvate (PEP) acts as a phosphate donor for enzyme I (EI), which together with HPr and EIIA and EIIB proteins, performs phosphorylation cascade that results in the transport of the carbohydrate bound to enzyme II BC (EIIBC) into the cell (Von Wright &Axelsson, 2012; Deutscher et al., 2014).

Proteolytic system

Although less extensively studied, the main characteristics of the proteolytic system of lactobacilli appear to be similar to that of *Lactococcus lactis* (Savijoki et al., 2006).

The proteolytic system is essential for bacterial growth, in this way, all species belonging to the genus *Lactobacillus* require at least three amino acids (e.g. *L. plantarum*) for development, others require a larger amount, in the case of *L. acidophilus* that requires 14 amino acids. Accordingly, they have a functional proteolytic system for acquiring amino acids from the growth medium or natural habitat (Barrangou et al., 2012).

According to the protein functions, the proteolytic system of lactic acid bacteria (LAB) can be divided into three components: (I) membrane-anchored proteinase (PrtP), which initiate the extracellular degradation of protein in oligopeptides; (II) transport systems, which carry the peptides through the cytoplasmic membrane and (III) several intracellular peptidases, which degrade the peptides to smaller sizes and amino acids (Kunji et al., 1996).

Proteolysis is an important mechanism for generating peptides and amino acids for bacterial growth and for forming metabolites that contribute to the development of the flavor of fermented products. Amino acids can be converted into various compounds responsible for flavor, such as aldehydes, alcohols, and esters (Liu et al., 2008, 2010).

Lactobacillus bulgaricus and *L. helveticus* have a vast arsenal of proteolytic enzymes, which is compatible with previous knowledge of the proteolytic activity thereof. *L. bulgaricus* is the main proteolytic organism in yogurt, with activity superior to *Streptococcus thermophilus*. L. *helveticus* is known as an adjuvant culture that has an important proteolytic activity in the degradation of peptides in cheese (Liu et al., 2010). These proteolyses promote the increase in the digestibility of milk and the increase in the nutritional quality of these foods (El-Ghaish et al., 2010).

Proteolytic activity is based on cell wall-associated serine proteinase (PrtP). This enzyme breaks down the protein into oligopeptides of varying sizes. Large peptides (4-18 amino acids) are transported by an oligopeptide transport system (Opp- an ABC transporter), while di- and tripeptides are transported by the Dpp (ABC transporter) and DtpT (MFS symporter) transport systems. Within the cell, the peptides are degraded to amino acids by specific intracellular peptidases (Savijoki et al., 2006; Von Wright & Axelsson, 2012).

Studies using *L. lactis* have shown that a pool of the amino acids isoleucine, leucine and valine stimulate binding of CodY, the transcriptional regulator which represses the expression of the genes involved in the proteolytic system (Savijoki et al., 2006). The regulatory mechanism of the proteolytic system of lactobacilli is poorly studied, and some research indicates that some components of the culture medium, such as glucose, may influence the production of enzymes involved in this mechanism (Savijoki et al., 2006; Wang et al., 2013).

Some enzymes are found only in a few strains of LAB, such as PrtP that are found only in *L. acidophilus*, *L. johnsonii*, *L. bulgaricus*, *L. casei*, *L. rhamnosus, S. termophilus* and *L. lactis*. Endopeptidases (PepE/PepG), proline peptidase (PepI, PepR, PepL, PepX, PepQ) and aminopeptidases (PepC, PepN and PepM). The endopeptidases and proline peptidases are present in the bacilli of the LAB group and absent in the cocci of the same group, whereas the aminopeptidases are present in all the genomes (Liu et al., 2010; Von Wright & Axelsson, 2012).

PepP, PepQ and PepM belong to the M24 peptidase family and require metal ions for their catalytic activities, for example, PePM requires cobalt and PepQ has a preference for manganese (Christensen et al., 1999).

In general, peptidases can remove the N-terminal amino acid from a peptide; the specificity will depend on the size of the peptide and the nature of the N-terminal amino acid residue (Savijoki et al., 2006).

Lactobacillus acidophilus, *L. brevis*, *L. casei*, *L. rhamnosus*, and *L. lactis* have the three LAB transport systems: di/tripeptides DPP and DtpT and the Oppoligopeptide system. In contrast, *L. reuteri* has only one functional transport of peptides, the DtpT system (Liu et al., 2010).

Lactobacilli increase the catabolism of free amino acids, generating energy (ATP) especially from the stationary phase or under conditions of environmental stress (acidity, lack of nutrients) (De Angelis et al., 2016).

Lipid metabolism: Tween 80 as growth factor

The standard MRS (Man, Rogosa & Sharpe) medium, used for the non-specific cultivation of lactobacilli, contains 0.1% Tween 80 (cis-9-octadecenoic acid), which is a surfactant derived from oleic acid and known to optimize the growth of many LAB (De Man et al., 1960). However, it is not always required for the growth of microorganisms. According to Al-Naseri et al. (2013), Tween 80 is used as the carbon source after depletion of the following priority sources: citrate, amino acids, acetate and carbohydrate traces present in the yeast extract.

In many LABs, octadecanoic acids are converted in the cell membrane into the cyclopropane fatty acids: oleic acid and cis-vaccenic acid (cis-11-octadecanoic acid), which are methylated to form dihydrosterculic acid (9,10-methylene octadecanoic acid), in the presence of the enzyme cyclopropane synthase and lactobacillic acid (11,12-methylene-octadecanoic acid), respectively (Polacheck et al., 1966; Johnsson et al., 1995; Partanen et al., 2001, Broadbent et al., 2014). Nevertheless, *L. plantarum*, *L. brevis*, and *L. delbrueckii* do not synthesize lactobacillic acid from cis-vaccenic acid. Due to this fact, it is still unclear whether there are two different enzymes for the conversion of oleic and vaccenic acids to their corresponding cyclopropane fatty acids. Another question is whether this conversion occurs at different sites in the cell (Johnsson et al., 1995).

Oleic acid and cis-vaccenic acid are the most predominant octadecanoic acids in lactobacilli, making up 14-67% of total fatty acids. However, linoleic acid can be found at trace levels up to 20%, although it is relatively uncommon (et al., 2004).

Some authors believe that dihydrosterculic acid promotes increased cellular membrane fluidity in LAB, and protects against the adverse effects of the environment, such as low temperatures in the freezing process and low pH (Partanen et al., 2001; Ananta et al., 2004). However, other authors believe that the presence of fatty acids, such as oleic acid, may confer to these bacteria a greater rigidity of the plasma membrane and this characteristic would promote an increase in bile tolerance and adhesion to the intestinal epithelium (Corcoran et al., 2007). These disagreements occur because the mechanism of Tween 80 in cellular physiology has not yet been fully elucidated and requires further research (Al-Naseri et al., 2013).

Genetics

The loss and gain of genes played a major role in the evolution and adaptation of these organisms to different environmental niches (Klaenhammer et al., 2008).

A phylogenetic study demonstrated that the common ancestor of the genus *Lactobacillus* had from 2,100 to 2,200 genes and registered a loss of 600 to 1,200 genes after the divergence from the genus *Bacillus*. These lost genes, particularly related to cofactor biosynthesis and sporulation, are indicative of the shift to a more nutrient-rich environment (Makarova et al., 2006). Currently, it is known that *Lactobacillus* genome size varies from 1.23 Mb (*L. sanfranciscensis*) to 4.91 Mb (*L. parakefiri*) (Sun et al., 2015).

The genetic gain among species during the evolution occurred through the horizontal gene transfer (HGT) that contributed to the evolution of these microorganisms and occurs continuously (Fang & O'Toole, 2009; Morelli et al., 2012).

This transfer of genetic material between bacteria occurs using bacteriophages and transposons and between different taxonomic groups, which are the main responsible for the various bacterial genetic rearrangements (Rossi et al., 2014; Stefanovic et al., 2017). The genomic regions that were acquired via horizontal transfer are called genomic islands (Bellanger et al., 2014).

According to some studies, genes encoding proteins involved in the transport and metabolism of several carbohydrates have been acquired by horizontal transfer and this may explain the great catabolic potential of *Lactobacillus* and the great adaptability of some species (e.g. *L. plantarum*) to different environments (Barrangou et al., 2003; Klaenhammer et al., 2005).

*Lactobacillus plantarum*can use a wide variety of carbohydrates, and this is why this species can inhabit several environmental niches. Analysis of *L. plantarum* genome revealed the presence of many transporters, particularly PTS, which can be correlated with the ability to metabolize a wide variety of carbohydrates. All these characteristics are a reflection of the large genomic size of this species (3.4 Mpb), one of the largest of the genus (Klaenhammer et al., 2005; Stefanovic et al., 2017).

Adaptation mechanisms

Soil and plants were the first hypothetical niches attributed to the first LAB, and obviously, it was assumed that the second habitat would be the intestine of herbivorous animals (Morelli et al., 2012). Three major genomic adaptations were necessary for these bacteria to survive and multiply in the intestines of animals: resistance to low gastric pH and intestinal bile salts, adhesion to intestinal epithelium to resist intestinal flow and ability to ferment some substrates more efficiently than pathogenic bacteria (Lebeer et al., 2008).

Species of this genus are present in dairy products (*L. delbrueckii* subsp. *bulgaricus, L. helveticus*), gastrointestinal tract of humans and animals (*L. acidophilus* and *L. gasseri*), or in a variety of niches (*L. plantarum, L. pentosus*, *L. brevis,* and *L. paracasei*) (Smokvina et al., 2013).

Adhesion of lactobacilli to the intestinal epithelium is one of the most important characteristics, as it allows colonization and stimulates host-microorganism interaction, forming an intestinal barrier and consequent protection through several mechanisms, including antagonistic activity against pathogens (Servin, 2004).

The cellular envelope is the first target of physical-chemical and environmental stress (Sengupta et al., 2013). Lactobacilli present great diversity in the cell surface structure and are known to modify their structural properties in response to changes in the environment (Taranto et al., 2003; Fozo et al., 2004). Different macromolecules constitute the cell wall of these bacteria and contribute to maintaining the integrity of the bacterial cell during environmental stress (Guerzoni et al., 2001).

Cell wall of lactobacilli consists of multiple layers of peptidoglycan (PG), with teichoic acids (WTA – wall teichoic acids, anchored to the cell wall) and/or lipoteichoic acids (LTA - bound to the cell membrane), exopolysaccharides (EPS), protein filaments called pili, and proteins anchored to the cell wall. Some species may also present an additional paracrystalline layer of proteins that surrounds the PG layer, referred to as S-layer. These macromolecules together may play a key role in determining species and specific characteristics of the lactobacilli strains, influencing host-microorganisms interactions and microbial adaptations to the new environment (Sengupta et al., 2013).

Lactobacilli face several environmental stress factors during their passage through the gastrointestinal tract, such as low pH and the presence of bile salts. Survival in acidic environments occurs by adaptation to low pH values through a mechanism called acid tolerance response (ATR) (Sengupta et al., 2013).

Three main mechanisms regulate intracellular pH (pHi) homeostasis in fermentative bacteria. The most important is the translocation of protons (H^+) through ATPase; this enzymatic complex plays a major role in the regulation of pHi by these microorganisms, promoting the extrusion of H^+ protons, which results in the increase of pHi (De Angelis & Gobbetti, 2004; Cotter & Hill, 2003).

Another pathway is the arginine deiminase (ADI), which catalyzes the conversion of the amino acid arginine into ornithine, ammonia and CO_2, resulting in the rise of pH by the formed ammonia and also by the expulsion of protons from the cytoplasm by the ATPase complex, with consequent generation of ATP (Lebeer et al., 2008).

The third mechanism is the glutamate decarboxylase (GAD) system that internalizes the amino acid glutamate, which decarboxylate in the cytoplasm, resulting in the intracellular consumption of a proton. The product of this reaction is gamma-amino-butyrate (GABA), which is exported from the cell via antiporter. As a result, there is an increase in intracellular pH due to the extrusion of H^+ ions and a small increase in extracellular pH by the release of GABA in the medium (Higuchi et al., 1997; Cotter & Hill, 2003).

To reach the colon in a viable state, the lactobacilli must survive besides stomach acidity, and the presence of bile in the upper part of the small intestine (Ruiz et al., 2013). The main mechanisms responsible for the resistance of these microorganisms are: active efflux of bile acid/salts (Pfeiler & Klaenamamer, 2009; Bustus et al., 2011), bile salt hydrolysis (Lambert et al., 2008) and modifications in structure/composition of the membrane and cell wall (Taranto et al., 2003).

The active expulsion of bile acids and salts accumulated in the cytoplasm occurs through an efflux system, belonging to the family of multidrug resistance (MDR) transporters (De Angelis & Gobbetti, 2004). Another mechanism used to neutralize the harmful effect of bile is the activity of the enzyme bile salt hydrolase (BSH) (Lebeer et al., 2008). Bile is composed of bile acids, which are synthesized from cholesterol, and conjugated with the amino acids glycine or taurine in the liver, to generate conjugated bile salts that are released into the intestine (De Angelis & Gobbetti, 2004). BSHs

are intracellular enzymes that catalyze the hydrolysis of the amide bond between the steroid and the bile acid chain (Lebeer et al., 2008).

Bile salts are amphipathic molecules with potent antimicrobial activity, acting as detergents and destructuring biological membranes (De Angelis & Gobbetti, 2004). Due to this lipophilic characteristic, bacterial membranes represent one of the main targets of bile that destroys the structure of the bacterial envelope, affecting cell and cellular morphology (Ruiz et al., 2013).

A study on the response to acidity and bile salts in lactobacilli has identified genes involved in the synthesis of peptidoglycan and the cell envelope (Sengupta et al., 2013). Other cell surface structures (LTA, WTA, and EPS) have been suggested to play important roles in cellular integrity in acidic environments containing bile (Neuhaus & Baddiley, 2003).

Antimicrobial compounds production

Lactobacilli are known to produce a wide array of compounds that exert a direct antimicrobial action against viruses and bacteria. These compounds include organic acids, hydrogen peroxide and bacteriocins (Lebeer et al., 2008; Yusuf& Hamid, 2013; Liévin-Le Moal & Servin, 2014).

Acidity is an important environmental stressor for acid-lactic bacteria during the fermentation of food and beverages (De Angelis & Gobbetti, 2004). Lactic acid in the undissociated form crosses the plasma membrane of pathogenic bacteria by diffusion or through a carrier into their cytoplasm and dissociates itself by releasing protons into the cell because the intracellular pH is more alkaline than the extracellular medium. This influx of protons induces cytoplasmic acidification, dissipating the membrane proton potential (ΔpH) and reducing the activity of enzymes sensitive to acidity, resulting in damage to protein, DNA and consequent inhibition of energy supply processes and macromolecule synthesis. Acetic acid also promotes the same mechanism (Ogawa et al., 2001; Gobetti et al., 2005; Lebeer et al., 2008; Broadbent et al., 2010).

The antimicrobial action of peroxide is associated with its toxicity, exerted through the molecule itself or by hydroxyl and superoxide radicals, which lead to oxidative stress and impair bacterial cell function (Tomás et al., 2003).

Bacteriocins are antimicrobial peptides produced by bacteria, which have bactericidal or bacteriostatic activity against other microorganisms (Balciunas et al., 2013). Most of the bacteriocins of lactobacilli have a broad spectrum of action on several bacterial groups, such as anaerobes (*Clostridium* spp*., Bacteroides* spp*., Bifidobacterium* spp.), Gram-positive bacteria (*Staphylococcus* spp*., Streptococcus* spp*., Listeria* spp.) and Gram-negative bacteria (*Salmonella* spp*., Campylobacter* spp*., Bacteroides* spp*., Enterobacter* spp*., Pseudomonas* spp.) (Drissiet al., 2016). The production and activity of these peptides will depend on some physical-chemical factors, such as pH, a nutrient source and chemical composition of the medium (Pérez et al., 2014).

Bacteriocins can be divided into three classes according to molecular weight and genetic properties: class I, class II and class III (Cotter et al., 2013).

Class I or lantibiotics are small peptides (<5kDa, 19-38 amino acid residues), with rare thermostable amino acids in their composition. They can bind to the membrane lipids, causing cell death by blocking cell wall synthesis. Nisin is the major representative of the group, produced by some species of *Lactococcuslactis* subsp. lactis, composed of 34 amino acid residues (Balciunas et al., 2013; Drissi et al., 2016).

Class II or non-lantibiotics are also small thermostable peptides (<10kDa) with an amphiphilic helical structure that allows their insertion into the cytoplasmic membrane of the target cell, promoting membrane depolarization and cell death. They are subdivided into subclasses IIa, IIb, IIc and IId (Cotter et al., 2013).

Class III are thermolabile with high molecular weight (>30kDa) and promote lysis of the cell wall of the target microorganism. One of its representatives is helveticin I produced by *Lactobacillus helveticus* (Zacharof & Lovitt, 2012).

Given these characteristics, bacteriocins have a great biotechnological potential, some of them are used as food preservatives (Cotter et al., 2005). In the meantime, several studies are still being conducted with the aim of optimizing production, purification and efficacy *in vivo* and *in vitro* (Drissi et al., 2015; Malheiros et al., 2015).

Conclusion

Lactobacilli are extensively studied because of their ability to promote health benefits to the host. Due to these beneficial effects, probiotic microorganisms have been essential in the pharmaceutical and functional food industries, such as yogurts, cheeses, milk, ice creams and kefir. Besides that, health awareness and the search for healthy, and functional foods have grown substantially. There are still uncertainties, and divergences about the biochemical metabolism of lactobacilli, however many genomic and proteomic

studies are being developed and published. Knowledge of these molecular mechanisms may contribute to the development of probiotic lineages and products with greater health benefits.

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