UNIVERSIDADE DE SÃO PAULO

FACULDADE DE CIÊNCIAS FARMACÊUTICAS DE RIBEIRÃO PRETO

UNIVERSITÉ DE BRETAGNE OCCIDENTALE

ÉCOLE DOCTORALE SANTÉ, INFORMATION-COMMUNICATION, MATHEMATIQUES, MATIÈRES

Isolation of lactic acid bacteria from milk and cheese with potential for food biopreservation and utilization for increasing whey digestibility

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Ribeirão Preto

2014

RESUMO

TULINI, F. L. **Isolamento de bactérias láticas de leite e queijo com potencial para bioconservação de alimentos e utilização no aumento da digestibilidade de proteínas do lactosoro**. 2014. 182 f. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto (Brasil), e École Doctorale Santé, Information-Communication, Mathematiques, Matières – Université de Brest, Brest (França), 2014.

As bactérias láticas (BAL) têm sido utilizadas pela humanidade há séculos devido às suas propriedades tecnológicas e potencial para conferir características sensoriais agradáveis aos alimentos. Além disso, é cada vez maior a demanda por alimentos de qualidade. Neste contexto, BAL tem grande potencial para serem utilizadas na produção de alimentos. Uma das principais características destas bactérias é a produção de substâncias que inibem a multiplicação de agentes patogênicos e micro-organismos deteriorantes em alimentos, tais como ácidos orgânicos, H_2O_2 e bacteriocinas. Estas últimas são um peptídeos antimicrobianos produzido via ribossomo por algumas bactérias e possuem pequeno espectro inibição. As bacteriocinas podem reduzir a multiplicação de bactérias-alvo, aumentando a segurança alimentar e a vida de prateleira de alimentos. Essas substâncias inibitórias produzidas por BAL podem também inibir fungos, que são em grande parte responsáveis pela deterioração dos alimentos. Outra importante propriedade das BAL é capacidade de modificar as proteínas do leite durante o processo de fermentação. Isto é importante para indivíduos alérgicos devido à alteração de potencial alergênico das proteínas do leite, e também é importante para a produção de peptídeos bioativos. Recentemente, resultados demonstraram que os peptídeos obtidos a partir da hidrólise de proteínas do leite podem ter diferentes atividades biológicas, tais como anti-hipertensiva, antioxidante, antimicrobiana e imunomodulatória. Em resumo, BAL apresentam potencial para a produção de alimentos de alta qualidade, o que estimula a busca de novas linhagens com propriedades tecnológicas de interesse. Assim, no presente estudo, BAL com atividade antimicrobiana e / ou proteolítica foram isoladas de leite e queijo de vaca, búfala e cabra, obtidos na região sudeste do Brasil. A partir de 156 amostras de leite e queijo, foram obtidos 815 isolados em ágar seletivo para BAL. A maioria eram cocos ou bacilos Gram-positivos, e não produziam a enzima catalase. Culturas puras destes novos isolados foram avaliadas quanto a atividade antimicrobiana por testes de antagonismo em ágar (*spot-on-the-lawn*), e quanto a atividade proteolítica sobre proteínas do leite pelo cultivo em placas de ágar BHI (*Brain Heart Infusion* suplementado com leite desnatado). Os isolados com maior atividade proteolítica também foram testados pelo cultivo em leite desnatado seguido de análise do leite fermentado por eletroforese em gel de poliacrilamida com dodecil sulfato de sódio (*sodium dodecyl sulfate polyacrylamide gel electrophoresis* SDS-PAGE). Entre os 815 isolados testados, quatro deles foram identificados como produtores de bacteriocinas, *Lactobacillus paraplantarum* FT259 (uma linhagem) e *Streptococcus uberis* (três linhagens, FT86, FT126 e FT190), enquanto quatro outros identificados como *Weissella confusa* FT424, *W. hellenica* FT476, *Leuconostoc citreum* FT671 e *Lactobacillus plantarum* FT723, os quais apresentaram atividade antifúngica em ensaios preliminares. Análises complementares mostraram que a linhagem com maior atividade antifúngica foi *L. plantarum* FT723, o qual inibiu *Penicillium expansum* em ágar MRS modificado (De Man, Rogosa, Sharpe, sem acetato) e em

modelo de leite fermentado. No entanto, nenhuma inibição foi observada contra *Yarrowia lipolytica*. A atividade proteolítica foi detectada em 205 isolados por testes em ágar, sendo que 123 isolados com intensa atividade proteolítica foram submetidos a confirmação da atividade por SDS-PAGE. As atividades proteolíticas de três isolados identificados como *Enterococcus faecalis* (FT132 e FT522) e *Lactobacillus paracasei* FT700 foram confirmadas por SDS-PAGE, como visualizado pela digestão de caseínas e proteínas de soro de leite (β-lactoglobulina e α-lactalbumina). No entanto, devido à alta semelhança entre as linhagens, apenas *E. faecalis* FT132 (juntamente com *L. paracasei* FT700) foram selecionados para os próximos estudos utilizando proteínas do leite como substratos em diferentes condições, seguidas de análises por SDS-PAGE e cromatografia líquida de alta eficiência (HPLC, *high-performance liquid chromatography*). Ambos *E. faecalis* FT132 e *L. paracasei* FT700 apresentaram atividades proteolíticas em pH 6,5, entre 37 e 42 °C. A atividade proteolítica das linhagens foi devida à presença de metaloproteases. Em seguida, para avaliar as possíveis atividades biológicas dos peptídeos derivados da atividade proteolítica de *E. faecalis* FT132 e *L. paracasei* FT700 em proteínas do leite, o sobrenadante de leite fermentado produzido por estas linhagens foi purificado em cartucho C_8 e liofilizado. Desse modo, os sobrenadantes de leite fermentado produzidos por estas linhagens foram adicionados às culturas de células (monócitos e macrófagos) para avaliar a sua citotoxicidade, os mecanismos de morte celular, propriedades imunomoduladoras (diferenciação de monócitos em macrófagos) e quantificação de TNF-α (do inglês *tumor necrosis factor*). Os sobrenadantes apresentaram toxicidade após 72 h de exposição a 10 mg/mL por apoptose. Abaixo das concentrações citotóxicas, ambos os sobrenadantes de leite fermentado estimularam a diferenciação de monócitos em macrófagos, como observado pelo aumento da expressão do marcador CD71. Esta estimulação imune não foi inflamatória visto que houve pouca produção de TNF-α. BAL também podem contribuir para a saúde dos consumidores quando utilizadas como probióticos. No entanto, algumas características das linhagens devem ser verificadas antes de serem utilizadas como probióticos, especialmente com relação aos fatores de virulência. Lactobacilos geralmente possuem um status GRAS (do inglês *generally recognized as safe*), ao contrário dos enterococos. Neste estudo, foi demonstrado que *E. faecalis* FT132 possuía três genes de virulência, *asa*1, *ace* e *gel*E, e que era resistente à eritromicina e à tetraciclina, indicando que esta linhagem não pode ser adicionada em alimentos. No entanto, *L. paracasei* FT700 seria um potencial candidato para ser utilizada como probiótico, bem como a linhagem bacteriocinogênica descrita anteriormente, *L. paraplantarum* FT259. As linhagens foram testadas quanto à sobrevivência em meio ácido (pH 2,0, 2,5 e 3,5), tolerância *in vitro* aos sais biliares, viabilidade em suco gástrico sintético e sensibilidade a antibióticos. Além disso, o peptídeo antimicrobiano produzido por *L. paraplantarum* FT259 foi parcialmente purificado em coluna preenchida com resina XAD-16, seguido de extração em fase sólida com cartucho de C_{18}, e analisados por SDS-PAGE. Reações em cadeia da polimerase (PCR, do inglês *polymerase chain reaction*) com *primers* para os genes estruturais da plantaricina NC8, plantaricina S e plantaricina W, seguidas de sequenciamento de DNA, foram realizados para detectar genes responsáveis pela produção de bacteriocinas. Os resultados mostraram que *L. paraplantarum* FT259 foi resistente ao pH 3,5 e a 0,3% de sais biliares por até 180 minutos, mas a população bacteriana em pH 2,0 e 2,5 após 90 minutos estava abaixo do limite de detecção do método (2 log UFC/mL). Em testes utilizando suco gástrico sintético, a população de *L. paraplantarum* FT259 reduziu de 8,6 log UFC/

mL para 4,4 log UFC/mL após 180 minutos. Por outro lado, *L. paracasei* FT700 sobreviveu bem em quase todas as condições. Depois de 180 minutos em pH 2,0 e em suco gástrico sintético, a população bacteriana reduziu 4 e 3 log UFC/mL, respectivamente. Também foi demonstrado que *L. paraplantarum* FT259 e *L. paracasei* FT700 foram sensíveis à maioria dos antibióticos testados. A análise de SDS-PAGE indicou que a bacteriocina parcialmente purificada apresentava uma massa molecular de aproximadamente 3900 Da, e o sequenciamento de DNA do produto de amplificação obtido por PCR mostrou a presença do gene que codifica a produção da plantaricina NC8. De modo geral, os resultados indicaram que ambas as linhagens possuem potencial probiótico. Além disso, a produção de bacteriocinas (*L. paraplantarum* FT259) e a atividade proteolítica (*L. paracasei* FT700) podem ser características interessantes para aplicações em alimentos. As BAL obtidas neste estudo podem ser úteis na indústria de alimentos para a produção de novos produtos lácteos com maior vida de prateleira e aumento da digestibilidade de proteínas do leite, assim como para a produção de peptídeos bioativos comercializados como fórmulas parcialmente purificadas.

Palavras-chave: bactérias láticas, antimicrobianos, proteólise, leite, queijo.

1. Introduction

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Lactic acid bacteria (LAB) are a phylogenetically diverse group of Gram-positive and non-sporulating bacteria that have in common the metabolism with production of lactic acid from glucose. They include different genera of the order Lactobacillales such as *Streptococcus*, *Lactococcus*, *Enterococcus*, *Pediococcus*, *Leuconostoc*, *Lactobacillus*, *Carnobacterium*, *Aerococcus*, *Tetragenococcus*, *Vagococcus*, *Oenococcus* and *Weissella* (PFEILER; KLAENHAMMER, 2007).

The LAB predominates in the natural microbiota of many food products (*e.g.*, milk, meat, vegetables, and cereals) and is of high economic importance to the food industry due to their use as starter and non-starter LAB (NSLAB) as well as in food preservation or protection against spoilage processes (STILES; HOLZAPFEL, 1997). Also, antagonistic activity of LAB is important for inhibition of foodborne pathogens (DE VUYST; LEROY, 2007). Autochthonous NSLAB are implicated in cheese ripening and generally consist of mesophilic lactobacilli, pediococci, enterococci and leuconostoc (CASEY et al., 2006). Their role in cheese production is not completely understood, in contrast to the well-known starter LAB. Nevertheless, it is known that NSLAB increase the level of free amino acids, peptides and free fatty acids, which contributes to flavor intensity and to the ripening of cheese. (DE ANGELIS et al., 2001).

Nowadays, researchers have different approaches to identify bacteria in food samples, such as the classical culture-dependent method (followed by phenotypic and/or genotypic identification), and also culture-independent methods (*e.g.* polymerase chain reaction with denaturing gradient gel electrophoresis, PCR-DGGE). Thereby, van Hoorde et al. (2008) evaluated the diversity of lactic acid bacteria in two Flemish artisanal Gouda-type cheeses by culture-dependent and the culture–independent method PCR-DGGE. When using culture-dependent methods, they detected *Lactobacillus paracasei*, *Lactobacillus plantarum*, *Lactobacillus brevis*, *Lactobacillus rhamnosus* and *Pediococcus pentosaceous*. However, when using PCR-DGGE, those authors found three species (*Enterococcus faecalis*, *Lactobacillus parabuchneri* and *Lactobacillus gallinarum*) that were not detected in culture-dependent methods. Despite culture-independent methods may result in more accuracy concerning the diversity of microbial population, culture-dependents methods are still very useful for the determination of a number of viable

microorganisms from different microbial groups and their isolation for further studies (ALEGRIA et al., 2012)

Dairy products are important sources of new LAB strains with technological properties. In 2010, Nespolo and Brandelli isolated LAB from sheep milk and cheese with proteolytic, lipolytic and antimicrobial activities. Among the isolates, *L. plantarum* and *L. rhamnosus* presented antimicrobial activity against both Gram-positive and Gram-negative bacteria. Similarly, in 2012, Yang et al. isolated 138 LAB strains from cheese and yogurts, and 20% presented antimicrobial activity against bacteria and fungi. Overall, LAB comprise an important group of microorganisms for the production and development of new food products.

1.1 Safety issues about lactic acid bacteria

From immemorial times, LAB are important for the production of fermented foods so they may be recognized as safe (CLEMENTI; AQUILANTI, 2011). However, the possibility of exchanging genes encoding antibiotic resistance has highlighted the importance of a correct safety evaluation when selecting strains for food application (DICKS; BOTES, 2010). There is also a concern whether these bacteria may transfer their resistance genes to the microbiota of the gastrointestinal tract, or even acquire virulence factors from pathogens (VAN REENEN; DICKS, 2011).

Rare cases of infections by LAB have been reported in patients receiving antibiotic treatment or severely immune compromised (VAN REENEN; DICKS, 2011). Recently, Franko et al. (2013) reported an infectious endocarditis and bacteremia by *L. paracasei* in a 77-year-old male consumer of probiotics, after being submitted to a colonoscopy. The patient was recovered after administration of amoxicillin and gentamicin. Moreover, according to those authors, probiotic may have contributed to this case and its use should be discontinued before digestive surgery and colonoscopy. In 2014, Sadowska-Krawczenko et al. reported that *Lactobacillus rhamnosus* GG caused infection in a newborn child. That infant had been treated empirically with antibiotics and the probiotic *L. rhamnosus* GG to avoid antibiotic-associated gastrointestinal complications. Those authors, however, stated that the use of probiotics should not be discouraged, but their use should be carefully evaluated. Similarly, cases of endocarditis have frequently been reported in elderly people where the causative agent was *Lactococcus garvieae*, a fish pathogen related

to different opportunistic infections in humans such as bacteremia, endocarditis, osteomyelitis, liver abscess and peritonitis (NAVAS; HALL; EL BEIJANI, 2013; ORTIZ et al., 2014; RASMUSSEN et al., 2014; WATANABE et al., 2011).

The safety issues for *Enterococcus* spp. remains controversial as isolates of this genus have emerged as opportunistic pathogens for humans (OGIER; SERROR, 2008). In addition, enterococci have been recognized as important hospital-acquired pathogens in recent years, and isolates of *Enterococcus faecium* and *E. faecalis* are the third- to fourth-most prevalent nosocomial pathogen worldwide (WERNER et al., 2013).

Antibiotic resistance is also a concern when selecting LAB for food applications. *L. plantarum*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactobacillus leishmannii*, *Lactobacillus acidophilus*, pediococci and *Leuconostoc* spp. carry intrinsic resistance to vancomycin but, usually, they are not resistance to other antibiotics of clinical interest, which encourage their use in food (BERNARDEAU et al., 2008; OGIER et al., 2008). Most of lactococci species are intrinsically resistant to metronidazole, trimethoprim, cefoxitin, gentamicin and kanamycin, but they are susceptible to antibiotics targeting Gram-positive bacteria, broad-spectrum antibiotics, and also to beta-lactams (DEVIRGILIIS; ZINNO; PEROZZI, 2013). Enterococci are intrinsically resistant to cephalosporins and low levels of aminoglycoside and clindamycin (MATHUR; SINGH, 2005). However, when located on mobile genetic elements (plasmids and transposons), antibiotic resistance traits may be transferred to commensal microbiota and pathogenic bacteria, which reinforce the need of a complete evaluation of safety aspects of LAB before its use for human or animal nutrition (KLARE et al., 2007). In this context, the most concerning LAB are the enterococci. In this genus, mobile elements or foreign DNA within a particular genome (chromosomes and plasmids) may account for 38 % and more than 25 % of the total genome of *E. faecium* and *E. faecalis*, respectively (WERNER et al., 2013). Also, enterococcal antibiotic resistance is well documented and there is evidence of infections by vancomycin resistant enterococci caused by strains acquired through the food chain (FISHER; PHILLIPS, 2009). According to Rubinstein and Keynan (2013), enterococcal infection can be caused by vancomycin-susceptible strains, mainly *E. faecalis*, and vancomycin-resistant strains, mainly *E. faecium*.

1.2 Main foodborne bacterial pathogens and spoilage microorganisms in dairy products

Foodborne pathogens represent a real problem for public health throughout the world (BAJPAI et al., 2008). In a recent review done by Gomes, Franco and De Martinis (2013), *Salmonella* spp., *Staphylococcus* spp., *Bacillus cereus*, *Clostridium perfringens*, *Shigella* spp. and *Clostridium botulinum* were presented as the most common foodborne pathogens reported in outbreaks in Brazil. However, according to those authors, for up to 50% of the registered outbreaks the etiological agent may remain undefined. In Europe, the main foodborne pathogens are *Salmonella* and *Campylobacter*, and their incidence may greatly vary according to the country and year (PIRES et al., 2010). Similarly, according to data from the Centers for Disease Control and Prevention (2011), the bacteria causing the most illnesses, hospitalizations, and deaths in the United States of America (USA) are *Campylobacter* spp., *C. perfringens*, *Escherichia coli* (STEC, Shiga toxin-producing *E. coli*) O157, *Listeria monocytogenes*, nonthyphoiddal *Salmonella* and *Staphylococcus aureus*. Among them, *L. monocytogenes* deserves special attention due to the high mortality associated with listeriosis (MILILLO et al., 2012).

L. monocytogenes, *Listeria marthii*, *Listeria innocua*, *Listeria welshimeri*, *Listeria seeligeri*, *Listeria ivanovii*, *Listeria fleischmannii*, *Listeria aquatica*, *Listeria floridensis*, *Listeria rocourtiae*, *Listeria weihenstephanensis*, *Listeria cornellensis*, *Listeria grandensis*, *Listeria riparia* and *Listeria grayi* compose the genus *Listeria*, but only *L. monocytogenes* and *L. grayi* have been generally considered as pathogens (DEN BAKKER et al., 2014; GASANOV; HUGHES; HANSBRO, 2005). *L. monocytogenes* is a nonspore-forming Gram-positive rod, facultative anaerobic, motile due to peritrichous flagella, and tolerates adverse environmental conditions such as low temperature, high concentration of sodium chloride and low pH (GANDHI; CHIKINDAS, 2007). *L. monocytogenes* can easily contaminate products such as pasteurized milk, soft cheeses, meat products, and ready-to-eat food that are stored at refrigeration temperatures and consumed without previous treatment (MARTINEZ; BRAVO; RODRIGUEZ, 2005). This bacterium is ubiquitous in the environment and it is well adapted to both lives in soil and into the cytosol of eukaryotic host cells (FREITAG; PORT; MINER, 2009). When infecting mammalian hosts, *L. monocytogenes* is able to cross the intestinal, feto-placental and blood brain

barriers and disseminate throughout the organism (COSSART; LEBRETON, 2014). Listeriosis is a relatively rare life-threatening disease (fatality rate of 20 - 30%) that mostly affects immunocompromised individuals, elderly, pregnant women and unborn or newly delivered infants (NEWELL et al., 2010). *Listeria monocytogenes* is one of the main pathogens of concern for the dairy industry, along with *S. aureus*, *E. coli*, and *Salmonella* spp. (GÁLVEZ et al., 2008).

Besides foodborne pathogens, the control of spoilage microorganisms in food is also important. In dairy products, *Pseudomonas* and *Bacillus* may contribute to food deterioration (FRANCO; LANDGRAF, 2005). *Pseudomonas* is a Gram-negative, aerobic, rod-shaped bacterium that grows rapidly in low temperatures and dominates the spoilage microbiota of proteinaceous foods such as milk, meat, poultry and fish, stored aerobically at refrigeration temperatures (MCMEEKIN; ROSS, 1996). In milk, *Pseudomonas* spp. have strong proteolytic and lipolytic activities (SØRHAUG; STEPANIAK, 1997). However, this microorganism usually contaminates pasteurized milk in post-process stages, and milk may also spoil due to psychotropic heat resistant spore of *Bacillus* (GRAM et al., 2002).

Some members of LAB may also be responsible for the spoilage of vacuum packaged refrigerated processed meats and some dairy products (HOLZAPFEL, 1992). In milk, *Lactobacillus* spp. and *Lactococcus lactis* may increase viscosity, and *Lactobacillus lactis* var. *maltigenes* may alter milk aroma (FRANCO; LANDGRAF, 2005).

Microbial contamination of food by fungi (*e.g. Aspergillus*, *Fusarium* and *Penicillium*) represents a real problem to food safety due to the production of mycotoxins, a toxic metabolite produced by certain fungi that may be carcinogenic, immunotoxic, teratogenic, neurotoxic, nephrotoxic and hepatotoxic (DALIÉ; DESCHAMPS; RICHARD-FORGET, 2010). In addition, yeasts may also contaminate food products and are recognized as the main factor for food spoilage. The foodborne yeasts *Candida*, *Debaryomyces*, *Kluyveromyces*, *Rhodotorula*, *Trichosporon* and *Yarrowia* are found quite frequent, and the contamination of food by these yeasts results in changes of food texture, colour and flavor (KUNICKA-STYCZYNSKA, 2011). Poor factory hygiene, lack of preservatives, inadequate pasteurizing temperatures and/or use of poor quality raw materials may contribute for the contamination of spoilage yeasts (GORETTI et al., 2009).

1.3 Potential of lactic acid bacteria for use in food biopreservation

The high demand for healthy food with extended shelf-life is a real challenge for food industry. Traditional strategies used to control microbial contamination in food includes drying, freeze-drying, cold storage, modified atmosphere storage and the additives acetic, lactic, propionic, sorbic and benzoic acids (SCHNÜRER; MAGNUSSON, 2005). LAB may help in biopreservation approaches alternatives or combined with physical and chemical methods to control pathogenic bacteria and spoilage microbiota, due to the production of antimicrobials (DALIÉ; DESCHAMPS; RICHARD-FORGET, 2010).

Microbial inhibition exerted by LAB is generally due to production of increased acidity, competition for substrates, production of antimicrobial compounds such as low-weight non-proteinaceous compounds (organic acids, H_2O_2, and others), bacteriocins and/or antifungal compounds (PARENTE; RICCIARDI, 1999).

1.3.1 Bacteriocins

Bacteriocins are antimicrobial peptides synthesized by bacteria via ribosomes and represent a defense strategy (OSCARIZ; PISABARRO, 2001). These compounds represent a potential alternative to chemical food preservatives because they are generally considered as safe, since they are destroyed by proteolytic enzymes in the gastrointestinal tract (ABRIOUEL et al., 2003; GUINANE et al., 2005). Moreover, many bacteriocins can be detected in fermented meat and dairy products as LAB represent a significant population of these food microbiota. This suggests that they have been consumed by humans for many years, reinforcing safety issues. For example, the antimicrobial peptide nisin (available for commercial use) is produced by certain *Lactococcus lactis* strains, and it is approved for use in food in more than 40 countries for *ca*. five decades (CLEVELAND et al., 2001). Formulations containing bacteriocins such as Nisaplin® (nisin) and ALTA® 2351 (pediocin PA-1) have been added to food to extend shelf-life and increase food safety (MILLS et al., 2011a)

Bacteriocins usually have a narrow spectrum of activity, and the bacteriocinogenic strains are immune to their own bacteriocins (CLEVELAND et al., 2001). The widely used classification system of Cotter, Hill and Ross (2005) divides bacteriocins into classes I, II and III, based on a previous system proposed by

Klaenhammer (1994). The class I bacteriocins (lantibiotics) are extensively post-translationally modified, with unusual amino acids such as lanthionine, methyllanthionine, dehydroalanine, and dehydrobutyrine. Many lantibiotics interfere with bacterial cell wall synthesis and promote pore formation (ROSS; VEDERAS, 2011). Class II comprises thermostable bacteriocins with molecular weight lower than 10 kDa and no modified amino acids. These bacteriocins usually act by permeabilizing the target cell membrane and this class is divided into four subgroups: (i) class IIa bacteriocins, such as pediocin, with the amino-acid sequence motif YGNGV and a disulfide bridge near the N-terminus; (ii) class IIb, that comprise two-peptides bacteriocins; (iii) class IIc bacteriocins with N- and C- termini covalently linked (circular bacteriocins); (iv) in the class IId are allocated the remaining bacteriocins that do not fit in the other subgroups. Finally, class III (bacteriolysins) comprises thermolabile proteins with molecular weights greater than 30 kDa that catalyze the hydrolysis of bacterial cell wall (COTTER; HILL; ROSS, 2005). Figure 1.1 illustrates the three mode of action of each bacteriocin group proposed by Cotter, Hill and Ross (2005).

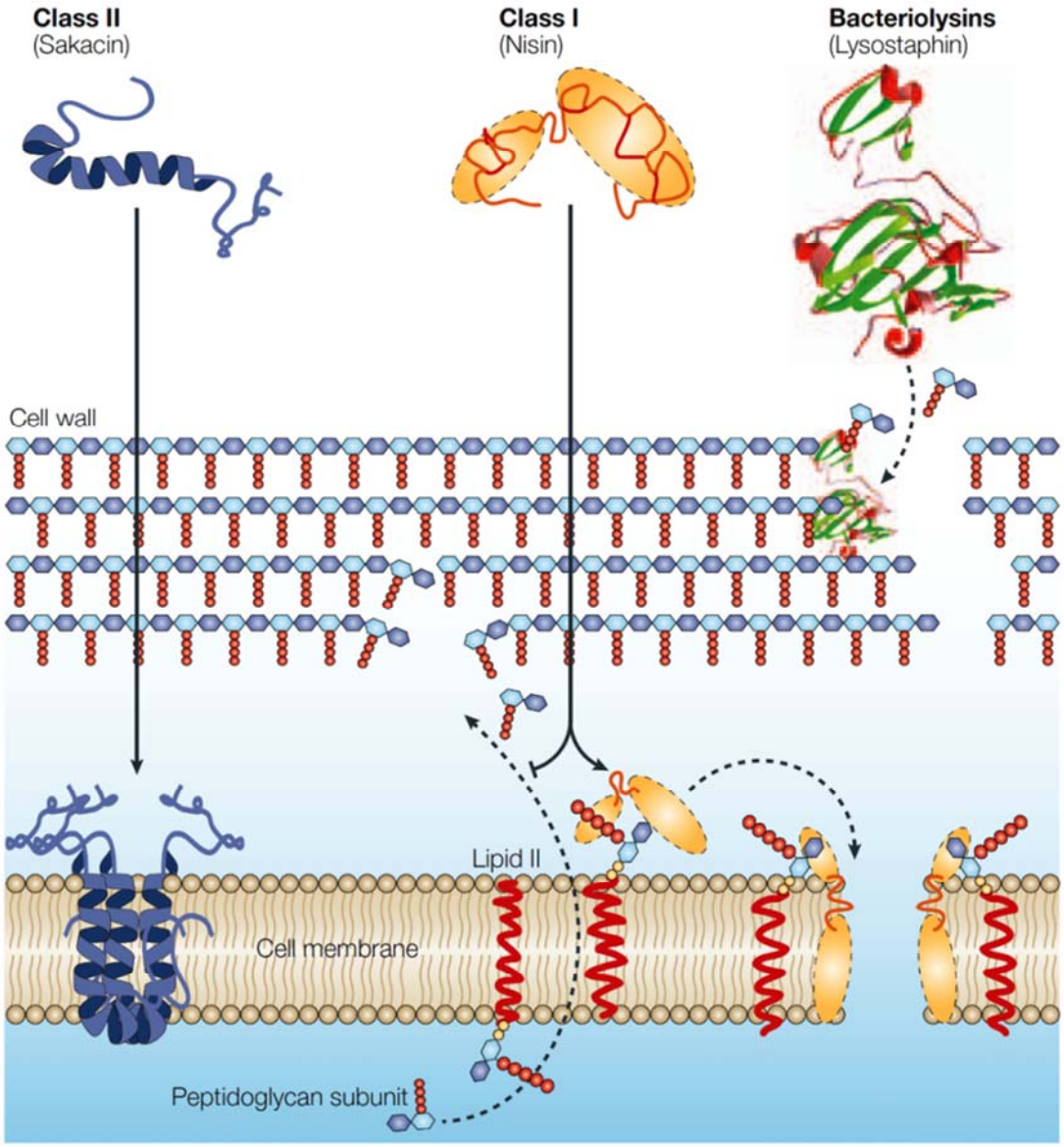

Figure 1.1 Mode of action of bacteriocins from classes I, II and III. In the class I (lantibiotics), the peptides can bind to lipid II (transporter of peptidoglycan subunits from the cytoplasm to the cell wall) and prevent the correct cell wall synthesis, leading to cell death. In addition, lantibiotics can use the lipid II as a tool to initiate the process of membrane insertion and pore formation, also leading to cell death. Bacteriocins allocated in class II have amphiphilic helical structures that allow them to insert into bacterial membrane and cause depolarization, which leads to cell death. In the third class, the bacteriolysins catalyze the hydrolysis of cell wall of Gram-positive bacteria, leading to bacterial lysis and death (COTTER; HILL; ROSS, 2005).

1.3.2 Phenyllactic acid

Phenyllactic acid may be produced by LAB and has broad antibacterial spectrum, antifungal action and it is not toxic to animal and human cells (CROWLEY; MAHONY; VAN SINDEREN, 2013).

Lavermicocca, Valerio and Visconti (2003) evaluated the effects of phenyllactic acid on the growth of 23 strains of *Aspergillus*, *Penicillium* and *Fusarium* isolated from bakery products. Those authors found that less than 7.5 mg/mL of phenyllactic acid was required to inhibit 90% of the growth of all strains, and less than 10 mg/mL was necessary for fungicidal activity in 19 strains. Ndagano et al. (2011) investigated the production of phenyllactic acid by LAB grown in MRS broth without acetate. Those authors detected 0.065 mg/mL (0.48 mM), 0.014 mg/mL (0.10 mM) and 0.018 mg/mL (0.13 mM) of phenyllactic acid, respectively, in the cell free supernatant of the LAB *L. plantarum* VE56, *Weissella cibaria* FMF4B13 and *Weisella paramesenteroides* LC11. Similarly, Cortés-Zavaleta et al. (2014) evaluated the production of phenyllactic acid by 13 lactobacilli with known antifungal activity. According to those authors, the production of phenyllactic acid by these lactobacilli ranged from 0.003 mg/mL (0.021 mM) to 0.037 mg/mL (0.275 mM). These concentrations of phenyllactic acid are lower than the minimal inhibitory concentration (MIC) reported by Lavermicocca et al. (2003), and antimicrobial activity detected suggests there is a synergistic effect with organic acids (CORTÉS-ZAVALETA et al., 2014; NDAGANO et al., 2011).

Mu et al. (2009) evaluated the production of phenyllactic acid by *Lactobacillus* sp. SK007 using batch and fed-batch fermentation. Those authors suggested phenylpyruvic acid is an important substrate to improve the phenyllactic acid production.

1.3.3 Reuterin and reutericyclin

Reuterin is a low-molecular-mass broad spectrum antimicrobial substance originally described in *Lactobacillus reuteri*. It is active against several microorganisms including Gram-positive and Gram-negative bacteria, yeasts and fungi (TOBAJAS et al., 2007). Arqués et al. (2004) evaluated the antimicrobial spectrum of reuterin (8 AU/mL) and observed activity against *L. monocytogenes*, *S.*

aureus, *E. coli* O157:H7, *Salmonella enterica* subsp. *enterica* serotype Typhi, *Yersinia enterocolitica*, *Aeromonas hydrophila* and *Campylobacter jejuni*. According to Schaefer et al. (2010), reuterin acts by inhibiting bacterial growth by modification of thiol groups, probably in a large number of cell targets.

The production of reuterin is influenced by the presence of glycerol and low concentrations of glucose during the anaerobic growth under pH and redox conditions similar to the small and large intestine (CLEUSIX et al., 2008; SCHNÜRER; MAGNUSSON, 2005).

Reuterin is water-soluble, active in a wide range of pH, and it is resistant to proteolytic and lipolytic enzymes, which indicates its potential use as biopreservative in food (ÁVILA et al., 2014). Despite the addition of reuterin in food is not legislated, the addition of glycerol plus *L. reuteri* to produce reuterin *in situ* is an alternative, as demonstrated by Langa et al. (2013). Those authors detected the production of reuterin in dairy products added of glycerol and reuterin-producing *L. reuteri*.

Some strains of *L. reuteri* also produce reutericyclin, a highly hydrophobic antimicrobial compound active against Gram-positive bacteria (GÄNZLE, 2004; REIS et al., 2012).

1.3.4 Antifungal peptides

There is evidence of production of antifungal peptides by lactic acid bacteria (DALIÉ; DESCHAMPS; RICHARD-FORGET, 2010). Rouse et al. (2008) described four LAB species (*L. plantarum*, *Weissella confusa*, *P. pentosaceous* and *W. cibaria*) with antifungal activity due to the production of antimicrobial peptides. Those authors also showed that the *P. pentosaceous* was effective to prevent the growth of *Penicillium expansum* in apple models.

The occurrence of antifungal cyclic peptides produced by LAB has been reported in the literature. In 2002, Ström et al. identified antifungal compounds produced by *L. plantarum* MiLAB 393 as phenyllactic acid and cyclic peptides. Similarly, Magnusson et al. (2003) investigated the nature of the antifungal activity of several LAB and isolated active compounds produced by *Lactobacillus coryniformis* Si3 (phenyllactic acid and the cyclic peptides cyclo Phe-Pro and cyclo Phe-4-OH-Pro).

Together, these findings indicate the potential use of lactic acid bacteria and their metabolites in food preservation strategies.

1.4 Proteolytic system of lactic acid bacteria

LAB are fastidious saccharolytic bacteria that require numerous essential growth factors. In milk, there is a low concentration of peptides and free amino acids, and LAB growth rate depends on proteinases and peptidases to hydrolyze milk proteins to support their growth (SOUSA; ARDO; MCSWEENEY, 2001). The LAB proteolytic system comprises three main components: (i) cell wall proteinases that initiate the degradation of casein into oligopeptides (ii) peptide transporters that carry peptides into the cell, (iii) peptidases that hydrolyze intracellular peptides into smaller peptides or amino acids, which can be converted into various flavor compounds such as aldehydes, alcohols and esters (LIU et al., 2010; SAVIJOKI; INGMER; VARMANEN, 2006).

Milk provides all the essential amino acids for protein metabolism, and milk proteins are considered one of the highest quality proteins in human diet (KANWAR et al., 2009). Bovine milk is basically composed by caseins and whey proteins, which include immunoglobulins, α-lactalbumin, β-lactoglobulin, bovine serum albumin and lactoferrin (MILLS et al., 2011b). Native caseins, β-lactoglobulin and α-lactalbumin present in milk may have different biological activities such as ion carrier, retinol carrier, antioxidant, Ca^{2+} carrier, immunomodulatory and anticarcinogenic (KORHONEN; PIHLANTO, 2007). Moreover, these proteins may release bioactive peptides after hydrolysis by the action of LAB, with different activities such as antihypertensive, antioxidant, antimicrobial, immunomodulatory and mineral binding activities (BENKERROUM, 2010; DZIUBA; DZIUBA, 2014; PEPE et al., 2013; RICCI; ARTACHO; OLALLA, 2010).

On the other hand, consumption of milk protein (*e.g.*, α-lactalbumin and β-lactoglobulin) may represent a hazard for some individuals because of allergenicity. Cow milk allergy (CMA) especially affects children under 3 years of age and can reach 7% of incidence within this consumer group (CEBALLOS et al., 2009). In that context, fermented milk by LAB may help to reduce allergenicity. In 2010, Bu et al. demonstrated that fermentation of skim milk with *Lactobacillus helveticus* and *Streptococcus thermophilus* reduced allergenic potential of α-lactalbumin and β-

lactoglobulin. Similarly, in 2012, Ahmadova et al. demonstrated that proteolytic activity of *L. helveticus* A75 reduced the IgE binding ability of α_{S1}- and β-caseins. Thus, bacterial fermentation may be an alternative to reduce antigenic and/or allergenic properties of milk proteins due to the production of proteolytic enzymes by these organisms, specially the lactic acid bacteria (EL-GHAISH et al., 2011).

The association of the high nutritional value of milk with the effect of bacteria that positively modify milk proteins could result in new dairy products with benefits for human health and nutrition.

1.5 Lactic acid bacteria as probiotics

In early 20th century, Eli Metchnikoff observed the long life of Bulgarian and Eastern Europe peasants that had the habit of consuming fermented dairy products (AZIZPOUR et al., 2009). He isolated *Lactobacillus bulgaricus* (formerly *Bacillus bulgaricus*) from those fermented dairy products and postulated this microorganism was linked to health benefits (VIEIRA; TEIXEIRA; MARTINS, 2013). Eli Metchnikoff also hypothesized colonic bacteria produce toxic compounds involved in aging process. According to him, consumption of fermented milk would coat the colon with LAB, decreasing the intestinal pH and the number of 'putrefactive' bacteria in the gut (VERNA; LUCAK, 2010). Nowadays, the most commonly used probiotic strains belong to the *Bifidobacterium* and *Lactobacillus* genera (ROKKA; RANTAMAKI, 2010).

World Health Organization (WHO) and the Food and Agriculture Organization (FAO) define probiotic as "live microorganisms that when administered in adequate amounts confer health benefits to the host" (FOOD AND AGRICULTURE ORGANIZATION; WORLD HEALTH ORGANIZATION, 2002).

Probiotics may interfere with gut microbiota and re-establish it after antibiotic therapy, improve gut resistance to the colonization by pathogenic bacteria, produce antimicrobial substances into the intestinal lumen, increase of lactose digestion in lactose intolerant individuals, vitamins production, immune system stimulation and they may also alleviate symptoms of intestinal inflammatory diseases (SAAD et al., 2013; WALSH et al., 2014). Other potential probiotic effects may be related to decreased risk of intestinal disorders and reduction of serum cholesterol levels (PAVLOVIC; STANKOV; MIKOV, 2012).

Some authors have studied the role of probiotic in the modulation of immune system. Peng, Lin and Lin (2007) evaluated the effect of probiotic intake in rats for a period of 6 months, and showed that there was a decrease of the levels of specific anti-ovalbumin immunoglobulin E (IgE). These data indicates that probiotics may be beneficial in the treatment of food allergy, which is mainly mediated by IgE and leads to immediate type hypersensitivity or type I reaction (KUMAR et al., 2012). In addition, Pochard et al. (2002) evaluated the effect of probiotic on Th2 cytokine production in peripheral blood mononucleated cell (PBMC) of allergic patients. Those authors observed that probiotics reduced the production of interleukin-4 (IL-4) and interleukin-5 (IL-5) in PBMC only when the cells were stimulated with the specific allergen. Th2 cells have a key role in the immunity to extracellular parasites and all forms of allergic inflammatory responses, regulating B cell class switch to IgE by the production of IL-4 (PAUL; ZHU, 2010). Also, some probiotic strains may increase interleukin-12 (IL-12) production in dendritic cells and macrophages, converting a Th2 response into a Th1-dominated response in mice (KAWASHIMA et al., 2011). Thus, the Th1 cells produce interferon gama (IFN-γ) that suppresses antigen-specific IgE production in B cells (FUJIWARA et al., 2004). These data showed the potential of probiotic bacteria on modulating immune system, especially in allergic diseases. Otherwise, certain probiotic strains may increase the production of interleukin-10 (IL-10), an anti-inflammatory cytokine that downregulates the expression of Th1 pro-inflammatory cytokines (*e.g.* INF-γ), and decrease the production of the pro-inflammatory cytokines TNF and IL-8 (BAI et al., 2006; FERNANDEZ et al., 2011). INF-γ seems to play a key role in the pathogenesis of inflammatory bowel disease and other gastrointestinal disorders, thereby specific probiotics strains could be an additional strategy to alleviate symptoms in such conditions (CHIBA et al., 2006; REIFF; KELLY, 2010).

Probiotics may also contribute to protect against infectious agents, especially enteropathogens. Castillo et al. (2013) compared the ability of probiotic and non-probiotic lactobacilli strains to protect against *Salmonella enterica* serovar Typhimurium infection using a mouse model. Those authors reported that only the probiotic strain was able to protect against the pathogen by increasing intestinal barrier function and decreasing local inflammatory response. The intestinal barrier is a dense mucous layer containing secretory IgA cells, antimicrobial peptides and

dynamic junctional complexes that regulate the permeability between cells (OHLAND; MACNAUGHTON, 2010). Thus, probiotics may increase IgA secretion in these sites leading to an increased intestinal barrier function (PARVEZ et al., 2006).

An equilibrated gut flora also contributes to prevent the overgrowth of pathogens by the production of volatile fatty acids and decrease in pH of the luminal contents (SURAWICZ, 2003). However, antibiotic therapy can disrupt intestinal microbial imbalance and results in a variety of undesirable side effects, such as antibiotic-associated diarrhea (AAD), which occurs in as many as 30 % of patients (HEMPEL et al., 2012; KATZ, 2010). The mechanisms of AAD include disruption of the gut flora, effects of altered bacterial breakdown of carbohydrates and increased gastrointestinal effects of certain antibiotics (CREMONINI; VIDELOCK, 2013). In some patients, the pathogen *Clostridum difficile* grows to large numbers and produces toxins that cause colonic damage (SURAWICZ, 2003). Probiotics can positively contribute to prevent and alleviate symptoms of AAD, and treatment with *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* seemed to have the most significant efficacy (KATZ, 2010). There are several possible mechanisms by which probiotics may exert beneficial effects on AAD, including the synthesis of antimicrobial substances, competition for nutrients required for the growth of pathogens, competitive inhibition of adhesion of pathogens, and modification of toxins or toxin receptors (SONG et al. 2010).

It is important for strains used as probiotics to be able to adhere to epithelial cells, reduce adhesion of pathogenic bacteria on gut wall, tolerate gastrointestinal tract (GIT) conditions, production of antimicrobial substances, to be safe, noninvasive, noncarcinogenic and nonpathogenic, and to contribute on achieving a balanced intestinal microbiota (FOOD AND AGRICULTURE ORGANIZATION; WORLD HEALTH ORGANIZATION, 2002). In addition, the incorporation of probiotics in foods requires technological processes to maintain microbial viability under diverse conditions of acidity, oxygen level, presence of naturally or artificially added antimicrobial substances and nutrient availability (FORTIN et al., 2011; MINERVINI et al., 2012). One of the strategies to increase probiotic viability in food is the microencapsulation, where the bacterial cells are incorporated into a matrix to form microparticles. This approach not only protects the cells against harsh conditions in food, but also provides an additional resistance to adverse conditions in the GIT, leading to a site-specific release of probiotic cells in the intestine (BURGAIN et al.,

2011). It is also recommended to monitor probiotic functionality throughout all stages of production, storage and consumption of food products (VINDEROLA et al., 2011).

Overall, this literature review indicates there is an increasing demand for safe and high quality food, low in chemical preservatives and with health promoting properties. In this context, LAB are very attractive to improve food quality, safety and sensorial characteristics. LAB are part of the autochthonous microbiota of dairy products, and these represent good sources for the isolation of new strains of technological interest. Moreover, cheese and milk from different animals (*e.g.* cow, buffalo and goat) have a very diverse microbiota. The production of bacteriocins and other antimicrobial compounds by new isolates are of great interest, as these microorganisms (or their metabolites) may be applied in food biopreservation. There is also a current concern with regard to food allergenicity and cow milk allergy, which affects especially children under 3 years of age. Some LAB strains are able to hydrolyze milk proteins into small peptides and this may reduce allergenic potential of milk proteins, and also generate different bioactive peptides with health promoting properties. Moreover, data from literature indicate that LAB strains may present probiotic potential to benefit the health of consumers. Thus, it is important to search for new LAB isolates with potential to increase food safety and sensorial characteristics, and also to be used in the development of new products that can contribute to improve health and life quality.

7. Closing remarks

- In this study, 156 samples of cow, buffalo and goat milk were analyzed to isolate LAB with antimicrobial or proteolytic activity. The isolates with interesting properties were identified by *16S rRNA* gene sequencing.

- Four LAB produced bacteriocins, and they were identified as *Streptococcus uberis* FT86 (isolated from cow milk), *S. uberis* FT126 (isolated from cow milk), *S. uberis* FT190 (isolated from cow milk) and *Lactobacillus paraplantarum* FT259 (isolated from cow cheese).

- *L. paraplantarum* FT259 presents the gene for the production of plantaricin NC8, and SDS-PAGE showed the antimicrobial peptide produced by this strain has *ca*. 3,900 Da, similar to one of the units of plantaricin NC8, previously described in the literature. So, it is very likely *L. paraplantarum* FT259 produces the plantaricin NC8.

- In addition, *L. paraplantarum* FT259 presented probiotic potential, since it survived at in acidic pH and in the presence of bile salts, which shows that this strain has high potential to be used in food products.

- Two strains (*Weissella confusa* FT424 and *Lactobacillus plantarum* FT723) presented antifungal activity toward *Penicillium expansum*. Moreover, *L. plantarum* FT723 inhibited *P. expansum* in a fermented milk model, indicating the potential of this strain for preservation of dairy products.

- *Enterococcus faecalis* FT132 and *Lactobacillus paracasei* FT700 were proteolytic in milk with the best activity at pH 6.5 and in the range of 37 to 42 °C.

- Fermented milk supernatant produced by *E. faecalis* FT132 and *L. paracasei* FT700 stimulated the differentiation of monocytes into macrophages with low production of TNF-α (no inflammatory process). This suggests that beneficial immune response could be stimulated by the hydrolyzed milk proteins, which could be obtained by the production of fermented dairy products.

- *E. faecalis* FT132 harbored the virulence genes *asa*1, *ace* and *gel*E, it was resistant to erythromycin and tetracycline, discouraging its application in food. However, the

purified peptides derived from milk protein hydrolysis by this LAB may be further evaluated for food applications.

- *L. paracasei* FT700 presented probiotic potential due to survival at pH 2.0 and tolerance to bile salts. This is strain was not resistant to any of the antibiotics tested, except for those of intrinsic resistance (vancomycin and ciprofloxacin). *L. paracasei* has the potential to be used to produce a fermented drink with probiotic benefits and immune system stimulatory properties.

- In summary, it was isolated several LAB from milk and cheese samples that could be candidates for production of bioactive compounds and development of new dairy products with increased shelf-life and health promoting claims.

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