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MINI-REVIEW

Conditions of nisin production by *Lactococcus lactis* subsp. *lactis* and its main uses as a food preservative

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Abstract

Nisin is a small peptide produced by *Lactococcus lactis* ssp *lactis* that is currently industrially produced. This preservative is often used for growth prevention of pathogenic bacteria contaminating the food products. However, the use of nisin as a food preservative is limited by its low production during fermentation. This low production is mainly attributed to the multitude of parameters influencing the fermentation progress such as bacterial cells activity, growth medium composition (namely carbon and nitrogen sources), pH, ionic strength, temperature, and aeration. This review article focuses on the main parameters that affect nisin production by *Lactococcus lactis* bacteria. Moreover, nisin applications as a food preservative and the main strategies generally used are also discussed.

Keywords Nisin · Lactic acid bacteria (LAB) · *Lactococcus lactis* · Fermentation · Production yields · Food preservation

Introduction

Lactic acid bacteria (LAB) are Gram-positive, non-spore forming, and catalase-lacking bacteria with cocci or rods morphology. LAB produce lactic acid as a main end product during carbohydrates fermentation. They grow only in complex environments, where fermentable carbohydrates and polyols are used as an energy source. Homofermentative LAB degrade hexoses to lactate, whereas heterofermentative ones degrade hexoses to lactate and other products such as CO_2, acetate, formate, succinate or ethanol (Mattarelli et al. 2014).

LAB are widely used as starter-cultures in the food industry to produce fermented foods, including dairy products (yogurt, cheese), meat (sausage), grains (bread and drinks such as beer), fruits (malolactic fermentation in wine) and vegetables (sauerkraut, kimchi, silage). Most LAB are generally recognized as safe (GRAS) (George et al. 2018). Moreover, LAB are used to develop new sensory properties, improve the nutritional quality of foods, but also to preserve and ensure food safety. In fact, LAB have a strong antimicrobial activity against many related and unrelated microorganisms, including food spoiling microorganisms and pathogenic bacterial strains such those belonging to *Listeria*, *Staphylococcus*, *Clostridium*, and *Bacillus* spp. The antimicrobial effect of LAB is mainly due to the food pH lowering, competition for nutrients, and production of inhibitory metabolites (Wedajo 2015; Srivastava 2018; Bintsis 2018; Kaczmarek et al. 2019).

Bacteriocins are protein molecules with a broad activity spectrum but mainly against species phylogenetically close to the producing strain. Among the bacteriocin producing bacteria, strains belonging to the genera of *Lactococcus*, *Lactobacillus*, *Pediococcus*, *Leuconostoc* and *Enterococcus* are the most studied (Table 1). *Lactococcus lactis* subsp *lactis* produces nisin and lacticin 3147, two of the most extensively characterized lantibiotics (Table 1). Nisin is a one peptide antimicrobial composed of 34 amino acids. Lacticin 3147 is a two-peptide lantibiotic consisting of both LtnA1 and LtnA2, composed of 30 and 29 amino acids, respectively (Piper et al. 2009). Nisin has a wide spectrum of activity against gram-positive bacteria, such as *Staphylococcus aureus*, *Listeria monocytogenes* and *Clostridium* species (Vukomanović et al. 2017). Indeed, lacticin 3147 has shown

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Table 1 Some well-characterized bacteriocins produced by LAB. Adapted from Parada et al. (2007)

Bacteriocin	Producing species	Spectrum of activity	Properties
Nisin	*Lactococcus lactis* ssp. *lactis*	Gram-positive bacteria	Lantibiotic, 3.5 kDa, 34 amino acids
Lacticin 3147	*Lactococcus lactis* ssp. *lactis*	*Clostridium* *Listeria monocytogenes* *Staphylococcus aureus*	Lantibiotic, 4.2 kDa, heat stable, active under acidic and physiological pH
Lactococcin B	*Lactococcus lactis* ssp. *cremoris*	*Lactobacillus*	Approx. 5 kDa, narrow spectrum of action
Lactacin F	*Lactobacillus acidophilus*	*Lactobacillus fermentum* *Enterococcus faecalis* *Lactobacillus delbrueckii* *Lactobacillus helveticus*	6.3 kDa, 57 amino acids, heat stable at 121 °C for 15 min
Lactacin B	*Lactobacillus acidophilus*	*Lactobacillus delbrueckii* *Lactobacillus helveticus* *Lactobacillus.bulgaricus* *Lactococcus lactis*	6.3 kDa, heat stable, detected only in cultures maintained between pH 5 and 6
Lactocin 705	*Lactobacillus casei*	*Listeria monocytogenes* *Lactobacillus plantarum*	Class-II two-component bacteriocin (33 amino acids component each), 3.4 kDa
Mesentericin Y 105	*Leuconostoc mesenteroides*	*Enterococcus faecalis* *Listeria monocytogenes*	3.8 kDa, 37 amino acids, heat stable (60 °C for 120 min at pH 4.5)
Pediocin F	*Pediococcus acidilactici*	Gram-positive bacteria	4.5 kDa, sensitive to proteolytic enzymes, resistant to heat and organic solvents, active under a wide range of pH
Pediocin A	*Pediococcus pentosaceous*	*Lactobacillus* *Lactococcus* *Leuconostoc* *Staphylococcus* *Enterococcus* *Listeria* *Clostridium*	2.7 kDa, sensitive to proteolytic enzymes and heat stable (10 min 100 °C)
Enterocin A	*Enterococcus faecium*	*Listeria monocytogenes* *Pediococcus*	4.8 kDa, 47 amino acids, heat stable
Lactocin S	*Lactobacillus sake*	*Lactobacillus* *Leuconostoc* *Pediococcus*	3.7 kDa, active between pH 4.5 and 7.5
Sakacin P	*Lactobacillus sake*	*Listeria monocytogenes*	4.4 kDa, heat stable
Helveticin J	*Lactobacillus helveticus*	*Lactobacillus bulgaricus* *Lactococcus lactis*	37 kDa, sensitive to proteolytic enzymes, reduction of activity after 100 °C for 30 min

an inhibitory activity against *Listeria monocytogenes, Bacillus cereus*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis*, penicillin-resistant *Pneumococcus*, *Propionibacterium acnes* and *Streptococcus mutans* (Ryan et al. 1996; Galvin et al. 1999). Unlike nisin which is poorly soluble, and thus less active, at pH 7, lacticin 3147 demonstrated greater potential as a therapeutic agent regarding its high activity at physiological pH 7 (Galvin et al. 1999; Cotter et al. 2005).

Bacteriocin producing bacteria are often used for all their above mentioned classic properties together, became the last few decades to be used for the production of bacteriocins. To achieve this goal, several basic and applied studies have helped to identify, categorize and better understand the biosynthesis mechanisms of these macromolecules. Bacteriocins are peptides produced by LAB to defend themself and are a part of innate immunity possessed by certain bacterial species. The main differences between bacteriocins and antibiotics are that antibiotics are not ribosomally synthesized, their mode of action is quite different, their antimicrobial spectrum is very diverse, and their applications are rather clinical than for food preservation (Cleveland et al. 2001; Cotter et al. 2013). However, bacteriocins are extracellular proteins synthesized by ribosomal pathways and having a bactericidal activity directed mainly against Gram-positive bacteria and the productive strain has specific protective mechanisms against their own bacteriocins (Cotter et al. 2013).

Nisin is the only bacteriocin which is used in currently permitted food products. This peptide was added to the list of food additives under the European number E234. In the present review, we give some properties and uses of nisin and we focus particularly on the main factors influencing the synthesis of nisin by lactic acid bacteria strains grown in controlled reactors.

Nisin production by *Lactococcus lactis* ssp. *lactis*

Nisin is an antimicrobial peptide of 34 amino acids produced by some strains of *Lactococcus lactis* ssp. *lactis*, which was discovered as a result of difficulties in delayed acidification experienced during cheese making by Rogers & Whittier (1928). A few years later the unidentified substance was found to be proteinaceous (Whitehead 1933), and in 1947 (Mattick and Hirsch 1947) it was called "NISIN" (group *N Streptococcus I*nhibitory *S*ubstance, *-IN* ending indicating an antibiotic). Nisin contains four unusual amino acids: dehydroalanine (DHA), dehydrobutyrine (DHB), lanthionine, and β-methyllanthionine that form thioether bridges in five positions (Fig. 1).

Lactococcus lactis is a Gram-positive, non-motile, and non-sporulating bacterium, measuring ordinarily between 0.5 and 1.5 µm. Cells of this bacterium are usually grouped in pairs or short chains. *L. lactis* metabolism is heterotrophic and facultative anaerobic (Song et al. 2017). Its optimum growth temperature is around 30 °C (Chen et al. 2015). *L. lactis* is classified into two major species: *L. lactis* ssp. *lactis* and *L. lactis* ssp. *cremoris*. Among the two subspecies, strains of *L. lactis* ssp. *lactis* are known for their better resistance to environmental changes such as pH and temperature. For example, *L. lactis* ssp. *lactis* can grow at 40 °C, pH 9.2 and even at a NaCl concentration up to 4%, whereas *L. lactis* ssp. *cremoris* cannot withstand any of these extreme conditions (Kim et al. 1999). In this same study, the authors showed that upon the *L. lactis* ssp. *lactis* medium acidification, the sub-lethal level is reached at pH 4.5, while the lethal level is reached at pH 2.5. Other specific properties of *L. lactis* ssp. *lactis* are summarized in Table 2. *L. lactis* ssp. *lactis* is very important commercially because of its wide use in the preparation of fermented dairy products. The main role of this bacterium during fermentation is acidification mainly through lactic acid production. It can also contribute to food texture modification by the production of exopolysaccharides and aroma improvement by the production of alcohols, ketones and aldehydes. *L. lactis* ssp. *lactis* can also be used for food preservation because of its ability to produce organic acids, hydrogen peroxide, diacetyl, as well as bacteriocins.

Pure nisin or nisin preparations can be obtained by culturing nisin-producing strains of *L. lactis* ssp. *lactis* followed

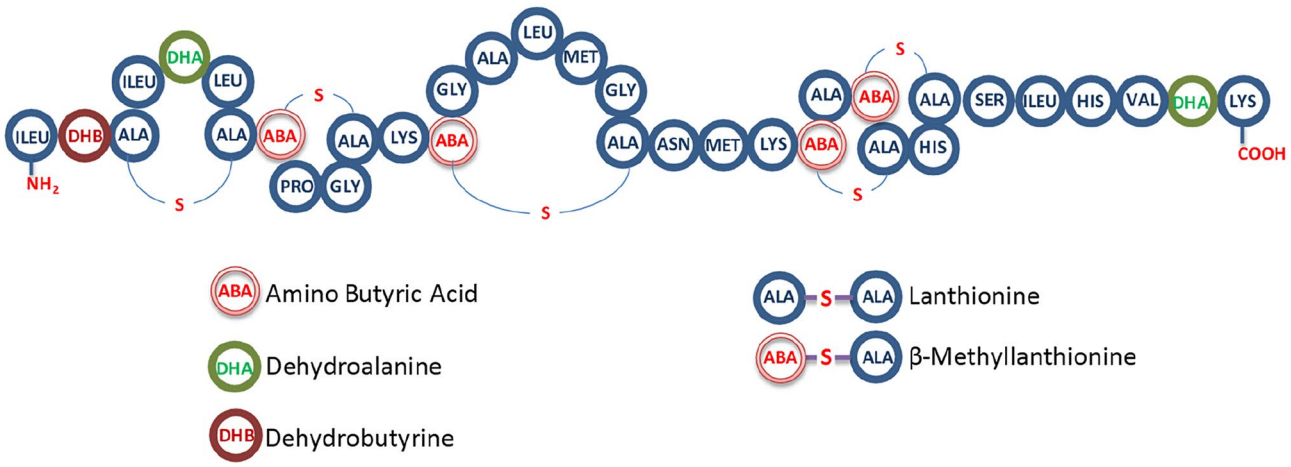

Fig. 1 Primary structure of nisin

Table 2 Main properties of *Lactococcus lactis* ssp. *lactis* bacteria

General properties	Non-pathogenic and GRAS (Generally Recognized As Safe) Gram-positive bacteria Spherical shaped (cocci), non-spore forming, and nonmotile
Main food uses	Starter in fermentation of dairy products
Optimum growth temperature	~30 °C (mesophilic)
Metabolism	Facultative anaerobic Homolactic fermentation under anaerobic conditions Heterolactic fermentation under aerobic conditions Production of L^+ lactic acid
Denomination	Current: *Lactococcus lactis* ssp. *lactis* Former: *Streptococcus lactis*

by suitable extraction and purification methods. The study of 40 wild-type strains of *L. lactis* showed that 35 were capable of producing nisin (Hurst 1981). Several types of nisin have been identified. The main variants are called A, Z, and Q and possess different biological activities. Nisin A and Z are the most active forms that are often marketed. Nisin Z is produced by some subspecies such as *L. lactis* ssp. *lactis* biovar. *diacetylactis* and differs from nisin A by a single amino acid at position 27. Although the nisin A and Z have the same antimicrobial properties, nisin Z has better solubility at pH > 6 which is important for food applications (Angela Faustino Jozala 2015).

For a long time, it was believed that nisin is synthesized during the stationary phase when nutrients are exhausted (Hurst 1981). However, it has been reported that in batch fermentation, the nisin production follows a primary metabolite kinetic (Guerra et al. 2007): a production during the exponential growth phase and a full stop when the bacteria enter the stationary phase (De Vuyst and Vandamme 1992). It was observed that nisin was detected in the growth medium during the exponential phase and its production rate peaked at the end of this phase which confirms that the synthesis of this peptide follows a primary metabolite kinetic (Chinachoti et al. 1998; Zhu 2017).

Although nisin synthesis occurs during the growth phase of cultured cells, the relationship between cell number and the amount of nisin produced is not linear in both batch and continuous modes (Abbasiliasi et al. 2017). This phenomenon can be explained by the complexity of the mechanism of nisin biosynthesis and its genetic regulation process. Genetically, a few remarks on the nisin biosynthesis stimulation deserve to be mentioned. Indeed, nisin is a molecule that self-regulates its own production (Hols et al. 2019). In cases of nisin A producing strains, two inducible promoters are located before genes nisA and nisF and a third before nisR gene (Kuipers et al. 1995). However, strains that produce nisin Z have two operons (nisZBTCIPRK and nisFEG) that are also nisin inducible (Qiao et al. 1996). In addition to these mechanisms based on genetic signal transduction, other studies have shown that the carbon source may also have a role in regulating nisin synthesis (Cheigh and Pyun 2005; Müller-Auffermann et al. 2015). During fermentation, the decreased production of nisin, even before the end of the exponential phase can also be attributed to its adsorption on the surface of producing cells: nisin is produced but remains adsorbed to cell surfaces (Parente and Ricciardi 1999). This adsorption becomes lower when pH decreases, which results in maintaining higher nisin concentrations in the reactor when the pH is not controlled (De Vuyst and Vandamme 1992). On the other hand, it was demonstrated that nisin production can be inhibited by high nisin concentrations when cells are cultured in a medium containing an excess of nutrients. This inhibition occurs even if the bacterial growth continues thanks to this excess of nutrients. However, it was also clearly observed that if the medium is deficient in nutrients, the production of nisin is limited by this nutrient depletion (Todorov and Dicks 2004).

A decrease in the amount of produced nisin can also be explained by the acidification due to lactate production. This acidification inhibits bacterial growth and consequently the synthesis of nisin. To avoid the inhibition related to acidification, several studies that have tried to remove lactate from the medium were published. Among the proposed strategies, we can mention fermentation in a mixed-culture system with another microorganism (Bouksaim et al. 2000), continuous separation of lactic acid-producing bacteria using a ceramic microfiltration membrane (Persson et al. 2001), using an anion exchange resin (Yu et al. 2002), changes in metabolic pathways of lactic acid synthesis (Wardani et al. 2006a; Hugenholtz 2008) or also the application of a magnetic field during fermentation for diverting the metabolism towards nisin synthesis (Alvarez et al. 2006).

Factors affecting nisin production by *Lactococcus lactis* ssp. *lactis*

Industrial nisin production

Nisin production by *Lactococcus lactis* demands optimized growth conditions. The complexity of the nisin purification step makes its industrial production a costly procedure. In addition, regarding the poor stability of nisin, the commercial nisin preparations contain only 2.5 wt% pure nisin, stabilized with denatured milk proteins and NaCl. The International Unit (IU) is defined as the amount of nisin dissolved in 1 mL of broth allowing the inhibition of one single *Streptococcus agalactiae* cell (Gharsallaoui et al. 2016). Cleveland et al. (2002) tested several commercial preparations standardized with salt and milk proteins. Results mainly demonstrated that the presence of insoluble substances influences the quantification and the activity of nisin. The authors considered that the low antimicrobial activity of commercial preparations may be due to nisin adsorption to milk proteins resulting in a decrease in its apparent activity.

Several industrial media were used to improve cell growth, neutralize the produced lactic acid, and increase nisin production. However, the multitude of parameters to control makes the nisin production conditions today far from being optimized. Papagianni et al. (2007) suggested that the optimum conditions that allow high production seem to be different from those that permit cell growth. Other authors such as Guerra et al. (2007) have even tried to use pseudo-mechanistic models to simulate the growth of *L. lactis* and its nisin production as a function of several experimental parameters. Development of such models can be seen as a

necessary step towards controlling the nisin production at industrial scale.

The effect of carbon and nitrogen sources, minerals intake, pH, and various other parameters has been extensively studied. However, these studies were often criticized because they do not differentiate between factors that influence the nisin production and those that influence the growth of producing bacteria (Chandrapati and O'Sullivan 1998). The difficulty of this operation is also due to the lack of precision and the diversity of nisin quantification strategies used during all growth stages of *L. lactis*. In fact, the first nisin quantification method based on diffusion in a semi-solid matrix was developed by Mocquot and Lefebre (1956) and was subsequently improved by Tramer and Fowler (1964). However, Chandrapati and O'Sullivan (1998) have proposed a rapid method for nisin quantification during the growth of *L. lactis* based on the diameter of inhibition of a *Micrococcus luteus* strain. Other rapid methods based on nisin specific antibodies and specific microtitrer based bioassays have also been developed (Daoudi et al. 2001; Immonen and Karp 2007).

In the following sections, the effect of the main experimental parameters on nisin biosynthesis by *L. lactis* ssp. *lactis* will be summarized and Table 3 gives some examples of nisin produced amounts obtained during the last two decades.

Nisin producing strains

Several strains of *L. lactis* are able to produce nisin but not with the same yield (Alegria et al. 2010). The performance difference between these strains was attributed to gene expression intensity, the activity of enzymes that provide post-translational maturation, and resistance of the producing strain to nisin. Regarding this last factor, the introduction of a plasmid containing nisin resistance genes has improved nisin production and growth rate of *L. lactis* (López-González et al. 2018; Dzhavakhiya et al. 2018). In fact, the surface properties of the producing strains are different (Giaouris et al. 2009) and may influence the adsorption of nisin to the cell surface during production. The surface hydrophobicity should thus be a criterion for strains producing bacteriocin selection. Aiming to improve the nisin production, research is also currently active in the screening of new strains able to produce high amounts of this bacteriocin. These attempts include the encouraging results obtained by cultivation of the strain *L. lactis* UQ2 isolated from a Mexican cheese (García-Almendárez et al. 2008). Later, the same research team developed a medium based on whey powder for the culture of this strain. Using this optimized medium, they achieved a maximum nisin activity of 575 IU/mL (Gonzalez-Toledo et al. 2010). In addition to strain screening, nisin production by *Lactococcus* could be

Table 3 Examples of nisin production by *Lactococcus lactis* ssp. *Lactis*

Strain	Specific experimental conditions	Yield (IU mL^{-1})	References
NIZO 22186	Batch fermentation; 10 g sucrose L^{-1}	1200	De Vuyst and Vandamme (1992)
NIZO 22186	pH 6.8; 50 g L^{-1} K_2HPO_4	3500	De Vuyst and Vandamme (1993)
IO-1	30 °C, pH 5.0–5.5; Stimulation by 0.1 M $CaCl_2$	3150	Matsusaki et al. (1996)
IO-1	Aeration: 320 rpm	3940	Chinachoti et al. (1998)
	Aeration: 1 000 rpm	3410	
IO-1	10 g glucose L-1, 12 h, 30 °C	737	Chinachoti et al. (1998)
	10 g xylose L-1, 18 h, 30 °C	810	
ATCC 11454	M17 media with glucose	975 (IU nisin/10^6 CFU)	Chandrapati and O'Sullivan (1998)
ATCC 11454	Fed-batch culture; Sucrose slow feeding	3887	Lv et al. (2004)
	Fed-batch culture; Nitrogen source slow feeding	4131	
ATCC 11454	Batch culture, 30 g sucrose L^{-1}	2658	Lv et al. (2005)
	Fed-batch (2 g sucrose L^{-1})	4961	
ATCC 11454	Batch culture, 30 °C, pH 6.0; aeration (1 L min^{-1}); 20 h	8000	Wardani et al. (2006a)
ATCC 11454	Batch culture, 25 g glucose L^{-1}	3122	Papagianni et al. (2007)
	Fed-batch, 10 g glucose L^{-1}	6100	
ATCC 11454	Milk whey; 2nd transfer; 30 °C/36 h/ 100 rpm	444,805	De Arauz et al. (2008)
ATCC 11454	Fermented barley by-product; 30 °C/pH 5.5/250 rpm	1488	Furuta et al. (2008)
UQ2	Whey medium supplemented by soybean peptone, $MgSO_4/MnSO_4$, and Tween 80	575	Gonzalez-Toledo et al. (2010)
CGMCC NO. 3050	Fermentation medium optimized by computer modeling	22,216	Guo et al. (2010)
MTCC 440	MRS and milk medium, 30 °C; 100 rpm, 0.15 µg initial nisin mL^{-1}	8244	Mall et al. (2010)

further optimized if the mechanisms and cellular pathways that guide the synthesis of this polypeptide were well understood (Wardani et al. 2006b).

Carbon source

The initial concentration of carbohydrates (carbon source) influences the amount of nisin produced by *L. lactis* at a given pH. The experiments performed by De Vuyst and Vandamme (1992) showed that the amount of produced nisin decreased from 19.1 to 10.9 mg per gram of produced biomass when sucrose concentration increased from 10 to 40 g L^{-1}. In this study, it was also shown that the optimum concentration of sucrose that can produce the maximum amount of nisin is 30 g L^{-1}. Beyond this sucrose level (30 g L^{-1}), nisin production decreased, while bacterial growth was not significantly influenced (Lv et al. 2005). This imbalance between nisin production, biomass production, and substrate availability has been explained in terms of gene expression or posttranslational modifications regulation by carbon source (De Vuyst and Vandamme 1992).

Higher nisin production (4000 IU mL^{-1}) was obtained using glucose as carbon source (Chinachoti et al. 1998). Compared to sucrose and fructose, glucose is the carbon source allowing the optimal production of nisin (Chandrapati and O'Sullivan 1998). It has also been shown, in this study, that glycerol exerts a suppressive action on the production of nisin. Xylose was also considered as a valuable carbon source for nisin production (3000 IU mL^{-1}) by *L. lactis* simultaneously with lactic acid production. Nisin production was 4 times higher when the *L. lactis* ssp. *lactis* A164 strain was cultured in M17 medium supplemented with 3% lactose (Cheigh et al. 2002). Papagianni et al. (2007) showed that using the glucostat system to maintain a 10 g L^{-1} glucose concentration in the reactor causes a very significant nisin production increase (6100 IU mL^{-1}) compared to that obtained in a batch growth medium containing an initial glucose concentration of 25 g L^{-1}. The authors postulated that beyond a certain concentration, glucose transport inside the cell is saturated which leads to a decrease in the nisin synthesis.

Nitrogen source

After carbon, the most abundant element in the bacterial cell is nitrogen. A typical cell contains about 12% nitrogen (dry weight) which is the main component of nucleic acids, proteins, and other cell molecules such as antimicrobial peptides (OpenStax 2019). LAB are fastidious bacteria that require an exogenous source of amino acids or peptides which are provided by the hydrolysis of proteins in the growth medium. In addition, LAB are able to respond to changes in nitrogen availability by regulating their metabolism to ensure a nitrogen balance in the cell.

Usually, during LAB culture for the production of bacteriocins, semi-synthetic media and readily commercially available media such as MRS, TGE and APT are recommended (Abbasiliasi et al. 2017; Yang et al. 2018). Some authors consider that the role of proteins in nisin synthesis is limited and that the problem can be solved by the use of inorganic nitrogen (Guerra and Pastrana 2001). However, other studies have suggested that protein sources, particularly peptides, can act as inducers for nisin synthesis (Cheigh and Pyun 2005; Jenssen et al. 2006; Venegas-Ortega et al. 2019). This partly explains the results obtained by Kim et al. (1997) which show that the produced nisin concentration increases with the supply of organic nitrogen. In another study, De Vuyst and Vandamme (1993) have tested various organic nitrogen sources (cotton-seed meal, yeast extract, fish meal…). The obtained results showed that the concentration of produced nisin varies significantly depending on the nitrogen source. A proteolytic activity is first required for slow-metabolisable nitrogen sources, before making nitrogen available, in the fermentation medium. This nitrogen limitation state may result in the suppression of metabolic regulatory mechanisms and consequently to a low growth rate. Moreover, De Vuyst and Vandamme (1993) reported a positive correlation between nisin production levels and cell yield which is influenced by the organic nitrogen content.

Cheigh et al. (2002) confirmed this study by showing that the use of 3% yeast extract, as an organic nitrogen source, allows to produce higher nisin amounts. In general, slowly metabolizable organic nitrogen sources can cause a low specific growth rate, but promote the nisin biosynthesis (De Vuyst and Vandamme 1992).

In addition to this nutritional role, stimulating nisin and other bacteriocins production by organic nitrogen sources has been reported (Aasen et al. 2000; Vázquez et al. 2004). These studies have proposed several explanations such as enzyme induction by amino acids or the simultaneous need for many amino acids for the synthesis of the lanthionine ring. Other studies have provided more details, showing, for example, that cysteine and tryptophan stimulate nisin production, whereas proline inhibits it (Vázquez et al. 2004). Cabo et al. (2001) suggested that even if there is no induction of nisin synthesis by individual amino acids, tryptone and yeast extract may contain peptides that are essential to the synthesis of this bacteriocin or can act as inducers of its production. The effect of glycine on nisin production is debatable. Indeed, De Vuyst (1995) showed that the addition of glycine to the growth medium did not influence the production of nisin by *L. lactis* ssp. *lactis* NIZO 22,186 while later, Guerra and Pastrana (2001) showed that this amino acid exerts an inhibitory effect on cell growth and nisin production by *L. lactis* ssp. *lactis* CECT 539. According

to the authors, this inhibitory action may be due to the synthesis inhibition of some membrane components such as peptidoglycan.

The use of some byproducts such as whey can significantly decrease the cost of nisin production and improve its production (Jozala 2011). Indeed, a nisin concentration of 11,120 mg L^{-1} was obtained by cultivation of *L. lactis* in bovine whey. This concentration is 22 times higher than that obtained in skim milk (De Arauz et al. 2008). The use of fermented barley extract enriched with glucose can also be considered as an alternative for the nisin production with lower costs (Furuta et al. 2008). The use of low/negative value soy whey (SW) was demonstrated as an alternative, inexpensive fermentation substrate to culture *L. lactis* for nisin production in MRS medium (Mitra et al. 2010).

pH

As mentioned above, nisin synthesis is associated with the growth phase. Thus, maintaining the optimal pH for *L. lactis* growth also improves nisin production. The optimal pH for nisin production is generally located around 5–6, slightly below the optimal pH for growth. Besides, Jozala (2011) explained that pH values could influence the extracellular liberation of nisin. The authors detected the highest nisin activity at pH < 5 for *Lactococcus lactis* ATCC 11,454 strain in milk whey. At pH values lower than 6.0, 80% of the nisin expressed by the cells were released in the culture medium. On the other hand, at pH values higher than 6.0, most of the nisin was retained in the cellular membrane or inside the cells.

However, the exact value of the optimum pH for nisin production may vary depending on the carbon source. For example, nisin Z production was highest at pH 6.0 in a medium containing xylose and 5.5 in a medium containing glucose (Parente and Ricciardi 1999).

Temperature

Usually, the growth optimal temperature allows the optimum production of nisin (Yang et al. 2018). This can easily be explained by the fact that production is associated with cell growth. However, Cheigh et al. (2002) showed that if the maximum growth temperature of the *L. lactis* ssp. *lactis* A164 strain was 37 °C, the optimum temperature for nisin and nisin-like bacteriocins production was 30 °C. In addition, heat stress can cause an increased nisin/biomass ratio (Lejeune and Crabbé 1998).

Ions

Some studies have shown that the presence of divalent cations like Ca^{2+} and Mg^{2+} may have a remarkable effect on the amount of produced nisin but the intensity of this effect is different from one strain to another. The Mg^{2+} ions preserve nisin from adsorption to *L. lactis* ssp. *lactis* ATCC 11,454 cells causing an increase in the apparent concentration of nisin (Meghrous et al. 1992). The addition of Ca^{2+} has helped to boost the nisin Z production, and the highest nisin production (3150 IU mL^{-1}) was obtained with 0.1 M $CaCl_2$ in a controlled pH reactor (Matsusaki et al. 1996). Like with Mg^{2+}, this effect was explained by the displacement of nisin Z on the cell surface. Phosphate ions enhance the production of nisin by *L. lactis* ssp. *lactis* NIZO 22,186 to reach 3500 IU ml^{-1} (De Vuyst and Vandamme 1993).

Cell immobilization

The concordance of many studies, showing that nisin is synthesized simultaneously with cell growth, suggests that the improvement of nisin production requires a high concentration of cells in the medium (Parente and Ricciardi 1999). The immobilization of *L. lactis* cells may be a good alternative to increase cell density in fermentors and ensure the continued production of nisin (Desjardins et al. 2001) (Table 4). LAB immobilization in solid matrices for nisin production has been studied since the early 1990s (Zezza et al. 1993; Pasini et al. 1995; Wan et al. 1995). Overall, the results of these studies have shown that cell confinement in alginate beads enhances nisin production. By contrast, Sonomoto et al. (2000) reported that the use of alginate as a carrier did not improve the production of nisin when compared to the free cells. According to Sonomoto et al. (2000) the highest nisin production yielding good commercial satisfaction was mainly due to cell entrapment in chitosan beads (Table 3).

Since then, several studies aiming at finding new materials and new techniques to immobilize cells in a stable support having a better transfer of substrates and metabolites objectives were conducted. For instance, Sonomoto et al. (2000) tested several methods and matrices for immobilization of the *L. lactis* IO-1 strain. Results showed that the adsorption of cells in the pores of commercial chitosan beads can lead to a 1.7 times higher nisin production than by free cells. This study also showed the importance of the beads size. Indeed, small size beads have a higher specific surface permitting the adsorption of a larger amount of nisin mainly through hydrophobic interactions. On the other hand, cells incorporation in gels often leads to problems of nutrients transfer resulting in poor cell growth and hence low nisin production (Sonomoto et al. 2000). However, the release of nisin from alginate beads to the outside environment is less influenced by diffusion due to the small size of this peptide. Indeed, calcium alginate beads have a molecular cut-off point of about 20 kDa which is much higher than the molecular weight of nisin (Scannell et al. 2000).

Table 4 *Lactococcus lactis* immobilization for nisin production

Immobilized strain	Material used for immobilization	Aim	References
Lactococcus lactis subsp. *lactis* DPC 3147 *Lactococcus lactis* DPC 496	Sodium alginate	Production of nisin and lacticin 3147	Scannell et al. (2000)
Lactococcus lactis IO-1	Sodium alginate Carrageenan Agar Alginate beads	Production of nisin Z	Sonomoto et al. (2000)
Lactococcus lactis subsp. *lactis* biovar. *diacetylactis UL179*	κ-Carrageenan/locust bean gum gel beads	Production of nisin Z	Bertrand et al. (2001) and Desjardins et al. (2001)
Lactococcus lactis subsp. *lactis* ATCC 11454	Spiral wound fibrous matrix	Production of nisin	Liu et al. (2005)
Lactococcus lactis MTCC B440	Alginate beads	Production of nisin 440	Sarika et al. (2012)

The use of continuous bioreactors containing immobilized bacteria did not significantly improve nisin production compared to cultures using free cells (Sonomoto et al. 2000; Desjardins et al. 2001). These results have led researchers to suggest the existence of one or more limiting steps in the synthesis of nisin such as post-translational modifications, transport, or maturation (Desjardins et al. 2001). The use of culture in the repeated batch cycle (RCB) characterized by a first stage of bead colonization has increased significantly the amount of produced nisin (Bertrand et al. 2001). The immobilization of *L. lactis* ssp. *lactis* ATCC 11,454 by natural adsorption on cotton fibers based support has allowed the production of nisin in a continuous reactor for at least 6 months without interruption (Liu et al. 2005). However, since produced nisin amounts are generally expressed in arbitrary units (AU), the yields obtained cannot be compared from one study to another.

Other factors

Other parameters such as agitation and/or aeration are among the factors to be optimized during nisin production in batch mode. Aeration is particularly important because LAB oxygen tolerance is associated with different metabolic pathways, which leads to a decrease of nisin productivity. In the available literature, the conditions of nisin production varied from anaerobiosis to atmospheres containing 60% O_2 (Fernández-Pérez et al. 2018). Several authors have determined the optimum rates of agitation and aeration (Desjardins et al. 2001; Mall et al. 2010; Jiang et al. 2015). However, it is not interesting to report these optimal values since they namely depend on the bioreactor size and design.

A comparison between the productions of different bacteriocins including nisin was published by Parente and Ricciardi (1999). This allowed to observe that continuous fermentations allow higher productivities compared to batch ones. This production can be improved by a factor of up to 4.5 times compared to batch culture by cell recycling (Taniguchi et al. 1994). Intermediate yields (~ 1.6–1.7 times higher than following batch mode) were also obtained by cultivating the strain *L. lactis* ssp. *lactis* ATCC11454 in a fed-batch mode by adding sucrose and organic nitrogen (yeast extract and soy peptone) (Lv et al. 2004). Continuous production of nisin is often confronted by the problem of bacterial cells loss (wash-out). This problem can be solved by immobilization or entrapment of *L. lactis* ssp. *lactis* cells in/on appropriate solid matrices as mentioned above.

Agustin Wardani et al. (2006a, b) have shown that a symbiotic process system composed of *L. lactis* ssp. *lactis* ATCC11454 and the yeast *Kluyveromyces marxianus* MS1 is effective in improving the nisin production. In another study, Kim (1997) showed that the addition of an organic phase (phenyl-methyl silicone oil) to the growth medium can increase nisin production by 24%. This improvement of nisin synthesis has been explained by an improvement in growth due to the elimination from the aqueous phase of inhibitory molecules such as lactic acid.

On the other hand, the presence of a small amount of nisin (0.15 µg mL^{-1}) in MRS medium seems necessary to stimulate the production of nisin by *L. lactis* ssp. *lactis* MTCC 440 (Mall et al. 2010). The autoregulating system of nisin allows transcription activation of the nisin structural gene by autophosphorylation of the histidine kinase enzyme (Chandrapati and O'Sullivan 1999; García-Parra et al. 2011). Besides, with the *Lactococcus lactis* UQ2 strain, García-Parra et al. (2011) added to the skim milk sub-inhibitory amounts of commercial nisin and a mixture of magnesium/manganese. The highest nisin production (75 ± 7 IU mL^{-1}) was achieved after 10 h of incubation in skim milk supplemented with 1.87 µg L^{-1} of nisin and 0.5/0.1 g L^{-1} of Mg/Mn, while only 3.5 ± 0.5 IU mL^{-1} were produced by control cultures at 6 h.

Guo et al. (2010) optimized composition of *L. lactis* growth medium using an experimental design and a computational model. Results showed that the optimum composition is as follows (g L^{-1}): 15.92 glucose; 30.57

peptone; 39.07 yeast extract; 5.25 NaCl; 10.00 KH_2PO_4; 0.20 $MgSO_4$ $7H_2O$. This composition has produced 21,423 IU mL^{-1} of nisin. This nisin concentration is about eight times higher than that obtained without computational optimization (Guo et al. 2010).

Nisin as a food preservative

Nisin is effective against several pathogenic Gram-positive bacteria, such as *Staphylococcus aureus* (Wang et al. 2020), *Listeria monocytogenes* (Zhao et al. 2020) and *Clostridium tyrobutyricum* (Ávila et al. 2020), but also against some Gram-negative pathogens such as *Salmonella enterica*, and *Pseudomonas fluorescens* when combined with chelators such as ethylenediaminetetraacetic acid (EDTA) (Liang et al. 2020) or heat treatment (Novickij et al. 2020). Indeed, the surface layer of Gram-negative bacteria, composed of lipopolysaccharides (LPS) acts as a barrier to the action of the nisin on the cytoplasmic wall. The action of chelating agents permits to confine the divalent magnesium and calcium ions of the LPS and destabilize the LPS layer. Thus, nisin can be transported through the LPS layer and create pores in the cytoplasmic membrane, causing a loss of the proton-motive force and a leakage of intracellular nutrients: its classical antimicrobial mechanism (Pattanayaiying et al. 2014).

This antimicrobial activity of nisin is largely dependent on its aqueous solubility and structural stability, which in turn depend on pH and temperature (Table 5). Nisin use for food preservation may offer several advantages: increasing the shelf life of the product, reducing the transmission risk of food-borne pathogens, reducing the use of chemical preservatives, salts, acids… and, permitting the use of soft treatments which better preserve vitamins and organoleptic properties. Moreover, it is important to highlight that nisin cannot be regarded as a "natural" preservative when used in concentrations higher than those naturally found in foods fermented with nisin-producing strains. Table 6 gives some recent examples of nisin amounts experimentally used for the shelf-life increase of some food products. When used for food preservation purpose, nisin can be directly added to food products (Younes et al. 2017), or incorporated in packaging films (Diblan and Kaya 2018), or also added as raw concentrates obtained from nisin-producer strain cultivated in milk or whey-derived substrates (Galvez et al. 2007).

The effect of direct addition of free nisin in dairy products is widely studied. Pinto et al., (2011) added nisin during Serro cheese manufacturing process against *Staphylococcus aureus* contamination. Pinto et al., (2011) observed that nisin did not affect the physicochemical and mechanical characteristics of obtained cheese. In the same way, Yoon et al. (2011) studied the inactivation of *Listeria monocytogenes* after adding nisin to the whole, low fat and skim milk. Their results showed that the anti-*Listeria* activity of nisin was dependent on fat contents in milk substrate. The anti-*Listeria* activity was moderate in whole milk, whereas remarkable in low fat and skim milk samples. The reaction between nisin and the listerial cell membrane was caused by hydrophobic interaction between amino acid residues of nisin and the fatty acids of the membrane phospholipids. So, the phospholipids present in milk fat could bind a large portion of the added nisin resulting in a reduced nisin amount available to interact with the cell membrane of *Listeria* spp. cells (Millette et al. 2004). This was not the case in skim milk where similar nisin concentrations were sufficient to cause disruption of the listerial cell membrane. This last case revealed that practical application of nisin can often be limited because of its variable solubility due to interactions with food components (such as protein and lipids) and its low activity at high pH, and consequently limited efficacy in certain food matrices (Malheiros et al. 2012). Moreover, the emergence of nisin tolerance in certain bacteria (*Listeria monocytogenes*) has been observed (Bergholz et al. 2013; Szendy et al. 2019). That is why several researchers combined nisin with other antimicrobial agents such as essential oil (Yoon et al. 2011), chitosan films (Cé et al. 2012) or with other antimicrobial treatments such as high-pressure processing (Marcos et al. 2013).

The second strategy for nisin use as a food preservative is its incorporation into polymeric films. The advantage of

Table 5 Some nisin properties that influence its application for food preservation

Structure	Cationic polypeptide, hydrophobic and heat stable Molecular weight is 3.5 kDa but nisin is capable of forming dimers (7 kDa, more stable) and tetramers (14 kDa)	Hurst (1981)
Aqueous solubility	Nisin is more soluble under acidic conditions (pH ~ 2–3)	Rollema et al. (1995)
Thermal stability	Thermal stability of nisin increases with decreasing pH (can resist to autoclaving at 121 °C and pH 2)	Davies et al. (1998)
Proteolytic enzymes	Inactivated by pancreatin, α-chymotrypsin, and ficin Not inactivated by trypsin, pepsin, and carboxypeptidase	Chollet et al. (2008)
Antimicrobial activity	Effective against Gram-positive bacteria and in particular the spore-forming ones Ineffective against yeast cells, fungi, viruses, and Gram-negative bacteria	Delves-Broughton (1993)

Table 6 Nisin uses in food preservation

Commodities	Target	Effective nisin concentration	Implementations	References
Dairy products	*Clostridium sporogenes*	400 IU. g^{-1}	Starter culture	Zottola et al. (1994)
	Listeria monocytogenes	2000 IU g^{-1}	Free nisin	Ferreira and Lund (1996)
	Listeria monocytogenes	100 IU g^{-1}	Free nisin	Davies et al. (1998)
	Bacillus cereus spores	4000 IU mL^{-1}	Free nisin	Wandling et al. (1999)
	Streptococcus thermophilus	20 IU mL^{-1}	Free nisin	Garde et al. (2004)
	Kocuria rhizophila ATCC 9341	40,000 or 20,000 IU g^{-1}	Free nisin	Chollet et al. (2008)
	Staphylococcus aureus ATCC 6538 *Listeria monocytogenes* ATCC 15313 *Penicillium* sp. *Geotrichum* sp.	20,000 IU.g^{-1}	Cellulose film	Dos Santos Pires et al. (2008)
	Cronobacter spp.	1600 IU mL^{-1}	Free nisin	Al-Nabulsi et al. (2009)
	Listeria innocua	1000 IU cm^{-2}	Sodium caseinate film	Cao-Hoang et al. (2010)
	Staphylococcus aureus ATCC 6538	100 or 500 IU mL^{-1}	Free nisin	Pinto et al. (2011)
	Listeria monocytogenes ATCC 19116	250 or 500 IU mL^{-1}	Free nisin	Yoon et al. (2011)
	Listeria monocytogenes	ND	Starter culture	Dal Bello et al. (2012)
	Listeria monocytogenes	ND	Liposomes	Malheiros et al. (2012)
	Listeria monocytogenes ATCC 25923 *Staphylococcus aureus* ATCC 19117	450 IU mL^{-1}	Chitosan-alginate nanoparticles	Zohri et al. (2013)
Meat	*Lactobacillus sake* and *curvatus*	1000 IU g^{-1}	Free nisin	Davies et al. (1999)
	Staphylococcus aureus ATCC 29213	500 or 1000 IU mL^{-1}	Sodium alginate film and beads	Millette et al. (2007)
	Enterobacteriaceae *Carnobacterium* spp. *Brochothrix thermosphacta*	ND	Plastic Film	Ercolini et al. (2010)
	Listeria innocua Li1	40,000 IU g^{-1}	Free nisin	Lauková and Turek (2011)
	L. monocytogenes	450 AU cm^{-2}	Polyvinyl alcohol film	Marcos et al. (2013)
Seafood	*Listeria monocytogenes*	500 or 2 000 IU cm^{-2}	Plastic Film	Neetoo (2008)

Table 6 (continued)

Commodities	Target	Effective nisin concentration	Implementations	References
Fruits and vegetables	*Lactobacillus*	100 IU.g^{-1}	Free nisin	Choi and Park (2000)
	Listeria monocytogenes ATCC 7644 *Bacillus cereus* ATCC 14579 *Staphylococcus aureus* ATCC 25923 *Escherichia coli* ATCC 25922 *Salmonella enteritidis* ATCC 13076 *Clostridium perfringens* ATCC 3624 *Lactobacillus acidophilus* ATCC 4356 *Aspergillus phoenicis* *Penicillium stoloniferum*	100 IU mL^{-1}	Edible chitosan film	Cé et al. (2012)
	Staphylococcus aureus ATCC 8095 *Listeria monocytogenes* ATCC 7644 *Alicyclobacillus acidoterrestris* DSMZ 2498 *Bacillus aureus* 4504	10^7 or 2.10^7 IU g^{-1} of cellulose	Cellulose film	Barbosa et al. (2013)
Not determined	*Listeria monocytogenes* V7	800 IU mL^{-1}	Phytoglycogen-based nanoparticles	Bi et al. (2011)
	Listeria innocua *Zygosaccharomyces bailii*	3000 IU mL^{-1}	Tapioca starch and hydroxypropyl methylcellulose edible films	Basch et al. (2013)
	Listeria innocua ATCC 33090 *Escherichia coli* JMP101 *Brochotrix thermosphacta* NCIB10018 *Enterococcus faecalis* (MXVK22)	450 IU mL^{-1}	Edible film of Whey protein isolate	Murillo-Martínez et al. (2013)

ND not determined

using bacteriocins in films, instead of their direct addition into food matrices, is associated with the increased stability of nisin and the control of its release (Barbosa et al. 2013). Nevertheless, as free nisin application, the effectiveness of antimicrobial packaging is dependent on the type of food packed, the film-forming polymer and the type and concentration of antimicrobial that will determine the release rate and therefore, the antimicrobial efficiency (Marcos et al. 2013). For example, Barbosa et al. (2013) formulated cellulose films containing nisin to improve the safety of minimally processed mangoes. Pathogen and spoilage microorganisms associated with fruit products were inhibited for 9 days without interfering in the organoleptic characteristics of mangoes appearance, texture, and nutritional value. This strategy was mainly beneficial to protect the product surface. Marcos et al. (2013) used nisin- polyvinyl alcohol film against *L. monocytogenes* for sliced fermented sausages.

As seen in Table 6, many studies have demonstrated the antimicrobial potential of polymeric gels, films, or plastic polymers containing nisin, but very few studies have reported the antimicrobial potential of immobilized living cells, potentially bacteriocin producers, on selected pathogenic bacteria (Millette et al. 2004; Gialamas et al. 2010; Brachkova et al. 2010; Concha-Meyer et al. 2011; Sánchez-González et al. 2013). To date, (Millette et al. 2004) are the only ones to have tested the antimicrobial potential of immobilized cells of a nisin-producing strain (*Lactococcus lactis* ATCC11454). They immobilized LAB cells in alginate-whey protein concentrate (WPC) beads with diameters between 1.6 and 2.2 mm. Their results showed that immobilization did not affect the inhibitory potential of *L. lactis* on Gram-positive bacteria *Enterococcus* sp., *Lactobacillus* sp., *Pediococcus*, *Kocuria* and *Staphylococcus*. The inhibition diameter measured ranged from 5 to 14 mm. To

verify whether the inhibition of Gram-positive bacteria was attributable to nisin, they added a proteolytic enzyme to the culture medium. In the presence of proteases, no inhibition area was observed, which demonstrated that the production of a proteinaceous antimicrobial agent (such as nisin) was responsible for the inhibition.

Conclusion

Nisin is the only bacteriocin approved for food preservation although other bacteriocins produced by LAB are also effective against pathogenic bacteria. However, the direct use of nisin in antimicrobial packaging is limited due to its high price and low purity. This situation is probably due to low production, which is about an average of 100 mg L^{-1}. The physicochemical properties of food matrix such as high-fat content, pH, and ionic force can reduce its activity of nisin. In addition to optimizing the composition of the growth medium, immobilization of *L. lactis* cells is today the most effective method that allows the reuse of cells, increasing the amount of produced nisin and the ease of its purification. The major developments occurring today in molecular biology could be used to improve both productions but also nisin stability without affecting its antimicrobial potency. However, the non-homogeneity of the units for measuring nisin production makes difficult the collection of global information concerning this bacteriocin production. On the other hand, nisin could be produced in situ in the preservation system. Recent development concerning food safety strategies revealed that immobilization of bacteriocin-producing LAB can preserve LAB ability to produce bacteriocins and to inhibit the growth of undesirable microorganisms.

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