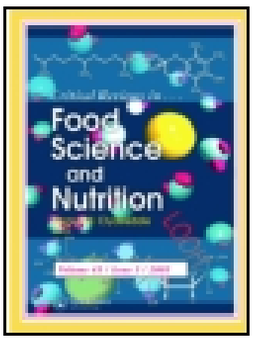

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REVIEW

Physical and nutritional conditions for optimized production of bacteriocins by lactic acid bacteria – A review

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ABSTRACT

There has been an increasing debate about the use of synthetic chemical compounds and the consequences of their use in food preservation. In this context, the utilization of some natural compounds produced by bacteria, showing an inhibitory effect against microorganisms associated with food contamination, have gained attention as preservation technology. In order to improve the production and yield costs of bacteriocins, detailed studies are necessary to determine the conditions that allow an optimized production and extraction of bacteriocins from lactic acid bacteria (LAB). In this context, this article aims to discuss the information regarding the main factors that influence bacteriocin production by LAB. The biosynthesis of bacteriocins can be influenced by various culture conditions, such as the composition of the medium, pH, temperature and growth kinetics of the microorganisms. One of the limiting factors for the use of bacteriocins on a large scale in food preservation is the economic factor. In order for the production costs of bacteriocins to be reduced, making them attractive, it is necessary to know the optimum parameters of production, thus maximizing productivity and making costs more attractive.

KEYWORDS

Antimicrobial; food; microorganisms; preservation

Introduction

Lactic acid bacteria (LAB) are characterized as Gram-positive *cocci* or *bacilli* that are non-aerobic but aerotolerant, capable of fermenting carbohydrates to produce energy and lactic acid (De Vuyst and Leroy 2007; Parada et al. 2007). The group of LAB comprise several genera like *Lactococcus, Lactobacillus, Leuconostoc, Enterococcus, Carnobacterium, Aerococcus, Pediococcus, Oenococcus, Streptococcus, Tetragenococcus, Vagococcus* and *Weissella* (Henning et al. 2015; Pennacchia, Vaughan, and Villani 2006). LAB are traditionally used as starter cultures for the fermentation of food and beverages, due to their contribution to the development of flavor and aroma and retarding deterioration. They also can break down proteins, fats and carbohydrates in food and helps in the absorption of nutrients increasing health (Settanni and Corsetti 2008; Teshome 2015; Zamfir et al. 2000). LAB are acknowledged as safe (Generally Recognized as Safe – GRAS) and its metabolites have been consumed by humans for thousands of years through fermented foods with no known adverse effect (Parada et al. 2007; Yang and Ray 1994).

Some of these bacteria produce substances of proteinaceous nature (both proteins and peptides) called bacteriocins, which are active against specific pathogenic microorganisms in small amounts (Holtsmark, Eijsink, and Brurberg 2008; Klaenhammer 1993). Bacteriocins differ from antibiotics by having a spectrum of antimicrobial activity against related species, while antibiotics have effect against a broad spectrum of microorganisms (Bharti et al. 2015; Dobson et al. 2012; Holtsmark et al. 2008). It is estimated that the majority of the bacteria can produce some kind of bacteriocin (Bharti et al. 2015; Dobson et al. 2012).

The main application of bacteriocins is intended for the food industry (Bharti et al. 2015; Zamfir et al. 2000). In industrialized countries, about 30% of the population is infected with pathogenic bacteria and fungi from food source (Gálvez et al. 2007). In addition, there is great concern regarding the use of chemical preservatives in food to control food spoilage and the risks associated with them. The long-term intake of foods with chemical preservatives can affect human health and alter significantly the gut microbiota, causing diseases, obesity and even cancer (Bharti et al. 2015; Yang et al. 2014). In this scenario, food biopreservation techniques using bacteriocins produced by LAB becomes a very attractive alternative to currently used chemical preservatives due their bactericidal effect against many food spoilage and pathogenic bacteria without any toxic effect to human health or change in the sensorial features of food (Bharti et al. 2015; Garsa et al. 2014).

Before they can be used as preservatives in foods, it is necessary to know the interaction of bacteriocin with food, their spectrum of action, effectiveness, stability, and attend to regulatory matters (Bharti et al. 2015; Yang and Ray 1994). Another important aspect for its effective use is the economic factor. For the production of bacteriocins become attractive and widespread, thoroughly investigation on the production parameters

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must be conducted to reach costs optimization (Van den Berghe et al. 2006; Yang and Ray 1994).

There is an intensive investigation for new antimicrobial substances produced by LAB (Cálix-Lara et al. 2014; Perez, Zendo, and Sonomoto 2014). However, aiming to achieve improvement of the production costs and bacteriocin yield, specific studies are needed to determine conditions that optimize the yields of bacteriocin production and extraction from LAB (Kumar et al. 2012b; Miao et al. 2015).

The production of bacteriocins can be influenced by different culture conditions such as medium composition, gaseous atmosphere, pH, temperature and growth kinetics of microorganisms (De Arauz et al. 2009; Mataragas, Metaxopoulos, and Drosinos 2002). In many occasions, the maximum production of bacteriocins is obtained working at different conditions of optimal conditions for growth of microorganisms (Aasen et al. 2000; De Vuyst, Callewaert, and Crabbé 1996; Parente, Ricciardi, and Addario 1994; Todorov and Dicks 2006; Todorov et al. 2010). Many authors found that good cell growth is directly related to the production of bacteriocins; however, the best cell growth rate does not necessarily imply better bacteriocin production rate (Biswas et al. 1991; De Vuyst et al., 1996; Kim, Hall, and Dunn 1997; Mataragas et al. 2002).

Currently, nisin A/Z and pediocin PA-1 are commercial bacteriocins approved as food additives and used in most major food producing countries. They are also the most studied bacteriocins because of their broad spectrum of activity, their bactericidal power at low concentrations and stability on food matrix (Anastasiadou et al. 2008b; Bharti et al. 2015; Deegan et al. 2006; Guerra and Pastrana 2002a; Settanni and Corsetti 2008; López and Belloso 2008). Besides every year a lot of new bacteriocins and producer strains are identified, there is a lack of studies proving safety for use and economic viability of the growing number of discovered bacteriocins (Anastasiadou et al. 2008b; Van den Berghe et al. 2006).

In view of the above, this work aims to discuss the information available in the literature regarding the main factors that influence bacteriocins productivity by LAB.

Kinetics of growth and fermentation time for bacteriocin production

The fermentation time is an important parameter for maximizing the bacteriocin production. The bacteriocin can be produced in different steps in a metabolic process (Cabo et al. 2001; Yang and Ray 1994) and have reduced activity on other (Ahmad et al. 2014). Thus, the knowledge of the growth kinetics is important for optimizing the production of bacteriocins, since this parameter can vary even between different strains of the same species (Martinez et al. 2013).

Bacteriocins produced by LAB are from a metabolic point of view, generally considered as primary metabolites, which are products formed during the exponential growth phase (Bharti et al. 2015; Cabo et al. 2001; Papagianni and Sergelidis 2013; Zamfir et al. 2000). Thus, cell production rates during the exponential growth phase is generally correlated with bacteriocin production rates (De Vuyst 1995; De Vuyst et al. 1996; Motta and Brandelli, 2003). A large number of papers available in the literature describe bacteriocins that follow this pattern, such as nisin A/Z (De Vuyst and Vandamme 1992; Parente et al. 1994), pediocin PA1/SA-1 (Anastasiadou et al. 2008a), mesenterocin 5 (Daba et al. 1993), Lactococcin 140 (Parente and Ricciardi 1994), lactostrepcin (De Vuyst, 1994), lactocin 705 (Vignolo et al. 1995), and leucocin (Geisen, Becker, and Holzapfel 1993).

However, some authors reported that bacteriocin production do not always correlate directly with the cell concentration or growth rate of producer microorganism (Dominguez et al. 2007; Kim et al. 1997; Kumar et al. 2012a). This premise is true in cases in which the optimal conditions for bacteriocin production are different from the optimal conditions for cell growth, such as pH or temperature conditions different than the optimal for cell growth (Aasen et al. 2000; Abo-Amer 2011; Parente and Ricciardi 1994; Todorov and Dicks 2005, 2006).

Metabolites with secondary character, produced during the stationary phase of bacterial growth, are generally regarded as antibiotic. However, studies indicate that some LAB can produce bacteriocins during the stationary growth phase, where a lower pH and reduced availability of nutrients takes place (Biswas et al. 1991). Some examples of these microorganisms are *Lactobacillus plantarum* LPCO10 (Jiménez-Díaz et al. 1993), *Lactococcus lactis* subsp. *lactis* (Cheigh et al. 2002), *Lactobacillus pentosus* B96 (Delgado et al. 2005).

There is a consensus that a loss in the production yield of bacteriocins occurs during the beginning of stationary phase, for bacteriocins produced during the exponential growth phase, or at the end of the stationary phase, for bacteriocins produced in the stationary phase (Ahmad et al. 2014; Leroy et al. 2006; Mataragas et al. 2002). This apparent loss is mainly attributed to the adsorption of bacteriocins by the surface of producing cells and to increased proteolytic activity (Aasen et al. 2000; De Vuyst et al. 1996; Lejeune et al. 1998; Mataragas et al. 2002; Parente et al. 1994). In has been described that this process can be facilitated by higher values of temperature and pH (Messens et al. 2002; Neysens et al. 2003).

Thus, knowledge on the growth kinetics and metabolic nature of the bacteriocin, as primary or secondary metabolite, becomes important for an effective increase in bacteriocin productivity. An extensive cultivation time generate lower amounts of cells and bacteriocins, when compared with the initial phase of the fermentation process, which can generate a relationship between cost and benefit unfavorable (Guerra, Bernárdez, and Castro 2008).

Influence of growth medium on bacteriocin production

One of the most influential factors in bacteriocin production is the medium. Supplementation of the medium with limiting growth substrates, such as carbohydrates, nitrogen sources, vitamins and salts can increase bacteriocin production levels (Settanni et al. 2008; Todorov and Dicks 2005). Besides the impact that nutrients have on the production of bacteriocins, there is also the economic impact, since complex medium and rich in nutrients have high costs. In this sense, the use of simple media with proper supplementation appears as a feasible alternative to the production of bacteriocins (Leães et al. 2011).

Several studies use MRS medium as a basis for the production of bacteriocins, since it can meet adequately the nutritional

needs of LAB. However, this is a complex and expensive medium, and contains a lot of proteins that can interfere in the downstream process of bacteriocin purification (Garsa et al. 2014). In this regard, some studies with alternative culture media, such as TGE (Yang and Ray 1994), M17, APT, Elliker (Cheigh et al. 2002), U-10, E-Sweet (Pattnaik, Grover, and Batish 2005), have achieved significant production of bacteriocins. Thus, several media can be studied to optimize the bacteriocin production.

A very attractive option is to use some by-products of food industry as raw material for the culture media. Some by-products from dairy industry like milk whey and mussel-processing wastes can be used as an inexpensive medium for fermentation by LAB that requires minimum nutritional supplementation. The by-products from dairy industry are a rich source of sugar, proteins and peptides that works as inducers for bacteriocins synthesis (Cladera-Olivera, Caron, and Brandelli 2004; Garsa et al. 2014; Guerra and Pastrana 2002b; Motta and Brandelli, 2008; Sood and Sinha 2009).

Some media need to be supplemented to attend the nutritional demand of some strains of LAB. Different carbohydrate sources are available for supplementation of culture medium, among the most common are glucose, lactose, sucrose, xylose, fructose, maltose, mannose, galactose, arabinose and raffinose (Cheigh et al. 2002; Miao et al. 2015; Settanni et al. 2008). Some examples of studies with supplementation using different sugar sources and concentrations and the impact on the bacteriocin production are summarized in Table 1.

Supplementation of glucose is indicated in some studies as an impact factor for the production of bacteriocins (Guerra et al. 2008; Miao et al. 2015; Papagianni, Avramidis, and Filiousis 2007), as can be observed in Table 1. This is explained by the fact that glucose allows increased production of enzymes and metabolic compounds that promote increased biomass and consequently the production of bacteriocins when compared with sucrose and fructose (Luesink et al. 1998; Papagianni et al. 2007). However, high concentrations of glucose may not generate a cumulative effect on biomass production due to the increased lactic acid production and inhibition of cell growth, as well as reduced production of bacteriocins. This effect was reported for nisin A production by *L. lactis* (Table 1), where the microorganism appears to be sensitive to the moderate sugar amounts (10 g/L) producing more bacteriocins when compared with more elevated sugar levels (25–35 g/L) and having a significant decreased on bacteriocin production when sugar levels reached 50–75 g/L (Papagianni et al. 2007). A similar effect was reported for the enterocin SD1/SD2/SD3/SD4 produced by four strains of *Enterococcus faecium* where the high glucose and lactose concentration (50 g/L) generate a decrease of the enterocins production (Schirru et al. 2014).

The supplementation of culture media containing different sugars such as maltose, lactose, sucrose and xylose were also studied and some examples are reported on Table 1 (Anthony et al. 2009; Cheigh et al. 2002; Settanni et al. 2008). The use of lactose as a carbon source showed significant increase on the cell growth and the amount of nisin-like bacteriocin produced by *L. lactis* subsp. *lactis* (Cheigh et al. 2002) and bacteriocin by *Bacillus licheniformis* AnBa9 (Anthony et al. 2009). During the production of bovicin HC5 by *Streptococcus bovis* HC5 it was showed that the increase of the sugar concentration have a positive effect considering levels of sugar supplementation up to 8 g/L (De Carvalho et al. 2009). Most of studies report that a high concentration of carbon source has a negative impact on the bacteriocin production when compared with moderated levels (Cheigh et al. 2002; Miao et al. 2015; Papagianni et al. 2007). Another important point was demonstrated by a study with *Enterococcus mundi* (Table 1), where different strains of the same species were sensitive to different carbon sources and showed a significant difference for bacteriocin production in response to each carbon source (Settanni et al., 2008). Based on these results, it could be suggested that the ideal carbon source and the optimal concentration of sugar to promote the highest bacteriocin production must be studied and defined for each producer strain.

Nitrogen sources also have a large impact on bacteriocin production. The amount of amino acids and peptides available in the cultivation medium prove to be a limiting factor for cell growth that are related to the bacteriocin production (Aasen et al. 2000; Anthony et al. 2009; Cheigh et al. 2002; Dominguez et al. 2007; Moretro et al. 2000). Some peptides can work as an inducer to producer cell starts bacteriocin synthesis process, so an appropriate source of nitrogen must have a variety of amino acids and peptides to promote the cell growth and induce the bacteriocin production (Aasen et al. 2000; Guerra and Pastrana 2001; Kim et al. 1997; Parente and Hill 1992; Vignolo et al. 1995).

Different studies investigated the impact of nitrogen sources on the production of bacteriocins, including peptone, tryptone, meat extract, yeast extract, fish meal, soybean protein, ammonium nitrate and ammonium sulfate, casein and soy protein. Some examples are detailed in the Table 2.

As shown in Table 2, one of the most efficient component for increase the bacteriocin production is the yeast extract, which have a lot of amino acids and peptides that can promote the cell growth and induce the bacteriocin production (Abo-Amer 2011; Pattnaik et al. 2001). The use of tryptone as nitrogen source could also achieve very good bacteriocin production levels for the bacteriocin production by *Lactococcus lactis* subsp. *lactis* A164 and achieve the best bacteriocin production levels as a single nitrogen source for enterocins SD1, SD2, SD3 and SD4 (Cheigh et al. 2002; Schirru et al. 2014). Another important point demonstrated in the studies for the enterocins and bovicin HC5 production is the use of a combination of different nitrogen sources, which in some cases can increase the bacteriocin production when compared with a single nitrogen source (De Carvalho et al. 2009; Schirru et al. 2014).

The presence of salts in the culture medium can have a significant effect on the production of cells and bacteriocins (Delgado et al. 2007; Hugas et al. 2002; Settanni et al. 2008; Verluyten, Messens, and De Vuyst 2004). Neysens et al. (2003) and Delgado et al. (2005) evaluated the influence of NaCl concentration for cell growth and bacteriocin production by *L. amylovorus* DCE 471 and *L. pentosus* B96, respectively. It was observed that high salt concentrations have a negative effect on

Table 1. Effect of different carbon source supplementation on bacteriocin production by LAB.

Producer Strain	Bacteriocin	Base medium	Carbon Source	Concentration	Bacteriocin production/activity	References
L. paracasei subsp. *tolerans* FX-6	Not specified	Sterilized milk	Lactose	2% (w/v)	20 mm*	(Miao et al. 2015)
			Glucose		22 mm*	
			Maltose		22 mm*	
			Sucrose		20 mm*	
			Glucose	1% to 5% (w/v)	23,5 mm (maximum at 3%)*	
Lactococcus lactis subsp. *lactis* A164	Nisin-like bacteriocin	M17 broth	Glucose	0.5%	2048 AU mL^{-1}	(Cheigh et al. 2002)
			Lactose		16384 AU mL^{-1}	
			Sucrose		2048 AU mL^{-1}	
			Xylose		2048 AU mL^{-1}	
			Fructose		512 AU mL^{-1}	
			Maltose		4096 AU mL^{-1}	
			Galactose		2048 AU mL^{-1}	
			Arabinose		1024 AU mL^{-1}	
			Raffinose		4096 AU mL^{-1}	
Enterococcus mundi WGWT1-1A	Not specified	MRS	Fructose	20 g/L	640 AU mL^{-1}	(Settanni et al. 2008)
			Lactose		320 AU mL^{-1}	
			Maltose		640 AU mL^{-1}	
			Sucrose		320 AU mL^{-1}	
			Ribose		0 mL^{-1}	
			Na-gluconate		320 AU mL^{-1}	
			Mannose		640 AU mL^{-1}	
			Xylose		0 mL^{-1}	
Enterococcus mundi WGW11.2	Not specified	MRS	Fructose	20 g/L	2560 AU mL^{-1}	(Settanni et al. 2008)
			Lactose		2560 AU mL^{-1}	
			Maltose		2560 AU mL^{-1}	
			Sucrose		320 AU mL^{-1}	
			Ribose		0 mL^{-1}	
			Na-gluconate		1280 AU mL^{-1}	
			Mannose		2560 AU mL^{-1}	
			Xylose		0 mL^{-1}	
Enterococcus mundi WGJ20.1	Not specified	MRS	Fructose	20 g/L	1280 AU mL^{-1}	(Settanni et al. 2008)
			Lactose		2560 AU mL^{-1}	
			Maltose		1280 AU mL^{-1}	
			Sucrose		640 AU mL^{-1}	
			Ribose		0 mL^{-1}	
			Na-gluconate		1280 AU mL^{-1}	
			Mannose		2560 AU mL^{-1}	
			Xylose		0 mL^{-1}	
Enterococcus mundi WGJ40.2	Not specified	MRS	Fructose	20 g/L	5120 AU mL^{-1}	(Settanni et al. 2008)
			Lactose		10240 AU mL^{-1}	
			Maltose		5120 AU mL^{-1}	
			Sucrose		2560 AU mL^{-1}	
			Ribose		1280 AU mL^{-1}	
			Na-gluconate		10240 AU mL^{-1}	
			Mannose		10240 AU mL^{-1}	
			Xylose		0 mL^{-1}	
Enterococcus mundi WGK53	Not specified	MRS	Fructose	20 g/L	2560 AU mL^{-1}	(Settanni et al. 2008)
			Lactose		5120 AU mL^{-1}	
			Maltose		2560 AU mL^{-1}	
			Sucrose		1280 AU mL^{-1}	
			Ribose		0 mL^{-1}	
			Na-gluconate		5120 AU mL^{-1}	
			Mannose		5120 AU mL^{-1}	
			Xylose		0 mL^{-1}	
Lactococcus lactis subsp. *lactis* ATCC 11454	Nisin A	MCD medium	Glucose	2.5 g/L	830 IU mL^{-1}	(Papagianni et al. 2007)
				5 g/L	950 IU mL^{-1}	
				10 g/L	6100 IU mL^{-1}	
				25 g/L	5000 IU mL^{-1}	
				35 g/L	3100 IU mL^{-1}	
				50 g/L	2500 IU mL^{-1}	
				75 g/L	450 IU mL^{-1}	
Streptococcus bovis HC5	Bovicin HC5	Basal medium	Glucose	4 g/L	3048 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	(De Carvalho et al. 2009)
			Glucose	8 g/L	5446 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Sucrose	4 g/L	444 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Sucrose	8 g/L	1185 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	

(*Continued on next page*)

Table 1. (*Continued*)

Producer Strain	Bacteriocin	Base medium	Carbon Source	Concentration	Bacteriocin production/activity	References
			Mannose	4 g/L	1422 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Mannose	8 g/L	1970 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Maltose	4 g/L	410 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Maltose	8 g/L	805 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Cellobiose	4 g/L	1084 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Cellobiose	8 g/L	2370 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Lactose	4 g/L	1230 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Lactose	8 g/L	2461 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
Enterococcus faecium SD1	Enterocin SD1	Modified MRS broth	Glucose	5 g/L	12800 AU mL^{-1}	(Schirru et al. 2014)
			Glucose	10 g/L	12800 AU mL^{-1}	
			Glucose	30 g/L	25600 AU mL^{-1}	
			Glucose	50 g/L	1600 AU mL^{-1}	
			Lactose	5 g/L	25600 AU mL^{-1}	
			Lactose	10 g/L	51200 AU mL^{-1}	
			Lactose	20 g/L	25600 AU mL^{-1}	
			Lactose	30 g/L	12800 AU mL^{-1}	
			Lactose	50 g/L	6400 AU mL^{-1}	
			D-manitol	20 g/L	0 AU mL^{-1}	
			Mannose	20 g/L	25600 AU mL^{-1}	
			Rhamnose	20 g/L	0 AU mL^{-1}	
Enterococcus faecium SD2	Enterocin SD2	Modified MRS broth	Glucose	5 g/L	3200 AU mL^{-1}	(Schirru et al. 2014)
			Glucose	10 g/L	6400 AU mL^{-1}	
			Glucose	30 g/L	6400 AU mL^{-1}	
			Glucose	50 g/L	800 AU mL^{-1}	
			Lactose	5 g/L	51200 AU mL^{-1}	
			Lactose	10 g/L	51200 AU mL^{-1}	
			Lactose	20 g/L	51200 AU mL^{-1}	
			Lactose	30 g/L	51200 AU mL^{-1}	
			Lactose	50 g/L	25600 AU mL^{-1}	
			D-manitol	20 g/L	0 AU mL^{-1}	
			Mannose	20 g/L	51200 AU mL^{-1}	
			Rhamnose	20 g/L	6400 AU mL^{-1}	
Enterococcus faecium SD3	Enterocin SD3	Modified MRS broth	Glucose	5 g/L	200 AU mL^{-1}	(Schirru et al. 2014)
			Glucose	10 g/L	200 AU mL^{-1}	
			Glucose	30 g/L	400 AU mL^{-1}	
			Glucose	50 g/L	200 AU mL^{-1}	
			Lactose	5 g/L	800 AU mL^{-1}	
			Lactose	10 g/L	3200 AU mL^{-1}	
			Lactose	20 g/L	1600 AU mL^{-1}	
			Lactose	30 g/L	400 AU mL^{-1}	
			Lactose	50 g/L	200 AU mL^{-1}	
			D-manitol	20 g/L	0 AU mL^{-1}	
			Mannose	20 g/L	1600 AU mL^{-1}	
			Rhamnose	20 g/L	0 AU mL^{-1}	
Enterococcus faecium SD4	Enterocin SD4	Modified MRS broth	Glucose	5 g/L	200 AU mL^{-1}	(Schirru et al. 2014)
			Glucose	10 g/L	200 AU mL^{-1}	
			Glucose	30 g/L	200 AU mL^{-1}	
			Glucose	50 g/L	0 AU mL^{-1}	
			Lactose	5 g/L	400 AU mL^{-1}	
			Lactose	10 g/L	400 AU mL^{-1}	
			Lactose	20 g/L	200 AU mL^{-1}	
			Lactose	30 g/L	200 AU mL^{-1}	
			Lactose	50 g/L	200 AU mL^{-1}	
			D-manitol	20 g/L	0 AU mL^{-1}	
			Mannose	20 g/L	800 AU mL^{-1}	
			Rhamnose	20 g/L	0 AU mL^{-1}	

*Diameter of inhibition halo by agar diffusion assay.
**Activity obtained in a cell-associated fermentation system.

cell growth and bacteriocin production. However, lower concentrations of this salt generate a metabolic stress effect and increased acidification of the medium, resulting in increased cell growth rates and production of bacteriocins. The effect of NaCl has also been reported in other studies (Hugas et al. 2002; Leal-Sanchez et al. 2002), where it was found that it stimulated

Table 2. Effect of different nitrogen sources supplementation on bacteriocin production by LAB.

Producer Strain	Bacteriocin	Base medium	Nitrogen Source	Concentration	Bacteriocin production	References
L. paracasei subsp. *tolerans* FX-6	Not specified	Sterilized milk	Peptone	2% (w/v)	22 mm*	(Miao et al. 2015)
			Beef extract		25 mm*	
			Yeast powder		26 mm*	
			Fish meal		25 mm*	
			Soybean protein		23 mm*	
			Ammonium sulfate		19 mm*	
			Yeast powder	1% to 5% (w/v)	26 mm (maximum at 2%)*	
Lactococcus lactis subsp. *lactis* A164	Nisin-like bacteriocin	M17 broth	Basal medium	1%	32 AU ml^{-1}	(Cheigh et al. 2002)
			Beef extract		256 AU ml^{-1}	
			Tryptone		8192 AU ml^{-1}	
			Soytone		8192 AU ml^{-1}	
			Yeast extract		16384 AU ml^{-1}	
			Peptone		1024 AU ml^{-1}	
			Casitone		4096 AU ml^{-1}	
			Proteose peptone		8192 AU ml^{-1}	
			Casein		512 AU ml^{-1}	
			Yeast extract	0.5% to 5%	32768 AU ml^{-1} (maximum at 3%)*	
Streptococcus bovis HC5	Bovicin HC5	Basal medium	Yeast extract	1.5 g/L	2909 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	(De Carvalho et al. 2009)
			Trypticase	1.5 g/L	1347 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Soy peptone	1.5 g/L	552 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Meat peptone	1.5 g/L	1230 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Casein peptone	1.5 g/L	388 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Ammonium sulfate	1.5 g/L	0 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
			Trypticase plus yeast extract	1.0 + 0.5 g/L	9310 AU ml^{-1} mg^{-1} dry cell $mass^{-1}$ **	
Lactobacillus acidophilus AA11	Not specified	Basal medium	Beef extract	1%	200 AU ml^{-1}	(Abo-Amer 2011)
			Yeast extract		12000 AU ml^{-1}	
			Tryptone		7500 AU ml^{-1}	
			Peptone		1600 AU ml^{-1}	
			Proteose peptone		6000 AU ml^{-1}	
			Casitone		3000 AU ml^{-1}	
			Casein		400 AU ml^{-1}	
			Soytone		6000 AU ml^{-1}	
Enterococcus faecium SD1	Enterocin SD1	Modified MRS broth	Tryptone	20 g/L	25600 AU ml^{-1}	(Schirru et al. 2014)
			Meat extract	20 g/L	6400 AU ml^{-1}	
			Yeast extract	20 g/L	6400 AU ml^{-1}	
			Tryptone + Meat extract	12.5 g/L + 7.5 g/L	12800 AU ml^{-1}	
			Tryptone + Yeast extract	12.5 g/L + 7.5 g/L	6400 AU ml^{-1}	
			Meat extract + Yeast extract	10 g/L + 10 g/L	25600 AU ml^{-1}	
			Tryptone + Meat extract + Yeast extract	10 g/L + 5 g/L + 5g/L	25600 AU ml^{-1}	
Enterococcus faecium SD2	Enterocin SD2	Modified MRS broth	Tryptone	20 g/L	6400 AU ml^{-1}	(Schirru et al. 2014)
			Meat extract	20 g/L	6400 AU ml^{-1}	
			Yeast extract	20 g/L	1600 AU ml^{-1}	
			Tryptone + Meat extract	12.5 g/L + 7.5 g/L	3200 AU ml^{-1}	
			Tryptone + Yeast extract	12.5 g/L + 7.5 g/L	6400 AU ml^{-1}	
			Meat extract + Yeast extract	10 g/L + 10 g/L	3200 AU ml^{-1}	
			Tryptone + Meat extract + Yeast extract	10 g/L + 5 g/L + 5g/L	25600 AU ml^{-1}	
Enterococcus faecium SD3	Enterocin SD3	Modified MRS broth	Tryptone	20 g/L	1600 AU ml^{-1}	(Schirru et al. 2014)
			Meat extract	20 g/L	400 AU ml^{-1}	
			Yeast extract	20 g/L	400 AU ml^{-1}	
			Tryptone + Meat extract	12.5 g/L + 7.5 g/L	200 AU ml^{-1}	
			Tryptone + Yeast extract	12.5 g/L + 7.5 g/L	200 AU ml^{-1}	
			Meat extract + Yeast extract	10 g/L + 10 g/L	400 AU ml^{-1}	
			Tryptone + Meat extract + Yeast extract	10 g/L + 5 g/L + 5g/L	1600 AU ml^{-1}	

(*Continued on next page*)

Table 2. (*Continued*)

Producer Strain	Bacteriocin	Base medium	Nitrogen Source	Concentration	Bacteriocin production	References
Enterococcus faecium SD4	Enterocin SD4	Modified MRS broth	Tryptone	20 g/L	800 AU ml^{-1}	(Schirru et al. 2014)
			Meat extract	20 g/L	400 AU ml^{-1}	
			Yeast extract	20 g/L	400 AU ml^{-1}	
			Tryptone + Meat extract	12.5 g/L + 7.5 g/L	200 AU ml^{-1}	
			Tryptone + Yeast extract	12.5 g/L + 7.5 g/L	200 AU ml^{-1}	
			Meat extract + Yeast extract	10 g/L + 10 g/L	400 AU ml^{-1}	
			Tryptone + Meat extract + Yeast extract	10 g/L + 5 g/L + 5g/L	800 AU ml^{-1}	

*Diameter of inhibition halo by agar diffusion assay.
**Activity obtained in a cell-associated fermentation system

cell growth rate of *L. sakei*, but had no effect on bacteriocin production.

Castro et al. (2012) observed the effect of using food-grade gums as a supplement to the culture medium. The presence of xanthan gum, carrageenan and tragacanth gum induced a higher bacteriocin production as compared to a medium without gum. This effect is probably due to the chemical characteristics of gums, including side chains with high levels of substitution and repulsion effects. As several bacteriocins may remain associated with producing cells by hydrogen bonds, these charged hydrocolloids may interact with the cell membrane and release the bacteriocins to the fermentation medium, thus increasing the yield recovery of bacteriocins.

Influence of pH on bacteriocin production

There is a consensus that the pH has a significant effect on bacteriocin production (Aasen et al. 2000; Cabo et al. 2001; Mataragas et al. 2002; Van den Berghe et al. 2006; Vignolo et al. 1995). It is known that the pH has a direct effect on the enzymatic activity of microorganisms and consequently on cell growth rates and production of several metabolites, including bacteriocins (Aasen et al. 2000; Mataragas et al. 2002; Moretro et al. 2000). Moreover, there are many mechanisms that regulate the production of bacteriocins and its activity is pH-dependent (Guerra 2014). Some authors suggest a direct relationship of pH with transport of nutrients, so that a great increase in acidity can cause failure of important cytoplasmic processes (Bibal et al. 1989; Gonçalves et al. 1997). Mechanisms of aggregation, adsorption of bacteriocin on producing cells and proteolytic degradation by specific or non-specific proteases, as well as post-translational processes for producing active bacteriocins are also sensitive to acidification of the medium (Biswas et al. 1991; Guerra 2014).

In a very acidified medium, with high levels of lactic acid, cell growth and the production of bacteriocins are greatly reduced or stop (Zamfir et al. 2000). Once the immunity of bacteriocin producing cells is based in the production of immune peptides, which are co-transcribed with the structural genes of bacteriocins, once the production of bacteriocins ceases, the production of these peptides will decrease (Abee 1995). Thus, very low pH values due to high levels of lactic acid have a negative effect on cell growth and production of bacteriocins (Zamfir et al. 2000).

Another pH-related effect that has a direct impact on bacteriocin productivity is reducing its activity due to aggregation or adsorption effects (Sharma, Garg, and Singh 2010). The adsorption process or physical aggregation of bacteriocins occurs when the bacterial cell starts to aggregate the produced antimicrobial peptides, which generally occurs during the stationary growth phase in more acidic pH values (De Arauz et al. 2009; Messens et al. 2002; Van den Berghe et al. 2006; Yang, Johnson, and Ray 1992). Furthermore, given the proteinaceous nature of bacteriocins, denaturation of the peptide structure may also occur depending of the medium pH (Vignolo et al. 1995).

Regarding the ways of conducting the fermentation process, many studies have concluded that the use of pH control systems may increase the number of cells and productivity of bacteriocins. However, the production of bacteriocins is typical of fermentative processes without pH control, and negative effects are directly related to excessive acidification of the culture medium. Thus, pH control prevents over-acidification and provides a higher productivity of cells and bacteriocins (Cheigh et al. 2002; Guerra et al. 2008; Zamfir et al. 2000; Yang and Ray 1994).

Some bacteriocin production processes require acidification of the medium to stimulate the production of bacteriocins. In these cases, a buffered process can't maximize the production of bacteriocins (Cabo et al. 2001; Guerra et al. 2008). In this sense, some investigations show that the neutralization of the medium through a fed-batch process promotes continuous acidification, which allows a significant increase in bacteriocin production yields (Cabo et al. 2001; Callewaert and De Vuyst 2000; Guerra et al. 2005; Guerra et al. 2008; Guerra and Castro 2003; Paik and Glatz 1997; Rehaiem et al. 2011; Vázquez et al. 2004).

The optimal pH range for the production of bacteriocins should be considered. Although this range may be related to the optimum pH for cell growth (Cheigh et al. 2002), some studies indicate that the optimum pH for bacteriocin production may differ from the optimal pH for cell multiplication (Dominguez et al. 2007; Mataragas et al. 2002). Therefore, it is necessary to establish this relationship for optimizing bacteriocin production.

Influence of temperature on bacteriocin production

Generally, the production of bacteriocins by LAB is described as a process sensitive to temperature. The same way for the pH, the temperature has a direct effect on the enzymatic activity of microorganisms and consequently on cell growth rates (Aasen et al. 2000; Mataragas et al. 2002; Moretro et al. 2000).

Several studies suggest that better bacteriocin production rates are achieved at temperatures below the optimum temperature for cell growth (Delgado et al. 2005; De Vuyst et al. 1996; Hurtado et al. 2011; Moretro et al. 2000; Pattnaik et al. 2001; Todorov and Dicks 2005). In some cases, the optimum temperature for bacteriocin production can be found in significantly lower values than the optimum growth temperature. For example, the optimum temperature for the growth of *Streptococcus macedonicus* ACA-DC 198 is 42.3°C, while the optimum temperature for bacteriocin production is 20–25°C (Van den Berghe et al. 2006).

However, suboptimal temperatures are not a general rule. Investigations with microorganisms like *E. faecium* RZS C5 (Leroy and De Vuyst 2002), *Pediococcus acidilactici* 13 (Altuntas, Cosansu, and Ayhan 2010), showed no significant differences in the production of bacteriocins between the optimum temperature for growth and sub-optimal temperatures. Thus, to maximize the production of bacteriocins, it seems necessary to investigate the effects of optimal and suboptimal temperatures, which are inherent to each LAB strain.

Parameter optimization for bacteriocin production

As noted in previous sections, several factors have impact on the production of bacteriocins by LAB. Additionally, the determination of the optimum value for each parameter must be investigated for each specific fermentation process and producer strain. However, treating separately each factor that can influence the process is a very time consuming and costly work. This approach can also lead to experimental errors by not considering the combined effect of different factors, where two factors evaluated separately when run on their optimized values may not produce the best result (Li et al. 2002; Myers and Montgomery 2002).

Within this context, the use of factorial design methodology associated with the response surface analysis is a tool based in statistical theory, which provides techniques for design experiments, build mathematical models, evaluate the factor effects, and search the optimum conditions for the desired response (Abee 1995; Cladera-Olivera et al. 2004). Among the advantages related to this methodology, there is a reduction in the number of experiments or repetitions with an improved quality of the information obtained, and the possibility of evaluating factors simultaneously. The methodology also allows to optimize more than one answer at the same time besides to calculate and evaluate the experimental error. But as every methodology there are some risks associated, as example if the critic factors are not correctly specified or a wide range is being used for a critical factor the results obtained can take to wrong conclusions (Myers and Montgomery 2002). The major disadvantage of response surface analysis is to fit the data to a second order polynomial. For example, the effect of temperature on biochemical processes is described by symmetrical or nonsymmetrical bell-shaped curves. Thus, it is not possible to explain the effect of temperature with a second order polynomial, especially when the curve is nonsymmetrical. To overcome this limitation, the data can be converted into another form that can be explained by the second order model (Bas and Boyaci 2007).

Despite this technique was proposed in the 1950's, it has been more intensively exploited in recent years (Myers and Montgomery 2002) and is already used in some studies to determine the optimal parameters for the production of bacteriocins (Anthony et al. 2009; Cladera-Olivera et al. 2004; Delgado et al. 2005; Dominguez et al. 2007; Miao et al. 2015). A study that can exemplify it was performed by Li et al. (2002), which investigated the medium composition for bacteriocin production by *L. lactis* ATCC 11454. The authors used a factorial fractioned design to study the effect of six different nutritional components in the cultivation medium. It was determined which components were significant for the production of bacteriocin and the optimum medium composition to produce the bacteriocin. The optimized medium allowed bacteriocin yield to be doubled as compared to regular medium.

Conclusion

The production of bacteriocins by LAB has been suggested as a promising and safe alternative for use as alternative to chemical preservatives in food. Several studies have been conducted to identify and characterize new bacteriocins, however, their effective use by the food industry still need great advances in the development and optimization of production techniques in order to guarantee stability, safety and cost reduction. As discussed in this paper, many factors can significantly affect the production of bacteriocins and each bacterial strain have a different metabolic characteristic, which requires investigative studies to define what are the critical factors that affect the fermentation process and how to optimize each factor considering all costs involved in the process. One way to optimize these studies and understand the interaction that the various factors have on the productivity of bacteriocins is the use of factorial design methodology.

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