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The impact of cell-free supernatants of *Lactococcus lactis* subsp. *lactis* strains on the tyramine formation of *Lactobacillus* and *Lactiplantibacillus* strains isolated from cheese and beer

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ABSTRACT

Tyramine is one of the most toxic biogenic amines and it is produced commonly by lactic acid bacteria in fermented food products. In present study, we investigated the influence of selected nisin-producing *Lactococcus lactis* subsp. *lactis* strains and their cell-free supernatants (CFSs) on tyramine production by four *Lactobacillus* and two *Lactiplantibacillus* strains isolated from cheese and beer. Firstly, we examined the antimicrobial effect of the CFSs from twelve *Lactococcus* strains against tested tyramine producers by agar-well diffusion assay. Six *Lactococcus* strains whose CFSs showed the highest antimicrobial effect on tyramine producers were further studied. Secondly, we investigated the influence of the selected six *Lactococcus* strains and their respective CFSs on tyramine production by tested *Lactobacillus* and *Lactiplantibacillus* strains in MRS broth supplemented with 2 $g.L^{-1}$ of L-tyrosine. Tyramine production was monitored by HPLC-UV. The tyramine formation of all tested *Lactobacillus* and *Lactiplantibacillus* strains was not detected in the presence of *Lc. lactis* subsp. *lactis* CCDM 71 and CCDM 702, and their CFSs. Moreover, the remainder of the investigated *Lactococcus* strains (CCDM 670, CCDM 686, CCDM 689 and CCDM 731) and their CFSs decreased tyramine production significantly ($P < 0.05$) – even suppressing it completely in some cases – in four of the six tested tyramine producing strains.

1. Introduction

Nowadays, more and more consumers prefer the 'natural' food, especially that which is without additives, processed minimally, high quality and undoubtedly safe. Therefore, the importance of developing new approaches in food-preservation techniques has been increasing over the past few years (Lucera et al., 2012; Barberis et al., 2018). Several publications demonstrate the potential use of antagonistic microorganisms or their antimicrobial metabolites as natural preservatives against the common spoilage or pathogenic microorganisms in a variety of foodstuffs (Cizeikiene et al., 2013; Comi et al., 2016; Siroli et al., 2016; Ramos et al., 2020). The ability to produce an array of antimicrobial metabolites and a long history of using lactic acid bacteria (LAB) in fermented foods have great potential in the biopreservation of foods. The preservative effect of LAB correlates especially with the production of bacteriocins, organic acids, diacetyl, hydrogen peroxide and/or carbon dioxide (Reis et al., 2012). The use of bacteriocin-producing LAB or purified bacteriocins has been attracting much attention during recent years (Perez et al., 2014; Favaro et al., 2015).

The bacteriocins produced by LAB are ribosomally synthesized peptides, which commonly consist of 20–60 amino acid residues (Nes and Holo, 2000). These peptides are thermostable and retain their activity across a wide range of pH values. In general, they are degradable by proteases in the digestive tract, for instance nisin. Therefore, they do not significantly affect the composition of gut microflora (Perez et al., 2014). Hovewer, a study by Umu et al. (2020) suggests that some bacteriocins have potential to transiently modulate the relative abundance of specific bacterial populations in the human gut. To date, nisin is the only bacteriocin approved for use as a food additive in the European Union (EU) according to Annex II of Regulation (EC) 1333/2008

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(European Regulation, 2008). It is a polypeptide consisting of 34 amino acids and is generally produced by *Lactococcus lactis* subsp. *lactis* (European Food Safety Authority [EFSA], 2006). Nisin is mainly active against gram-positive bacteria due to its interaction with the membrane-bound cell wall precursor lipid II, resulting in the inhibition of peptidoglycan synthesis (Nes et al., 2007; Lucera et al., 2012).

Biogenic amines (BAs) are nitrogenous substances with biological activity (Silla Santos, 1996). Although these compounds perform important physiological roles in the human body, intaking them excessively can induce several adverse health effects (Ladero et al., 2010). Intoxication by BAs is a particular concern of the European Food Safety Authority, which has been underlined by Question No. EFSA-Q-2009-00829 (EFSA, 2011). Based on this qualitative risk assessment of BAs, the EFSA Panel on Biological Hazards has concluded that tyramine is considered to be one of the most toxic BAs (as is histamine), which is particularly relevant for food safety (EFSA, 2011).

The formation and accumulation of tyramine in foods requires the availability of free amino acids, the presence of microorganisms with tyrosine decarboxylases, and conditions allowing their growth and decarboxylating activity (Suzzi and Gardini, 2003). Intoxication by tyramine is often due to the consumption of cheese. Therefore, this form of intoxication is known as a 'cheese reaction' and it can cause several health problems; for instance, nausea, vomiting, migraine, neurological disorders, hypertension and respiratory disorders (del Rio et al., 2017). The production of tyramine in cheese is a very complex process and depends on several factors. However, BA concentrations in cheese can reach up to 2000 mg kg^{-1} (Roig-Sagués et al., 2002). The consumption of such cheeses and alcoholic beverages (for instance, beer) is a direct threat to the consumer. Since beer is commonly reported to be a source of tyramine and other BAs (Kalač et al., 2002; Buňka et al., 2012; Lorencová et al., 2012), and taking into account the amount of beer consumed in the Czech Republic (142 L per capita), tyramine intake can easily reach health-hazardous levels. Moreover, alcohol or other BAs present in beer can increase tyramine absorption, and thus enhances its vasopressor effect (EFSA, 2011).

Ensuring food safety is one of the main tasks of the food industry. The potential toxicity of BAs, especially tyramine and histamine, has led food manufacturers to consider the content of BAs during the hazard analysis carried out in the process of developing and maintaining food-safety management systems. Therefore, the researchers have investigated the possibilities for preventing the accumulation of BAs in food. To date, most studies have focused on the factors influencing the decarboxylase activity and isolation and characterization of microorganisms with amino-oxidase activity (Buňková et al., 2011; Capozzi et al., 2012; Eom et al., 2015). Additionally, very few studies have examined the effect of cell-free supernatants on BA-producing food-borne pathogens and bacteriophages to target the population of BA-producing bacteria (Ö;zogul, 2011; Kuley et al., 2012; Toy et al., 2015; Ö;zogul et al., 2017; del Rio et al., 2019). However, there are scarcely any studies on the interactions between bacteriocin-producing microorganisms and BA producers, and no information exists regarding the tyramine formation by LAB in the presence of bacteriocin-producing strains or their antimicrobial compounds. Therefore, the objectives of the present study were to examine the antimicrobial effect of nisin-producing *Lc. lactis* subsp. *lactis* strains on tyramine producers and to determine the impact of these strains and their cell-free supernatants (CFSs) on the tyramine (TYM) production of *Lactobacillus* and *Lactiplantibacillus* strains isolated from cheese and beer.

2. Material and methodology

The whole experiment consisted of two phases. In the first phase, the antimicrobial effect of CFSs from twelve *Lactococcus* strains was determined against four tyramine-producing *Lactobacillus* and two *Lactiplantibacillus* strains. The aim of the first phase was to select the *Lactococcus* strains showing the greatest amount of antibacterial activity against the tyramine-positive strains tested. In the second phase, the six *Lactococcus* strains (and their respective CFSs) that demonstrated the highest antagonistic effect against the observed tyramine producers were selected and investigated with respect to their impact on tyramine production.

2.1. Strains and growth conditions

Seven *Lc. lactis* subsp. *lactis* strains (CCDM 71, CCDM 414, CCDM 416, CCDM 418, CCDM 671, CCDM 702 and CCDM 731) and five *Lc. lactis* subsp. *lactis* biovar *diacetylactis* strains with the ability to produce nisin (CCDM 670, CCDM 686, CCDM 689, CCDM 695 and CCDM 698) and *Lactococcus lactis* subsp. *lactis* S32 as negative control (nisin-negative strain – nisin operon is no present) was obtained from were obtained from the Culture Collection of Dairy Microorganisms Laktoflora® (MILCOM) (Prague, Czech Republic). *Micrococcus luteus* CCDM 732 as positive (nisin-sensitive) control Czech Collection of Microorganisms (Brno, Czech Republic). Cheese isolates with tyrosine decarboxylase activity (*Lactobacillus curvatus* DEPE T3, DEPE T15 and DEPE T36) were acquired from the Collection of Microorganisms, Department of Environmental Protection Engineering (DEPE), Tomas Bata University in Zlín, Czech Republic. Tyramine-producing strains isolated from beer (*Lb. brevis* RIBM P93, and *Lactiplantibacillus plantarum* RIBM P89 and RIBM P96) were obtained from the Research Institute of Brewing and Malting (RIBM) Culture Collection (Prague, Czech Republic). All the tested bacteria was stored in the presence of 30% (v/v) glycerol (PENTA, Prague, Czech Republic) at −80 ± 1 °C and subcultured twice before use in the experiments. The tested lactococci were subcultured in M17 broth (Oxoid, Basingstoke, United Kingdom) at 30 ± 1 °C under aerobic conditions for 24 h. For the lactobacilli and *L. plantarum*, the broth used was De Man, Rogosa and Sharpe (MRS) (Merck, Darmstadt, Germany) containing L-tyrosine 2 $g.L^{-1}$ (Sigma-Aldrich, St Louis, USA) and it was cultivated anaerobically at 37 ± 1 °C for 48 h.

2.2. Screening of the antibacterial activity of the cell-free supernatants (CFSs) from Lactococcus strains

2.2.1. Preparation of cell-free supernatants (CFSs)

The twelve nisin-producing *Lc. lactis* subsp. *lactis* strains were cultivated in 20 mL of M17 broth (1% inoculum, v/v) at 30 ± 1 °C under aerobic conditions for 48 h. After the 48-h cultivation, the cells were removed using centrifugation at 10,000 × *g* for 10 min at 4 ± 1 °C. The obtained CFSs were adjusted to pH 6.0 ± 0.1 with 10% (w/v) NaOH (PENTA, Prague, Czech Republic) in order to eliminate the inhibition effect due to organic acids (under a low pH) according Hu et al. (2017). The CFSs were then sterilized by being filtered through a 0.22 μm membrane filter (Sigma-Aldrich, St Louis, USA) and used immediately in the experiments.

2.2.2. Agar-well diffusion assay

The antimicrobial activity of the CFSs from the tested *Lactococcus* strains against the tyramine-producing strains was investigated using agar-well diffusion assay (Pongtharangkul and Demirci, 2004). The overnight cultures of lactobacilli and *L. plantarum* were diluted serially in a 0.85% (w/v) NaCl (PENTA, Prague, Czech Republic) solution. A fraction (1 mL) of the dilution 10^{-2} was inoculated into a sterile Petri dish, then 20 mL of MRS agar was added and mixed with swirling. After solidification, five wells (6 mm in diameter) were punched using a sterile cork borer, and 100 μL of each tested CFS was added to the appropriate well. After incubation at 37 ± 1 °C for 24–48 h, the antimicrobial activities of the CFSs were determined by measuring the inhibition zones (mm). The test was performed six times. The inhibition was recorded as negative if no zone was observed around the agar well.

2.3. Determination of an impact of selected Lactococcus strains and their CFSs on tyramine production

The impact of selected nisin-producing *Lc. lactis* strains and their CFSs on tyramine production by *Lb. curvatus* (DEPE T3, DEPE T15 and DEPE T36), *Lb. brevis* (RIBM P93) and *L. plantarum* (RIBM P89 and RIBM P96) were examined using MRS broth supplemented with 2 $g.L^{-1}$ of L-tyrosine (MRS+). The first set of tubes with 7 mL of MRS+ was inoculated with only overnight cultures of tyramine-producers (100 μL; ca 10^7 CFU mL^{-1}) and used as control samples. The second set of tubes with 7 mL of MRS+ was inoculated with 100 μL of overnight cultures of tyramine-producing strains and with 100 μL of overnight cultures of nisin-producing *Lactococcus* strains. The third set of tubes with 7 mL of MRS+ was inoculated with 100 μL of overnight cultures of tyramine-producing strains and with 500 μL of neutralized CFSs from the investigated *Lactococcus* strains. After 24-h and 48-h cultivations at 37 ± 1 °C, samples were collected from which to determine the tyramine content. All factors were tested in triplicate.

The bacterial enumeration was determined by counting the cells (CFU.mL^{-1}) spread on the agar plates of MRS in the case of *Lactobacillus* and *Lactiplantibacillus* strains, and on agar plates of M17 in the case of *Lactococcus* strains. Serial tenfold dilutions were plated. The *Lactobacillus* and *Lactiplantibacillus* strains were incubated anaerobically at 37 ± 1 °C for 24–48 h. The lactococci were incubated at 30 ± 1 °C under aerobic conditions for 24 h.

2.3.1. Determination of tyramine content of samples

The tyramine content in samples were determined by HPLC-UV. The samples were collected after 24-h and 48-h cultivation and were centrifuged at 3500 × *g* for 20 min at 22 ± 1 °C.The acquired supernatant (600 μL) was diluted (1:1; v/v) with perchloric acid (1.2 $mol.L^{-1}$; Sigma-Aldrich, St Louis, USA). The acidified mixture was filtered (0.22 μm membrane filter; Sigma-Aldrich, St Louis, USA), and the filtrate was subjected to derivatization, according to Dadáková et al. (2009). The derivatized samples were filtered (0.22 μm membrane filter; Sigma-Aldrich, St Louis, USA) and applied on a column (ZORBAX RRHD Eclipse Plus C18, 50 × 3.0 mm, 1.8 μm, Agilent Technologies, Santa Clara, USA) of a chromatographic system (Thermo Fisher Scientific, Waltham, Massachusetts, USA). UV/VIS detection was carried out at a wavelength of 254 nm and a column temperature of 30 °C. The conditions for the separation and detection of BA are described by Smělá et al. (2004); 1.7-heptanediamine (Sigma-Aldrich, St Louis, USA) was used as an internal standard. Each of the three samples prepared for one tested microorganism was derivatized twice, and each derivatized mixture was also applied on the column twice (n = 12). Data were acquired and evaluated using Chromeleon™ 6.8 software (Thermo Fisher Scientific, USA).

Based on the determination of the colony-forming unit (CFU) and tyramine content, the yield factors ($Y_{TYM/CFU}$; mg × 10^{12} CFU^{-1}) were calculated. Similar approaches were applied by Emborg and Dalgaard (2008) or Buňková et al. (2011), for example.

2.4. Statistical analysis

The differences between the tyramine productions of the individual strains were evaluated statistically by Kruskall–Wallis and Wilcoxon tests using the Unistat 5.6 (Unistat Ltd., London, UK) statistical program. The significance level used in the tests was 0.05.

3. Results

3.1. Selection of Lactococcus strains based on antimicrobial activity of their CFSs on lactobacillus strains

In the present study, none of the tested *Lactococcus strains* and their CFSs increased the tyramine production by fermented-food isolates. Seven strains of *Lc. lactis* subsp. *lactis* and five strains of *Lc. lactis* subsp. *lactis* biovar *diacetylactis* that are able to produce nisin were screened for their antimicrobial activity on six tyramine-producing strains isolated from cheese and beer. The antibacterial activity was determined using agar-well diffusion assay. This initial phase of research was carried out to select the *Lactococcus* strains, based on the antimicrobial activity of the CFSs, for the further examination of their impact on the tyramine (TYM) production by the tested *Lactobacillus* and *Lactiplantibacillus* strains.

The CFSs from three *Lc. lactis* subsp. *lactis* strains (CCDM 414, CCDM 416 and CCDM 418) showed no inhibition effect with respect to the tested tyramine producers. Two controls was used: *Micrococcus luteus* CCDM 732 as positive (nisin-sensitive) control and inhibition zones was observed (19.1 ± 0.9 mm) in all tested lactococci. The second control was *Lactococcus lactis* subsp. *lactis* S32 as negative control (nisin-negative strain – nisin operon is no present) and inhibition effect was not shown in all tested strains, including *M. luteus* CCDM 732. The rest of the examined CFSs from the nine *Lactococcus* strains displayed different levels of antimicrobial activity on the tyramine producers. The inhibitory spectra of the tested CFSs are highlighted in Table 1. The cheese isolates (DEPE T3, DEPE T15 and DEPE T36) were highly sensitive to the antimicrobials present in the CFSs, particularly from strains CCDM 71, CCDM 670, CCDM 686, CCDM 689, CCDM 702 and CCDM 731. The diameters of the inhibition zones ranged from 15.0 to 19.0 mm (including the 6 mm diameter of the well). The biggest inhibition-zone diameter detected (19.0 mm) was obtained with CFSs from the strain *Lc. lactis* subsp. *lactis* CCDM 71 on *Lb. curvatus* DEPE T3. This strain also displayed great susceptibility to CFSs from the *Lc. lactis*

Table 1
Antimicrobial activity of cell-free supernatants (CFS) from tested *Lactococcus lactis* subsp. *lactis* strains (CCDM) on tyramine-producing *Lactobacillus* strains [mean value (mm) ± S.D.; n = 6; ND – no inhibition zone].

Lactococcus strains	Inhibition zones of tested *Lactobacillus* and *Lactiplantibacillus* strains					
	DEPE T3	DEPE T15	DEPE T 36	RIBM P89	RIBM P93	RIBM P96
CCDM 71	19.0 ± 0.0	17.0 ± 0.0	17.5 ± 0.7	16.0 ± 0.0	17.5 ± 0.7	16.5 ± 0.7
CCDM 414	ND	ND	ND	ND	ND	ND
CCDM 416	ND	ND	ND	ND	ND	ND
CCDM 418	ND	ND	ND	ND	ND	ND
CCDM 670	16.5 ± 0.7	15.5 ± 0.7	17.0 ± 0.0	14.5 ± 0.7	14.5 ± 0.7	14.5 ± 0.7
CCDM 671	10.5 ± 0.7	10.0 ± 0.0	10.0 ± 0.0	12.5 ± 0.7	13.5 ± 0.7	12.5 ± 0.7
CCDM 686	15.0 ± 0.0	15.5 ± 0.7	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	15.5 ± 0.7
CCDM 689	15.0 ± 0.0	15.5 ± 0.7	16.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0
CCDM 695	13.0 ± 0.0	14.5 ± 0.7	13.5 ± 0.7	10.0 ± 0.0	10.0 ± 0.0	9.5 ± 0.7
CCDM 698	13.0 ± 0.0	13.5 ± 0.7	13.0 ± 0.0	8.5 ± 0.7	9.5 ± 0.7	10.0 ± 0.0
CCDM 102	18.5 ± 0.7	17.5 ± 0.7	16.5 ± 0.7	16.5 ± 0.7	16.5 ± 0.7	16.5 ± 0.7
CCDM 731	17.0 ± 0.0	17.0 ± 0.0	17.0 ± 0.0	16.0 ± 0.0	17.0 ± 0.0	16.5 ± 0.7

subsp. *lactis* CCDM 702 and CCDM 731 (18.5 mm and 17.0 mm inhibition zones, respectively). Inhibition zones of similar sizes to those of these CFSs were also observed for *Lb. curvatus* DEPE T15 and DEPE T36. The weakest antimicrobial activity on the cheese isolates tested was displayed for the CFS from strain *Lc. lactis* subsp. *lactis* CCDM 671 (inhibition zones of 10.0–10.5 mm). On the other hand, the beer isolates (RIBM P89, RIBM P93 and RIBM P96) were the least inhibited by the CFSs from the *Lc. lactis* subsp. *lactis* biovar *diacetylactis* CCDM 698 (8.5–10.0 mm) and from the *Lc. lactis* subsp. *lactis* biovar *diacetylactis* CCDM 695 (9.5–10.0 mm). The inhibition zones for the remainder of the seven CFSs ranged from 12.5 to 17.5 mm. The growth of beer isolates, as well as cheese isolates, was greatly inhibited by the CFSs from the strains CCDM 71, CCDM 702 and CCDM 731 (16.0–17.5 mm).

Taking into account the results described previously, six strains (CCDM 414, CCDM 416, CCDM 418, CCDM 671, CCDM 695 and CCDM 698) whose CFSs showed the smallest or no inhibitory effect on tested tyramine producers were excluded from further study.

3.2. Effect of the selected Lactococcus strains and their CFSs on the tyramine production by Lactobacillus and Lactiplantibacillus strains

Based on the findings presented in section 3.1, six nisin-producing strains of *Lc. lactis* subsp. *lactis* (CCDM 71, CCDM 670, CCDM 686, CCDM 689, CCDM 702 and CCDM 731) and their CFSs (CFS 71, CFS 670, CFS 686, CFS 689, CFS 702 and CFS 731) were investigated regarding their impact on tyramine production by *Lb. curvatus* (DEPE T3, DEPE T15 and DEPE T36), *Lb. brevis* RIBM P93 and *L. plantarum* (RIBM P89 and RIBM P96). The amounts of TYM produced ($mg.L^{-1}$) by the tested cheese and beer isolates in the presence of the investigated *Lactococcus* strains and their CFSs are presented in Tables 2 and 3.

In the control samples, the formation of TYM by the tested cheese isolates varied from 14.7 ± 1.2 $mg.L^{-1}$ to 786.1 ± 47.4 $mg.L^{-1}$ after a 24-h cultivation, and from 15.1 ± 1.3 $mg.L^{-1}$ to 875.9 ± 62.1 $mg.L^{-1}$ after a 48-h cultivation. The highest concentrations of TYM detected were produced by strain *Lb. curvatus* DEPE T15 ($P < 0.05$). On the con-

Table 2
Tyramine production ($mg.L^{-1}$) by *Lactobacillus* strains isolated from cheese (DEPE T3, DEPE T15 and DEPE T36) in the presence of investigated *Lactococcus lactis* subsp. *lactis* strains (CCDM) and their cell-free supernatant (CFS) after a 24- and 48-h cultivation in MRS + broth (mean ± S.D.; n = 12; ND = not detected).

Lactococcus strains and their CFS	Tyramine producers					
	DEPE T3		DEPE T15		DEPE T36	
	24 h	48 h	24 h	48 h	24 h	48 h
Control	14.7 ± 1.2 ^{d}A*	15.1 ± 1.3 ^{e}A	786.1 ± 47.4 ^{c}A	875.9 ± 62.1 ^{c}A	16.4 ± 1.0 ^{c}A	18.1 ± 1.1 ^{d}B
CCDM 71	ND	ND	ND	ND	ND	ND
CFS 71	ND	ND	ND	ND	ND	ND
CCDM 670	ND	ND	722.7 ± 50.6 ^{c}A	793.5 ± 52.5 ^{c}A	ND	ND
CFS 670	ND	ND	759.0 ± 49.9 ^{c}A	873.1 ± 51.2 ^{c}B	ND	ND
CCDM 686	10.7 ± 0.9 ^{c}A	10.8 ± 0.9 ^{c}A	783.4 ± 59.7 ^{c}A	799.1 ± 60.3 ^{c}A	15.5 ± 1.3 ^{c}A	16.8 ± 1.4 ^{d}A
CFS 686	9.3 ± 0.8 ^{c}A	12.6 ± 1.0 ^{d}B	718.3 ± 50.7 ^{c}A	821.9 ± 61.4 ^{c}A	7.3 ± 0.3 ^{b}A	6.7 ± 1.3 ^{c}A
CCDM 689	6.9 ± 0.5 ^{b}B	2.69 ± 0.20 ^{a}A	758.0 ± 47.5 ^{c}A	852.5 ± 50.3 ^{c}B	6.1 ± 0.3 ^{a}B	3.8 ± 0.2 ^{b}A
CFS 689	5.1 ± 0.3 ^{a}B	4.30 ± 0.39 ^{b}A	705.2 ± 45.9 ^{c}A	875.8 ± 49.8 ^{c}B	6.1 ± 0.2 ^{a}B	1.8 ± 0.5 ^{a}A
CCDM 702	ND	ND	ND	ND	ND	ND
CFS 702	ND	ND	ND	ND	ND	ND
CCDM 731	ND	ND	29.1 ± 0.5 ^{a}A	31.1 ± 2.5 ^{a}A	ND	ND
CFS 731	ND	ND	56.6 ± 1.2 ^{b}A	64.8 ± 4.2 ^{b}B	ND	ND

* The means within a column (the difference between used protective strain or its cell-free supernatant and also between individual *Lactococcus* strains) followed by different superscript letters differ ($P < 0.05$). The means within a line (the difference between cultivation times) followed by different capital letters differ ($P < 0.05$); samples with different tyramine-positive strains were evaluated separately.

Table 3
Tyramine production ($mg.L^{-1}$) by *Lactobacillus* strains isolated from beer (RIBM P89, RIBM P93 and RIBM P96) in the presence of investigated *Lactococcus lactis* subsp. *lactis* strains (CCDM) and their cell-free supernatant (CFS) after a 24- and 48-h cultivation in MRS + broth (mean ± S.D.; n = 12; ND = not detected).

Lactococcus strains and their CFS	Tyramine producers					
	RIBM P89		RIBM P93		RIBM P96	
	24 h	48 h	24 h	48 h	24 h	48 h
Control	247.9 ± 18.7 ^{e}A*	331.1 ± 21.2 ^{e}B	588.5 ± 42.2 ^{f}A	727.9 ± 51.2 ^{f}B	15.2 ± 1.1 ^{d}A	16.4 ± 1.1 ^{c}A
CCDM 71	ND	ND	ND	ND	ND	ND
CFS 71	ND	ND	ND	ND	ND	ND
CCDM 670	19.1 ± 1.3 ^{c}A	27.6 ± 2.0 ^{c}B	35.2 ± 2.3 ^{b}A	38.2 ± 2.1 ^{b}A	2.4 ± 0.1 ^{a}A	3.9 ± 0.2 ^{a}B
CFS 670	14.8 ± 1.0 ^{b}A	17.8 ± 1.1 ^{b}B	21.2 ± 1.3 ^{a}A	22.1 ± 1.3 ^{a}A	ND	ND
CCDM 686	53.6 ± 4.0 ^{d}A	72.8 ± 5.9 ^{d}B	127.5 ± 10.0 ^{d}A	208.9 ± 12.4 ^{d}B	8.6 ± 0.6 ^{c}A	15.0 ± 1.0 ^{c}B
CFS 686	4.5 ± 0.4 ^{a}A	6.2 ± 0.4 ^{a}B	40.8 ± 2.0 ^{c}A	50.3 ± 4.0 ^{c}B	ND	ND
CCDM 689	232.9 ± 17.6 ^{e}A	326.1 ± 20.5 ^{e}B	274.0 ± 21.1 ^{e}A	490.4 ± 32.6 ^{e}B	6.1 ± 0.5 ^{b}A	7.3 ± 0.5 ^{b}B
CFS 689	226.4 ± 17.0 ^{e}A	314.5 ± 22.4 ^{e}B	279.8 ± 20.2 ^{e}A	510.3 ± 30.0 ^{e}B	5.9 ± 0.4 ^{b}A	6.5 ± 0.4 ^{b}B
CCDM 702	ND	ND	ND	ND	ND	ND
CFS 702	ND	ND	ND	ND	ND	ND
CCDM 731	ND	ND	ND	ND	ND	ND
CFS 731	ND	ND	ND	ND	ND	ND

* The means within a column (the difference between used protective strain or its cell-free supernatant and also between individual *Lactococcus* strains) followed by different superscript letters differ ($P < 0.05$). The means within a line (the difference between cultivation times) followed by different capital letters differ ($P < 0.05$); samples with different tyramine-positive strains were evaluated separately.

trary, the TYM accumulated by each of *Lb. curvatus* DEPE T3 and DEPE T36 was below 20 mg.L^{-1} after a 48-h cultivation. The TYM production by the strain DEPE T15 was not detected after the cultivation with the strain *Lc. lactis* subsp. *lactis* CCDM 71 and CCDM 702, and their CFSs. Moreover, strain CCDM 731 and its CFS reduced the amounts of tyramine to 4% and 7%, respectively, compared to the controls after a 48-h cultivation ($P < 0.05$). Similarly, if the absolute value of TYM formation was recalculated on production of individual cells (represented as yield factor, $Y_{TYM/CFU}$), the lowest yield of TYM per CFU was also detected in the presence of strain CCDM 731 and its CFS ($P < 0.05$; Table 4). No significant ($P > 0.05$) inhibition of TYM production was observed in the presence of the other tested *Lactococcus* strains and their CFSs. On the contrary, the formation of tyramine by strain DEPE T3 was significantly ($P < 0.05$) reduced in all cases. The cultivation of this lactobacilli with strain CCDM 689 and its CFS decreased the amounts of TYM to 18% and 29%, respectively, compared to the controls after 48 h ($P < 0.05$). An analogous reduction of TYM was also detected in strain *Lb. curvatus* DEPE T36. After a 48-h cultivation, strain CCDM 689 and its CFS decreased the TYM concentrations to 21% and 10%, respectively ($P < 0.05$). On the other hand, the TYM production by individual cells ($Y_{TYR/CFU}$) of these lactobacilli was equal in presence of strain CCDM 686 and its CFSs ($P > 0.05$). In the presence of the remainder of tested *Lactococcus* strains (CCDM 71, CCDM 670, CCDM 702 and CCDM 731) and their CFSs, tyramine production by these cheese isolates (DEPE T3 and DEPE T36) was not detected.

The tested beer contaminants (RIBM P89, RIBM P93 and RIBM P96) were able to accumulate TYM in concentrations from 15.2 ± 1.1 to 588.5 ± 42.2 mg.L^{-1} after a 24-h cultivation and from 16.4 ± 1.1 to 727.9 ± 51.2 mg.L^{-1} after a 48-h cultivation (Table 3). Among the beer isolates, the highest TYM production (727.9 ± 51.2 mg.L^{-1} after 48 h) was detected in strain *Lb. brevis* RIBM 93. It is noteworthy that the tyramine formation by this strain was significantly ($P < 0.05$) decreased by all tested *Lactococcus* strains and their CFSs. The TYM production by individual cells of this strain, represented as yield factor ($Y_{TYM/CFU}$), was very weak in the presence of CFS 670, CCDM 670 and CFS 686, for which the TYM concentration diminished to 4%, 6% and 7%, respectively, compared to the control samples after 48 h ($P < 0.05$; Fig. 1, part B). An equivalent reduction in TYM accumulation was also observed for *L. plantarum* RIBM P89. After a 48-h cultivation, strain CCDM 670 decreased the amount of TYM to 8%, the CFS 670 to 5% and the CFS 686 to 2% compared to the control samples ($P < 0.05$; Fig. 1, part A). The TYM production of the individual cells of strain RIBM P89 ($Y_{TYM/CFU}$) was the least affected ($P > 0.05$) in the presence of *Lc. lactis* subsp. *lactis* biovar *diacetylactis* CCDM 689 and its CFS. On the contrary, this strain and its CFS significantly ($P < 0.05$) diminished the formation of TYM by *L. plantarum* RIBM P96. Reductions in the amounts of tyramine to 48% and 40% after a 48-h cultivation were detected ($P < 0.05$; Fig. 1, part C). Furthermore, the TYM formation by this beer isolate was not observed after cultivation with the CFSs from strains CCDM 670 and CCDM 686. However, no significant effect ($P > 0.05$) on TYM formation was noticed in presence of *Lactococcus* strain CCDM 686. The tyramine production of all beer isolates tested was not detected in the presence of *Lc. lactis* subsp. *lactis* CCDM 71, CCDM 702 and CCDM 731, and their CFSs.

4. Discussion

To our knowledge, this is the first study describing the impact of nisin-producing Lactococcus strains and their CFSs on tyramine production by selected Lactobacillus and Lactiplantibacillus strains. Our results show that using nisin-producing Lactococcus strains or their CFSs can reduce significantly the accumulation of tyramine. This is suggesting that application of bacteriocinogenic strain or their CFSs can enhance the safety and quality of fermented products.

To preserve their existence or ecological niche, many species have established advanced antimicrobial defence systems against competitor microorganisms (Cleveland et al., 2001). The antimicrobial effect of LAB is due to the production of bacteriocins and other antagonistic compounds, such as organic acids, diacetyl and/or hydrogen peroxide (Reis et al., 2012). The antibacterial activity of LAB against BA-negative food spoilage and pathogenic microorganisms has been reported previously (Hwanhlem et al., 2017; Kondrotiene et al., 2018).

Table 4
The values of yield factor for tyramine formation $Y_{TYM/CFU}$ (mg × 10^{12}/CFU) of six *Lactobacillus* strains (DEPE T3, DEPE T15, DEPE T36, RIBM P89, RIBM P93 and RIBM P96) in presence of investigated protective *Lactococcus lactis* subsp. *lactis* strains (MO) and/or their cell-free supernatant (CFS) after a 24- and 48-h cultivation (mean ± S.D.; n = 12).

Protective strain	MO/CFS	Time of cultivation	$Y_{TYM/CFU}$ (mg × 10^{12}/CFU)					
			DEPE T3	DEPE T15	DEPE T36	RIBM P89	RIBM P93	RIBM P96
Control sample		24	24.1 ± 2.0 $^{a}E_{c}$	2067.6 ± 124.7 $^{a}C_{f}$	20.9 ± 1.3 $^{a}C_{b}$	188.0 ± 14.1 $^{b}E_{d}$	616.3 ± 44.2 $^{b}E_{e}$	9.4 ± 0.7 $^{a}D_{a}$
		48	24.2 ± 2.1 $^{a}E_{a}$	2006.6 ± 142.3 $^{a}C_{f}$	64.6 ± 4.1 $^{b}D_{d}$	52.5 ± 3.4 $^{a}E_{c}$	527.3 ± 37.1 $^{a}F_{e}$	27.8 ± 1.9 $^{b}C_{b}$
CCDM 670	MO	24	ND	1901.0 ± 133.2 $^{a}C_{d}$	ND	14.5 ± 1.0 $^{b}C_{b}$	36.8 ± 2.4 $^{b}B_{c}$	1.5 ± 0.1 $^{a}A_{a}$
		48	ND	1817.7 ± 120.2 $^{a}C_{d}$	ND	4.4 ± 0.3 $^{a}C_{a}$	27.7 ± 1.6 $^{a}B_{c}$	6.6 ± 0.3 $^{b}A_{b}$
	CFS	24	ND	1996.4 ± 131.2 $^{a}C_{c}$	ND	11.2 ± 0.8 $^{b}B_{a}$	22.2 ± 1.3 $^{b}A_{b}$	ND
		48	ND	2000.2 ± 117.2 $^{a}C_{c}$	ND	2.8 ± 0.2 $^{a}B_{a}$	16.0 ± 0.9 $^{a}A_{b}$	ND
CCDM 686	MO	24	17.6 ± 1.5 $^{a}D_{b}$	2060.4 ± 157.0 $^{a}C_{e}$	19.8 ± 1.6 $^{a}C_{b}$	40.6 ± 3.0 $^{b}D_{c}$	133.5 ± 10.5 $^{a}C_{d}$	5.3 ± 0.4 $^{a}C_{a}$
		48	17.3 ± 1.4 $^{a}C_{b}$	1830.5 ± 138.1 $^{a}C_{f}$	59.8 ± 4.9 $^{b}D_{d}$	11.5 ± 0.9 $^{a}D_{a}$	151.3 ± 9.0 $^{a}D_{e}$	25.5 ± 1.7 $^{b}C_{c}$
	CFS	24	15.2 ± 1.3 $^{a}C_{c}$	1889.4 ± 133.4 $^{a}C_{e}$	5.2 ± 0.4 $^{a}A_{b}$	3.4 ± 0.3 $^{b}A_{a}$	35.3 ± 2.1 $^{a}B_{d}$	ND
		48	20.1 ± 1.7 $^{b}D_{b}$	1882.8 ± 140.6 $^{a}C_{e}$	54.1 ± 4.7 $^{b}C_{d}$	1.0 ± 0.1 $^{a}A_{a}$	36.4 ± 2.9 $^{a}C_{c}$	ND
CCDM 689	MO	24	11.2 ± 0.9 $^{b}B_{c}$	1993.8 ± 125.0 $^{a}C_{f}$	7.8 ± 0.4 $^{a}B_{b}$	176.7 ± 13.3 $^{b}E_{d}$	286.9 ± 22.1 $^{a}D_{e}$	3.7 ± 0.3 $^{a}B_{a}$
		48	4.3 ± 0.3 $^{a}A_{a}$	1952.9 ± 115.1 $^{a}C_{f}$	13.7 ± 0.6 $^{b}B_{c}$	51.7 ± 3.3 $^{a}E_{d}$	355.2 ± 23.6 $^{b}E_{e}$	12.3 ± 0.9 $^{b}B_{b}$
	CFS	24	8.2 ± 0.5 $^{b}A_{b}$	1854.8 ± 120.6 $^{a}C_{e}$	7.8 ± 0.3 $^{a}B_{b}$	171.8 ± 12.9 $^{b}E_{c}$	293.0 ± 21.2 $^{a}D_{d}$	3.6 ± 0.2 $^{a}B_{a}$
		48	6.9 ± 0.6 $^{a}B_{a}$	2006.3 ± 114.1 $^{a}C_{e}$	6.5 ± 1.7 $^{a}A_{a}$	49.8 ± 3.5 $^{a}E_{c}$	369.7 ± 21.7 $^{b}E_{d}$	11.0 ± 0.7 $^{b}B_{b}$
CCDM 731	MO	24	ND	76.4 ± 1.4 ^{a}A	ND	ND	ND	ND
		48	ND	71.1 ± 5.8 ^{a}A	ND	ND	ND	ND
	CFS	24	ND	148.9 ± 3.2 ^{a}B	ND	ND	ND	ND
		48	ND	148.4 ± 9.6 ^{a}B	ND	ND	ND	ND

* The means within a column (the difference between the different cultivation times) followed by different superscript letters differ ($P < 0.05$); samples with different protective strains and their supernatants were evaluated independently. The means within a column (the difference between protective strains and their supernatants in concrete cultivation times) followed by different capital letters differ ($P < 0.05$); samples cultured during different cultivation times were evaluated independently. The means within a line (the difference between tyramine-positive strains) followed by different subscript letters differ ($P < 0.05$).

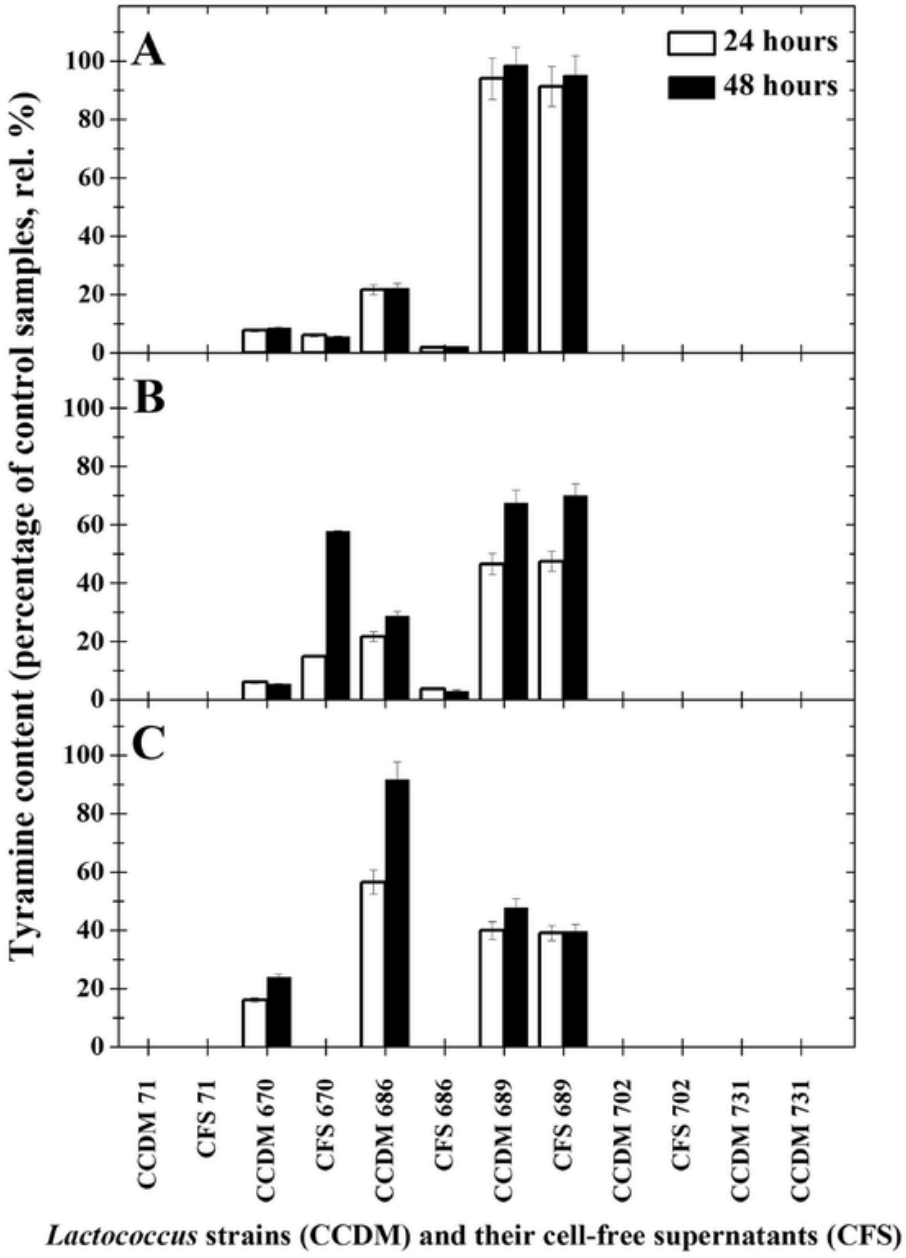

Fig. 1. Effect of tested *Lactococcus lactis* subsp. *lactis* strains (CCDM) and their cell-free supernatant (CFS) on tyramine production (rel. %) by *Lactobacillus plantarum* RIBM P89 (A), *Lb. brevis* RIBM P93 (B) and *Lb. plantarum* RIBM P96 (C) after a 24- and 48-h cultivation. Bars correspond to means ± SD (n = 12).

However, there are scarcely any studies on the interactions between bacteriocin-producing microorganisms and BA producers, and no information exists regarding the tyramine formation by LAB in the presence of bacteriocin-producing strains or their antimicrobial compounds. To our knowledge, this is the first study describing the impact of nisin-producing *Lactococcus* strains and their CFSs on tyramine production by selected *Lactobacillus* and *Lactiplantibacillus* strains.

The investigated *Lactobacillus* and *Lactiplantibacillus* strains were able to produce considerable amounts of TYM, in some cases reaching levels of up to 900 $mg.L^{-1}$ after a 48-h cultivation. The highest levels of TYM production were detected in *Lb. brevis* RIBM P93 and *Lb. curvatus* DEPE T15, which were able accumulate TYM in concentrations from 727.9 ± 51.2 $mg.L^{-1}$ to 875.9 ± 62.1 $mg.L^{-1}$ after a 48-h cultivation, respectively.

Such high amounts of tyramine in food can endanger human health. According to Rafehi et al. (2019), the oral administration of 400 mg of TYM can increase systolic blood pressure up to 100 mmHg in healthy individuals. However, a much smaller amount of dietary tyramine can have a toxic effect on those individuals treated with monoamine-oxidase inhibitor (MAOI) drugs. Only 6 mg of TYM could provoke a mild crisis and 10–25 mg of TYM causes a severe headache (EFSA, 2011).

The effect of bacteriocin-producing LABs and their supernatants on the reduction of biogenic amines varies depending on the BA-producing strain, as reported by many studies (Xie et al., 2016; Özogul et al., 2017; Saelao et al., 2018). Our results of this current study confirmed that the impact of the nisin-produsing *Lactococcus* strains and their CFSs on tyramine formation differed based on the tyramine producer. Nevertheless, the TYM production of all tested *Lactobacillus* and *Lactiplantibacillus* strains was not detected in the presence of *Lc. lactis* subsp. *lactis* CCDM 71 and CCDM 702, and their CFSs. Moreover, the rest of the investigated strains (CCDM 670, CCDM 686, CCDM 689 and CCDM 731) and their CFSs completely suppressed or significantly ($P < 0.05$) decreased TYM formation in four of the six tested food iso-

lates. The highest reductions in TYM detected were observed after the cultivation of *L. plantarum* RIBM P89 with CFSs from strain CCDM 686, *Lb. brevis* RIBM P93 with CFSs from strain CCDM 670 and *Lb. curvatus* DEPE T15 with CFSs from strain CCDM 731, for which the TYM concentrations after a 48-h cultivation decreased to 2%, 3% and 4% respectively, in comparison with the controls ($P < 0.05$). Table 4 shows the conversion of tyramine production per cell (represented as yield factor, $Y_{TYM/CFU}$). The table shows that in the presence of nisin-producing strains and their cell-free supernatants (compared to the control without nisin-positive strains) there was observed a reduction in tyramine production. The production of tyramine is thus taken into account due to the lower number of CFU in the presence of nisin-positive strains. These results are in good agreement with Xie et al. (2016) findings which suggest that CFS from *L. plantarum* reduced the accumulation of cadaverine and putrescine mainly through the inhibition of the cell number of amine-positive bacteria rather than related decarboxylase activities.

The study undertaken by Toy et al. (2015) observed that CFSs from LAB had a similar inhibition effect on tyramine production by food-borne pathogens, including *Salmonella* Paratyphi A, *Listeria monocytogenes*, *Staphylococcus aureus* and *Escherichia coli*. Two different concentrations of CFS (50% and 25%) were tested. Both concentrations of CFS from *Streptococcus thermophilus* and a 50% CFS of *Pediococcus acidophilus* inhibited the TYM production by *S.* Paratyphi A by up to 98%. The tyramine production by *E. coli* was also inhibited by a 50% CFS of *Lc. lactis* subsp. *lactis* and a 25% CFS of *Leuconostoc lactis* subsp. *cremoris*.

Different findings are reported by Ö;zogul (2011), who studied the influence of the *Lc. lactis* subsp. *lactis*, *Lc. lactis* subsp. *cremoris*, *L. plantarum* and *S. thermophilus* on BA formation by food-borne pathogens, such as *E. coli*, *Klebsiella pneumoniae*, *L. monocytogenes*, *S. aureus*, etc. In most cases, the TYM production of food-borne pathogens increased. Similarly, Kuley et al. (2012) also find that LAB has a stimulation effect on the TYM production of food-borne pathogens. In general, the activation of amino acid decarboxylation systems in BA-positive microorganisms are reported to be adaptive responses to energy depletion, but also strategies for withstanding acid stress (Barbieri et al., 2019). It is noteworthy that, in the present study, none of the tested *Lactococcus* strains and their CFSs increased the tyramine production by fermented-food isolates.

The influence of the investigated nisin-producing strains and their CFSs on TYM production by the tested *Lactobacillus* and *Lactiplantibacillus* strains is comparable. However, in some cases, the impact of CFSs on reducing TYM production was higher than the nisin-producing culture itself. In particular, the CFSs from strains CCDM 670 and CCDM 686 were more efficient at reducing TYM formation in all beer isolates tested. This phenomenon can be explained by the fact that the production of nisin by *Lc. lactis* is highly dependent on the availability of nutrients in the culture medium (González-Toledo et al., 2010). Therefore, the competition for nutrients between the nisin-producing strain and the lactobacilli might be resulting in the insufficient production of nisin and the higher production of tyramine. Other explanation may be due to the fact that the CFSs is concentrated by centrifugation, and thus there is a higher concentration of nisin. Similarly, Özogul et al. (2017) states that higher concentrations of cell-free supernatant may further reduce the production of biogenic amines.

Taken together, these findings suggest that nisin-producing lactococci and their CFSs could be a suitable tool for providing control measures to prevent a significant food-safety hazard (tyramine content) or reduce it to an acceptable level. It is a promising technological intervention that could enhance food safety, and it should be taken into account during the development and maintenance of food-safety management systems.

5. Conclusion

The findings in this study demonstrates that nisin-producing *Lactococcus* strains or their CFS can significantly reduce tyramine accumulation by *Lactobacillus* and *Lactiplantibacillus* strains tested. The tyramine production of all tested BA-positive strains was not detected in presence of *Lc. lactis* subsp. *lactis* CCDM 71 and CCDM 702, and their CFSs. Moreover, the remainder of the investigated *Lactococcus* strains (CCDM 670, CCDM 686, CCDM 689 and CCDM 731) and their CFSs significantly ($P < 0.05$) decreased TYM production in four of the six tested BA-positive strains. Consequently, in order to prevent formation and accumulation of tyramine in high concentration in fermented food products, such as cheese or beer, it is advisable to use nisin-produsing strain or its CFS to enhance safety and quality of these fermented food products. However, further research should be done in order to examine these *Lactococcus* strains and their CFSs in real food system.

Declaration of conflict interest

None.

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