Sjournals
Scientific Journals
Scientific Journal of Microbiology (2014) 3(9) 96-103
ISSN 2322-2948
doi: 10.14196/sjm.v3i9.1665

Contents lists available at Sjournals
Scientific Journal of Microbiology
Journal homepage: www.Sjournals.com

Original article

Antimicrobial activity of bacteriocin produced by *lactobacillus* bacteria against proteus spices

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ARTICLE INFO

Article history,
Received 03 September 2014
Accepted 21 September 2014
Available online 29 September 2014

Keywords,
Bacteriocin
Lactobacillus acidophilus
Lactobacillus plantarum
Proteus spices

ABSTRACT

Probiotics are from non-pathogenic bacteria that have beneficial effects for their host through producing anti-microbial compounds, such as bacteriocin. Bacteriocins are defined as antimicrobial proteins or peptides that have inhibitory effect. In this study *Lactobacillus plantarum* (ATCC 8014) and *Lactobacillus* acidophilus (ATCC 4356) were tested for production of bacteriocins in different pH, temperatures and enzymes treatment, then their activity against Proteus spices as a most common urinary tract infections evaluated. The results demonstrate that the cell-free supernatant from *L. plantarum* and *L. acidophilus* is effective in inhibiting the growth of different strains of Proteus. The inhibitory compound lost activity when heated to temperatures greater than 30°C and when subjected to pH changes that lowered the pH below 4 or above 5. In addition, the inhibitory protein was susceptible to digestion by various proteases. These findings support the idea that the inhibitory compounds in both studied stains can be considered as a bacteriocin by relative heat and pH stable and proteiaceous nature that can have inhibitory effect against Proteus spices.

1. Introduction

The term "probiotic" is a Greece word meaning "for life", that first used by Lilly and Stillwell in 1965 to describe the substances secreted by one microorganism that stimulate the growth of another (Lilly & Stillwell, 1965).

According to the Roy Fuller's definition (1989), probiotics are "live microbial feed supplement which beneficially affects the host by improving its intestinal microbial balance"(Fuller, 1989). This definition focuses on the live nature of probiotics.

Strains of lactic acid bacteria (LAB), members of the genera Lactobacillus, Bifidobacterium and also some strains of Propionic bacteria are the most common microbes employed as probiotics. Lactic acid bacteria although are from a normal protective bacteria of urinary tract, have a long history of safe use in fermented foods that now a days play an essential role in the majority of food fermentations (Huis in't veld, et al., 1998, Reid, et al., 2001, Reid, et al., 2010).

These bacteria produce lactic acid by fermentation of sugars through different pathways, homolactate and non-homolactate fermentation. Lactobacillus also is known as effective bacteria that can decompose proteins, carbohydrates and fats in foods and help absorption of necessary inorganic nutrient, amino acids and vitamins for human and animals. Lactobacilli have an antagonistic effect on different microorganisms, due to production of antimicrobial compounds such as bacteriocins or bacteriocin-like compounds (Piard & Desmazeaud, 1991, Axelsson, 2004, Picard, et al., 2005).

Bacteriocin are small proteins or peptides that are usually active against bacterial species closely related to the producer with the capacity to inhibit, even in low concentrations (Cleveland, et al., 2001). Bacteriocins are categorized in several ways, including producing strain, common resistance mechanisms, and mechanism of killing. The bacteriocins from lactobacilli are similar to classic colicins model (Tagg, et al., 1976, Cintas, et al., 2001).

Their inhibitory spectrum is mostly restricted to Gram-positive bacteria, but several *bacteriocins* like *bulgarisin*, *acidolin*, *lactoside* or *acidophiline* observed that have inhibitory activity against wide spectra of Gram-positive, Gram-negative bacteria, yeast and fungus (Nemcova, 1997).

Klaenhammer (1993) classified the bacteriocins of LAB by proposing four major classes: class 1: lantibiotics, class 2: small (<10 k Da) heat-stable, non-lanthionine containing bacteriocins, class 3: large (>30 k Da) heat-labile bacteriocins and class 4: complex bacteriocins composed proteins, lipids or carbohydrates (Klaenhammer, 1993). Bacteriocins produced by lactic acid bacteria have received considerable attention during recent years for their possible use as preservatives in food and controlling bacterial infections (Hanlin, et al., 1993). The aim of this study is to investigation the physiological characterization of *L. acidophilus* and *L. plantarum* bacteriocins and their antagonism activity against P. mirabilis and P. vulgaris as an important cause of urinary tract infections bacteria.

2. Materials and methods

2.1. Bacterial strains and growth conditions

L. acidophilus ATCC 4356 and L. plantarum ATCC 8014 were grown anaerobically in de Man Rogosa Sharpe (MRS) broth (Merck, Germany), overnight at 37°C. P. mirabilis and P. vulgaris strains were grown in BHI broth (Merck, Germany) and nutrient broth (Merck, Germany) at 37°Cat aerobic conditions. The used strains are listed in Table 1.

Table 1
Bacterial strains and growth conditions.

Bacterial strains	Relative properties	Source	Temperature	Medium incubation
Lactobacillus acidophilus	Wild type	ATCC 4356	37°C	MRS, anaerobic
Lactobacillus plantarum	Wild type	ATCC 8014	37°C	MRS, anaerobic
Proteus mirabilis	Indicator strain	ATCC 7002	37°C	BHI, aerobic
Proteus mirabilis OXK	Indicator strain	ATCC 15146	37°C	BHI, aerobic
Proteus vulgaris	Indicator strain	PTCC 1182	37°C	BHI, aerobic
Proteus vulgaris	Indicator strain	ATCC 7829	37°C	BHI, aerobic

2.2. Preparation of cell-free supernatant from Lactobacillus strains

Cell-free supernatant was obtained from an overnight culture of *L. acidophilus* and *L. plantarum* by centrifugation (Eppendorf, Centrifuge AG) at 10000 g for 10 min at 4°C. The Supernatant fluids neutralized to pH 7 with NaOH 1N and then filtered through 0.22 µm syringe filter (Millipore) to achieve a sterile cell-free supernatant (Mohankumar & Murugalatha, 2011).

2.3. Analysis of bacteriocins production and their inhibitory activity

The method of Lash et al. (2005) was used to detect bacteriocin antagonistic activity. Briefly, 15 µl of the appropriate culture broth of *Lactobacillus* strains were poured into a well of a microtitre plate (96 wells) and inoculated with about 100 µl of an indicator strain by 107cfu/ml. After 24 hours of incubation at 37° C in aerobic conditions, the plates were read using a microplate reader at a wavelength of 600 nm. Positive antimicrobial activity was evaluated by visual comparison with the control (media) and the experimental (15 ml of *L. plantarum* and L. acidophilus supernatant) to report antibacterial activity as percent difference in cell growth (Lash, et al., 2005).

2.4. Effect of temperature, pH and enzymes on antibacterial activity

The effect of temperature on the antibacterial activity was determined by heating neutralized cell-free supernatant fluids of L. acidophilus and *L. plantarum* at 100°C for 10, 30 and 60 min, and autoclaving at 121°C for 15 min, then the residual activity tested by previously described MODA (Lash, et al., 2005). The effect of pH on the antibacterial activity of L. acidophilus and *L. plantarum* products was tested using the MODA, by adjusting to a pH ranging from 1 to 14, in increments of one pH unit, using 1 N NaOH or 1 N HCl, where the original pH value of the spent supernatant served as a control. In order to determine the sensitivity to enzymes, neutralized cell-free, supernatant fluids were treated with the following enzymes: pepsin (1 mg/ml), trypsin (1 mg/ml), and catalase (5 mg/ml) and then the supernatant was incubated for 1 hours at 37°C and the digested cell-free supernatant was screened for antibacterial activity using MODA (Lash, et al., 2005).

2.5. Statistical analysis

The data from the study of the influence of heat, pH and enzymes treatment on the inhibitory effect of cell-free supernatant on L. acidophilus and *L. plantarum* were submitted to one-way ANOVA and the means were compared by the Newman-Keuls test ($p \leq 0.05$).

3. Results

3.1. Screening for antimicrobial activity

The *L. acidophilus* and *L. plantarum* cell-free supernatant were screened for antimicrobial activity using MODA method. Both lactobacilli strains exhibited an antibacterial effect against Proteus species. Table 2 shows the measured inhibitory activity of studied Lactobacillus strains supernatant using MODA. Cell-free supernatant from L. plantarum and L. acidophilus inhibited the Proteus mirabilis and Proteus vulgaris growth by values of 77.78% up to 97.78% compared to the untreated control. The MRS control showed no inhibitory effect on any of the test cultures (Table 2).

Table 2
MODA of cell-free supernatant from *L. acidophillus* and *L. plantarum*.

Cell free supernatant	Absorbance (A600)			
	Proteus mirabilis ATCC 7002	Proteus mirabilis OXK ATCC 15146	Proteus vulgaris PTCC 1182	Proteus vulgaris ATCC 7829
Cells (Growth control)	0.507	0.683	0.512	0.588
Media (Positive control)	0.463	0.540	0.505	0.493
L. acidophillus supernatant	0.053	0.012	0.070	0.033
Percent difference cell growth	88.55 %	97.78 %	86.13 %	93.30 %
L. plantarum supernatant	0.033	0.120	0.068	0.024
Percent difference cell growth	92.87 %	77.78 %	86.53 %	95.13 %

3.2. Effect of temperature, pH and enzymes on antibacterial activity

The effect of pH, temperature and enzymes on the stability of cell-free supernatant from L. plantarum and L. acidophilus were assessed by MODA. The neutralized cell-free supernatant was found to be heat-liable for both lactobacilli strains, because it loses activity when heated at 100°C more than 10 and 30 min in considering of L. acidophilus and L. plantarum respectively. Also autoclaving the cell-free supernatant at 121°C for 15 minutes lost the activity (Table 3).

Table 3
The effect of temperature on cell-free supernatant of *L. acidophillus* and *L. plantarum*.

Cell free supernatant	Pathogens	Temperature (°C)			
		100 °C for 10 min	100 °C for 30 min	100 °C for 60 min	121°C for 15 min
Lactobacillus acidophilus ATCC 4356	Proteus mirabilis ATCC 7002	+	-	-	-
	Proteus mirabilis OXK ATCC 15146	+	-	-	-
	Proteus vulgaris PTCC 1182	+	-	-	-
	Proteus vulgaris ATCC 7829	+	-	-	-
Lactobacillus plantarum ATCC 8014	Proteus mirabilis ATCC 7002	+	+	-	-
	Proteus mirabilis OXK ATCC 15146	+	+	-	-
	Proteus vulgaris PTCC 1182	+	+	-	-
	Proteus vulgaris ATCC 7829	+	+	-	-

+: Indicates inhibitory activity was seen when the supernatant was heat treated using MODA
-: Indicates inhibitory activity was not seen when the supernatant was heat treated using MODA.

At pH ranging from 5 to 8 the *L. acidophillus* supernatant remained stable, when the *L. plantarum* supernatant was adjusted to pH values below 5 and or above 7, activity was lost, suggesting that the inhibitory compound is only active at a very narrow pH range (Table 4).

Table 4
The effect of pH on cell-free supernatant of *L. acidophillus* and *L. plantarum*.

Cell free supernatant	Pathogens	Supernatant pH *						
		1-4	4.8	5	6	7	8	9-14
Lactobacillus acidophilus ATCC 4356	Proteus mirabilis ATCC 7002	-	+	+	+	+	+	-
	Proteus mirabilis OXK ATCC 15146	-	+	+	+	+	+	-
	Proteus vulgaris PTCC 1182	-	+	+	+	+	+	-
	Proteus vulgaris ATCC 7829	-	+	+	+	+	+	-
Lactobacillus plantarum ATCC 8014	Proteus mirabilis ATCC 7002	-	+	+	+	+	-	-
	Proteus mirabilis OXK ATCC 15146	-	+	+	+	+	-	-
	Proteus vulgaris PTCC 1182	-	+	+	+	+	-	-
	Proteus vulgaris ATCC 7829	-	+	+	+	+	-	-

*The *L. acidophillus* and *L. plantarum* supernatant was adjusted to pH values ranging from 1-14 using 1 N NaOH or 1 N HCl, pH values of 4.8 was included as a control.
+: Indicates inhibitory activity was seen when the supernatant was adjusted to specific pH using MODA
-: Indicates inhibitory activity was not seen when the supernatant was adjusted to special pH using MODA.

Inhibition due to acid and hydrogen peroxide were excluded by neutralization with NaOH and treatment of the supernatants with catalase respectively. Treatments by pepsin and trypsin also have been done to digest lactobacilli cell-free supernatants proteins compounds. It has been observed that upon treatment of the cell-free supernatant with any of the enzymes, a marked effect on the inhibitory activity have been seen and antibacterial activity was lost for all tested strains (Table 5).

Table 5

The effect of enzymes treatment (pepsin (1mg/ml), trypsin (1mg/ml) and catalase (5mg/ml) and NaOH neutralization on cell-free supernatant of *L. acidophillus* and *L. plantarum* by MODA (The results are from the absorbance of cultural supernatant at 600 nm (O.D.), visual comparison with the control (media) and the experimental (15 ml of lactobacilli supernatant in percent).

Cell free supernatant	Pathogens	Supernatant treatment *											
		Cells (Growth control)	Media (Positive control)	Neutralized supernatant (pH=7)		Un treated supernatant (pH= 4.8)		Pepsin		Trypsin		Catalase	
				OD	%	OD	%	OD	%	OD	%	OD	%
Lactobacillus plantarum ATCC 8014	Proteus mirabilis ATCC 7002	0.507	0.463	0.164	64.57%	0.053	88.55%	0.315	32.00%	0.247	46.60%	0.275	40.60%
	Proteus mirabilis OXK ATCC 15146	0.683	0.540	0.104	80.74%	0.012	97.78%	0.358	33.70%	0.214	60.38%	0.278	48.51%
	Proteus vulgaris PTCC 1182	0.512	0.505	0.201	60.20%	0.070	86.13%	0.386	23.56%	0.270	46.53%	0.251	30.00%
	Proteus vulgaris ATCC 7829	0.588	0.493	0.134	72.82%	0.033	93.30%	0.360	27.00%	0.246	50.10%	0.244	50.50%
Lactobacillus acidophilus ATCC 4356	Proteus mirabilis ATCC 7002	0.507	0.463	0.152	67.17%	0.033	92.87%	0.359	22.46%	0.232	49.90%	0.310	33.00%
	Proteus mirabilis OXK ATCC 15146	0.683	0.540	0.134	75.18%	0.120	77.78%	0.351	35.00%	0.246	54.44%	0.215	60.18%
	Proteus vulgaris PTCC 1182	0.512	0.505	0.253	50.00%	0.068	86.53%	0.376	25.5%	0.389	22.98%	0.252	50.00%
	Proteus vulgaris ATCC 7829	0.588	0.493	0.144	70.80%	0.024	95.13%	0.189	61.6%	0.211	57.20%	0.264	46.45%

4. Discussion

In this study the antagonistic activity of cell-free supernatant from *L. acidophilus* and *L. plantarum* against Proteus strains was investigated. Both studied Lactobacillus strain exerted inhibitory activity on all the examined bacteria with inhibitory activity between 77.78% and 97.78% of the untreated control (Table 2). Most notably was Proteus mirabilis OXK (ATCC 15146) with values of greater than 97% of the untreated control.

The large inhibitory activity of lactobacilli strains against Proteus spices, because of their significant role in pathogenesis of urinary tract infections is important. The inhibitory effect from Lactobacillus spices, against food born bacteria and nosocomial infections have been studied more before (Barefoot & Klaenhammer, 1983, Enan, et al., 1996, Franz, et al., 1998, Han, et al., 2002, Lash, et al., 2005, Sosan & Kawther Hkeem, 2009).

In the study that have been conducted by Lash et al. in 2005 on the extracted bacteriocin of *L. plantarum*, a wide range of inhibitory activity against Gram-positive and Gram-negative bacteria including, Staphylococcus *aureus*, *Escherichia coli*, *Listeria innocua*, and *Pseudomonas aeruginosa* have been observed , by more than 90% inhibitory activity in comparison to the untreated control by MODA (Lash, et al., 2005). This wide range spectrum could be result of the high sensitivity and easiest of the MODA test and also its possibility in liquid medium, because it is not affect by solid medium limitation which is exist in other methods (Lash, 2002).

It is observed that antimicrobial peptide or proteins that made through LAB usually have better antagonism activity against Gram positive bacteria than Gram negative bacteria. However, some studies have already reported bacteriocin activity against this group of bacteria (De Vuyst & Vandamme, 1994). While other small molecular weight compounds from LAB have been more effective against growth of Gram-negative bacteria (Strus, et al., 2000). This inhibitory activity of Lactobacillus spices against Proteus bacteria as a Gram negative bacteria because of its rare incidence is also important (Stevens, et al., 1991).

The LAB in this study has been reported to produce bacteriocins. Therefore, it is likely that bacteriocins are responsible for the antagonists effects observed for the cell-free supernatant. Further purification, identification and technological application should be pursued, in order to propose potential uses as natural preservatives. So in this study we were seeking for evaluate the nature of this antimicrobial compound.

After elimination the effect of acid and H2O2 by NaOH and catalase enzymes treatment, residual antimicrobial activity have been observed.

Addition of catalase to the lactobacilli supernatant did not eliminate the inhibitory effect, so the effect of potential production of hydrogen peroxide by *L. plantarum* and *L. acidophillus* was discounted (Table 5). The result of Toba and Yoshioka in 1991 was also compatible (Toba, et al., 1991).

Tagg et al (Tagg, et al., 1976) reported that most of the bacteriocin are resistance to the acidic conditions. The result of this study was also compatible, that cell-free supernatant had antimicrobial activity after neutralization by NaOH.

In this study after treatment of the cell-free supernatant by enzymes treatment good antimicrobial activity against Proteus spices have been observed .The susceptibility of the inhibitory compound to digestion by proteolytic enzymes and the inhibitory activity being completely lost upon exposure to proteolytic enzymes, also lends support to its characterization as a bacteriocin (Table 5).

In various investigations it is observed that L. acidophilus and *L. plantarum* through producing bacteriocin could prevent or reduce the growth of Proteus mirabilis as an important urinary tract infection. The survey that have been conducted by Mohankuamr in 2011 showed that L. acidophilus could inhibit growth of Proteus spices due to bacteriocin productions (Mohankumar & Murugalatha, 2011).

De Vuyst et al. (1994) showed that the produced bacteriocin by L. acidophilus on the growth of Gram-negative bacteria is more effective than Gram-positive. While this produced bacteriocins showed action against a wide range of Gram-positive and Gram-negative bacteria (De Vuyst & Vandamme, 1994). Other numerous investigators have also shown that bacteriocin activity is lost upon treatment by proteolytic enzymes (Tagg, et al., 1976, Klaenhammer, 1988, Han, et al., 2002, Lash, et al., 2005).

This inhibitory activity of the protein was highly sensitive during heating (Table 3) and during repeated the inhibitory activity after 10 min and 30 min heating at 100°C for L. acidophilus and *L. plantarum* respectively and also 121 °C for 15min have been lost. When cell free supernatant adjusted to pH values lower than pH 4 or above pH 8 all inhibitory activity was lost, so the inhibitory activity was seen only in a narrow pH range (Table 4).The finding that the inhibitory compound is heat and pH unstable is common among investigators (Tagg, et al., 1976,

Klaenhammer, 1988, Rammelsberg & Radler, 1990, Toba, et al., 1991, Enan, et al., 1996, Van Reenen, et al., 1998, Messi, et al., 2001, Lash, et al., 2005).

Our results showed that L. acidophilus ATCC 4356 and *L. plantarum* ATCC 8014 had good antimicrobial activity against *P. mirabilis* and *P. vulgaris* bacteria. This inhibitory activity was relatively heat and pH stable with a proteiaceous nature. So these results suggest that the anti-bactericidal compound was indeed a protein in nature that can have inhibitory effect against Proteus.

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