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Original Article

Antibacterial and Antibiofilm Activities of Nisin from Lactococcus Lactis and Alteration of the Bacteria-Induced Pro-Inflammatory Responses on Kidney and Bladder Tumor Cell Lines

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HIGHLIGHTS

- The bioactivities of Nisin cause a promising candidate as a further antimicrobial agent for targeting S. aureus infections.
- Nisin induced inflammatory responses in ACHN and 5637cells.
- Nisin inhibiting MRSA and MSSA strains.

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ABSTRACT

Introduction
The emergence of superbugs puts the world into an antibiotic-resistance era, and antimicrobial peptides could solve this severe problem. The aim of this study was the in vitro evaluation of the bactericidal effects of the Nisin on Staphylococcus aureus, probable cytotoxic effects, and its impact on host-microbe interactions.

Methods
The minimal inhibitory concentration of Nisin was determined, and Nisin-induced cell toxicity was assessed by MTT assay. Then, the pro-inflammatory effects of Nisin on ACHN (kidney tumor cell line), and 5637 (bladder tumor cell line) cell lines were analyzed by ELISA (enzyme-linked immunoassay). Finally, the sensitivity of two biofilm-producing S. aureus to Nisin was evaluated in planktonic and biofilm-resident cells by crystal violet assay.

Results
MIC for methicillin-sensitive S. aureus (MSSA) and methicillin-resistant S. aureus (MRSA) was 1 µg/ml and 2 µg/ml, respectively. A low concentration of Nisin demonstrated no cytotoxic effects on studied cell lines. However, high cytotoxicity was found at the following concentrations 330 and 430 µg/ml of Nisin compared to the negative control. Only a high dose of Nisin induced high levels of interleukin-6 (IL6) in ACHN cells. In contrast, low concentrations of Nisin in 5637 cells induced the secretion of high levels of IL-6. In cell culture, Nisin inhibited the S.aureus-induced cytotoxicity and the release of IL-6 from kidney and bladder cell lines.

Conclusions
Our results demonstrated that Nisin, efficiently inhibiting MRSA and MSSA strains, antagonized bacteria-induced inflammatory responses in ACHN and 5637 cells. In summary, the bioactivities of Nisin make it a promising candidate as a further antimicrobial agent for targeting S. aureus infections.

Keywords: Antimicrobial Peptide; Biofilm; Inflammatory Responses; Nisin

Introduction

After various medical treatments, such as organ transplantations, surgical procedures, and chemotherapy, infectious diseases are still high-risk adverse events with significant morbidity and mortality due to antimicrobial resistance (1). Moreover, the inappropriate use of antibiotics gave rise to the emergence of antibiotic-resistant bacteria, which brings a high economic burden to the public health care systems (2). Hence, there is an urgent need for developing novel antibacterial agents.

Antimicrobial peptides (AMP) are a promising candidate for exploring novel antibiotics, and bacteria are considered a rich source of them, denoted as bacteriocins. Bacteriocins are ribosomally synthesized peptides in a particular bacterium that negatively impact the other closely associated bacteria and can be harnessed to fight against bacterial infections (3). There are numerous groups of bacteriocins classified based on their biochemical characteristics. One of these classes is lanthionine-comprising antibiotics, basically abbreviated as lantibiotics (4). Lantibiotics possess antibacterial activity even against highly resistant superbugs such as vancomycin-resistant enterococci (VRE) or methicillin-resistant S. aureus (MRSA), and some of them passed pre-clinical studies with good results (5). The best-studied lantibiotic is Nisin, which Rogers reported previously in 1928 (6). Nisin prevents cell wall synthesis by pore formation via interaction with lipid II. Pore formation causes metabolites to efflux the bacterial cells and disturbance osmotic pressure and ion gradients (7).

This study aims to assess the bactericidal properties of Nisin on MRSA strain and the ability of Nisin to induce cytotoxic and proinflammatory responses in ACHN (human renal adenocarcinoma) and 5637 (human-grade II bladder carcinoma) cell lines. It was demonstrated that Nisin is a promising candidate for treating staphylococcal infections, especially MRSA.

Methods

Bacterial strains

Two biofilm-producing bacteria strains (MRSA and Methicillin-sensitive S. aureus (MSSA)) were kindly provided by the Department of Pathobiology, School of Public Health (TUMS). The selected strains were previously examined for biofilm formation ability and categorized as potent biofilm generators (8).

Nisin

Nisin (potency:1,000,000 per IU/g), one of the fermentation products of Lactococcus lactis, was purchased from Sigma-Aldrich (N5764). A stock solution of Nisin was prepared in ultrapure water at a 1mg/ml concentration and used for all experiments. Working solutions were prepared in a DMEM medium for the cell culture experiment.

Determination of minimal inhibitory concentration (MIC)

The MIC of Nisin for the planktonic cells of the selected strains was determined by the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) (9). Briefly, Nisin was serially diluted into a 96-well microtiter plate at a volume of 100µl. The overnight bacterial culture was then diluted to reach a bacterial density of approximately 1.5×108 CFU/ml. After adding 100µl of bacterial suspension to each well, wells with the final volume of 200µl, and different concentrations of Nisin (0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, 512 and 1024µg/ml) were made. The plate was incubated aerobically at 37°C for 18-24h. MIC was determined as the lowest concentration of Nisin that inhibited bacterial growth (3).

Effects of Nisin on the established biofilm

After biofilm formation by adding the cell suspensions in the selected wells, the supernatant of mature biofilm was removed, and biofilm was washed thoroughly with sterile PBS. Nisin solution was then added to the biofilms at the following concentration (0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, 512 and 1024µg/mL).

A series of Nisin-free wells were used as a control sample, further incubated for 24h at 37°C, and measured absorbance at 590 nm. The MICs of sessile cells were determined at 50% disruption (SMIC50) of the established biofilm, and the results were compared with those obtained from the Nisin-free control wells in the crystal violet assay (10).

Cell viability and cell cytotoxicity

Cell viability was biochemically assessed by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]. Briefly, ACHN and 5637 cell lines in 10% FBS DMEM were seeded in 96-well plates at a density of 50,000 cells/well. Cells in each well were then treated by different concentrations of Nisin solution (130µg/ml, 230µg/ml, 330µg/ml, and 430µg/ml) for 24h at 37°C. After 24h, microscopic images were taken at 100x magnification (Olympus CKX41, Olympus Optical, Solna, Sweden). For cell viability, 10µl MTT (5mg/ml) were added to each well for 4h. Next, the medium was removed, and 100µl DMSO was added to dissolve the intracellular purple precipitate relative to the number of viable cells. Then, the absorbance was read at 570 nm by an ELISA (Enzyme-Linked-Immuno-Sorbent Assay) reader (VersaMax ELISA Microplate Reader, CA, USA). Each experiment was performed in duplicate.

Determination of interleukin-6

To assess immune responses of renal and bladder cells (ACHN and 5637), Inter Leukin-6 (IL-6) was analyzed in

Table 1. Determination of MIC and SMIC50 (µg/ml) of Nisin against biofilm-forming isolates

Strains	MIC	SMIC50 (Established Biofilm)
MRSA	2	32
MSSA	1	16

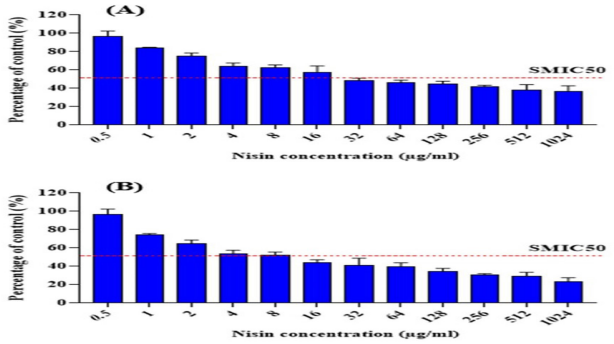

Figure 1. Effect of various concentrations of Nisin on the established biofilm of selected strains; A) MRSA; B) MSSA. The dotted line shows a range of possible SMIC50 values.

cell culture supernatants using concentrations mentioned above in the MTT assay. According to the manufacturer's instructions, the protein levels of IL-6, secreted by ACHN and 5637, were determined by ELISA using a commercial kit of the Karmania Pars Gene, Iran.

The effects of Nisin on bacteria-related activation of ACHN and 5637 cell lines

For bacterial stimulation of ACHN and 5637 cell lines, the cells were prepared as described above for the cytotoxicity test. Briefly, cells in 10% FBS DMEM were seeded at a density of 50,000 cells/well in 12-well plates. After overnight incubation, MRSA or MSSA suspension is added at a multiplicity of infection (MOI) of 1 and 10, with or without Nisin. The concentration of Nisin used was 2 µg/ml for MRSA and 1 µg/ml for MSSA. The selected Nisin concentrations are associated with the highest determined MIC value. The bacterial cell suspension was incubated for 24h at 37°C in 5% CO2, upon which microscopy images were taken at 100x magnification (Olympus CKX41, Olympus Optical). Culture supernatants were divided and stored at −80°C for additional analysis. Concentrations of IL-6 were determined as described above.

Statistical analysis

Data of performed experiments are presented as mean with standard error of the mean (SEM) indicated. Statistical comparisons between individual groups were made by one-way analysis of variance (ANOVA) with Bonferroni post hoc test using GraphPad Prism 8 (GraphPad Software, Inc).

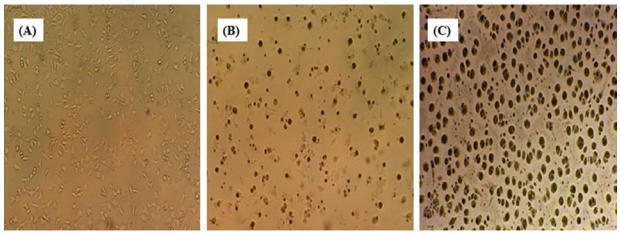

Figure 2. Morphological effects of Nisin on ACHN (human renal adenocarcinoma). A: negative control; B:330µg/ml, C:430µg/ml of Nisin. Cells without Nisin served as a negative control. Representative images are shown from one experiment.

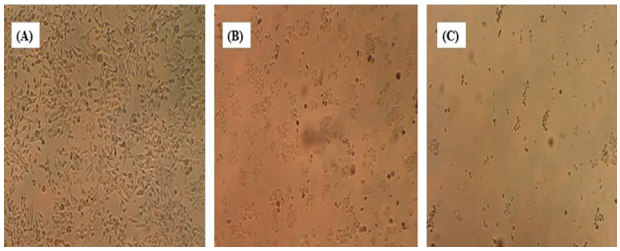

Figure 3. Morphological effects of Nisin on 5637 (human-grade II bladder carcinoma). A: negative control; B: 330 µg/ml, C:430µg/ml of Nisin. Cells without Nisin served as a negative control. Representative images are shown from one experiment.

Results

Determination of MIC

MIC is the lowest concentration of an antimicrobial compound that inhibits bacterial growth. MIC of Nisin for the two selected MRSA and MSSA strains was 2µg/ml and 1µg/ml, respectively. MIC results are summarized in Table 1.

Effect of Nisin on established biofilm.

The SMIC50 of Nisin for biofilm disruption for the MRSA and MSSA strains were 32 and 16µg/ml, respectively (Table 1). However, the concentrations of Nisin used in this assay were inadequate to remove the established biofilm altogether (Figure 1).

Determination cell cytotoxicity

Human Renal and bladder cancer cell lines (ACHN and 5637) were exposed to various doses of Nisin for 24 h to evaluate possible cellular effects. The cytotoxicity properties of Nisin on ACHN and 5637 cell line was measured by MTT assay. Compared to the negative control, no significant alterations of ACHN and 5637 cell density or morphology could be seen at 130–230µg/ml of Nisin. However, the highest tested concentrations, 330 and 430µg/ml, induced significant alterations in ACHN and 5637 morphologies, although the cell number visually appeared to be less than the control (Figures 2,3).

An MTT assay was performed to assess the cytotoxicity characteristics of Nisin in ACHN and 5637 cell lines. As shown in Figure 4, following concentration

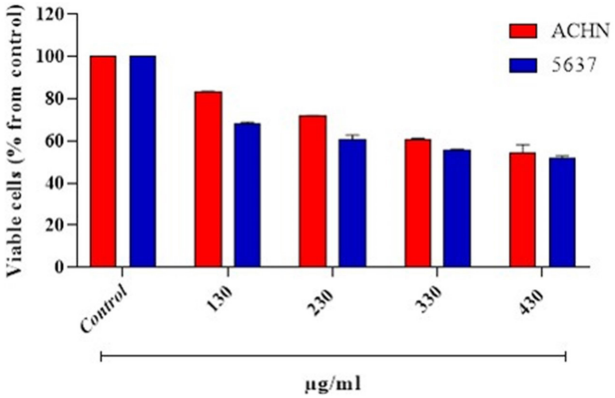

Figure 4. The effects of Nisin on the viability of ACHN and 5637 cell lines. Cancer cells (50,000 cells/well) were untreated (control) or treated with various concentrations of Nisin for 24 h. Viability was determined as an MTT assay.

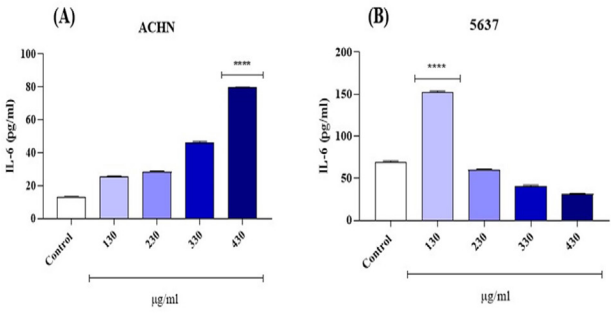

Figure 5. The effects of Nisin on immune responses of ACHN and 5637 cell lines. Data are presented as mean values with SEM indicated. Statistically significant differences were determined by using one-way ANOVA with Bonferroni post hoc test (****P-value<0.0001).

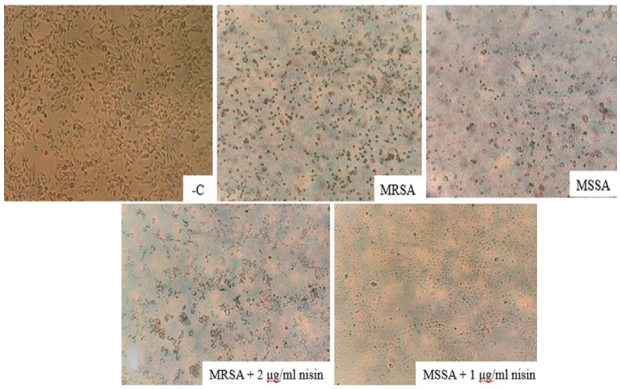

Figure 6. Morphological effects of MRSA and MSSA strains (MOI:10) on the 5637. Untreated cells were used as a negative control (−C).

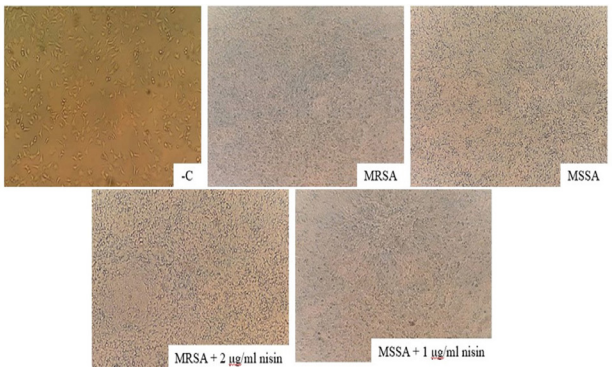

Figure 7. Morphological effects of MRSA and MSSA strains (MOI:10) on the ACHN. Untreated cells were used as a negative control (−C).

430, 330, 230, and 130µg/ml of Nisin led to a slight cytotoxic impact on ACHN cells (57.87, 60.98, 71.92, and 83.04%, respectively) in comparison with the negative control (100%) (P-value<0.05). 5637 cells showed a more significant decrease in cell density and were more susceptible to Nisin than ACHN cells. As shown in Figure 4, a significant cytotoxic impact on the 5637-cell line was seen at the following concentrations 330 and 430µg/ml of Nisin in comparison with the negative control (100%) (P-value<0.05). Nevertheless, the cell viability of ACHN cells was higher at concentrations of 130 and 230µg/ml of Nisin compared to the negative control(P-value<0.05).

Determination of interleukin-6

Analysis of ACHN release of the proinflammatory mediator IL-6 showed that only the highest tested dose of Nisin (430µg/ml) significantly increased the amount of this chemokine from 46 to 79pg/ml (Figure 4). A different outcome was found for the 5637-cell line, where the lowest concentration of Nisin (130µg/ml) caused a significant increase in chemokine amount about 150pg/ml (Figure 5).

The effects of Nisin on bacteria-induced activation of ACHN and 5637 cell lines

Both 5637 and ACHN cell lines were treated with MRSA and MSSA strains at both MOI:1 and MOI:10 to clarify the effect of the Nisin in vitro cell system. Microscopic images display significant bacterial growth once the studied strains were added to cell cultures at MOI:10. Though, in the presence of Nisin, the bacterial growth of both tested strains was limited (Figure 6,7). Similar results were found at MOI:1 (Data not shown).

Both MRSA and MSSA strains (MOI:1 and MOI:10) noticeably increased the release of IL-6 from both ACHN and 5637 cell lines (Figure 8). Both MRSA and MSSA strains released high amounts of IL-6 from ACHN (Figure 8A,8B). Based on the graph, Nisin significantly reduced bacteria-induced secretion of IL-6 from ACHN.

Similarly, Both MRSA and MSSA markedly increased the release of IL-6 from 5637, an effect that Nisin entirely abolished. MRSA and MSSA at MOI:1 induced IL-6 release from the 5637-cell line, but only MRSA induced statistically significantly higher rates than the control (Figure 8C). MRSA-induced IL-6 was intensely reduced by Nisin, which was not the case for MSSA. Surprisingly,

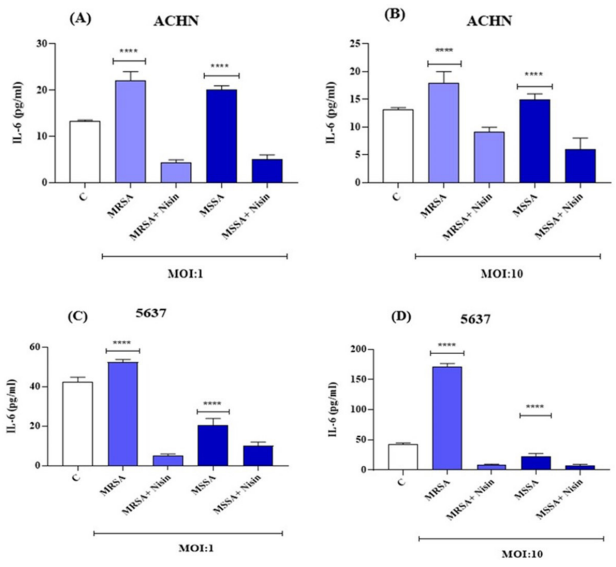

Figure 8. The effects of Nisin on immune responses of S. aureus-stimulated ACHN and 5637 cell lines. Data are presented as mean values with SEM indicated. Statistically significant differences were determined by using one-way ANOVA with Bonferroni post hoc test (****P-value< 0.0001).

MSSA at MOI:10 induced a lower release of IL-6 from 5637 compared to MRSA strain (Figure 8D). MRSA induced both MOI:1 and MOI:10 a substantial release of IL-6 from ACHN and 5637, whereas MSSA (MOI:1 and MOI:10) caused a more modest elevation from 5637.

Discussion

The extensive misuse of antibiotics causes the emergence of resistant bacteria and throws the world into a post-antibiotic era where medical care might stand effortless in combating multi-drug resistant pathogens. Therefore, antimicrobial peptides are a promising substitute for treating infections (11, 12). The present study investigated the bactericidal, anti-biofilm, and cell cytotoxic properties of the lantibiotic Nisin. MIC of Nisin was determined for two potent biofilm producer strains (MRSA and MSSA). Both strains showed susceptibility patterns to Nisin (Table 1). The results reveal that Nisin has a highly bactericidal effect against S. aureus. Dosler et al., (2012) showed a MIC value of 2–32µg/ml Nisin against S. aureus strains, whereas another study verified 2.1–3.0µg/ml (13, 14). In comparison, Saising et al. (2012) demonstrated a MIC of 4-8 µg/ml bacteriocin (gallidermin) for both S. aureus and S. epidermidis, which was consistent with another study that demonstrated similar susceptibilities to gallidermin for both S. epidermidis and S. aureus (6.25–12.5µg/ml) (7, 15-18).

A unique characteristic of antibiotics, which contributes to their promising potential as future beneficial antimicrobial agents, is that lantibiotics generally show low cell cytotoxicity (19). Our studied cell lines displayed slight changes in morphology when exposed to high concentrations of Nisin (130 and 230µg/ml), considerably higher concentrations than the attained MICs. Additionally, the viability of ACHN and 5637 cell lines was not influenced by Nisin and remained almost stable despite the high concentrations. Previously, another study by Bengtsson reported that the fibroblasts viability was not impressed by gallidermin, which was by our results (7). In the other study by Maher & McClean (2006), the cytotoxic effects of Nisin, gallidermin, and vancomycin were investigated on epithelial cells and demonstrated low cytotoxicity for these antibiotics (13). Their findings support our results, which establish that Nisin does not affect cell viability and is not toxic.

We also considered if Nisin can induce inflammatory responses in ACHN and 5637 cell lines and analyzed the pro-inflammatory cytokine IL-6. In the case of ACHN, minor amounts of IL-6 were induced by low concentrations of Nisin. On the other hand, the highest tested concentrations of Nisin (430µg/ml) significantly increased the amount of this chemokine in the ACHN cell line and indicates that Nisin has a minor capacity to raise an inflammatory response in these cells. The different outcome was realized in bladder cells where the highest IL-6 level was found at the lowest concentration (130µg/ml) and suggests that Nisin more efficiently induces inflammatory responses in bladder cells. At higher doses, less cytokine is produced due to the sensitivity of bladder cells to Nisin, and subsequently, more pronounced cell death results in lower cytokine production and secretion.

In this context, Kindrachuk et al. examined the innate immunity modulatory function of antibiotics, as well as Nisin and gallidermin, on human peripheral blood mononuclear cells and suggested that Nisin was able to modulate host immune responses, including the release of the pro-inflammatory cytokine such as CXCL8 (20, 21).

As anticipated, S. aureus infected the cells, triggering cell death and significant bacterial growth. Interestingly, these effects were more or less reversed by Nisin. Our studied cell lines release IL-6, markedly raised by the various staphylococcal strains at MOI:1 and MOI:10. Both MRSA and MSSA strains caused similar inflammatory responses in ACHN, with MRSA inducing a little higher response. Nisin effectively abolished MSSA and MRSA-induced secretion of IL-6 from both ACHN and 5637 cell lines. Our finding that Nisin abolishes bacteria-induced release of IL-6 is remarkable and significant since it thus may counteract harmful inflammatory processes. It seems that molecular patterns expressed by the bacteria would induce a release of cytokines from ACHN and 5637 as long as Nisin kills the bacteria. However, this might be since our studied cell lines are not professional immune cells.

On the other hand, this might also propose that Nisin has anti-inflammatory effects. Cells stimulated with MRSA released high amounts of IL-6, a result that Nisin efficiently antagonized. MRSA induced less IL-6

secretion at MOI:1 compared to MOI:10 in the 5637-cell line. MSSA caused a more modest secretion of the inflammatory mediators than the other strains.

Conclusions

Our results demonstrate that Nisin and efficiently inhibiting MRSA and MSSA strains antagonizes bacteria-induced inflammatory responses in ACHN and 5637cells. Nisin displays no cytotoxic properties on studied cells and has a little proinflammatory capacity. Briefly, the bioactivities of Nisin make it a promising candidate as a further antimicrobial agent for targeting S. aureus infections.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no potential competing or conflict of interest.

Funding

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Ethics statement

Not applicable.

Data availability

Data will be provided on request.

Abbreviations

AMP	Antimicrobial peptides
CLSI	Clinical and laboratory standards institute
ELISA	Enzyme-linked-immuno-sorbent assay
MIC	Minimal inhibitory concentration
MRSA	Methicillin-resistant S. aureus
MSSA	Methicillin-sensitive S. aureus
VRE	Vancomycin-resistant enterococci

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Author (s) biosketches

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