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REVIEW

# Anti-infective properties of bacteriocins: an update

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**Abstract** Bacteriocin production is a widespread phenomenon among bacteria. Bacteriocins hold great promise for the treatment of diseases caused by pathogenic bacteria and could be used in the future as alternatives to existing antibiotics. The anti-infective potential of bacteriocins for inhibiting pathogens has been shown in various food matrices including cheese, meat, and vegetables. However, their inhibition of pathogens in vivo remains unclear and needs more investigation, due mainly to difficulties associated with demonstrating their health benefits. Many bacteriocins produced by established or potential probiotic organisms have been evaluated as potential therapeutic agents and interesting findings have been documented in vitro as well as in a few in vivo studies. Some recent in vivo studies point to the efficacy of bacteriocin-based treatments of human and animal infections. While further investigation remains necessary before the possibilities for bacteriocins in clinical practice can be described more fully, this review provides an overview of their potential applications to human and veterinary health.

**Keywords** Bacteriocins · Anti-infective properties · Pathogens · Clinical therapy

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## Introduction

Bacteriocins are peptides of bacterial origin with relatively narrow spectra of bacteriostatic or bactericidal activity directed primarily against species closely related to the producing strain [55]. They make up a heterogeneous family in terms of heat stability, molecular mass, mode of release and action, microbial target, and mechanism conferring protection to the producing strain [48, 57]. Bacteriocins were first identified almost 100 years ago and have since been found among most families of eubacteria as well as many actinomycetes. Although they have been described as universally produced, including by some members of the Archaea [107, 117], the vast majority of known bacteriocins are products of Gram-positive bacteria. Known producers among Gram-negative bacteria are few, and their bacteriocins are of less diverse nature [53].

Bacteriocin classification has been based on biochemical properties, genetics, and bioactivity profiles. The initial scheme proposed by Klaenhammer [72] grew as new bacteriocins were identified and characterized, but eventually became the subject of debate [22, 26, 35, 43, 56, 66, 155]. Four main classes, reviewed over 10 years ago [22], are currently recognized. Class I bacteriocins, also called the lantibiotics, are heat-stable, low molecular mass peptides (<5 kDa) characterized by the presence of unusual amino acids such as lanthionine or β-methyllanthionine produced by post-translational modification [149]. Class II bacteriocins are small heat-stable, unmodified peptides (<10 kDa) comprising three subclasses, namely class IIa (pediocin-like), class IIb (two-chain), and IIc (non-pediocin-like single-chain) [39]. Class III bacteriocins are large (>30 kDa) heat-labile proteins, while class IV bacteriocins include cyclic peptides with covalently linked N and C termini. A special group contains the so-called high molecular weight

(HMW) bacteriocins, which have been shown by electron microscopy to be phage-tail-like molecules. Similarities between bacteriophages and HMW bacteriocins in terms of structure have been proven on the basis of morphological characters, immunological cross-reactivity, complementation, and DNA–DNA hybridization. The most thoroughly studied phage-tail-like bacteriocins, namely the F-type and R-type pyocins produced by *Pseudomonas aeruginosa*, have been reviewed [86]. A third type of pyocins called S, are colicin-like, soluble, and protease-sensitive proteins [86]. Archaea produce their own distinct family of bacteriocin-like antimicrobial substances known as archaeocins [116]. Known bacteriocins that have been isolated are listed in an online database called BACTIBASE [52, 53] at http://bactibase.pfba-lab-tun.org, which provides physicochemical, structural, microbiological, and taxonomic information on bacteriocins of both Gram-positive and Gram-negative bacteria.

The lethal action of bacteriocins begins with entry into the target cell by interaction with specific cell surface molecules that act as receptors (Fig. 1). Several such receptors have been identified, including mannose-phosphotransferase systems (man-PTS) and lipid II. Class IIa bacteriocins target a phylogenetically defined subgroup of man-PTS on sensitive cells of genera such as *Listeria*, *Enterococcus*, and *Lactobacillus* [71]. The N-terminal domain of class II bacteriocins plays a crucial role in electrostatic binding to the membrane surface [41], while the C-terminal region is important for determining target specificity. Lipid II, which has an essential role in cell wall synthesis, serves as an anchoring receptor for the vancomycin/teicoplanin family of glycopeptides, mannopeptimycins, ramoplanins, katanosins/plusbacins, and lantibiotics, a subject previously reviewed [23]. While vancomycin binds the D-Ala-D-Ala peptide side chain of lipid II, the lantibiotic nisin binds the highly conserved sugar-pyrophosphate moiety. Vancomycin-resistant strains thus remain sensitive to nisin [12, 60]. Binding to the membrane surface (through specific or non-specific receptors) leads to subsequent insertion of the bacteriocin into the cytoplasmic membrane to form ion-permeable channels and ultimately large pores. Three models of pore formation have been proposed, namely the barrel-stave model, the carpet model, and the wedge model. Lantibiotics may form pores according to the barrel-stave or

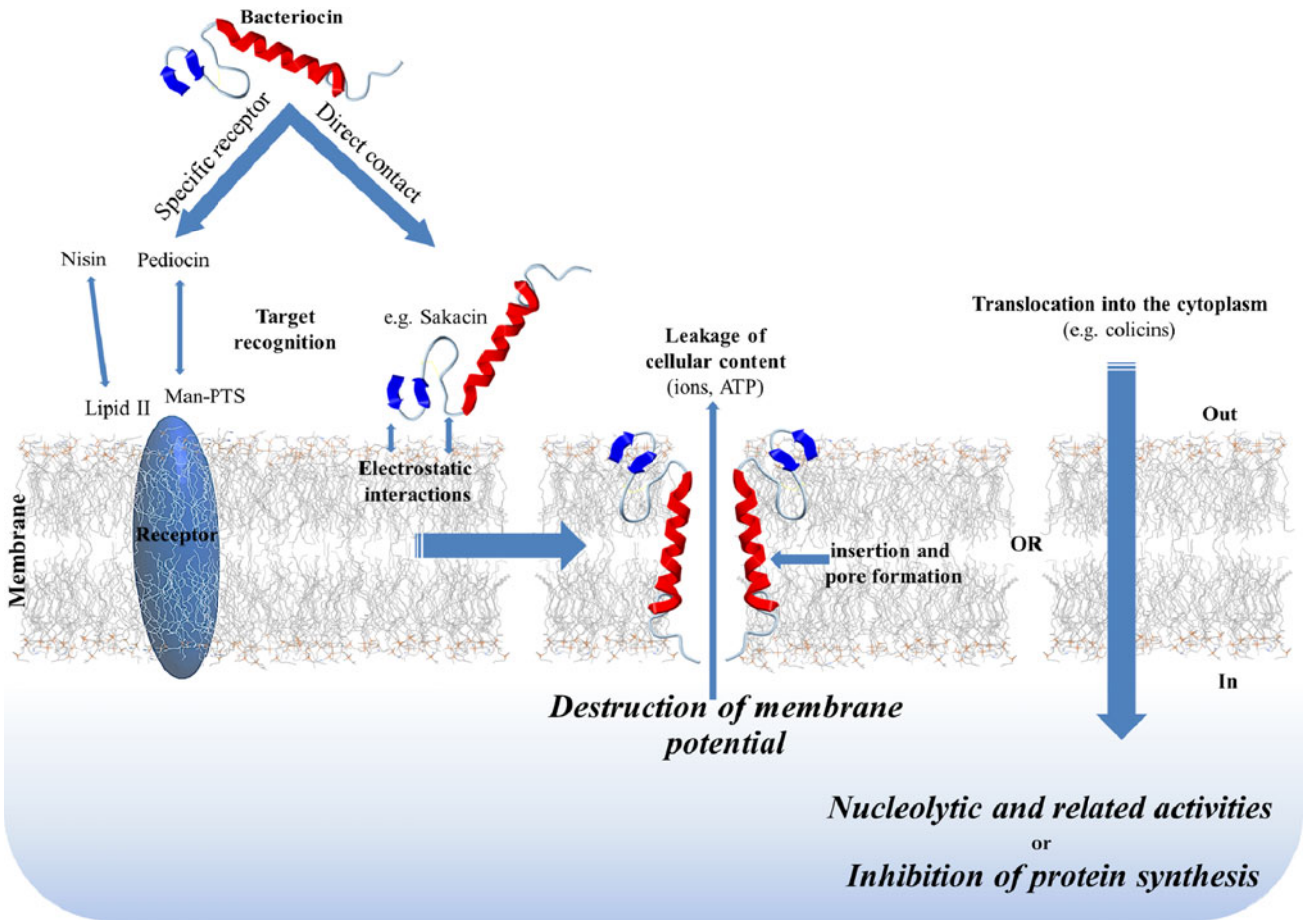


**Fig. 1** Overview of the mode of action of bacteriocins

wedge models, while class II bacteriocins may function according to the barrel-stave or carpet models. These mechanisms have been previously reviewed [13, 21, 87]. Microbial cell death may result from efflux of metabolites, dissipation of vital ion gradients, leakage of cell contents, non-specific degradation of cellular DNA, inhibition of protein synthesis through specific cleavage of 16S rRNA, or by cell lysis resulting from inhibition of peptidoglycan synthesis [148]. For example, after translocation into the periplasmic space, colicin E2 kills the target cell by non-specific DNA cleavage, colicin E3 kills through inactivation of the ribosome, and colicin M inhibits murein biosynthesis by hydrolyzing the pyrophosphate linkage between bactoprenol and the murein precursor. These mechanisms have been reviewed previously [46, 73]. The modes of intracellular action of antibiotics and bacteriocins thus differ considerably. For example, macrolides are an important class of antibiotics that block protein synthesis by binding to the nascent peptide exit tunnel of the ribosome [69], while RNase-type colicins inhibit protein synthesis by cleaving a specific site near the 3′ end of 16S rRNA. The action of these colicins is the subject of a review [93].

First-generation antibiotics have long been misused in human and veterinary medicine and in agriculture and are losing their effectiveness. The emergence of pathogens resistant to them is relentless and has long been a serious public health threat [118]. Of particular notoriety are ubiquitous pathogens such as *Salmonella* typhimurium, *Staphylococcus aureus*, and *Listeria monocytogenes*, all of which are having a major impact on human health and food safety. Many scientists have therefore tested bacteriocins as alternatives to antibiotics. While the effectiveness of bacteriocins and their producer strains as inhibitors of pathogens in food matrices has been shown repeatedly, their inhibitory activity in vivo remains uncertain and needs more investigation. Recent advances in bacteriocin identification and characterization have renewed interest in the study of their use as therapeutic agents, and support is accumulating for their efficacy in treating infections in humans and animals [30, 31, 69]. New bacteriocins with promising in vitro antimicrobial profiles and in vivo effectiveness are being identified and the use of this category of antimicrobial agent as alternatives or adjuncts to help alleviate the current problem of antibiotic overuse and resistance may now be seriously envisaged [37]. This review focuses on progress in bacteriocin applications since 2005.

## Human applications

In recent years, bacteriocins have attracted increasing attention in medicine, since they are active at nanomolar concentrations and non-toxic to humans. Furthermore, their unique mechanism of action, highly specific activity, and their low propensity to generate resistance are attractive properties. Many bacteriocins have been assessed for potential application as therapeutic agents [139]. Bacteriocins have been used successfully to fight skin infections as well as oral, respiratory, gastrointestinal, and urogenital tract infections (Fig. 2; Table 1).

### Hospital-acquired infections

The increasing emergence of antibiotic resistance among nosocomial and community-acquired pathogens is a serious public health threat and will have a major impact on antimicrobial treatments in the future [118]. Currently, the greatest cause for concern is infection by *S. aureus*, enterococci and pneumococci strains displaying acquired resistance to six or more antibiotics. Advances in bacteriocin identification and characterization have prompted renewed interest in the use of these molecules as anti-infective agents. An increasing number of bacteriocins are reportedly potent inhibitors of staphylococci of clinical relevance. Of particular interest are the modes of action of bacteriocins, which differ markedly from those of antibiotics. In a recent study, the antimicrobial activities of lacticin 3147 and nisin A against a common set of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) were assessed [99]. The minimum inhibitory concentration (MIC) is defined as the lowest concentration of antimicrobial agent that completely inhibits the growth of a test organism. Nisin A was thus found more effective against MRSA (MIC = 0.5–4.1 μg/ml), while lacticin 3147 was more potent against VRE (MIC = 2–8.3 μg/ml). More recently, the in vivo activity of lacticin 3147 against luminescent *S. aureus* was investigated using BALB/c mice infected via the intraperitoneal route with $10^6$ colony-forming units (CFUs) of *S. aureus* Xen 29, and treated subcutaneously with the lantibiotic (50.85 mg/kg of Ltnα and 43.8 mg/kg of Ltnβ) after 1.5 h. Lacticin 3147 treatment brought a significant reduction of pathogen levels in the liver, spleen, and kidneys. The capacity to inhibit systemic infection by *S. aureus* makes lacticin 3147 a promising candidate for potential therapeutic applications [98].

In a prior study, Piper and coworkers evaluated the in vitro activity of nisin variants A, F, Q, and Z against MRSA [100], finding variant F the most active, inhibiting strains ST 525 (MIC = 1.2 μg/ml), EC 676 (MIC = 5.1 μg/ml), EC 725 (MIC = 2.5 μg/ml), VISA 22900 (MIC = 41.4 μg/ml), VISA 22781 (MIC = 82.8 μg/ml), hVISA 35197 (MIC = 2.5 μg/ml), *S. aureus* 8325-4 (MIC = 5.1 μg/ml) and *Lactococcus lactis* HP (MIC = 0.064 μg/ml). The ability of nisin F to control *S. aureus* infection in the peritoneal cavity was assessed in a murine model

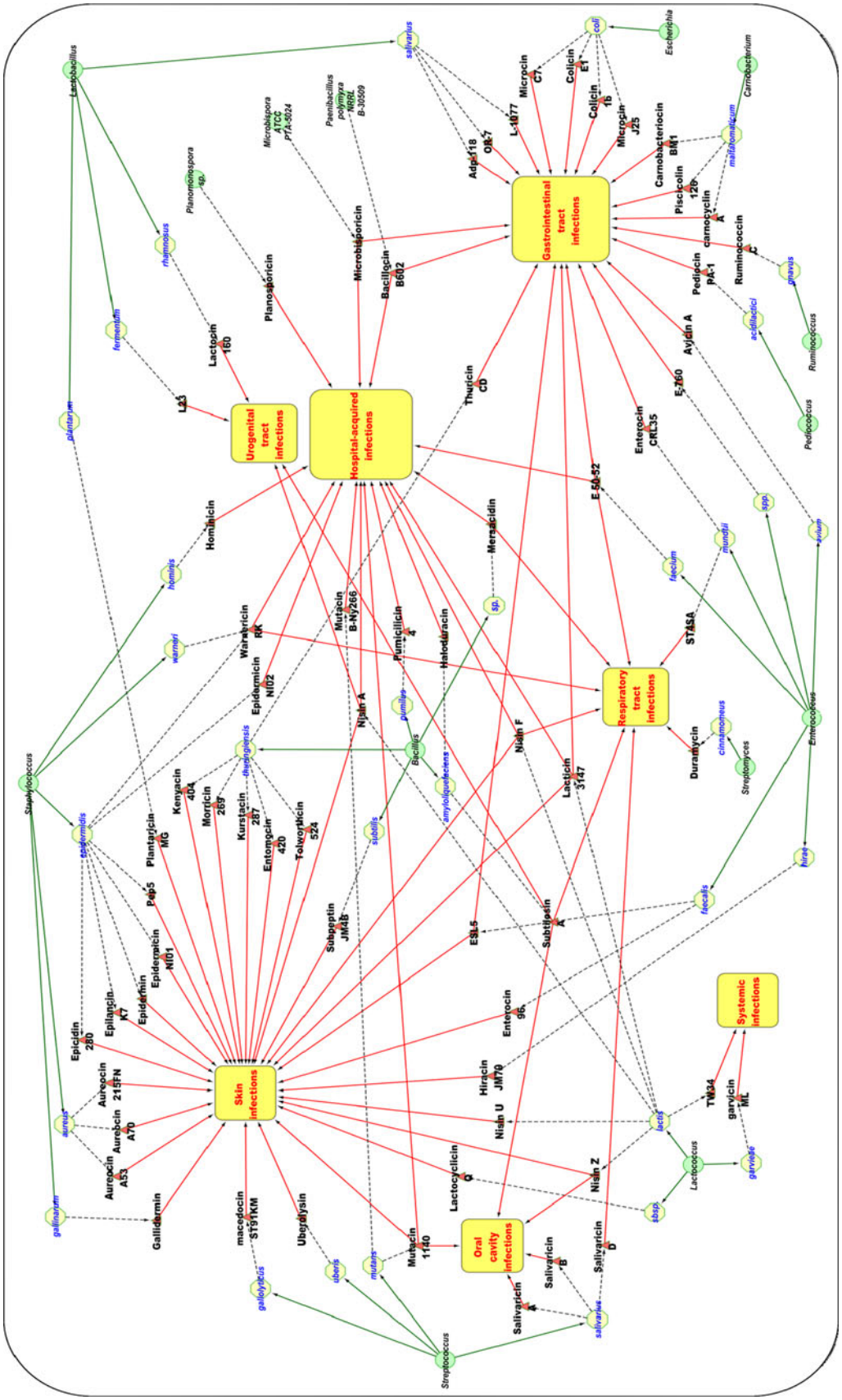


**Fig. 2** Review of therapeutic potential of bacteriocins (in vitro and in vivo studies). *Green circles* producer genus; *yellow circles* producer strain; *red triangles* bacteriocins; *yellow rectangles* anti-infective properties of bacteriocins

**Table 1** Summary list of the bacteriocins discussed in this article

| Bacteriocin | Producer strain | Class | Anti-infective effects | In vitro/vivo | Reference |
|---|---|---|---|---|---|
| Nisin A | *Lactococcus lactis* subsp. | Ia | Multidrug-resistant strain | In vitro | [99] |
| | | | Human mastitis | In vivo (human model) | [40] |
| | | | Spermicidal activity | In vitro | [105] |
| | | | Bovine mastitis | In vivo (bovine model) | – |
| Nisin F | *Lactococcus lactis* subsp. | Ia | Multidrug-resistant strain | In vitro | [100] |
| | | | Multidrug-resistant strain | In vivo (murine model) | [11, 140, 141] |
| | | | Cutaneous diseases | In vivo (murine model) | [34] |
| | | | Pneumonia | In vitro/in vivo (rat model) | [32, 33] |
| Nisin Z | *Lactococcus lactis* subsp. | Ia | Bovine mastitis | In vivo (bovine model) | [17, 152] |
| | | | Oral candidiasis | In vitro | [2] |
| Ruminococcin C | *Ruminococcus gnavus* E1 | Ia | Gastrointestinal disease | In vivo (rat model) | [29] |
| Microbisporicin | *Microbispora* ATCC PTA-5024 | I | Multidrug-resistant strain | In vitro/in vivo (animal model) | [20, 65] |
| | | | Gastrointestinal disease | In vitro | [78] |
| Mutacin 1140 | *Streptococcus mutans* | I | Cutaneous infection | In vitro | [45] |
| | | | Multidrug-resistant strain | In vitro | [45] |
| | | | Oral caries | In vitro/in vivo (animal + human models) | [58, 59, 154] |
| Hominicin | *Staphylococcus hominis* MBBL2-9 | I | Multidrug-resistant strain | In vitro | [70] |
| Gallidermin | *Staphylococcus gallinarum* Tü3928 | I | Cutaneous infection | In vitro/in vivo (rat model) | [83] |
| Mutacin B-Ny266 | *Streptococcus mutans* ATCC 202022 | I | Multidrug-resistant strain | In vitro/in vivo (murine model) | [88] |
| Mersacidin | *Bacillus* sp. strain HIL Y-85,54728 | I | Rhinitis/multidrug-resistant strain | mouse model | [76] |
| Duramycin | *Streptomyces cinnamomeus* NRRL B-1699 | I | Cystic fibrosis | In vivo (human model) | [49, 123] |
| Salivaricin A<br>Salivaricin B | *Streptococcus salivarius* K12 | I | Halitosis | In vitro/in vivo (animal + human models) | [14–16] |
| Salivaricin D | *Streptococcus salivarius* 5M6c | I | Pneumoniae | In vitro | [8] |
| Nisin U | *Lactococcus lactis* spp. | I | Bovine mastitis | In vitro | [150] |
| Macedocin ST91KM | *Streptococcus gallolyticus* subsp. *macedonicus* ST91KM | I | Bovine mastitis | In vitro | [96, 97] |
| Pep5 | *Staphylococcus epidermidis* 5 | I | Bovine mastitis | In vitro | [142] |
| Epidermin | *Staphylococcus epidermidis* | I | Bovine mastitis | In vitro | [142] |
| Epilancin K7 | *Staphylococcus epidermidis* | I | Bovine mastitis | In vitro | [142] |
| Epicidin 280 | *Staphylococcus epidermidis* | I | Bovine mastitis | In vitro | [142] |
| Lacticin 3147 | *Lactococcus lactis* DPC 3147 | Ib | Multidrug-resistant strain | In vitro | [99] |
| | | | Multidrug-resistant strain | In vivo (murine model) | [98] |
| | | | Gastrointestinal disease | In vitro (fermentation model) | [102] |
| | | | Bovine mastitis | In vivo (bovine model) | [27, 28, 74] |
| Thuricin CD | *Bacillus thuringiensis* DPC 6431 | Ib | Gastrointestinal disease | In vitro/distal colon model | [103, 104] |
| Haloduracin | *Bacillus halodurans* C-125 | Ib | Multidrug-resistant strain | In vitro | [91] |
| Planosporicin | *Planomonospora* sp. DSM14920 | IB | Multidrug-resistant strain | In vitro/in vivo (mouse model) | [19] |
| Avicin A | *Enterococcus avium* | IIa | Gastrointestinal disease | In vitro | [7] |

**Table 1** continued

| Bacteriocin | Producer strain | Class | Anti-infective effects | In vitro/vivo | Reference |
|---|---|---|---|---|---|
| Piscicolin 126 | *Carnobacterium maltaromaticum* UAL307 | IIa | Gastrointestinal disease | In vitro | [85] |
| Carnobacteriocin BM1 | | IIa | Gastrointestinal disease | | |
| Epidermicin NI01 | *Staphylococcus epidermidis* 224 | II | Cutaneous infection | In vitro | [112] |
| | | | Multidrug-resistant strain | | |
| | | | Cutaneous infection | | |
| Pediocin PA-1 | *Pediococcus acidilactici* UL5 | IIa | Gastrointestinal disease | In vivo (murine model) | [31] |
| Enterocin CRL35 | *Enterococcus mundtii* CRL35 | IIa | Gastrointestinal disease | In vivo (murine model) | [109] |
| ST4SA | *Enterococcus mundtii* | IIa | Middle ear infection | In vitro | [75] |
| Bacillocin B602 | *Paenibacillus polymyxa* NRRL B-30509 | IIa | *Campylobacter* infection | In vivo (Chickens + turkey models) | [24, 125] |
| | | | Multidrug-resistant strain | In vitro | [130] |
| E 50-52 | *Enterococcus faecium* NRRL B-30746 | IIa | Gastrointestinal diseases | In situ (chicken) | [132] |
| | | | Tuberculosis | mouse model | [122] |
| | | | Multidrug-resistant strain | In vitro | [130] |
| L-1077 | *Lactobacillus salivarius* NRRL B-50053 | IIa | Gastrointestinal diseases | In vitro/in situ (chicken model) | [131] |
| Enterocin 96 | *Enterococcus faecalis* WHE96 | II | Cutaneous infections | In vitro | [64] |
| Hiracin JM79 | *Enterococcus hirae* DCH5 | II | Cutaneous infections | In vitro | [111] |
| Adp-118 | *Lactobacillus salivarius* UCC118 | IIb | Gastrointestinal disease | In vivo (murine + pig models) | [25, 106] |
| E-760 | *Enterococcus* spp. NRRL B-30745 | IIb | *Campylobacter* infection | In situ (chicken model) | [79] |
| Carnocyclin A | *Carnobacterium maltaromaticum* UAL307 | Cyclic | Gastrointestinal disease | In vitro | [85] |
| Subtilosin A | *Bacillus amyloliquefaciens* | Cyclic | Periodontal disease | In vitro | [119] |
| | | | Pneumonia | In vitro | [119] |
| | | | Bacterial vaginosis | In vitro | [129] |
| | | | Spermicidal activity | In vivo (animal model) | [120, 127] |
| Garvicin ML | *Lactococcus garvieae* DCC43 | Cyclic | Lactococcosis | In vitro | [9, 110] |
| Microcin J25 | *Escherichia coli* | | Gastrointestinal disease | In vivo (murine model) | [81] |
| Microcin C7 | *Escherichia coli* H22 | | Gastrointestinal disease | In vitro/in vivo (murine model) | [30] |
| Colicin 1b | | | | | |
| Colicin E1 | | | | | |
| Plantaricin MG | *Lactobacillus plantarum* KLDS1.0391 | UN | Cutaneous infection | In vitro | [47] |
| Subpeptin JM4B | *Bacillus subtilis* JM4 | UN | Cutaneous infection | In vitro | [153] |
| ESL5 | *Enterococcus faecalis* SL-5 | UN | Cutaneous infection | In vitro/in vivo (human model) | [68] |
| | | | Gastrointestinal disease | | |
| Pumicilicin 4 | *Bacillus pumilus* WAPB4 | UN | Multidrug-resistant strain | In vitro | [5] |
| Warnericin RK | *Staphylococcus warneri* RK | UN | Multidrug-resistant strain | In vitro | [3] |
| | *Staphylococcus epidermidis* A487 | | Pneumonia | In vitro | [146] |
| Lactocin 160 | *Lactobacillus rhamnosus* 160 | UN | Bacterial vaginosis | In vitro/in-vivo (rabbit model) | [38, 138] |
| L23 | *Lactobacillus fermentum* L23 | UN | Bacterial vaginosis | In vitro | [94] |
| TW34 | *Lactococcus lactis* TW34 | UN | Lactococcosis | In vitro | [115] |
| Lactocyclicin Q | *Lactococcus* ssp. QU12 | UN | Cutaneous infections | In vitro | [113] |

**Table 1** continued

| Bacteriocin | Producer strain | Class | Anti-infective effects | In vitro/vivo | Reference |
|---|---|---|---|---|---|
| Uberolysin | *Streptococcus uberis* strain 42 | UN | Bovine mastitis | In vitro | [151] |
| Aureocin A70 | *Staphylococcus aureus* A70 | UN | Bovine mastitis | In vitro | [142] |
| Aureocin A53 | *Staphylococcus aureus* A53 | UN | Bovine mastitis | In vitro | [142] |
| Aureocin 215FN | *Staphylococcus aureus* 215FN | UN | Bovine mastitis | In vitro | [142] |
| Morricin 269 | *Bacillus thuringiensis* subsp. *Morrisoni* (LBIT 269) | BLIS | Bovine mastitis | In vitro | [6] |
| Kurstacin 287 | *Bacillus thuringiensis* subsp. *Kurstaki* (LBIT 287) | BLIS | Bovine mastitis | In vitro | [6] |
| Kenyacin 404 | *Bacillus thuringiensis* subsp. *Kenyae* (LBIT 404) | BLIS | Bovine mastitis | In vitro | [6] |
| Entomocin 420 | *Bacillus thuringiensis* subsp. *Entomocidus* (LBIT 420) | BLIS | Bovine mastitis | In vitro | [6] |
| Tolworthcin 524 | *Bacillus thuringiensis* subsp. *Tolworthi* (LBIT 524) | BLIS | Bovine mastitis | In vitro | [6] |
| OR-7 | *Lactobacillus salivarius* NRRL B-30514 | | *Campylobacter* infection | In vitro (chicken model) | [126] |

*UN* unclassified, *BLIS* bacteriocin-like inhibitory substance

[11]. In this trial, C57BL/6 mice were infected intraperitoneally with $10^8$ CFU of *S. aureus* Xen 36 and treated with a single dose of nisin F (640 AU) 4 h postinfection. Growth of the pathogen was inhibited for only 15 min, after which re-emergence of pathogen bioluminescence was observed. It was presumed that degradation by proteolytic enzymes and/or inactivation through non-specific binding at physiological pH values limited the inhibitory activity. Injected into the peritoneum, nisin F did not alter bacterial diversity in the mouse gastrointestinal tract [141].

More recently, the feasibility of nisin F-loaded brushite cement was evaluated [140]. Incorporation of nisin F into the formula did not cause substantial changes in cement structure or chemistry. The resulting bone cement clearly inhibited in vitro the growth of *S. aureus* Xen 36 for at least 72 h. In vivo studies were then carried out using BALB/c mice infected with bioluminescent *S. aureus* Xen 36 [140]. Nisin F-loaded brushite cement was implanted in a subcutaneous pocket and the mice were then infected with the pathogen. As expected, nisin-F-loaded cement protected the mice from *S. aureus* infection for 7 days and no viable bacterial cells were detected in the implants. Incorporation of nisin F into brushite cement resulted in a high burst release, followed by a slow steady release. However, the release trend was slightly more rapid than reported for other drugs. Release kinetics could be improved by altering porosity of the cement or by incorporating polymeric molecules associated with the desired bacteriocin. A two-peptide lantibiotic called haloduracin, produced by *Bacillus halodurans* C-125, was also compared to nisin [91]. Some of the tested strains (vancomycin-resistant *Enterococcus*) were more sensitive to haloduracin (MIC = 781 nM) than to nisin (MIC = 12,500 nM). Conversely, nisin was more effective than haloduracin against methicillin-resistant *S. aureus* C5 in the micromolar range (MIC = 4,690 and 1,560 μM, respectively). Haloduracin was more stable at physiological pH than was nisin, which is of interest for therapeutic applications. E 50-52 and B602, two pediocin-like bacteriocins produced respectively by *Enterococcus faecium* NRRL B-30746 and *Paenibacillus polymyxa* NRRL B-30509, were shown to be active against multidrug-resistant bacteria (MDR) [130]. All tested MRSA isolates were highly sensitive to both B602 (MIC $<$ 0.025 μg/ml) and E 50-52 (MIC $\leq$ 0.05–0.2 μg/ml). E 50-52 was active against isolates of Gram-negative *Acinetobacter baumannii* and *Proteus* spp., while *S. aureus* isolates showed susceptibilities in narrower ranges, with MIC ranging from $\leq$0.05 to 0.2 μg/ml. Similarly, isolates of Gram-negative organisms such as *A. baumannii*, *Citrobacter freundii*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus* spp. were sensitive to B602, with MIC from $\leq$0.025 to 0.05 μg/ml. MRSA isolates were similarly susceptible to this bacteriocin, with MIC $\leq$0.025 μg/ml. Compared to published MIC of nisin for MRSA and

methicillin-sensitive *S. aureus* (MSSA), varying from 0.5 to 4.1 μg/ml [99], these isolates were 100 times more sensitive.

Planosporicin is a type B lantibiotic produced by *Planomonospora* sp. DSM14920 and displaying a wide antimicrobial spectrum [19]. Patented as antibiotic 97518, planosporicin has MIC values of 2–16 μg/ml against *S. aureus* (including MRSA), 4 μg/ml against *Streptococcus pneumoniae* and ≤0.25 μg/ml against *Clostridium perfringens*. Although no known lipid II binding motif is present in planosporicin, its mechanism of action involves inhibition of cell wall biosynthesis. The authors developed a murine model of *Streptococcus pyogenes* infection to evaluate the in vivo antibiotic activity of planosporicin (MIC = 0.5 μg/ml). The peptide protected mice with an $ED_{50}$ of 3.75 mg/kg by both intravenous and subcutaneous administration. No acute toxicity was observed during this trial. Castiglione and coworkers [19, 20] reported comparisons of the bioactivity of microbisporicin, planosporicin, actagardine, mersacidin, and nisin. Microbisporicin is produced by *Microbispora* ATCC PTA-5024 and secreted as isoforms A1 and A2 with distinguishing post-translational modifications 5-chloro-trypthopan and mono (in A2) or bis-hydroxylated (in A1) proline [20]. The activity of microbisporicin appeared comparable to or better than those of reference lantibiotics such as planosporicin, actagardine, mersacidin, and nisin. Microbisporicin, also called NAI-107 or antibiotic 107891, was active against Gram-positive bacteria including MRSA, glycopeptide-intermediate *S. aureus* (GISA) and VRE [65] and against Gram-negative bacteria including *Moraxella catarrhalis*, *Neisseria* spp. and *Haemophilus influenzae*, which were insensitive to most of the lantibiotics and only moderately susceptible to nisin. The strong bactericidal activity of microbisporicin observed in vitro was also confirmed in vivo in animal models of severe infection induced by MDR Gram-positive pathogens [20, 65].

Kim and coworkers [70] purified a lantibiotic from *Staphylococcus hominis* MBBL 2–9. Hominicin showed potent activity against MRSA ATCC 11435 (MIC = 0.96 μg/ml) and VISA CCARM 3501 (MIC = 3.82 μg/ml), but none against VRE CCARM 5024. The authors also compared the potency of hominicin and other antimicrobial peptides against MRSA, VISA, and *S. aureus*, obtaining an MIC of 0.06 μg/ml for hominicin against *S. aureus,* just slightly higher than that of nisin (0.05 μg/ml) and lower than those of gramicidin (1.76 μg/ml), polymyxin B (0.16 μg/ml), colistin (0.13 μg/ml) and bacitracin (0.16 μg/ml) [70]. Hominicin was more active than nisin against MRSA and VISA. Similarly, pumilicin 4, a 2-kDa bacteriocin produced by *Bacillus pumilus* WAPB4 isolated from water [5] showed broad spectrum antibacterial activity including MRSA and VRE. Pumilicin 4 (at 80 AU/ml) induced 3 and 2.5 log reduction of MRSA and VRE counts, respectively. Mutacin B-Ny266, a lantibiotic produced by *Streptococcus mutans* Ny266 (ATCC 202022) was shown to be active in vitro against VREF 0032 (MIC = 2.7 μg/ml), MRSA 0034 (MIC = 2 μg/ml) and *E. coli* 0025 (MIC = 1.7 μg/ml) but not active at the highest tested concentration (64 μg/ml) against *Candida albicans* or *Pseudomonas aeruginosa* [88]. The efficacy of mutacin B-Ny266 against staphylococci infection was also shown, protecting mice infected intraperitoneally with $3.1 \times 10^7$ CFU of *S. aureus* Smith (MSSA) and injected with a single intraperitoneal dose of bacteriocin (1 mg/kg) immediately after infection [88].

## Respiratory infections

Community-acquired pneumonia is a frequent infectious respiratory disease that remains a major cause of morbidity in both the developing and developed world [82, 101]. While *S. pneumoniae* is the most frequently isolated pathogen, pneumonia may be caused also by a wide variety of pathogens including *H. influenzae* and *M. catarrhalis*, *S. aureus*, *Enterobacteriaceae* and *P. aeruginosa*. Less common pneumonia etiologies include *S. pyogenes*, *Neisseria meningitidis*, *Pasteurella multocida*, and *H. influenzae* type b. [82]. *Legionella pneumophila*, another pathogen responsible for a severe pneumonia, infects humans through inhalation of contaminated aerosols [89]. Produced by *Staphylococcus warneri* RK, warnericin RK was the first bacteriocin found to have anti-*Legionella* activity [146]. This peptide exhibits a very narrow spectrum of activity almost limited to the *Legionella* genus, and a hemolytic activity. More recently, *Staphylococcus epidermidis* strain A487 was shown to produce the same bacteriocin (called peptide 487 by the authors) with strong activity against MRSA in vitro [3]. Bacteriocins inhibitory to *S. pneumoniae*, *S. aureus*, and *P. aeruginosa* in vitro have been purified recently and characterized microbiologically, including subtilosin A [119], L23 [94], mutacin 1140 [45], and salivaricin D [8]. *Acinetobacter baumannii*, *P. aeruginosa*, *S. pneumonia*, *S. aureus*, and *E. faecium,* all known to cause otitis media, one of the most common infections in young children [114], are inhibited by a class IIa bacteriocin called peptide ST4SA, produced by *Enterococcus mundtii* [75]. Peptide ST4SA was more active than other antibiotics in vitro and remained active when incubated in blood and middle ear fluid and could thus be useful for the treatment of middle ear infections.

Nisin F has been reported to inhibit clinical strains of *S. aureus* in vitro [33]. In a recent in vivo trial, Nisin F administered intranasally for four consecutive days inhibited the growth of *S. aureus* in the respiratory tract of immunocompromised Wistar rats [32] and prevented the

onset of symptoms of pneumonia, mucosal hyperplasia, blood contamination, or necrotic lesions. The authors concluded that nisin F is nontoxic and could be used to treat respiratory tract infections caused by *S. aureus*. However, these findings remain to be confirmed in humans. The in vivo activity of the bacteriocin mersacidin was assessed against MRSA colonizing nasal epithelia in a mouse rhinitis and MRSA carrier model recently developed by Kruszewska and collaborators [76]. Administered intranasally twice daily over three days, mersacidin completely killed MRSA. Furthermore, no bacteremia was detected in animals post-treated with the bacteriocin.

The antimycobacterial activity of bacteriocin E50-52 was evaluated in vivo using a murine model of tuberculosis infection developed by Sosunov and collaborators [122]. C57BL/6JCit (B6) mice were challenged with *Mycobacterium tuberculosis* strain H37Rv to induce acute tuberculosis. During this trial, bacteriocin E50-52 was compared to rifampicin, a clinically used antibiotic. A 5-day treatment with bacteriocin/liposome complex was sufficient to increase animal life span. The effect was slightly weaker than that of rifampicin injected at tenfold higher concentrations. Carroll and coworkers [18] have reported the in vitro susceptibility of clinically relevant strains of mycobacteria to the lantibiotics lacticin 3147 and nisin A. Lacticin 3147 was particularly active against *M. tuberculosis* H37Ra ($MIC_{90}$ = 7.5 μg/ml; $MIC_{90}$ values are defined as the lowest concentration of bacteriocin that prevent the growth of >90 % of the bacterial population), *M. avium* subsp. *paratuberculosis* ATCC 19698 ($MIC_{90}$ = 15 μg/ml) and *M. kansasii* CIT11/06 ($MIC_{90}$ = 60 μg/ml). Although inhibitory, nisin A was less potent against the tested mycobacteria, with $MIC_{90}$ values of 60 μg/ml for *M. kansasii* and >60 μg/ml for *M. avium* subsp. *paratuberculosis* and *M. tuberculosis* H37Ra.

In patients with cystic fibrosis (CF), chronic lung infection with *P. aeruginosa* occurs in infancy and early childhood, damaging the epithelial surfaces. The company AOP Orphan Pharmaceuticals AG have developed a therapeutic product for CF treatment based on the lantibiotic duramycin (Moli1901). A phase II placebo-controlled, double-blind, single-center trial was successfully completed using an inhaled aerosol Moli1901 in 24 patients with CF and stable lung disease [49]. Pulmonary pharmacokinetics and safety of nebulized duramycin were studied in healthy human volunteers [123]. Pyocin S2, a HMW bacteriocin isolated recently from *P. aeruginosa* PA01, was found more effective than aztreonam or tobramycin (two approved antibiotics for treatment of chronic CF lung infection) against biofilms of *P. aeruginosa* clinical isolate YHP14, showing 4-log reductions in cell survival at a concentration equivalent to the highest concentration of antibiotic. The ability of pyocin S2 to provide protection against an infectious dose ($10^4$ CFU) of *P. aeruginosa* YHP14 in the caterpillar *Galleria mellonella* was then tested. Viable counts of pathogen 3 h post-infection in larvae treated with pyocin S2 (27 μg/g) were as low as 10–40 CFU, compared to 5–10 × $10^8$ CFU in untreated larvae at the time of death. The authors also found pyocin S2 to be nontoxic to the host in the absence of infection [121].

## Skin infections

Community-acquired MRSA infection has become epidemic, with skin and soft-tissue infections being the most frequent forms of disease. *S. aureus* may colonize intact skin only transiently and remain present in nasal mucosa without the occurrence of any pathogenic event [63]. However, the bacteria can colonize broken skin to utilize the nutrient-rich bloodstream, express a wide range of virulence factors that disrupt the epithelial barrier, and diminish neutrophil functions and cell-mediated immune responses [63]. Staphylococci cause an array of cutaneous and systemic infections including impetigo, furuncles, subcutaneous abscesses, staphylococcal scalded skin syndrome (SSSS), toxic shock syndrome, and neonatal toxic shock syndrome-like exanthematous disease or NTED [63]. Acne vulgaris is another common human skin disease, mostly caused by pathogenic *Propionibacterium acnes* and *S. epidermidis* [90]. C57BL/6 mice challenged with a bioluminescent strain of *S. aureus* (Xen 36) and then treated with subcutaneous administration of nisin F (256 AU at 24 and 48 h) did not resist subcutaneous skin infections any better than did control mice [34], although the lantibiotic did appear to stimulate the immune system. The authors concluded that nisin F is ineffective as a treatment for deep dermal staphylococcal infections. Previously, strains of *Streptococcus salivarius* that produce a bacteriocin-like substance (BLIS) have been shown to inhibit growth of *P. acnes* [10]. In this study, the prevalence of *S. salivarius* in the oropharynx of patients with acne vulgaris was evaluated. A total of 33 human clinical isolates of *S. salivarius* were tested for BLIS-producing capacity based on antagonism of three streptococci and *P. acnes*. One-third of the isolated *S. salivarius* strains inhibited growth of *P. acnes* [10]. *Enterococcus faecalis* SL-5 isolated from fecal specimen of a healthy Korean adult was found to produce bacteriocin ESL5, which inhibited *P. acnes*, *Bacillus cereus*, *Bacillus subtilis*, *L. monocytogenes*, and *S. aureus* [68]. A double-blind, randomized, placebo-controlled phase III trial was then conducted to evaluate the therapeutic effect of *E. faecalis* SL-5 in patients suffering from mild to moderate acne using a lotion containing *E. faecalis* SL-5. With a twice-per-day treatment, the lotion significantly reduced inflammatory pustule-like lesions in patients. However, the

authors noted the presence of a mild unpleasant odor and skin dryness, reported by both treated and untreated patients.

Gallidermin is a well-characterized lantibiotic that has shown great therapeutic potential against several pathogens including *P. acnes* and *S. aureus*. Entrapped in anionic niosomes incorporated into a gel, gallidermin was used to treat *P. acnes* and *S. aureus* infections in rats by transdermal absorption [83]. The gel formulation provided superior cumulative flux into the skin with no risk of systemic effects. The entrapment efficiency was about 45 %. However, the gallidermin–niosome system decreased the in vitro antibacterial activity by half compared to nonencapsulated gallidermin. Several antistaphylococcal class II bacteriocins, including enterocin 96 from *E. faecalis* WHE96 [64], hiracin JM79 from *Enterococcus hirae* DCH5 [111] and lactocyclicin Q from *Lactococcus* subsp QU12 [113] have been purified and characterized in vitro in recent years. These have been shown to possess a wide spectrum of activity inhibitory also to enterococci, lactobacilli, and *L. monocytogenes*.

Mutacin 1140 (MU1140), a 22-amino-acid lantibiotic produced by *S. mutans*, has a promising role in promoting colonization of the oral cavity by the producer strain [45]. All tested Gram-positive bacterial strains ($n = 30$) were sensitive to MU1140, while none of the 28 Gram-negative species or the yeasts tested showed sensitivity. MU1140 was particularly active against *E. faecalis* (MIC = 16–32 μg/ml), *S. aureus* (MIC = 16 μg/ml), *S. epidermidis* (MIC = 16 μg/ml), *Streptococcus agalactiae* (MIC = 4 μg/ml), *S. pneumoniae* ATCC 49619 (MIC = 4 μg/ml), and *S. pyogenes* (MIC = 0.5 μg/ml). This study also demonstrated the susceptibility of vancomycin-resistant and oxacillin-resistant *S. aureus*, *E. faecalis*, and *E. faecium* strains to this lantibiotic [45]. Initially isolated from fermented cream, *Lactobacillus plantarum* KLDS1.0391 produces plantaricin MG, another bacteriocin with a broad spectrum of activity [47]. Partially purified plantaricin MG inhibited *S. aureus*, *Pseudomonas fluorescens* ATCC 17485, *Pseudomonas putida* ATCC 13525, *E. coli*, and *S.* typhimurium during in vitro studies. Likewise, Wu and coworkers [153] reported the susceptibility of *Shigella flexeneri* to subpeptin JM4B, a dodecapeptide bacteriocin obtained from *B. subtilis* JM4. Subpeptin JM4B was also active in vitro against *S. aureus*, *P. aeruginosa*, *Salmonella* sp., and *E. faecalis*. More recently, a new class II bacteriocin produced by *S. epidermidis* 224 isolated from human skin has been identified [112]. Epidermicin NI01 has been shown to be active against a range of clinically relevant pathogens including *S. epidermidis* (MIC = 0.063–4 μg/ml), *Staphylococcus saprophyticus* (MIC = 0.5–1 μg/ml), *S. hominis* (MIC = 1 μg/ml), *S. warneri* (MIC = 1 μg/ml), *E. faecalis* (MIC = 1 μg/ml), VRE (MIC = 0.5–2 μg/ml), MRSA (MIC = 1–2 μg/ml) and *S. aureus* 1195 (MIC = 2 μg/ml). Toxicity data indicate that peptide NI01 at 100 × MIC has no adverse effects on human blood cells or on human fibroblast cell lines, which is encouraging with respect to clinical applications.

Mastitis is an inflammation of the breast, usually caused by an infection during lactation. *Staphylococcus albus* and *S. aureus* are the pathogens most commonly associated with human mastitis, while *E. coli* and streptococci are involved less frequently. Fernández and collaborators [40] have found nisin effective for the treatment of staphylococcal mastitis during lactation. During this trial, eight women who did not respond to cloxacillin, clindamycin, amoxicillin/clavulanic acid and/or erythromycin were treated with nisin solution (6 μg/ml) applied to the nipple and mammary areola after each suckling episode for 2 weeks. The treatment reduced staphylococcal counts considerably and led to the complete disappearance of clinical signs of mastitis.

## Gastrointestinal tract infections

### *Oral cavity*

The oral cavity is not simply the entrance to the gastrointestinal tract, but harbors some of the most varied and extensive indigenous microbiota in the human body. The oral cavity provides a continuous source of infectious agents. Oral disorders can lead to dental caries (cavities), periodontal diseases, gingivitis, halitosis, and periodontitis. Probiotics have been used successfully to control gastrointestinal diseases, as reviewed in [42]. Much attention has been given recently to the health-promoting properties of probiotics in the treatment of periodontal disease, reviewed in [136]. *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Actinobacillus actinomycetemcomitans* are regarded as the principal potential periodontal pathogens [4]. Therapy consists of replacing resident pathogens with a nonpathogenic bacteriocin-producing variant. Described by Shelburne and collaborators [119], subtilosin A inhibited in vitro growth of *P. gingivalis* (MIC = 3.125–6.25 μg/ml). The *Lactobacillus paracasei* strain HL32 produces a 114-kDa bacteriocin that has been shown to inhibit *P. gingivalis* selectively, making it a candidate for periodontal treatment [92]. However, this bacteriocin appears toxic to human erythrocytes and would therefore not be suitable for systemic use. Since the creation of *S. mutans* BCS3-L1 (in the year 2000, using recombinant DNA technology) for use in the prevention of dental caries, Hillman and collaborators have improved this producer of mutacin 1140 but not lactic acid [59]. Additional mutations have been introduced to allow rapid elimination of the strain in case of adverse side effects and to increase genetic

stability. The newly transformed strain A2JM has been tested in vitro and in vivo in animal models. The authors believe that based on the apparent safety and efficacy, A2JM is ready for testing in human clinical trials [59]. They have also developed and patented a probiotic mouthwash called ProBiora3. The product consists of a blend of *Streptococcus uberis KJ2*, *Streptococcus oralis KJ3*, and *Streptococcus rattus* JH145 (MU1140 producing and lactic acid-deficient). Studies of ProBiora3 in rats [58] and human volunteers [154] have been carried out to assess its safety and effectiveness as a mouthwash.

Halitosis or oral malodor results from metabolic activity of oral bacteria that produce volatile sulphur compounds, valeric acid, butyric acid, and putrescine [80]. *S. salivarius* K12 produces two lantibiotics, salivaricin A, and salivaricin B and has been shown active against bacterial species involved in halitosis, inhibiting *Micrococcus luteus* I1, *Streptococcus anginosis* T29, *Eubacterium saburreum* ATCC 33271, and *Micromonas micros* ATCC 33270 [15]. Further toxicology studies in animals have not revealed any negative effect of multiple dosing [14]. Meanwhile, *S. salivarius* K12 has been evaluated for safety and human tolerance in a randomized, placebo-controlled, double-blind trial [16]. Clinical trials of *Lactobacillus salivarius* strain WB21 [62] for probiotic control of halitosis and *Lactobacillus reuteri* (Prodentis) for preventing periodontal disease [147] have also been carried out. In a recent screening, 357 oral strains of *Lactobacillus* isolated from children were evaluated as inhibitors of oral pathogens [135]. Six of these were strong inhibitors of *P. gingivalis* and *A. actinomycetemcomitans* in vitro. Further characterization and safety analyses are necessary before testing any of these isolates in clinical trials.

Oral candidiasis and denture-associated stomatitis are oral infections caused by *C. albicans*. Nisin Z has been evaluated in vitro for efficacy against *C. albicans* adhesion and transition following contact with normal human gingival cells [2]. At concentrations of 25 μg/ml, nisin Z reduced *C. albicans* adhesion to gingival monolayer cultures and inhibited germ tube formation in vitro.

### *Gastric and intestinal infections*

The human gastrointestinal (GI) tract harbors trillions of microorganisms (approximately $10^{11}$ per gram of feces) that carry out vital processes for normal digestive functions of the host and play an important albeit not yet fully understood role in the maturation of human immunity and defense against pathogens [145]. Intestinal floral equilibrium may be altered by several factors, such as infection or antibiotic therapy, resulting in diarrhea and hence exposure of the subject to additional and often more dangerous infections, for example *C. difficile* [84]. Several bacteriocins have been tested as inhibitors of GI pathogenic bacteria such as *Helicobacter pylori*, *C. difficile*, *L. monocytogenes*, and *Salmonella* (Fig. 1).

### *Clostridium difficile*

*C. difficile* is the most common identifiable cause of bacteria-associated diarrhea in developed nations and the major cause of gastroenteritis in nursing homes and other long-term-care facilities [67]. Microbisporicin shows promising activity in vitro against several clostridia, with MIC values <0.125 μg/ml against *C. difficile*, *C. perfringens*, *Clostridium butyricum*, *Clostridium beijerinckii*, and *Clostridium septicum* [78]. Microbisporicin also inhibits *L. monocytogenes* (MIC = 0.125 μg/ml). The impact of this bacteriocin on the intestinal microbiota needs to be studied in vivo before it can be considered for use as an orally administered therapeutic agent.

Lacticin 3147, a two-component lantibiotic produced by *L. lactis*, has significant antimicrobial activity against pathogenic isolates of *C. difficile* [102], bactericidal in the same concentration range as vancomycin and metronidazole, the most commonly used antibiotics. At 18 μg/ml, it totally eliminated *C. difficile* ($10^6$ CFU/ml) from a model fecal environment within 30 min with only minor effects on commensal flora such as *Lactobacillus* and *Bifidobacterium*. However, porcine studies indicate that gastric acidity is a hurdle for lacticin 3147, to be overcome by suitable technology (e.g., encapsulation) before it can be considered for use as an orally administered therapeutic agent [44]. Despite the effectiveness of lacticin 3147 against *L. monocytogenes* in vitro, its producer strain failed to prevent infection by the pathogen in a mouse model [37]. *Bacillus thuringiensis* DPC 6431, isolated from human feces, has been shown to produce thuricin CD [104]. Identified as a two-peptide lantibiotic, thuricin CD has impressive in vitro activity against clostridia including 21 clinical isolates of *C. difficile*, *Clostridium histolyticum* NCIMB 503, *Clostridium indolis* NCIMB 9731, *Clostridium lituseburense* NCIMB 10637, *C. perfringens* LMG 10468, *C. perfringens* LMG 11264, and *Clostridium tyrobutyricum* NCIMB 8243. It has little impact on most other genera, including gastrointestinal commensals such as *Bifidobacterium*, *Enterococcus*, and *Lactobacillus*. Comparing the impact of vancomycin, metronidazole, lacticin 3147, and thuricin CD on microbiota composition in a model of the human distal colon, Rea and coworkers [103] found that although effective against *C. difficile*, the antibiotics and lacticin 3147 had a broad spectrum of activity making them less suited to therapeutic use in the gastrointestinal tract. In contrast, the narrow spectrum of activity of thuricin CD represents a therapeutic advantage, killing *C. difficile* but having little impact on microbiota composition.

Recently isolated directly from the dominant fecal microbiota of a healthy man, *Ruminococcus gnavus* E1 was used to colonize the digestive tract of axenic rats. Under these conditions, it was found to express the rumA genes weakly and produce a bacteriocin called ruminococcin C or RumC in the cecum [29]. RumC is active against *C. perfringens* and resistant to high temperature and acidic pH.

### *Listeria monocytogenes*

*Listeria monocytogenes* is an opportunistic and invasive pathogen transmitted to animals and humans by ingestion of contaminated food. It causes listeriosis, an infection with serious consequences (septicemia, meningitis, encephalitis, spontaneous abortion) among high-risk individuals (the elderly, immunocompromised individuals, pregnant women) and potentially fatal outcome [143]. One strain of particular note is *Carnobacterium maltaromaticum* UAL307, isolated from fresh pork. Strain UAL307 produces several bacteriocins, including piscicolin 126, carnobacteriocin BM1, and carnocyclin A, and exhibits potent activity against a number of Gram-positive organisms, including numerous *Listeria* species [85]. While piscicolin 126 and carnobacteriocin BM1 belong to subclass IIa, carnocyclin A has a cyclic structure consisting of 60 amino acids. This cyclic peptide inhibited all of the Gram-positive strains tested, including pathogens such as *L. monocytogenes* and *S. aureus*. Likewise, *Enterococcus avium* isolated from feces of healthy infants was found to produce avicin A, a class IIa bacteriocin active (MIC $<$ 1.33 μg/ml) against *L. monocytogenes* [7]. The bacteriocin Abp-118 is a broad-spectrum class IIb bacteriocin produced by *L. salivarius* strain UCC118, which was originally isolated from the intestine of a human patient. This bacteriocin has been shown to protect in vivo against *L. monocytogenes* invasion [25]. Mice fed *L. salivarius* UCC118 for 3 days and then challenged with *L. monocytogenes* were significantly protected against infection of the liver and spleen [25]. It was later shown that feeding *L. salivarius* UCC118 for 7 days affected intestinal microbiota diversity in mice and pigs less than antibiotic treatment did [106].

Previously, the efficacy of pediocin PA-1 and its producer strain *Pediococcus acidilactici* UL5 was assessed in vivo in a murine model of *L. monocytogenes* infection ($2 \times 10^9$ CFU) [31]. In this trial, the intragastric administration of $10^{10}$ CFU of *P. acidilactici* UL5 failed to protect against pathogen infection in mice. Researchers were surprised to note increased invasiveness of *L. monocytogenes* in the intestine, liver, and spleen tissues of *P. acidilactici*-treated mice compared to control mice. However, they did note a 2-log reduction of fecal listerial counts following post-infection administration of pediocin PA-1 in three daily doses of 250 μg. Enterocin CRL35 is a class IIa bacteriocin produced by *E. mundtii* CRL35 and active against *Listeria*. In this instance, the effectiveness of enterocin CRL35 and its producing strain were evaluated in a murine model of pregnancy-associated *L. monocytogenes* infection [109]. Oral administration of 65 μg of enterocin CRL35 (every 12 h for 3 days) provided 1.6-log and 1-log decreases in *L. monocytogenes* FBUNT (MIC = 1.6 ng/ml) in spleen and liver respectively on day 3 postinfection. By day 7, *L. monocytogenes* was undetectable in these organs in CRL35-treated animals. Furthermore, no bacteria were recovered from the bloodstream of mothers or fetuses. Administering $2 \times 10^9$ CFU of *E. mundtii* CRL35 5 h prior to infection resulted in reduced counts of *L. monocytogenes* FBUNT in liver and spleen. Although *E. mundtii* CRL35 was shown to inhibit or delay *Listeria* translocation, it did not prevent it completely. Both pediocin PA-1 and enterocin CRL35 were shown more effective than their producer strains as inhibitors of *L. monocytogenes* translocation.

### Salmonella

*Salmonella* is a major foodborne pathogen that causes gastroenteritis, enteric fever, bacteremia, and subsequent focal infections [1]. In recent years, the emergence of antibiotic-resistant *Salmonella* due to the overuse of antimicrobial agents has become a public health concern. Bacteriocins could replace antibiotics currently used to treat infections. The efficacy of microcin J25 (MccJ25) has been evaluated in a murine model of *Salmonella* infection [81]. In mice receiving an intraperitoneal dose of $10^6$ CFU of *Salmonella* Newport and treated with MccJ25 2 h later and then daily for the next 6 days, reductions in pathogen viable count were 2–3 log in both the spleen and the liver compared to control mice. The authors also reported low hemolytic activity for MccJ25.

*E. coli* H22 has been shown to produce several bacteriocins, including microcin C7 and colicins 1b and E1, and to inhibit several pathogenic or potentially pathogenic enterobacteria [30]. Pathogens *Enterobacter agglomerans*, *E. coli*, *K. pneumoniae*, *Morganella morganii*, *Salmonella enterica*, *S. flexeneri*, and *Yersinia enterocolitica* were inhibited in vitro by strain H22. The in vitro inhibition of *S. flexeneri* was shown mediated by microcin C7. A further trial involving a germ-free mouse model confirmed the efficacy of H22 in reducing fecal population of *S. flexneri* to undetectable levels.

### Urogenital tract infections

Bacterial vaginosis (BV) is a common vaginal infection associated with a variety of serious health risks in women of

reproductive age. BV is characterized by a decrease in the lactobacilli population and by an increase in the number of other organisms. Several bacteria have been implicated in BV, in particular *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Mobiluncus curtisii* [77]. One of the greatest concerns in conventional treatment with antibiotics such as clindamycin and metronidazole is inhibition of healthy vaginal microflora along with the pathogens. Clinicians and microbiologists are therefore looking for alternative approaches that treat BV without killing *Lactobacillus*. Lactocin 160, a bacteriocin produced by *Lactobacillus rhamnosus* 160 (a healthy vaginal isolate), specifically inhibits BV-associated pathogens such as *G. vaginalis* and *Prevotella bivia* without affecting the healthy microflora [138]. Furthermore, both in vitro and in vivo toxicity studies have shown that lactocin 160 does not irritate vaginal epithelial tissue, is neither hemolytic for human erythrocytes nor toxic to vaginal lactobacilli and therefore could be safe for use in BV treatment [38]. More recently, Turovskiy and Chikindas [137] reported that zinc lactate and soap-nut extract act synergistically with lactocin 160 against *G. vaginalis*. Produced by *Bacillus amyloliquefaciens* isolated from a fermented dairy beverage, subtilosin A [128] has been shown in vitro to inhibit *L. monocytogenes*, *G. vaginalis*, and *S. agalactiae* without affecting healthy vaginal lactobacilli. Moreover, synergy with glycerol monolaurate, lauric arginate, and ε-poly-L-lysine make it effective at lower concentrations [129]. Its safety, nontoxicity, and specificity toward pathogenic *G. vaginalis* make subtilosin A a promising candidate for the treatment of BV. Obtained in partially purified form from *Lactobacillus fermentum* L23, an isolate from vaginal flora of healthy women, bacteriocin L23 (at 640 AU/ml) inhibits several Gram-positive and Gram-negative pathogenic strains and *Candida* species [94], producing large zones of inhibition of *E. coli* (∅ = 41 mm), *P. aeruginosa* (∅ = 44 mm), *Proteus mirabilis* (∅ = 40 mm), *K. pneumoniae* (∅ = 34 mm), *Klebsiella oxytoca* (∅ = 30 mm), *Enterobacter aerogenes* (∅ = 49 mm), *S. epidermidis* (∅ = 21 mm), *S. saprophyticus* (∅ = 30 mm), *S. aureus* (∅ = 36 mm), *C. albicans* (∅ = 15 mm), and *Candida glabrata* (∅ = 13 mm). This bacteriocin has good potential for inactivation of pathogens in the urogenital tract and its activity should be confirmed in vivo.

### *Spermicidal activity*

The spermicidal activity of bacteriocins has received much attention in conjunction with their potent antibacterial activity and lack of harmful effects on human tissues. Although nisin has significant spermicidal activity [105], it appears harmful to healthy vaginal microbiota, making it unsuitable for this type of commercial application [127]. In contrast, subtilosin appears inoffensive to vaginal lactobacilli and is lethal to horse/pony, cattle, boar, rat [120], and human [127] spermatozoa. Subtilosin therefore appears to have great potential for use as a contraceptive.

## Animal applications

As the incidence of disease caused by drug-resistant pathogens increases in the human population, debate grows around the systematic use of antibiotics to protect livestock and enhance growth performance. This use of antibiotics is being blamed increasingly for the emergence of antibiotic resistance and is regarded more and more as an unnecessary risk to human health [36]. The use of bacteriocins and their producer strains (probiotics) in animal feed is proposed as a safe alternative to running such risks (Fig. 2; Table 1).

### Skin infections

Mastitis is the most significant and costly disease of dairy cattle. It is caused by bacterial intramammary infection, *S. aureus*, *S. uberis*, and *Streptococcus dysgalactiae* being the pathogens most frequently involved [51]. The strong activity of many of bacteriocins against mastitis pathogens has spurred interest in their potential application to the control of udder infections, as reviewed in [95]. Although bacteriocin-based products have been developed successfully in the past, only nisin and lacticin 3147 have been applied to the control of mastitis on a commercial scale. Nisin is used in the product Wipe Out® Dairy Wipes (Immucell, Portland, ME, USA), marketed as a teat disinfectant prior to milking. Nisin Z has been tested in the treatment of clinical [17] and subclinical mastitis [152]. The nisin Z used in these studies was only about 50 % pure, and some udder irritation was observed. Another commercial product, Mast Out® (Immucell, Portland, ME, USA) has been submitted recently for FDA approval. An intramammary infusion product, Mast Out contains pharmaceutical-grade nisin A to lessen irritation. Lacticin 3147, a lantibiotic produced by *L. lactis* DPC3147 and highly inhibitory to many mastitis-causing pathogens, has received much attention in this regard. Lacticin 3147 has been evaluated for use as a dry cow therapy in teat seal formulations [27, 28]. Two patents were filed in 2010 for this use of the bacteriocin. In recent trials, Klostermann and collaborators [74] found that 10-min treatment with teat dip containing lacticin 3147 reduced counts of *S. aureus*, *S. dysgalactiae*, and *S. uberis* on the teats of lactating cows by 80, 97, and 90 %, respectively. In recent years, several potential antimastitis bacteriocins, such as nisin U [150], uberolysin [151], and bacteriocin ST91KM [96, 97], have been characterized. Varella Coelho and collaborators [142] report the activity of several staphylococcal bacteriocins

(Pep5, epidermin, epilancin K7, epicidin 280, aureocins A70, A53, and 215FN) against *S. aureus* and *S. agalactiae* involved in bovine mastitis. Bacteriocins (morricin 269, kurstacin 287, kenyacin 404, entomocin 420, and tolworthcin 524) produced by different isolates of *B. thuringiensis* have been tested against a collection of *S. aureus* isolates involved in subclinical bovine mastitis [6]. While *S. aureus* isolates have shown a high level of resistance to commercial antibiotics, they appear sensitive to bacteriocins, in particular morricin 269 and kurstacin 287. Several bacteriocins are being evaluated for their efficacy in treatment or prevention of infections. Mastitis treatment could be enhanced by using a mixture of bacteriocins displaying synergistic antimastitis activity.

### Systemic infection

Lactococcosis is an emerging disease worldwide that causes systemic septicemia in numerous fish species and major economic losses both in marine and freshwater aquaculture. *Lactococcus garvieae* is the etiological agent of the disease [144]. A novel circular bacteriocin called garvicin ML (GarML), produced by *L. garvieae* DCC43 isolated from Mallard ducks (*Anas platyrhynchos*) [110], has been shown to inhibit various Gram-positive bacterial strains in vitro including *L. garvieae*, *C. perfringens*, *L. monocytogenes*, and *S. pneumoniae* [9]. However, no activity against any Gram-negative bacteria was noted. The bacteriocin producer *L. lactis* TW34 isolated from the intestinal tract of *Odontesthes platensis* also inhibits *L. garvieae* [115]. Crude TW34 bacteriocin was also found to inhibit *Lactococcus piscium*, *Carnobacterium piscicola*, *Streptococcus iniae*, *E. faecalis*, and *L. monocytogenes*. *L. lactis* TW34 and *L. garvieae* DCC43 could provide an alternative for the control of lactococcosis and should therefore be considered for future challenge experiments with fish.

### Gastrointestinal tract infections

*Campylobacter* infection is a leading cause of diarrheal disease and foodborne gastroenteritis worldwide. *Campylobacter jejuni* or *Campylobacter coli* are the species typically involved. Transmission of *Campylobacter* to humans occurs by ingestion of contaminated food or water, including undercooked poultry, fresh produce, and unpasteurized milk, or by direct contact with animals. The bacterium is zoonotic and poultry is considered a major reservoir for transmission to humans [61]. Considerable progress towards isolation of anti-*Campylobacter* poultry commensal bacteria and associated bacteriocins has been made in the past few years, as reviewed in [133]. Several potent anti-*Campylobacter* bacteriocins produced by commensal bacteria isolated from the chicken intestine have been purified and characterized, including bacillocin B602 from *P. polymyxa* [134], E50-52, and E-760 from *Enterococcus* spp. [24, 79], OR-7 and L-1077 from *L. salivarius* [126, 131]. Purified B602 from *P. polymyxa* NRRL B-30509 has been microencapsulated in polyvinylpyrrolidone and incorporated into chicken [125] and turkey [24] feed. In both trials, B602 feeds reduced *Campylobacter* colonization to undetectable levels in chickens and turkeys experimentally infected with *C. jejuni* and *C. coli*, respectively. Similar results were obtained with bacteriocin E50-52, which reduced *Campylobacter* counts by six log cycles in the ceca of broiler chickens infected with *C. jejuni* and *Salmonella enteritidis* [132]. Moreover, this class IIa bacteriocin inhibited *Yersinia* spp., *Salmonella* spp., *E. coli* O157:H7, *Shigella dysenteriae*, *M. morganii*, *Staphylococcus* spp. and *Listeria* spp., with MIC ranging from 0.025 to 32 μg/ml. Similar use of purified bacteriocin E-760 with broad-spectrum activity against both Gram-positive and Gram-negative bacteria has also been reported [79], with an impressive 8-log reduction of *Campylobacter* counts in broiler chickens. Svetoch and coworkers isolated a bacterial strain identified as *L. salivarius* 1077 (NRRL B-50053) from poultry intestinal material and found that it produces a class IIa bacteriocin (L-1077) found most active against *C. jejuni* L-4 (MIC = 0.09 μg/ml) and also active against *Salmonella* sp., *E. coli* O157:H7, *Yersinia* sp., *Staphylococcus* sp., *L. monocytogenes*, and *C. perfringens*, with MIC values ranging from 0.09 to 1.5 μg/ml [131]. Administration of L-1077-containing feed significantly reduced colonization of broiler chickens experimentally challenged with *C. jejuni* and *S. enteritidis* by more than four CFU log cycles. Previously, Stern and collaborators [124] found that the producer strain was ineffective for controlling *C. jejuni* by competitive exclusion in broiler chicken trials. The mechanism for *C. jejuni* colonization control is independent of the bacteria-producing bacteriocins but rather seems to be related on the secreted and purified bacteriocin [124].

## Data mining of bacteriocin anti-infective properties

The increasing interest of researchers in bacteriocins is reflected in the number of papers that can be found in PubMed describing them [54]. The BACTIBASE database offers a more complete picture of bacteriocins. Peptide sequence data stored in the database have been accumulating rapidly [53, 54]. However, data relating to therapeutic applications of bacteriocin have been scattered in separate resources for many years. To address this deficiency, we have developed a literature area in BACTIBASE, which groups papers focused on bacteriocins and

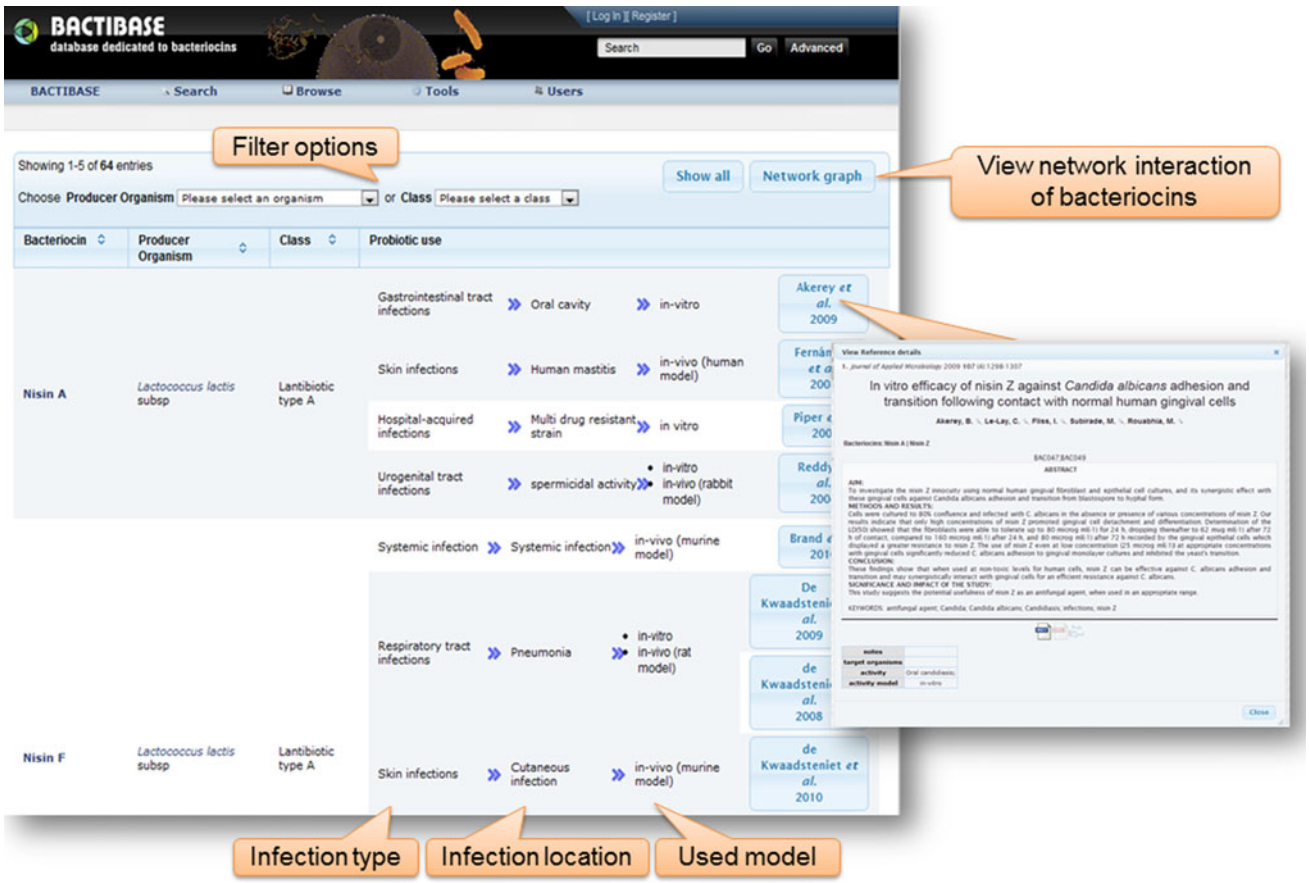


**Fig. 3** Web-based user interface for therapeutic application of bacteriocins

bacteriocin-like substances (BLIS) that have been evaluated as potential therapeutic agents. Compilation of documents relevant to the anti-infective properties of bacteriocins was achieved using various knowledge databases including PubMed, Google Scholar, and ISI Web of Science. A Web-based interface was developed and made available at http://bactibase.pfba-lab-tun.org/antiinfective. As illustrated in Fig. 2, data are displayed in tabular format. The Web interface also hosts an interactive copy of the network graph presented in Fig. 2. The table can be sorted or filtered according to producer organism or class. If it exists, detailed information for each entry in BACTIBASE can be viewed by clicking on the peptide name. A link is also provided to all bacteriocins produced by a specific organism in BACTIBASE. The right column includes infection type and location, model used (in vitro, or in vivo + animal) and publications by author name. The user can also click on the publications button to get detailed information on the study, including the abstract, studied bacteriocins, targeted strains, infection type and location, and experimental model (Fig. 3). These visualization techniques help users explore the data more conveniently.

## Conclusions

Bacteriocin production is a widespread phenomenon among prokaryotes. The anti-infective potential of bacteriocins for inhibiting pathogens has been shown in various food matrices including cheese, meat, and vegetables. However, the nature of their in vivo inhibitory activities against pathogens remains unclear and needs more investigation, mainly because of difficulties associated with demonstrating their health benefits. Many bacteriocins produced by established or potential probiotic strains have been assessed for potential application as therapeutic agents in studies in vitro as well as a few in vivo. Some in vivo studies carried out over the past decade point to the efficacy of bacteriocin-based treatments of human and animal infections [30, 31, 68]. Furthermore, investigation of the pharmacokinetics and pharmacodynamics of lantibiotics demonstrated their high therapeutic efficacy (e.g., MU1140), as reviewed in [140]. Although extensive progress has been made with respect to our understanding of bacteriocin structure/function, regulation and immunity, additional thorough investigation of the factors influencing cell survival, bacteriocin production, and bacteriocin

activity is required in order to obtain greater consistency between observed in vitro inhibition and in vivo results. One concern regarding the use of bacteriocins as anti-infective agents would be the possible occurrence of spontaneously acquired or natural resistance. Such phenomena could result from the failure of the bacteriocin to bind to the target strain (altered receptor or membrane composition) or from rapid inactivation of the bacteriocin by proteases produced by the target organism. However, experience shows that this occurs at very low frequencies, for example, $10^{-8}$ to $10^{-9}$ CFU observed for lacticin 3147 [50]. In addition, resistance acquired against one bacteriocin does not make a strain resistant to many other bacteriocins. Only bacteriocins sharing the same mode of action might lose their effectiveness. The use of mixtures of bacteriocins having different mechanisms of action would make the development of resistance highly unlikely.

Several challenges must still be met before more bacteriocins can be brought to the market. All drug candidates must be cleared of potential toxicity issues as well as questions regarding in vivo stability and appropriate delivery route. Loss of peptide activity in vivo due to proteolytic action is also of concern. For example, nisin shows promising activities in vitro and in animal models against numerous clinically relevant bacteria strains. However, its inherent chemical instability and poor solubility at pH 7.0 place a technological hurdle before its application as a therapeutic agent. Unlike nisin, lacticin 3147 is soluble and active at physiological pH and therefore might be more suitable for human clinical applications. Both nisin and lacticin 3147 are broad-spectrum antimicrobials with activity against most Gram-positive species, including those that would be considered beneficial to human gut health, such as *Lactobacillus* and *Bifidobacterium*, which constitutes a concern for their application in GI tract diseases. It is noted with interest that thuricin CD did not produce major alterations of GI populations, a contributing factor in recurrent *C. difficile* infection [108]. Similarly, class IIa bacteriocins are less disruptive to the intestinal microbiota equilibrium. For example, the safety of pediocin PA-1 and its producer strain for common intestinal bacterial equilibrium has been demonstrated in a murine model [31]. Several factors influence the in vivo effectiveness of bacteriocins produced in situ, including producer strain survival, specific activity, the animal model, and the targeted pathogen. The efficacy of bacteriocin production in vivo still remains a challenge, in spite of generally high bacteriocin specific activities, due mainly to low production levels and non-specific interactions with other hydrophobic molecules.

While further investigation remains necessary before the possibilities for bacteriocins in clinical practice can be described more fully, this review provided an overview of their potential applications to human and veterinary health. Bacteriocins hold great promise for the treatment of diseases caused by pathogenic bacteria and may eventually be employed as alternatives to existing antibiotics. Bacteriocins will have to go through the same rigorous and expensive research and validation process as all other compounds before they can be approved for use as therapeutic agents.

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