DOI:10.21276/sjpm

Saudi Journal of Pathology and Microbiology
Scholars Middle East Publishers
Dubai, United Arab Emirates
Website: http://scholarsmepub.com/

ISSN 2518-3362 (Print)
ISSN 2518-3370 (Online)

Review Article

Bacteriocins: A Novel Weapon against Emerging Resistance

Hannana Maryam[2], Sana Maqsood[2], Umer Farooq[1*]
[1]Riphah Institute of Pharmaceutical sciences, Riphah International University, Lahore, Pakistan
[2]Institute of Industrial Biotechnology, Government College University, Lahore, Pakistan

***Corresponding Author:**
Umer Farooq
Email: mufgohar@yahoo.com

Abstract: Increasing problem of resistance to conventional antibiotics has initiated an alarming situation for entire world and hence there exist an immediate need to explore better alternatives for combating resistance. This exploration of substitutes led to discovery of bacteriocins which are considered as natural antimicrobial agents. Bacteriocins are proteinaceous substances ribosomally synthesized from certain bacteria. Bacteriocins producing bacteria include both gram positive and gram negative bacteria. Bacteriocins have been classified in various classes on the basis of amino acids present, producer bacteria, and molecular masses. There are four classes of bacteriocins produced from gram positive bacteria and two classes produced from gram negative bacteria. Bacteriocins exhibit all four mechanisms of microbial inactivation used by conventional antibiotics which are inhibition of cell wall synthesis, disruption of membrane structure and integrity, interference in protein and DNA synthesis. In addition to these conventional drug targets, bacteriocins show novel mechanism of septum formation which results in termination of cell cycle. Bacteriocins have shown a wide range of applications in pharmaceutical industry as an excellent drug for multidrug resistant bacteria as well as against methicillin resistant staphylococcus aureus (MRSA). They have also displayed inhibitory effects against peptic ulcer causing H.pylori and skin infections causing gram positive bacteria. They possess antimicrobial activity not only against bacteria but viruses and fungi are also susceptible to bacteriocins.
Keywords: Bacteriocins, antimicrobial activity, resistance.

INTRODUCTION

The period from 1940-1960 has been described as “Golden era” for discovery of antibiotics during which lot of antibiotics were discovered and produced from natural, semisynthetic or synthetic ways. Nalidixic acid is considered as most recently discovered antimicrobial which was discovered almost 30 years ago. As the process of discovering new antibiotics is declining, development of resistance is emerging as a huge problem [1]. Development of resistance against traditional antibiotics is a phenomenon that is effecting the entire world and needs an immediate concern and public awareness policies [2].Resistance is not a new problem but it is a threat which is haunting scientists since discovery of Penicillin[3,4].

Gram negative bacteria such as *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* cause serious diseases and are constant threats for human population as reported by US intensive care units in 2008 that 13,74,13 and 17% respectively ,of isolates of these bacteria were resistant to multidrug[5]. While among these resistant pathogens *E.coli* and *K.pneumoniae* are notorious for producing extended spectrum β lactamases and carbapenemases making them resistant to β lactam drugs, carbapenems and cephalosporins, that are supposed to be last hope for such resistant bacteria[6,7,8]. Chronic infections like cystic fibrosis caused by *P.aeruginosa* and urinary tract infections caused by *E.coli* strains are difficult to treat with present antibiotics. Hence, available antibiotics and treatments for gram negative bacterial infections are confined [9, 10].

The main causes of resistance are inappropriate use of antibiotics and resistance mechanisms exploited by bacteria. In addition to cause problem of resistance, overuse of antibiotics also disturbs normal microbiota of gut. Hence this is need of time to dig and explore alternatives for traditional resistant antibiotics which are natural and safe for human consumption resistance. Many sources and substances like plant derived compounds, probiotics, microbial peptides and bacteriophages have been explored for novel and innovative antimicrobial properties.

Bacteriocins which are ribosomally produced peptides of bacterial origin particularly stand out as an excellent and viable substitute for resistant antibiotic

strains. They are proteinaceous substances that inactive and kill bacteria other than producer strains. They are secondary metabolites of bacteria produced during stationary phase of bacterial growth cycle. Both gram positive and gram negative bacteria produce bacteriocins but lactic acid bacteria (LAB) are most important producers. There are numerous bacteriocins produced by wide range of bacteria and classified on basis of their mode of action, producer bacteria, spectrum of activity and molecular masses [11]. Bacteriocins possess narrow spectrum of activity showing activity against specific bacteria but spectrum can be enhanced to other bacterial species. Bacteriocins are natural antimicrobials as compared to other antibiotics and have been part of human food since old times [12]. Bacteriocins, particularly nisin, are declared as safe for human consumption and have showed variety of applications in medicine and food preservation technology.

Bacteriocins are now considered as better substitute for treating chronic and multidrug-resistant infections. It has been observed that bacteriocins encoding genes are present in many gram negative pathogens like *E.coli*, *P.aeruginosa* and *K.pneumoniae* [13].Bacteriocins are very specific antibacterial as they kill only those bacteria which are closely related to producer strains because they compete with close bacteria for nutrients and inhibit them in process [14]. This competition is cause of bacteriocins dependant killing of highly pathogenic gram negative rods. This extraordinary specific nature of bacteriocins makes them highly attractive therapeutic agents against chronic infections caused by gram negative bacteria. One basic issue related to traditional antibiotic treatment is killing of broad range of bacteria resulting in impaired microbiota [15]. But narrow spectrum of activity of bacteriocins acts like blessing in disguise in this scenario and only bacteria responsible for infections are identified and targeted specifically [15].

Classification

Bacteriocins are present in both gram positive and gram negative bacteria and bacteriocins from both types of bacteria are classified in various classes. Bacteriocins from gram positive bacteria are divided into four classes. In class I, there are bacteriocins with unusual peptides, lanthionine and methyllanthionine. They are also called lantibiotics because of presence of lanthionine and methyllanthionine [16]. Most prominent bacteriocin included in class I is nisin which was discovered in 1928 and only bacteriocin which is declared safe by FDA. Other examples of class I bacteriocins include subtilin, enterocin AS-48, enterocin A and pediocin Ach.

Class II bacteriocins contain unmodified peptides with usual amino acids and hence group is called as non lantibiotics. This class is further divided into four subclasses. Bacteriocins included in this class are less than 10kDa and examples include pediocin, pediocin PA-1 and lactacin.

Class III bacteriocins are heat labile and larger than 10kDa [17]. This class is subdivided into bacteriolysins that lyses bacteria and non-lytic bacteriocins. One well studied example of bacteriolysins is lysostaphins. Bacteriocins included in class IV are complicated molecules as they contain lipid and carbohydrates. Examples of class IV bacteriocins are leuconocin and plantaricin S.

Bacteriocins of gram negative bacteria are mostly produced by *enterobacteriaceae*. These bacteriocins are divided in two classes on the basis of molecular masses. High molecular mass bacteriocins include colicins and low molecular mass bacteriocins include microcins.

Mechanism of action

Traditional antibiotics exhibit five major mechanisms for inactivation of microbes. These mechanisms are (i) Inhibition of cell wall synthesis; (ii) inhibition of cell membrane function (iii) Disruption in protein synthesis (iv) Inhibition of DNA transcription and replication and (v) Folate synthesis inhibition. Bacteriocins can inactivate bacteria by using four of these reported antibiotic targets and some innovative mechanisms of their own such as septum formation. Figure-1 shows targets of traditional antibiotics and bacteriocins with examples of each.

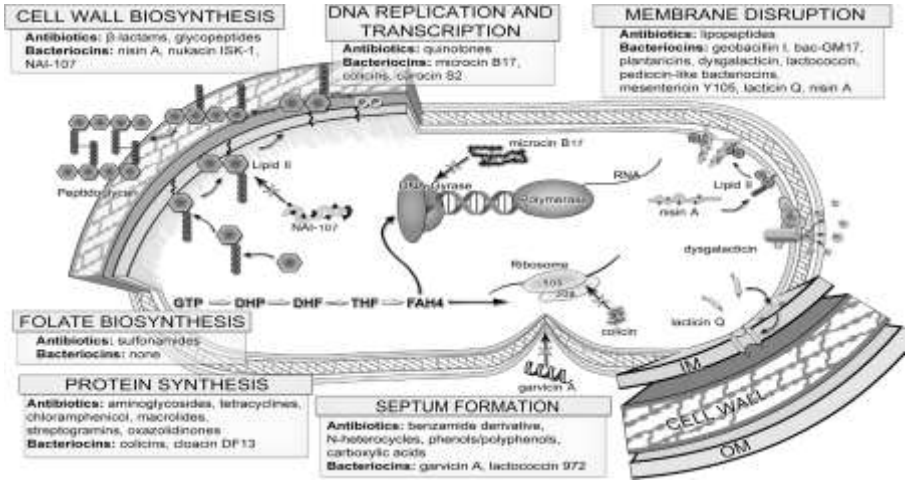

Fig-1: Various targets for antimicrobial agents

Bacteriocins show antimicrobial activity against bacteria which are closely related to each other, spores and even fungi [18].

Action on cell wall synthesis

Cell wall is considered as an excellent target for antibacterial activity as it is structure which is conserved to only bacteria and not exists in mammalian cells. β lactam drugs that include penicillin, cephalosporin, monobactam and carbapenems inhibit cell wall synthesis by inhibiting transpeptidation during final cross linking. But bacteria have developed resistance against these drugs by producing degrading enzymes such as penicillinases and carbapenemases [19]. Due to this emerging problem of resistance it is strongly needed to explore other antimicrobials. In this regard, bacteriocins have proved to be an applicable alternative particularly lantibiotics but still sub inhibitory levels of lantibiotics for longer periods can induce resistance [20].

Nisin A, synthesized by *Lac. lactis*, is bacteriocin which inhibit cell wall synthesis either by docking to lipid II in membrane which is precursor in cell wall synthesis or by forming pores in membrane leading to death of cells. First mechanism is bacteriostatic and second is bactericidal at high concentration [21]. Nisin exhibit an effective antimicrobial activity against gram positive bacteria making it useful in pharmaceutical as well as food industry.

Inhibition of DNA synthesis

There is structural difference between human and bacterial DNA gyrase and thus suitable site for antibiotic action [22].Quinolones are antibiotics that inhibit DNA synthesis by preventing decatenation of DNA during replication. Bacteriocins such as microcin B17 possess same mechanism of inhibition but it is still not applicable for human use [22].

Interference with protein synthesis

Another important mechanism exploited by antimicrobial agents is inhibition of protein synthesis. They inhibit protein synthesis at 30S ribosomal unit such as tetracycline and amino glycosides and some inhibit by binding at 50S ribosomal unit that include chloramphenicol, clindamycin, erythromycin and linezolid. These antibiotics interfere in protein synthesis at various steps like inititiation (linezolid), elongation including aminoacyl tRNA entry (tetracycline), proofreading (aminoglycosides), peptidyl transfer (chloramphenicol, macrolides) ribosomal translocation(macrolides, clindamycin) and termination(macrolides).

Bacteriocins particularly colicins also inhibit protein synthesis by interfering with translation of proteins at various steps. These bacteriocins including colicins E3-E6 and cloacin DF13 exhibit rRNase activity at 16S [23,24]. Group E colicins possess endonuclease activity and they inhibit translation by acting on 3' end of the coding sequence and cleaving 16S rRNA [25]. Some colicins like D and E5 are tRNases and they act by increasing exhaustion of tRNA resulting in limited protein synthesis [26].

Disruption of membrane structure

Some antimicrobials inactivate bacteria by interfering with synthesis of peptidoglycan layer that culminate into poor membrane integrity. These antibiotics include β lactam drugs which are so far most susceptible to resistance. Bacteriocins cause disruption in integrity of membrane by docking to lipid II site and forming pores those results in leakage of cell contents. One prominent bacteriocin in this regard is nisin and others are Bac-GM17, PlnJ/K, PlnE/F, Pep5, geobacillin I and epidermin. Some bacteriocins like lacticin Q do not act by docking on lipid II rather they act by formation of toroidal pores through lipid flip flop resulting in leakage of proteins and other contents from cell that causes cell death[27,28].Similarly another

bacteriocins, carnocyclin A, directly interacts with lipid bilayer and forms ion specific pores in membrane[29].

Septum formation: An unconventional target

Bacteriocins not only exploit all four mechanisms used by traditional antibiotics but they also exhibit unconventional mechanism of inactivating bacteria which makes them highly attractive alternative of traditional antibiotic. This novel mechanism is formation of septum which is in growth of mucopeptide layer and cytoplasmic membrane during mitosis. Bacteriocins act during cytokinesis resulting in formation of bulge and termination of cell cycle [30]. Two bacteriocins have been known yet to demonstrate this mechanism of antimicrobial inactivation. These two bacteriocins are lactococcin 972 that shows activity against closely related lactococcus species and garvicin that inhibit lactococcus graviae strains [31,32].

Applications of bacteriocins as an alternative to the antibiotics

Bacteriocins against Multidrug Resistant Bacteria

Due to the excessive use of antibiotics, emergence of antibiotic resistant bacteria has become the major issue. Some bacteria like methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VREs) are tremendously causing nosocomial infections as they are resistant to a number of antibiotics that are usually used to treat these infections [33]. Control and treatment of multidrug resistant organisms induced infections is the major challenge in pharmaceutical industry. Bacteriocins can be an alternative of conventional drugs against these resistant bacteria [34]. Class 1 bacteriocins (Nisin) are most common and most studied bacteriocins. Nisin has ability to cause lysis of many resistant organisms including different strains of *S. aureus*, *Streptococcus pneumoniae* and vancomycin-resistant *E. faecalis* and *E. faecium* **[**35]. Nisin when used in combination with other antibiotics (cell wall synthesis inhibitor) shows synergistic effects [36]. Combination of nisin and vancomycin is also effective different strains of VRE. Other bacteriocins which are effective against multidrug resistant strains include Lacticin 3147, leucocin A, microbisporicin, pediocin and mersacidin [37]. Lacticin 3147 and pediocin have activity against VRE while Nisin has activity against MRSA [38]. Another bacteriocin, produced by *Streptococcus mutans*, lantibiotic mutacin 1140 has bactericidal activity against vancomycin- and oxacillin- resistant *S. aureus*, while it has bacteriostatic activity against vancomycin-resistant *E. faecium* [39].

Bacteriocins for Peptic Ulcers Treatment

Helicobacter pylori are a major cause of duodenal and gastric ulcers. Usually, a combination of two or three drugs is used for treatment of infection caused by *H. pylori.* In a study done by Ishihara in 1997 it was shown that some oral bacteria have inhibitory effects on *H. pylori* [40].The research showed that some strains of oral *streptococcus* (*S. mutans, S. sobrinus*) can inhibit the growth of *H. pylori.* Inhibitory effect of these stains was affected after trypsin treatments which showed that the responsible molecules were bacteriocins. Some bacteriocins have been tested already. As bacteriocins are stable at acidic pH, their use *in vivo* can be advisable. Bacteriocins do not affect gut normal flora as they are sensitive to digestive proteases. Several lantibiotics (class I bacteriocins) have shown *in vitro* activity against different strains of *H. pylori*. These bacteriocins include Lacticins A164, nisin A, JW3, NK24, pediocin PO2, and leucocin K [41]. Some class II bacteriocins (non lantibiotic) have also been tested *in vitro*, like bulgaricin BB-18 which is a pediocin-like molecule (class IIa) or class IIb bacteriocin, the putative lactacin F, a two-component bacteriocins [42].These bacteriocins can reduce side effects of chemical therapy when used in combination with antibiotics.

Bacteriocins in the Oral Cavity

Plaque-related oral diseases are the most common bacterial infection in the oral cavity affecting human. Different species of Gram-positive bacteria, the *Streptococcus mutans* and *S. sobrinus*, are the causative agents. 95% of the world population is affected by dental caries. Gram-negative microorganisms like *Porphyromonas* and *Prevotella* are cause of inflammatory oral diseases. Dental caries can also be a cause of cardiovascular complications when the patient is immunocompromised. Conventionally, acrinol and chlorhexidine have been used for treating such infections but due to emergence of resistance, some additional treatment is required [43]. Bacteriocin producing bacteria can replace oral pathogens. In the oral cavity, bacteriocin producing bacteria may have advantageous effects as they produce some antimicrobial peptides that can inhibit pathogens by stimulating of the immune system and reducing the formation of biofilms [44]. For instance, colonization of a mutacin-producing strain of *S. mutans* can compete with other plaque-forming strains for growth and survival. For treating pharyngeal infections and dental caries caused by *Streptococcus pyogenes*, bacteriocin (Salivaricin) producing strains of *S. salivarius* have also been successfully assayed [45]. Purified baceriocins Combination of purified bacteriocin and traditional antimicrobial drugs like triclosan, chlorhexidine have also been tested. Lobos showed positive results *in vitro* on combination of antibiotics and *Pseudomonas* sp. PsVP-10 bacteriocin [46]. Moreover, Nisin is also effective in gingivitis. Researchers are trying to develop delivery systems of antimicrobial peptides for the mouth. An antimicrobial peptide, KSL-W, is tested in chewing gums for the delivery in to oral cavity [47**]**.

Bacteriocins in Skin

S. aureus and *Streptococcus* spp. cause a number of skin and soft tissue diseases like abscesses, mastitis, cellulites, folliculites, impetigo, furuncles, or

erysipela. *Enterobacter*, *pseudomonas*, *Klebsiella*, or *Proteus* can also cause skin diseases in the immunocompromised patients. Most strains of these organisms are resistant. Bacteriocins application is best replacement of antibiotics. For instance, bacteriocin produced by *Lactococcus*sp. HY 449 has shown inhibitory effects on some common skin pathogens such as *S. aureus, S. epidermidis,* several streptococci, *Propionibacterium acnes*, and some strains of *Pseudomonas* [48]. When enterocin ESL5 was used in an ointment for *P. acnes* induced infections, it showed a reduction in the inflammation [49].

Bacteriocins against *Mycobacterium*

Tuberculosis (TB) is one of the most infectious diseases in the world. Emergence of multidrug resistant strains due to long duration of the antibiotic treatment is the major challenge in medicine. Moreover, mycobacterium has ability to escape phagocytosis as it survives inside the macrophages. Bacteriocins are more effective against mycobacterium than other antimicrobial drugs. When nisin was tested against *Mycobacterium smegmatis*, nisin formed pores in membrane causing loss of intracellular ATP but the effect of nisin was dependent on its concentration and time duration [50]**.**Many other bacteriocins have shown positive results *in vitro* against mycobacterium as well. Carroll *et al.* compared the effect of lacticin 3147 and nisin on three isolates of mycobacteria [51]. Lacticin 3147 inhibited the bacterium growth more effectively. Development of a drug-delivery system for bacteriocins which have activity against TB can help in the treatment for this disease.

Bacteriocins as Antiviral Agents

Wachsman (2003) showed that a bacteriocin (enterocin CRL35) produced by *E. faecium*CRL35, had antiviral activity [52]. It was able to inhibit different strains of herpes simplex virus type 1 and 2 in Vero cells. Exact mechanism of action of enterocin CRL35 was unknown but it was reported that late stages of viral replications were affected. Qureshi *et al.* assayed activity of two bacteriocins, enterocins AAR-71 and AAR-74, produced by *E. faecalis*AAR-71 and AAR-74 [53]. These bacteriocins had activity against phages mostly coliphage HAS. Another bacteriocin that was isolated from a Turkish fermented beverage boza also showed activity *in vitro* against herpes simplex virus type 1(HSV) [54]. Recently, different strains of lactic acid bacteria have been isolated from human breast milk that is affective against HIV-1 isolates [55]. The results show that bacteriocins have ability to control and prevent viral transmission in lactant children.

Bacteriocins as Antifungal

A few bacteriocins have been reported as antifungal agent due to their inhibitory effects on yeast and molds. They are now commonly used as food preservatives. A subspecies *Lactobacillus* is reported to produce a proteinaceous compound with antifungal activity. The compound had similar characteristics as that of class II bacteriocins [56]. Another bacteriocin (Pentocin TV35b) that is produced by *Lactobacillus pentosus* also has antifungal effects especially against *Candida albicans* [57]. Recently, it is reported that Nisin Z has ability to inhibit the growth *C. albicans* by interfering with its adhesion and transition [58].The results showed that Nisin can be used as antifungal peptide.

CONCLUSION

Emergence of antibiotic resistance has become a serious issue due to inappropriate use of antibiotics. So scientists are trying to find some alternative to antibiotics. Bacteriocins are antimicrobial peptides which are safe to use as they are naturally produced ribosomally. Besides having applications in food industry, bacteriocins have been proved useful in the pharmaceutical industry. Bacteriocins are effective against many bacteria including MRSA, VRE and MTB. Recent studies show that bacteriocins can also serve as antiviral and antifungal peptides. Effect of bacteriocins in cancer therapy is also under investigation. Combination of bacteriocins with conventional drugs has shown synergistic effects.

Eventually, bacteriocin has become helpful tool in therapeutic field due to its multifunctional properties. Bacteriocins proved as a replacement of antibiotics. An understanding of its proper production and isolation is important to use it in clinical settings.

REFERENCES

1. Travis, J. (1994). Reviving the antibiotic miracle?. *Science*, *264*(5157), 360-363.
2. Michael, C. A., Dominey-Howes, D., & Labbate, M. (2014). The antimicrobial resistance crisis: causes, consequences, and management. *Frontiers in public health*, *2*.
3. Gillor, O., Nigro, L. M., & Riley, M. A. (2005). Genetically engineered bacteriocins and their potential as the next generation of antimicrobials. *Current pharmaceutical design*, *11*(8), 1067-1075.
4. Lages, M. C. A., Beilharz, K., Morales Angeles, D., Veening, J. W., & Scheffers, D. J. (2013). The localization of key Bacillus subtilis penicillin binding proteins during cell growth is determined by substrate availability. *Environmental microbiology*, *15*(12), 3272-3281.
5. Center for Disease Control and Prevention (2011) Gram-negative bacteria infections inhealthcare settings [Internet]. http://www.cdc.gov/hai/organisms/gram-negative-bacteria.html.
6. Cadman H, Marinez L. (2014) Antimicrobial Resistance Global Report on Surveillance (eds) World Health Organization (pp. 1–42).
7. Pitout, J. D., Nordmann, P., & Poirel, L. (2015). Carbapenemase-producing Klebsiella pneumoniae, a key pathogen set for global nosocomial

dominance. *Antimicrobial agents and chemotherapy*, *59*(10), 5873-5884.
8. Willyard, C. (2017). Drug-resistant bacteria ranked.
9. Soto, S. M. (2014). Importance of biofilms in urinary tract infections: new therapeutic approaches. *Advances in Biology*, *2014*.
10. Costerton, J. W., Stewart, P. S., & Greenberg, E. P. (1999). Bacterial biofilms: a common cause of persistent infections. *Science*, *284*(5418), 1318-1322.
11. Klaenhammer, T. R. (1993). Genetics of bacteriocins produced by lactic acid bacteria. *FEMS microbiology reviews*, *12*(1-3), 39-85.
12. Cleveland, J., Montville, T. J., Nes, I. F., & Chikindas, M. L. (2001). Bacteriocins: safe, natural antimicrobials for food preservation. *International journal of food microbiology*, *71*(1), 1-20.
13. Holt, K. E., Nga, T. V. T., Thanh, D. P., Vinh, H., Kim, D. W., Tra, M. P. V., ... & Thuy, C. T. (2013). Tracking the establishment of local endemic populations of an emergent enteric pathogen. *Proceedings of the National Academy of Sciences*, *110*(43), 17522-17527.
14. Majeed, H., Gillor, O., Kerr, B., & Riley, M. A. (2011). Competitive interactions in Escherichia coli populations: the role of bacteriocins. *The ISME journal*, *5*(1), 71-81.
15. Cotter, P. D., Ross, R. P., & Hill, C. (2013). Bacteriocins—a viable alternative to antibiotics?. *Nature Reviews Microbiology*, *11*(2), 95-105.
16. Nissen-Meyer, J., & Nes, I. F. (1997). Ribosomally synthesized antimicrobial peptides: their function, structure, biogenesis, and mechanism of action. *Archives of microbiology*, *167*(2), 67-77.
17. Savadogo, A., Ouattara, A. C., Bassole, H. I., & Traore, S. A. (2006). Bacteriocins and lactic acid bacteria-a minireview. *African Journal of Biotechnology*, *5*(9).
18. Majeed, H., Lampert, A., Ghazaryan, L., & Gillor, O. (2013). The weak shall inherit: bacteriocin-mediated interactions in bacterial populations. *PloS one*, *8*(5), e63837.
19. O Gutkind, G., Di Conza, J., Power, P., & Radice, M. (2013). β-lactamase-mediated resistance: A biochemical, epidemiological and genetic overview. *Current pharmaceutical design*, *19*(2), 164-208.
20. Modi, K. D., Chikindas, M. L., & Montville, T. J. (2000). Sensitivity of nisin-resistant Listeria monocytogenes to heat and the synergistic action of heat and nisin. *Letters in applied microbiology*, *30*(3), 249-253.
21. Allard, J. F., & Rutenberg, A. D. (2007). Steady-state helices of the actin homolog MreB inside bacteria: Dynamics without motors. *Physical Review E*, *76*(3), 031916.
22. Collin, F., Thompson, R. E., Jolliffe, K. A., Payne, R. J., & Maxwell, A. (2013). Fragments of the bacterial toxin microcin B17 as gyrase poisons. *PLoS One*, *8*(4), e61459.
23. Ng, C. L., Lang, K., Meenan, N. A., Sharma, A., Kelley, A. C., Kleanthous, C., & Ramakrishnan, V. (2010). Structural basis for 16S ribosomal RNA cleavage by the cytotoxic domain of colicin E3. *Nature structural & molecular biology*, *17*(10), 1241-1246.
24. Akutsu, A., Masaki, H., & Ohta, T. (1989). Molecular structure and immunity specificity of colicin E6, an evolutionary intermediate between E-group colicins and cloacin DF13. *Journal of bacteriology*, *171*(12), 6430-6436.
25. Walker, D. C., Georgiou, T., Pommer, A. J., Walker, D., Moore, G. R., Kleanthous, C., & James, R. (2002). Mutagenic scan of the H-N-H motif of colicin E9: implications for the mechanistic enzymology of colicins, homing enzymes and apoptotic endonucleases. *Nucleic acids research*, *30*(14), 3225-3234.
26. Ogawa, T., Inoue, S., Yajima, S., Hidaka, M., & Masaki, H. (2006). Sequence-specific recognition of colicin E5, a tRNA-targeting ribonuclease. *Nucleic acids research*, *34*(21), 6065-6073.
27. Li, M., Yoneyama, F., Toshimitsu, N., Zendo, T., Nakayama, J., & Sonomoto, K. (2013). Lethal hydroxyl radical accumulation by a lactococcal bacteriocin, lacticin Q. *Antimicrobial agents and chemotherapy*, *57*(8), 3897-3902.
28. Yoneyama, F., Imura, Y., Ohno, K., Zendo, T., Nakayama, J., Matsuzaki, K., & Sonomoto, K. (2009). Peptide-lipid huge toroidal pore, a new antimicrobial mechanism mediated by a lactococcal bacteriocin, lacticin Q. *Antimicrobial agents and chemotherapy*, *53*(8), 3211-3217.
29. Gong, X., Martin-Visscher, L. A., Nahirney, D., Vederas, J. C., & Duszyk, M. (2009). The circular bacteriocin, carnocyclin A, forms anion-selective channels in lipid bilayers. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *1788*(9), 1797-1803.
30. Lages, M. C. A., Beilharz, K., Morales Angeles, D., Veening, J. W., & Scheffers, D. J. (2013). The localization of key Bacillus subtilis penicillin binding proteins during cell growth is determined by substrate availability. *Environmental microbiology*, *15*(12), 3272-3281.
31. Maldonado-Barragán, A., Cárdenas, N., Martínez, B., Ruiz-Barba, J. L., Fernández-Garayzábal, J. F., Rodríguez, J. M., & Gibello, A. (2013). Garvicin A, a novel class IId bacteriocin from Lactococcus garvieae that inhibits septum formation in L. garvieae strains. *Applied and environmental microbiology*, *79*(14), 4336-4346.
32. Martínez, B., Rodríguez, A., & Suárez, J. E. (2000). Lactococcin 972, a bacteriocin that inhibits septum formation in lactococci. *Microbiology*, *146*(4), 949-955.

33. Murray, B. E. (2000). Vancomycin-resistant enterococcal infections. *New England Journal of Medicine*, *342*(10), 710-721.
34. Sang, Y., & Blecha, F. (2008). Antimicrobial peptides and bacteriocins: alternatives to traditional antibiotics. *Animal Health Research Reviews*, *9*(02), 227-235.
35. Severina, E., Severin, A., & Tomasz, A. (1998). Antibacterial efficacy of nisin against multidrug-resistant Gram-positive pathogens. *Journal of Antimicrobial Chemotherapy*, *41*(3), 341-347.
36. Brumfitt, W., Salton, M. R., & Hamilton-Miller, J. M. (2002). Nisin, alone and combined with peptidoglycan-modulating antibiotics: activity against methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. *Journal of Antimicrobial Chemotherapy*, *50*(5), 731-734.
37. Millette, M., Cornut, G., Dupont, C., Shareck, F., Archambault, D., & Lacroix, M. (2008). Capacity of human nisin-and pediocin-producing lactic acid bacteria to reduce intestinal colonization by vancomycin-resistant enterococci. *Applied and environmental microbiology*, *74*(7), 1997-2003.
38. Piper, C., Draper, L. A., Cotter, P. D., Ross, R. P., & Hill, C. (2009). A comparison of the activities of lacticin 3147 and nisin against drug-resistant Staphylococcus aureus and Enterococcus species. *Journal of Antimicrobial Chemotherapy*, *64*(3), 546-551.
39. Ghobrial, O. G., Derendorf, H., & Hillman, J. D. (2009). Pharmacodynamic activity of the lantibiotic MU1140. *International journal of antimicrobial agents*, *33*(1), 70-74.
40. Ishihara, K., Miura, T., Kimizuka, R., Ebihara, Y., Mizuno, Y., & Okuda, K. (1997). Oral bacteria inhibit Helicobacter pylori growth. *FEMS microbiology letters*, *152*(2), 355-361.
41. Kim, T. S., Hur, J. W., Yu, M. A., Cheigh, C. I., Kim, K. N., Hwang, J. K., & Pyun, Y. R. (2003). Antagonism of Helicobacter pylori by bacteriocins of lactic acid bacteria. *Journal of food protection*, *66*(1), 3-12.
42. Simova, E. D., Beshkova, D. B., & Dimitrov, Z. P. (2009). Characterization and antimicrobial spectrum of bacteriocins produced by lactic acid bacteria isolated from traditional Bulgarian dairy products. *Journal of Applied Microbiology*, *106*(2), 692-701.
43. Yamamoto, T., Tamura, Y., & Yokota, T. A. K. E. S. H. I. (1988). Antiseptic and antibiotic resistance plasmid in Staphylococcus aureus that possesses ability to confer chlorhexidine and acrinol resistance. *Antimicrobial agents and chemotherapy*, *32*(6), 932-935.
44. Perdigón, G., Fuller, R., & Raya, R. (2001). Lactic acid bacteria and their effect on the immune system. *Current issues in intestinal microbiology*, *2*(1), 27-42.
45. Tagg, J. R. (2004). Prevention of streptococcal pharyngitis by anti-Streptococcus pyogenes bacteriocin-like inhibitory substances (BLIS) produced by Streptococcus salivarius. *Indian journal of medical research*, *119*, 13.
46. Lobos, O., Padilla, A., & Padilla, C. (2009). In vitro antimicrobial effect of bacteriocin PsVP-10 in combination with chlorhexidine and triclosan against Streptococcus mutans and Streptococcus sobrinus strains. *archives of oral biology*, *54*(3), 230-234.
47. Faraj, J. A., Dorati, R., Schoubben, A., Worthen, D., Selmin, F., Capan, Y., ... & DeLuca, P. P. (2007). Development of a peptide-containing chewing gum as a sustained release antiplaque antimicrobial delivery system. *AAPS PharmSciTech*, *8*(1), E177-E185.
48. Oh, S., Kim, S. H., Ko, Y., Sim, J. H., Kim, K. S., Lee, S. H., ... & Kim, Y. J. (2006). Effect of bacteriocin produced by Lactococcus sp. HY 449 on skin-inflammatory bacteria. *Food and chemical toxicology*, *44*(4), 552-559.
49. Kang, B. S., Seo, J. G., Lee, G. S., Kim, J. H., Kim, S. Y., Han, Y. W., ... & Park, Y. M. (2009). Antimicrobial activity of enterocins from Enterococcus faecalis SL-5 against Propionibacterium acnes, the causative agent in acne vulgaris, and its therapeutic effect. *The Journal of Microbiology*, *47*(1), 101-109.
50. Montville, T. J., Chung, H. J., Chikindas, M. L., & Chen, Y. (1999). Nisin A depletes intracellular ATP and acts in bactericidal manner against Mycobacterium smegmatis. *Letters in applied microbiology*, *28*(3), 189-193.
51. Carroll, J., Draper, L. A., O'Connor, P. M., Coffey, A., Hill, C., Ross, R. P., ... & O'Mahony, J. (2010). Comparison of the activities of the lantibiotics nisin and lacticin 3147 against clinically significant mycobacteria. *International journal of antimicrobial agents*, *36*(2), 132-136.
52. Wachsman, M. B., Castilla, V., de Ruiz Holgado, A. P., de Torres, R. A., Sesma, F., & Coto, C. E. (2003). Enterocin CRL35 inhibits late stages of HSV-1 and HSV-2 replication in vitro. *Antiviral research*, *58*(1), 17-24.
53. Qureshi, H. U. M. A. I. R. A., Saeed, S. A. D. I. A., Ahmed, S. A. M. I. A., & Rasool, S. A. (2006). Coliphage hsa as a model for antiviral studies/spectrum by some indigenous bacteriocin like inhibitory substances (BLIS). *Pak J Pharm Sci*, *19*, 182-185.
54. Todorov, S. D., Botes, M., Guigas, C., Schillinger, U., Wiid, I., Wachsman, M. B., ... & Dicks, L. M. T. (2008). Boza, a natural source of probiotic lactic acid bacteria. *Journal of applied microbiology*, *104*(2), 465-477.
55. Martín, V., Maldonado, A., Fernández, L., Rodríguez, J. M., & Connor, R. I. (2010). Inhibition of human immunodeficiency virus type 1 by lactic acid bacteria from human breastmilk. *Breastfeeding Medicine*, *5*(4), 153-158.

56. Magnusson, J., & Schnürer, J. (2001). Lactobacillus coryniformis subsp. coryniformis strain Si3 produces a broad-spectrum proteinaceous antifungal compound. *Applied and Environmental Microbiology*, *67*(1), 1-5.
57. Okkers, D. J., Dicks, L. M. T., Silvester, M., Joubert, J. J., & Odendaal, H. J. (1999). Characterization of pentocin TV35b, a bacteriocin-like peptide isolated from Lactobacillus pentosus with a fungistatic effect on Candida albicans. *Journal of Applied Microbiology*, *87*(5), 726-734.
58. Akerey, B., Le-Lay, C., Fliss, I., Subirade, M., & Rouabhia, M. (2009). In vitro efficacy of nisin Z against Candida albicans adhesion and transition following contact with normal human gingival cells. *Journal of applied microbiology*, *107*(4), 1298-1307.