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Review

Expanding Layers of Bacteriocin Applications: From Food Preservation to Human Health Interventions

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Abstract: Bacteriocins, ribosomally synthesized by bacteria, have long been recognized for their role in ensuring food safety and security due to their antibacterial effects against foodborne pathogens and spoilage bacteria. However, recent advancements have unveiled their expanding potential beyond food applications, with increasing evidence of their efficacy against clinically significant pathogenic bacteria, biofilm formation, viral infections, and even cancer. These emerging discoveries have continuously added new layers to the application of bacteriocins, extending their relevance from food preservation to broader human health interventions. To further harness this expanding potential, various innovative strategies have been developed to overcome traditional limitations associated with bacteriocin use. Instead of directly employing bacteriocins or bacteriocin-producing bacterial cultures, novel approaches, such as incorporating them into films and packaging materials or coupling them with nanoparticles, have demonstrated enhanced effectiveness. In this review, we examine the evolving landscape of bacteriocin applications and shed light on the expanding functional spectrum of bacteriocins for both food safety and human health, although some important challenges and limitations remain. By analyzing the recent literature and innovative technological advancements, we highlight how bacteriocins are continuously evolving, opening new frontiers for their use and reinforcing their significance beyond their conventional roles.

Keywords: bacteriocins; food safety; health applications; antimicrobial peptides; innovative bacteriocin delivery

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1. Introduction

It is known that almost all living things can produce low molecular weight antimicrobial peptides as part of their defense mechanisms [1]. Among these antimicrobial peptides, bacteriocins are ribosomally synthesized by almost all bacterial groups, especially Gram-positive bacteria, which are peptides that may be multifunctional [2]. Although bacteriocins are basically effective against bacterial species closely related to the producer species and especially against Gram-positive bacteria [3], various studies conducted in recent years have shown that different bacteriocins also have antimicrobial properties against some Gram-negative bacteria [4], and even some viruses [5]. Moreover, the understanding that

some bacteriocins also have anticancer properties [6] has led to the emergence of bacteriocins as important candidates that can be used not only to ensure food safety but also to protect human health.

In recent years, increasing antibiotic resistance among bacteria has made the treatment of many bacterial infections difficult, and, if alternatives to antibiotics cannot be developed, there is a significant potential threat on a global scale [7]. In this context, the effectiveness of bacteriocins against both various foodborne and clinical bacterial infections indicates that bacteriocins have the potential to be used as an alternative to antibiotics [8]. In addition, the fact that bacteriocins have different mechanisms of action than antibiotics and can be easily degraded in nature reduces the possibility of bacteria developing resistance to bacteriocins, which makes bacteriocins stand out as a substitute for antibiotics [9]. Moreover, it has been understood that various bacteriocins are effective against biofilms, which can cause significant problems in both the food industry and medical devices, in addition to contributing to the increase in antibiotic resistance [10]. However, some important obstacles limit the use of bacteriocins in foods. Lactic acid bacteria (LAB) are frequently used as starter or adjunct cultures in fermented foods, and the use of bacteriocins that are effective against these cultures in these foods can cause various disadvantages in food production and quality. In addition, bacteriocins with peptide structures are affected by proteolytic enzymes, and the stability of bacteriocins in various foods may be low [11]. To eliminate all these limitations, various studies [12,13] conducted in recent years have shown that successful results can be obtained by adding bacteriocins or bacteriocin-producing bacteria with GRAS (Generally Recognized as Safe) status to film and coating materials used in foods. Additionally, successful results have been obtained by using bacteriocins encapsulated with various nanoparticles, such as silver [14]. The number of studies in the literature on the innovative use of bacteriocins is increasing day by day, and promising results are being obtained.

This review explores the expanding frontiers of bacteriocin applications, highlighting how recent advancements have introduced new layers of use beyond food safety. By examining the latest findings, we emphasize the growing potential of bacteriocins not only in food preservation but also in broader applications for human health protection. Additionally, we discuss innovative strategies that enhance their effectiveness, paving the way for novel applications in medical, pharmaceutical, and biotechnological fields. From this perspective, we aim to show how bacteriocins are continuously evolving and expanding their scope of action far beyond their traditional roles, although there are still some important challenges and limitations to be overcome.

2. Classification of Bacteriocins

Bacteriocins are classified based on various properties, such as molecular weight, antimicrobial spectrum, mode of action, thermal stability, amino acid composition, and post-translational modifications [15]. In addition, bacteriocins can be classified into two main groups, those produced by Gram-positive bacteria and those produced by Gram-negative bacteria, depending on the cell wall structure of the producing bacteria.

2.1. Gram-Positive Bacteriocin Producers and Their Bacteriocins

Bacteriocins produced by Gram-positive bacteria are divided into four main classes based on criteria such as structural properties, size, biosynthesis mechanisms, and biological activities (Figure 1) [16].

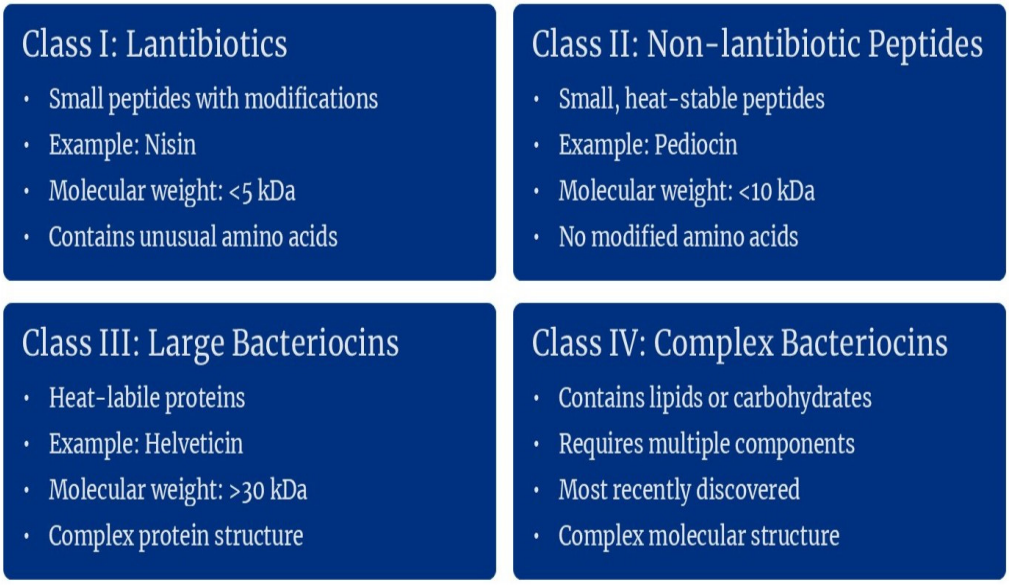


Figure 1. Classification and prominent features of bacteriocins produced by Gram-positive bacteria.

2.1.1. Class I Bacteriocins

Many bacteriocins are produced by Gram-positive bacteria. Among this class, LAB stand out as bacteriocin producers. Nisin produced by *Lactococcus lactis* was the first bacteriocin found to be produced by LAB. Lantibiotics are a specific subgroup of bacteriocins characterized by their content of post-translationally modified amino acids, including lanthionine and/or β-methyl-lanthionine. Nisin is an example of a type I lantibiotic, the most frequently studied bacteriocin and the first bacteriocin authorized for use as a food preservative in many countries. Nisin A and Z are produced by *L. lactis* and Nisin U by *Streptococcus uberis* [17]. Lacticin 3247, also produced by *L. lactis*, is included in type II lantibiotics [18].

Staphylococcus epidermidis APC 3775 and APC 3810 strains were found to produce lantibiotics included in class IA, which were found to be similar to epilancin 15X and epidermin [19]. Other important bacteriocins in this class are lacticin 481, mutacin A, and duramycin produced by *L. lactis*, *Streptococcus mutans*, and *Streptomyces cinnamoneus*, respectively [19–21].

Carnocyclin A produced by *Carnobacterium maltaromaticum* UAL307 [20], enterocin AS-48 produced by *Enterococcus faecalis* [21], and cytolysin, a two-component bacteriocin produced by *E. faecalis* APC 3825, are included in class IB. Apart from these, gasserin A, reutericin 6, enterocin 4, and lactocyclicin Q are produced by LAB, while sirularin A is produced by *Clostridium beijerinckii* [22], butyrivibriocin AR10 is produced by *Butyrivibrio fibrisolvens* [23], romsacin is produced by *Staphylococcus haemolyticus* [24], and a bacteriocin produced by *Staphylococcus hominis*, APC 3824, are bacteriocins produced outside LAB belonging to class IB [19].

Class IC includes subtilocin A, thuricin CD, and H bacteriocins. Subtilocin A is produced by *Bacillus subtilis* [25] and is included in this class because it contains a post-translational modification. The two-peptide bacteriocin thuricin CD produced by *Bacillus thuringiensis* 6431 contains alpha carbon bridges and has antimicrobial activity against *Clostridioides difficile* [26]. Streptolysin S, produced by *Streptococcus pyogenes*, is a class ID bacteriocin [27], while glycocin F, the first identified glycocin, produced by *Lactiplantibacillus plantarum*, is a class IE bacteriocin [28]. Lariatin A from *Rhodococcus jostii*, streptomonomicin from *Streptomonospora alba* YIM 90003, and sviceucin from *Streptomyces sviceus* ATCC 2908

are referred to as lasso peptides in class IF produced by Gram-positive bacteria that have been structurally determined by NMR analysis [29].

2.1.2. Class II Bacteriocins

Class IIA includes pediocins and pediocin-like bacteriocins that are effective on *Listeria*. *Pediococcus acidilactici*, *P. pentosaceus*, and *P. damnosus* are LAB reported to produce pediocins. The bacteriocins pediocin PA-1, enterocin A, leucocin A-UAL 187, mesentericin Y105, sakacin P, and curvacin A are produced by *P. acidilactici* [30], *Enterococcus faecium* [31], *Leuconostoc gelidum* UAL 187 [32], *Leuconostoc mesenteroides* [33], *Latilactobacillus sakei*, and *Latilactobacillus curvatus* LTH1174 [34], respectively, and are included in this class. *E. faecium* APC 3830, 3833, 3835, and 3880 strains isolated from milk samples were found to produce class IIA bacteriocins 100% similar to enterocin P [19].

To date, 16 bacteriocins containing two peptides have been identified, and these bacteriocins belong to class IIB. Lactococcin G produced by *L. lactis* [35], and thermophilin produced by *Streptococcus thermophilus*, are the best-known examples of two-peptide bacteriocins [36]. *E. faecalis* strain APC 3825 was found to produce a class IIB bacteriocin 100% similar to enterocin 1071 bacteriocin [19].

Enterocin L50 is a class IIC bacteriocin produced by *E. faecium* L50, which has been studied many times. It has also been reported that *E. faecium* strain produces a class IIC bacteriocin similar (95.4%) to enterocin NKR-5-3B bacteriocin [19,37].

Lactococcin A, produced by *L. lactis*, is the first bacteriocin to be included in class IID [36]. It has been reported that this bacteriocin does not have a homologous sequence like other bacteriocins. Bacteriocins produced by *Propionibacterium* spp. are also included in class IID. Bactofencin A is a novel class IID bacteriocin produced by *Ligilactobacillus salivarius* DPC6502 that is effective against medically important pathogens, including *Staphylococcus aureus* [38]. In addition, lactococcin 972-like bacteriocins have been found to be produced by *S. epidermidis* and *S. aureus* strains [19].

2.1.3. Class III Bacteriocins

Class III bacteriocins are called bacteriolysins. Helveticin J, produced by *Lactobacillus helveticus* [39], linocin M18, produced by *Brevibacterium linens* [40], enterolysin A, produced by *E. faecalis*, dysgalacticin, produced by *Streptococcus dysgalactiae* subsp. *equisimilis* W2580 [16], millericin B, produced by *Streptococcus milleri* [41], and zoocin A, produced by *Streptococcus zooepidemicus* [42], are bacteriocins in this class. Caseicin, also in this class, is produced by *Lacticaseibacillus casei* and has a different antimicrobial mechanism [16]. Lysostaphin, produced by *Staphylococcus simulans*, is also included in this class [43]. Class III bacteriocins also include enterolysin A, helveticin M, and helveticin J, produced by *E. faecalis*, *Lactobacillus crispatus*, and *L. helveticus*, respectively [16,44].

2.1.4. Class IV Bacteriocins

Class IV bacteriocins are distinguished by their complex structures, which include covalently bonded non-protein components such as lipids or carbohydrates. These moieties are integral to their antimicrobial function, contributing to their unique structural and functional properties. The incorporation of these non-proteinaceous groups often results in cyclic peptide structures, where the N-terminal and C-terminal ends are covalently linked, forming a continuous loop. This cyclization can enhance the stability and activity of the bacteriocin. However, the presence of lipid or carbohydrate components also renders these bacteriocins susceptible to enzymatic degradation by glycolytic or lipolytic enzymes, which can affect their stability and activity profiles [45–47].

Notable examples of Class IV bacteriocins include leuconocin S and plantaricin S produced by *Leuconostoc paramesenteroides* OX and *L. plantarum*. Leuconocin S is a complex

bacteriocin incorporating lipid or carbohydrate components. It has been identified as a bacteriolysin due to its structural intricacies and functional properties. Plantaricin S exhibits antimicrobial activity against a variety of Gram-positive bacteria. Its lipid or carbohydrate modifications contribute to its stability and specificity [46,47].

The structural complexity of Class IV bacteriocins, characterized by the integration of lipid or carbohydrate groups and cyclic peptide backbones, not only contributes to their potent antimicrobial properties but also presents challenges in large-scale production and stability. Ongoing research aims to engineer more stable variants and develop efficient production methods to harness their full potential as natural food preservatives and therapeutic agents [45].

2.2. Gram-Negative Bacteriocin Producers and Their Bacteriocins

Bacteriocins are mostly produced by Gram-positive bacteria, mainly LAB, but some Gram-negative bacteria can also produce bacteriocins. Gram-negative bacteriocins consist of colicins and microcins produced by *Escherichia coli*. In addition to these, colicin and microcin-like bacteriocins are also present (Figure 2) [48].

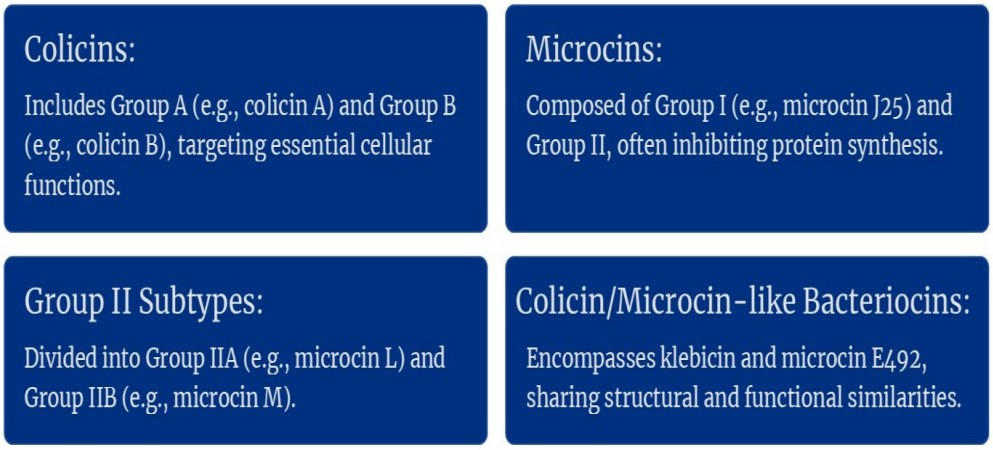


Figure 2. Classification and prominent features of bacteriocins produced by Gram-negative bacteria.

Colicins are divided into two groups. Group A requires Tol proteins to act on the cell membrane and Group B requires Ton proteins. Group A includes bacteriocins such as colicin A, E1-E9, K, N, U, and S4, while Group B includes colicin B, D, Ia, M, 5, and 10 [49]. Colicin-like bacteriocins are also produced by Gram-negative bacteria other than *E. coli*. Cloacin DF13, klebicin, bacteriocin 28b, and alveicin [50] are produced by *Enterobacter cloacae*, *Klebsiella pneumoniae* [51], *Serratia marcescens* N28b, and *Hafnia alvei* [52], respectively, and are included in Group A, while pesticin, produced by *Yersinia pestis* [53], and pyocin, produced by *Pseudomonas aeruginosa* [54], are included in Group B.

Similar to colicins, microcins are divided into two groups. Group I consist of microcins B17, C7-C51, D93, and J25 [55]. Group IIA includes microcins L, V, and N, while Group IIB includes microcins E412, M, and H47 [26]. Gram-negative bacteria other than *E. coli* have been found to produce microcin-like bacteriocins. Microcin E492 is a microcin-like bacteriocin produced by *K. pneumoniae* [48].

3. Mechanisms of Action of Bacteriocins

Bacteriocins exert their antimicrobial effects against Gram-positive and Gram-negative bacteria through various mechanisms. These mechanisms include disruption of cell wall integrity and inhibition of protein and nucleic acid synthesis [56].

3.1. Mechanisms of Action of Gram-Positive Bacteriocins

The mechanisms of action of Gram-positive bacteriocins are inhibition of cell wall synthesis, disruption of cell membrane structure, and inhibition of septum formation (Figure 3) [57].

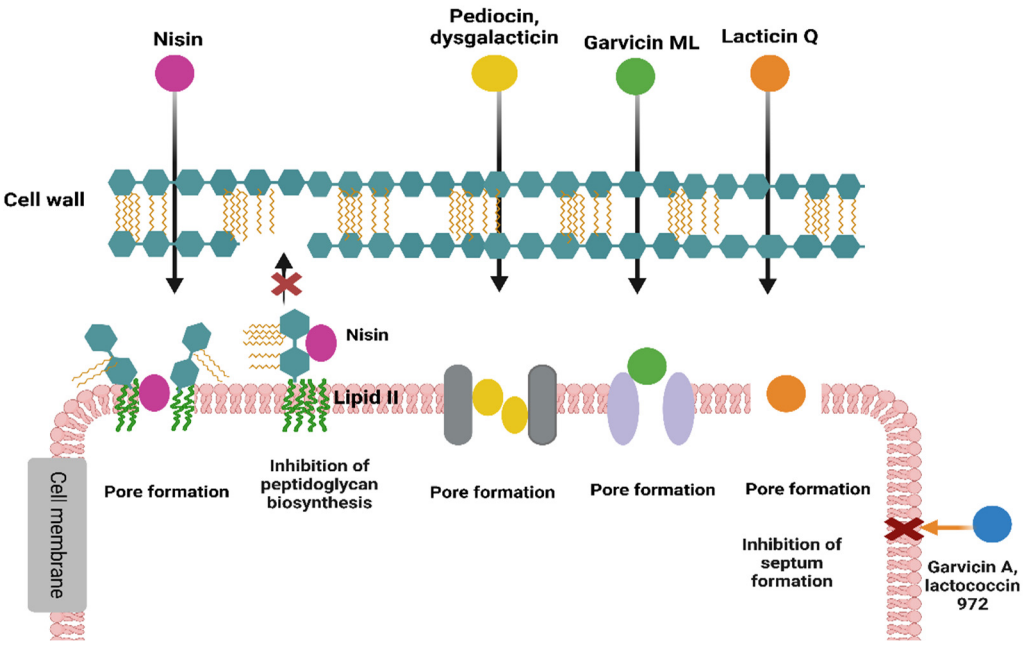


Figure 3. Antimicrobial mechanism of action of bacteriocins produced by Gram-positive bacteria (adapted from Kaya et al. [58]).

3.1.1. Inhibitors of Cell Wall Synthesis

The cell wall has vital functions, such as ensuring cellular integrity, forming cell morphology, and regulating intracellular osmotic pressure. Therefore, inhibition of cell wall biosynthesis becomes a critical target [57].

Nisin A targets cell wall biosynthesis. Nisin A is a membrane-binding precursor and performs inhibition by binding to the lipid II molecule, which transports peptidoglycan subunits from the cytoplasm to the cell wall. It shows activity by binding to phosphate groups in the lipid II molecule. The formed nisin-lipid II complex acts by forming a pore in the cell wall at high concentrations [44].

Similarly, nukacin ISK-1, produced by *Staphylococcus warneri*, inhibits cell wall biosynthesis by binding to lipid II molecules. However, it was reported that different concentrations of nukacin ISK-1 did not form pores in the cell membrane [57]. Again, NAI-107, a lantibiotic produced by *Microbispora* sp. ATCC-PTA-5024, was reported to bind to lipid II molecules and inhibit the growth of vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) [57]. Lacticin 481 contains a lipid II binding motif and exerts its antimicrobial effect by inhibiting peptidoglycan synthesis catalyzed by penicillin-binding protein [59].

3.1.2. Disruptors of Bacterial Membrane Integrity

Bacteriocins have two main effects on the target cell membrane. First, they exert an inhibition by disrupting the structure of the cell membrane by mass action, without the need for a specific binding site. This effect is realized in the presence of high concentrations of bacteriocin. The other mode of action is inhibition by the presence of a specific binding site, similar to that of anti-listerial bacteriocins [57].

After binding the nisin to the lipid II molecule, it is translocated to the cytoplasmic membrane. Pores are formed and amino acids, potassium ions, and ATP leak out of the

cell. As a consequence, the proton motive force is disrupted and ion losses and a decrease in cellular electrolytes occur [57]. This effect is similarly mediated by bacteriocins such as epidermin (produced by *S. epidermidis* Tu3298), geobacillin I (produced by *Geobacillus thermodenitrificans* NG80-2), plantaricin (E, F, J and K produced by *L. plantarum*), and Pep5 (produced by *S. epidermidis* 5), and they perform this activity by binding to lipid II molecule [60]. Bac-GM17 is a bacteriocin with bactericidal and fungistatic activity produced by *Bacillus clausii* GM17 [61].

However, not all bacteriocins that disrupt membrane integrity act by binding to the lipid II molecule. Dysgalacticin produced by *S. dysgalactiae* subsp. *equisimilis* W2580 acts by binding to the glucose molecule and/or man-PTS system in the membrane. Dysgalacticin disrupts the structure of the cytoplasmic membrane and causes leakage of potassium ions and the membrane loses its function. Lactococcins A, B, pediocin and pediocin-like bacteriocins show activity by binding to the man-PTS system [62].

Apart from binding to lipid II and the man-PTS system, some bacteriocins cause pore formation in different ways. Lacticin Q is produced by *L. lactis* QU 5. It displaces lipids in the cytoplasmic membrane and causes the formation of toroidal pores [62]. Through the toroidal pores, proteins leak out of the cell, and cell death occurs without the need for special structures. For garvicin ML produced by *Lactococcus garvieae*, the maltose ABC transporter system on the cell surface is recognized as the target receptor site and shows its effect by causing pore formation because of its interaction [62]. Enterocin AS48 is a bacteriocin produced by *E. faecalis* [62]. It forms a dimer on the cell membrane without the need for any special receptor to form a pore, and this dimer then becomes membrane-bound and causes pore formation. Here, enterocin AS48 interacts directly with the lipid bilayer. Carnocyclin A, which also interacts with the lipid bilayer to form ion-specific pores [20].

3.1.3. Inhibitors of Septum Formation

Bacteriocins act on metabolic activities that are vital for the cell, such as replication, transcription, translation, and cell wall biosynthesis. New mechanisms of action for bacteriocins, i.e., new cellular targets, are being uncovered every day. For example, garvicin A is produced by *L. garvieae* and lactococcin 972 by *L. lactis*; both bacteriocins show antimicrobial effects by blocking septum formation in closely related species [62–64].

3.2. Mechanisms of Action of Gram-Negative Bacteriocins

Gram-negative bacteriocins target DNA replication, transcription, and protein synthesis in addition to Gram-positive bacteriocins' targets of inhibition of cell wall synthesis, disruption of cell membrane structure, and inhibition of septum formation (Figure 4) [57].

3.2.1. Inhibitors of Cell Wall Synthesis

Colicin M causes cell lysis by inhibiting peptidoglycan biosynthesis. Colicin M binds to lipid II molecule and causes its degradation. In this way, peptidoglycan subunits are lost in the periplasmic space, peptidoglycan synthesis is inhibited, the cell is lysed, and the cell dies [55].

3.2.2. Pore Formers in the Cytoplasmic Membrane

Colicin A, B, E1, Ia, Ib, K, N, and microcin E492 form pores on the cytoplasmic membrane, causing leakage of vital cytoplasmic components out of the cell, disruption of the electrochemical gradient, loss of ions, and, ultimately, cell death [48]. It has been reported that colicins do not require a target cell protein to attach to the lipid membrane, localize to the membrane, and form pores. With electrostatic interactions, the positively charged side chain ring of colicins interacts with the phospholipid layer, and an open umbrella-shaped pore structure (umbrella pore model) is formed [65]. Microcin E492 forms

cation-selective channels on the phospholipid bilayer. It requires TonB protein for transport across the outer membrane and proton motive force for its antimicrobial activity [66].

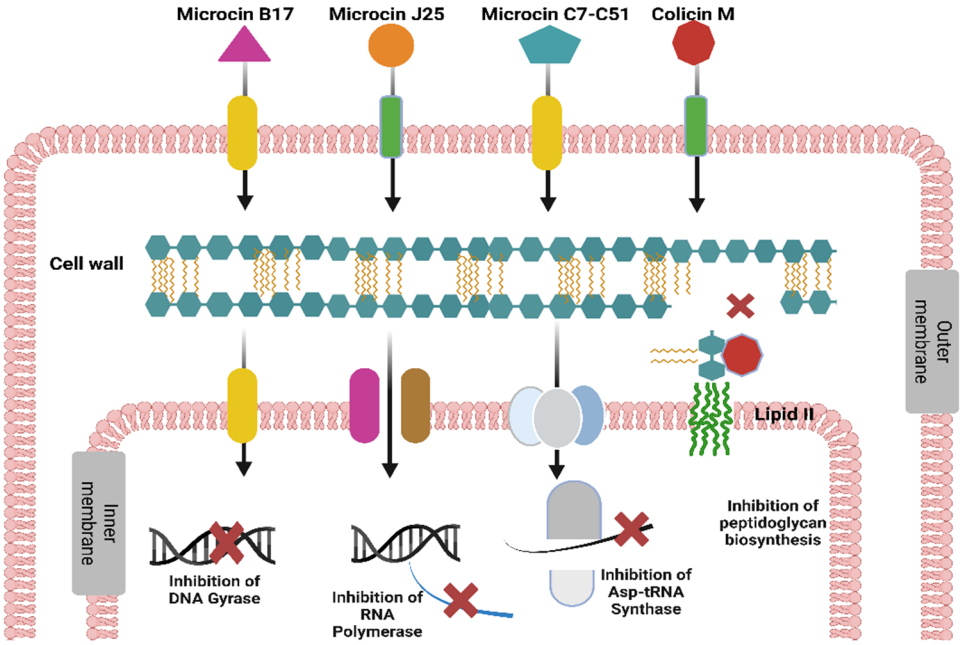


Figure 4. Antimicrobial mechanism of action of bacteriocins produced by Gram-negative bacteria (adapted from Kaya et al. [58]).

3.2.3. Inhibitors of DNA Replication

Colicins, microcins, and other bacteriocins produced by Gram-negative bacteria (carocin S2, etc.) show bactericidal antimicrobial activity by non-specifically cleaving the DNA molecule [55].

Among the DNase colicins, colicins E2, E7, E8, and E9 are metal ion-dependent bacteriocins that cleave DNA molecules at random sites [44,65]. They bind to the BtuB receptor on the outer membrane and then pass into the periplasmic space. They also enter the cell by binding to Tol proteins on the inner membrane. They act by forming nicks on double-stranded DNA and cell death usually occurs as a result of excessive nicking [67]. Colicin E9 acts on both single-stranded and double-stranded DNA. DNase Colicins require metals, such as nickel, cobalt, copper, and often zinc, to bind to DNA [68].

Microcin B17 has a decatenation mechanism of action and acts as a DNA gyrase inhibitor. It crosses the outer membrane through the OmpF pores and then enters the cytoplasm through the Sbm A protein on the inner membrane. By targeting DNA gyrase, it prevents the formation of the DNA supercoil [57,69].

3.2.4. Inhibitors of Protein Synthesis

Colicins have 16S rRNase and tRNase activity, microcins have RNase and tRNase activity. Carocin S2, produced by *Pectobacterium carotovorum*, is a bacteriocin with RNAase activity. Colicin E3, E4, E6, and cloacin DF13 show 16S rRNAase activity, while colicin D and E5 show tRNAase activity [70]. Group E colicins show endonuclease activity. They require BtuB protein to cross the outer membrane and Tol protein to cross the inner membrane. They cause translation inhibition by cleaving phosphodiester bonds at the 3′ end of the 16S rRNA coding sequence. Colicin E3 acts specifically on the 30S subunit of the bacterial ribosome, while Colicin D and E5 act by cleaving phosphodiester bonds in the anticodon loop of tRNAs involved in protein synthesis. Colicin D binds to the FepA protein on the outer membrane and Ton protein on the inner membrane [68,70].

Microcin J25 inhibits transcription and microcin C7/C51 inhibits translation [44]. Microcin J25 is transferred to the periplasmic space via the iron-chromium-containing FhuA receptor on the outer membrane. In the inner membrane, it requires the TonB protein complex for this process. It reaches inside the cell as a result of its interaction with the SbmA protein in the cytoplasmic membrane. It causes inhibition of RNA polymerase by causing a blockage in its second channel and targets mitochondria and the respiratory chain with increasing concentration [71]. Microcin C7/C51 interacts with the OmpF molecule on the outer membrane and the YejI molecule on the inner membrane and passes into the cell. As a result of its activity, it mimics the aspartyl adenylate molecule and inhibits tRNA aminoacylation, thus inhibiting protein synthesis [69].

4. Innovative Approaches to the Application of Bacteriocins in Food Systems

No doubt, bacteriocins have a huge contribution to food safety because of their effectiveness against some important foodborne pathogenic bacteria, and to food security by preventing the growth of spoilage bacteria. In addition, consumers' increasing prejudices against synthetic antimicrobials in recent years have led to increased interest in natural preservatives, such as bacteriocins. However, bacteriocins can also have a negative effect, especially against lactic starter cultures, and this limits their use in fermented foods. Therefore, it is generally desirable that the antimicrobial effects of bacteriocins are specific to foodborne pathogens and spoilage bacteria. In addition, proteases secreted into the medium by starter cultures during fermentation should not inhibit the activity of bacteriocins [72]. Additionally, although food safety is a priority issue, the bacteriocins or bacteriocin-producing bacterial cultures to be used should not adversely affect the sensory properties of the food.

Bacteriocin applications in foods can be by adding pure bacteriocin or semi-purified bacteriocin (such as fermentates containing bacteriocin) to food, or by using bacteriocin-producing bacterial culture as a starter or bioprotective culture in food production. Among the bacteriocins, nisin is undoubtedly the most used as a food preservative, and nisin producer *L. lactis* is also frequently used as a starter and preservative culture, especially in cheesemaking. For example, the problem of the late blowing, which causes economic loss, by *Clostridium butyricum* and *Clostridium tyrobutyricum* in pasta filata group cheeses, such as mozzarella, cheddar, and kashar, can be eliminated with nisin or a nisin-producing starter culture [73]. Although nisin is known to be less effective in meat products compared to dairy products [74], nisin can be used as an alternative to nitrate/nitrite salts against the risk of *Clostridium botulinum*, which causes severe diseases, such as paralysis and blindness or death, in meat products, such as sausages [75]. Apart from nisin, other bacteriocins that have been used in foods with successful results, especially against foodborne pathogens, and are permitted to be used by their producers are pediocin (PA-1) and lacticin. It is well known that pediocin has a strong inhibitory effect against *L. monocytogenes*, another important pathogen that causes serious foodborne diseases and even death [76]. Morgan et al. [77] determined that, in the presence of lacticin 3147 powder, there was a 99.9% decrease in the amount of *L. monocytogenes* in yogurt and 85% in cottage cheese within two hours, and that the number of *Bacillus cereus* in soup decreased by 80% within three hours. In addition, there are examples of using bacteriocins as cocktails or using multi-bacteriocin-producing starter cultures. For example, Kaya and Simsek [78] used a bacteriocin cocktail obtained from *L. plantarum*, *E. faecalis*, and *Lactobacillus delbrueckii* subsp. *lactis* (each at a concentration of 100 AU/mL) and reported that the bacteriocin cocktail caused a decrease of 1.5, 3, and 2 log CFU/mL against *B. cereus*, *L. monocytogenes*, and *S. aureus* inoculated

at a concentration of 5 log CFU/mL in a milk model system, respectively, after one week of storage.

There are many studies in the literature examining the individual use of bacteriocins or bacteriocin-producing starter or bioprotective cultures in foods, as well as their use with different hurdles such as heat treatment [79], high pressure [80], pulsed electric field [81], modified atmosphere packaging [82], bacteriophages [83], and other antimicrobials [84]. However, in recent years, there have been innovative approaches to the use of bacteriocins in edible films and coating materials and nanotechnology [85].

4.1. Use of Bacteriocin in Film and Coating Material

In recent years, the use of edible films and coatings in food packaging has become widespread due to the various advantages they provide as an alternative to traditional packaging. In this regard, the number of examples of the use of bacteriocin or bacteriocin-producing LAB strains in the edible film and coating matrix has also increased. For example, in a study [86] examining the effect of edible galactomannan coatings produced with nisin on the safety of ricotta cheese, it was determined that coatings containing nisin (50 IU/g) caused a significant decrease (by 2.2 log CFU/g) in the number of *L. monocytogenes* after seven days of storage at 4 °C compared to coatings without nisin. Another study [87] reported that, by applying enterocins (from *Enterococcus avium*) to agar coatings of soft and semi-hard cheeses contaminated with *L. monocytogenes*, there was a 1 log decrease in the number of *L. monocytogenes*, and also that this strategy was more effective by facilitating the diffusion of enterocins due to the higher moisture content in soft cheeses. Contessa et al. [88] reported that the use of chitosan/agar-agar bioplastic film containing purified bacteriocin extract of *L. sakei* in Minas Frescal cream cheese packaging contributed to an increase in microbiological stability during the storage period, resulting in a 53.4% greater reduction in microbial load compared to the film without bacteriocin extract. However, more successful results can be achieved at lower costs by using bacteriocin-producing bacterial strains in films and coatings instead of bacteriocins. For example, in a study conducted by Esposti et al. [85], nisin, enterocin, and bacteriocin-producing live *Enterococcus casseliflavus* were trapped in polyvinyl alcohol (PVOH)-based coatings applied to poly (ethylene terephthalate) (PET) films and tested for their effectiveness against *L. monocytogenes* during the storage of pre-cooked chicken fillets, and a live *Enterococcus*-doped film was determined to be more successful than nisin and enterocin-doped films for long periods at both 4 °C and 22 °C. It was reported that *L. monocytogenes* was completely inactivated with this film after seven days at 22 °C. Another study reported that a whey protein/inulin/gelatin-based film with the addition of the bacteriocin producer *L. curvatus* reduced the number of *Listeria innocua* in a cooked ham by approximately 2 log after 28 days of storage at 4 °C compared to control films, where the bacterial count increased from 5.77 to 6.47 log CFU/cm^2 at the end of the storage period [89]. In another example, enterocin-producing live *E. faecium* immobilized in sodium alginate film was observed to cause a 3-log CFU decrease in the number of *Salmonella enterica* in *S. enterica*-infected chicken after 34 days of storage at 7–8 °C [90].

In studies using bacteriocin producer live bacteria, it can be assumed that different antibacterial metabolites contribute to antibacterial activity in addition to bacteriocins, and, from all these results, it can be concluded that significant successes can be achieved in increasing food safety and food durability by using bacteriocins and/or bacteriocin-producing bacteria with GRAS-status in edible films and coatings. However, more comprehensive research is required, especially examining the long-term stability of bacteriocin-based film and coating materials.

4.2. Use of Bacteriocin in Nanotechnology

Various factors (such as high cost, low selectivity, easy degradation by proteases, and potential to affect the sensory properties of foods) limit the use of bacteriocins in foods, and different strategies are being sought to overcome these limitations. In this context, utilizing nanotechnology to maximize bacteriocin activity and utilization stands out as a new and promising approach. Significant successes in both food safety and food security can be achieved by developing new and effective antimicrobial agents without causing a change in the organoleptic properties of foods by encapsulating bacteriocins. The main advantage of encapsulating bacteriocins using nanomaterials is based on increasing the desired activity by changing their physical properties, such as solubility, half-life, and bioavailability [91]. For example, it has been shown that the hybrid prepared from nisin with chitosan/alginate nanoparticles can reduce *S. aureus* and *L. monocytogenes* populations by up to five- and seven-fold, respectively, on a logarithmic scale compared to free nisin [92]. Pandit et al. [93] reported that silver-nisin nanoconjugates were more effective against foodborne pathogens such as *L. monocytogenes* and *S. aureus* than nisin and silver nanoparticles separately. Similarly, the combination of nisin and silver nanoparticles was reported to have broad-spectrum activity compared to when used separately [94]. The use of bacteriocins together with materials such as silver, which are widely used in nanotechnology, not only increases the antibacterial effect spectrum but also may lead to a decrease in toxicity [95]. For example, enterocin-coated silver nanoparticles synthesized by Sharma et al. [96] showed broad-spectrum inhibition against foodborne pathogenic bacteria without any detectable toxicity to red blood cells. Nanoliposomes, which are vesicular or spherical structures composed of one or more phospholipid layers, can be used to transport active substances such as bacteriocins [97]. In a study [98] where pediocin was encapsulated into nanovesicles prepared from partially purified soybean phosphatidylcholine, it was observed that the antimicrobial activity and properties of free and encapsulated pediocin were maintained for 13 days at 4 °C, after which the encapsulated pediocin retained 50% of its initial activity. It was also reported that the effect of encapsulated pediocin on *L. monocytogenes* at 48 h of incubation resulted in viable counts that were 2.5 log and 1.0 log lower than those observed for empty liposomes and free pediocin, respectively, but, after this period, free pediocin showed a better inhibitory effect compared to encapsulated pediocin. In another study [99], where the bacteriocin produced by *L. sakei* 2a was encapsulated in phosphatidylcholine and 1,2-dioleoyloxy-3-trimethylammonium-propane liposomes and evaluated for their activities against *L. monocytogenes* in vitro and in contaminated milk during storage, it was determined that both free and encapsulated bacteriocins retarded the growth of *L. monocytogenes* at 7 °C and, after five days, 5 log lower bacterial loads were observed in both BHI (Brain Heart Infusion) medium and milk than in controls. The researchers reported that the activity of the bacteriocin was not affected when this bacteriocin was encapsulated from the results they obtained.

The use of bacteriocins with nanomaterials seems very promising. Significant gains in food safety can be achieved with different material–bacteriocin combinations. However, toxicity studies on the use of nanoparticles in foods are limited. Therefore, the toxicity of these combinations should be investigated in detail before they are used in foods. Additionally, the efficacy and stability of the nanomaterial-bacteriocin combination need to be confirmed by further studies.

In summary, the food industry can enhance food safety and shelf life by incorporating innovative approaches, such as using bacteriocins or GRAS-status bacteriocin-producing bacteria in film coatings and nanomaterials, to meet consumer expectations.

5. Use of Bacteriocins to Inhibit Biofilm Formation

Biofilms, according to Kokare et al. [100], are intricate microbial communities encased in a polysaccharide matrix. They play an important role in chronic bacterial infections, medical device contamination, and food spoilage. As summarized by Tilahun et al. [101], the process of biofilm formation involves reversible and irreversible attachment, maturation, and dispersal. Briefly, biofilms are bacterial communities that form on surfaces and are difficult to treat with antibiotics. Bacteria in biofilms are protected by a matrix that protects them from drugs [102].

The presence of biofilms on food contact surfaces can lead to the persistence of pathogenic species and recurrent cross-contamination of food, causing serious safety issues and economic losses. Every year, almost 600 million people worldwide are affected by foodborne diseases [103]. This is because the bacterial population that forms biofilms can include pathogens, such as *L. monocytogenes*, *S. aureus*, *E. coli* O157:H7, and *Salmonella*, which become more resistant to disinfectants used to prevent biofilms, pose a serious threat to food quality and safety and negatively affect the economic activity of food industry businesses due to food spoilage and equipment erosion [104]. Biofilm-forming isolates and their locations in the food industry are given in Table 1.

Table 1. Biofilm-forming isolates and places are commonly found in the food industry.

Biofilm-Forming Isolates	Common Locations in Food Industry	References
L. monocytogenes	Stainless steel surfaces, food processing equipment	[105]
S. aureus	Dairy equipment, meat processing plants, food contact surfaces	[106]
P. aeruginosa	Food processing equipment, water systems, fresh produce surfaces	[107,108]
E. coli	Food contact surfaces, stainless steel surfaces, dairy processing environments	[109]
Salmonella spp.	Food processing equipment, poultry processing environments, food contact surfaces	[110]
B. cereus	Dairy processing equipment, stainless steel surfaces	[111]

The resistance of biofilm cells to conventional disinfectants necessitates the development of natural alternatives to effectively inhibit biofilm formation and eliminate pre-existing biofilms [112]. Bacteriocins show promise in preventing biofilm formation and some bacteriocins may inhibit biofilm formation by disrupting the binding and maturation stages [102,112]. However, the use of bacteriocins in combination with classical antibiotics has shown great efficacy in inhibiting biofilm formation [113]. For example, Angelopoulou et al. [114] reported a synergistic effect between nisin A and vancomycin against biofilms of multidrug-resistant *S. aureus* strains. Similarly, Al Atya et al. [115] showed that the combination of enterocin DD28 and DD93 (from *E. faecalis* 28 and 93) with erythromycin or kanamycin had a significant synergistic effect against clinical MRSA-S1 strain and this combination inhibited the formation of MRSA-S1 biofilm on the surfaces of the glass and stainless steel. Additionally, integrating bacteriocins with bioactive agents, such as bacteriophages, essential oils, and nanoparticles, also increases their stability and expands their antibacterial activity. For example, adding bacteriocins to nanoparticles may make them more stable, resistant to enzymatic breakdown, and more bioavailable. Additionally, bacteriophages and essential oils help to increase the range of action of bacteriocins and

decrease the chance of resistance building. Several uses for these synergistic combinations are being investigated, such as antiviral, anticancer, and antibiofilm treatments. As a result, these combinations may contribute to increased efficacy in combating biofilms, increased therapeutic effect, reduced use of conventional antibiotics, and reduced the spread of antibiotic resistance [116].

There are several ways in which bacteriocins can be used to inhibit biofilm formation. The first is that bacteriocins directly inhibit the growth of biofilm-producing bacteria. Here, bacteriocins inhibit biofilm development by interfering with the adhesion of bacterial cells to other cells in the early stages of biofilm formation [117]. Direct inhibition of biofilm-producing bacteria by bacteriocins involves several mechanisms, including recognition, binding, membrane disruption, and, in some cases, enzymatic activity. Bacteriocins have been shown to recognize and bind to specific target cells, and this recognition is crucial for their inhibitory activity [118,119]. Furthermore, a membrane disruption mechanism of bacteriocins has been demonstrated, where they act by disrupting the bacterial cell membrane, leading to cell lysis and growth inhibition [120]. These findings collectively highlight mechanisms by which bacteriocins may directly inhibit biofilm-producing bacteria through different mechanisms. Second, bacteriocins can disrupt the structure of the biofilm and make established biofilm cells more susceptible to other antimicrobial agents. Bacteriocins have been shown to act on pre-formed biofilms and can prevent their formation [121]. The inhibitory effects of bacteriocins on biofilm formation have been attributed to their ability to disrupt the cell viability of bacteria within biofilms, making them valuable therapeutic tools in the biofilm-related fight [122]. Furthermore, some bacteriocins can also prevent biofilm formation by inhibiting a communication system known as "quorum sensing" [123,124]. Briefly, bacteriocins have been shown to possess anti-quorum sensing properties that can control biofilm formation at minimum inhibitory concentrations [125]. In addition, bacteriocins have been found to affect the expression of important biofilm-associated genes and the quorum sensing mechanism, thereby influencing biofilm formation [126].

Different modes of action of bacteriocins, such as pore formation and inhibition of cell wall synthesis, which are crucial in targeting biofilms formed by antibiotic-resistant bacteria, have been proposed and described. For example, bacteriocins such as nisin A, lacticin Q, and nukacin ISK-1 have demonstrated efficacy in disrupting biofilms, particularly those formed by MRSA [102,127].

In summary, in addition to their direct antimicrobial effects, they exert their mechanisms of action on biofilms through multiple pathways, including quorum sensing, interference with pore formation and ATP flow, disruption of bacterial cell viability, and modulation of gene expression associated with biofilm formation. These findings highlight the potential of bacteriocins as effective agents to prevent and disrupt biofilm formation, particularly in the context of biofilm control.

As food safety is becoming an increasingly important international concern, the application of bacteriocins derived from LAB that target pathogenic bacteria without major side effects has attracted great interest. Moreover, the immune mechanisms of LAB bacteriocins play an important role in protecting bacteriocin-producing cells from their own antimicrobial effects [128]. For example, in a study addressing biofilm formation—a significant challenge in the dairy industry—the BM173 bacteriocin from *Lactobacillus crustorum* MN047 demonstrated promising potential as a preservative. It effectively inhibited biofilm formation and exhibited broad-spectrum antibacterial activity against *E. coli* and *S. aureus*, with minimum inhibitory concentration (MIC) values of 14.8 μg/mL and 29.6 μg/mL, respectively. [129]. A study found that bacteriocin-producing *L. sakei* CRL1862 effectively inhibits *L. monocytogenes* biofilm formation, especially on stainless steel surfaces, suggesting that it is a safe and eco-friendly method to reduce food contamination [130]. A recent

study demonstrated partial purification of bacteriocin produced by *Levilactobacillus brevis* DF01 and investigated whether bacteriocin inhibits biofilm formation of *E. coli* and *Salmonella typhimurium*. Evaluation by microtiter plate method as well as fluorescence and scanning electron microscopy showed that biofilm formation of *E. coli* and *S. typhimurium* was reduced when bacteria were co-incubated with crude bacteriocin of *L. brevis* DF01 (DF01 bacteriocin). The result revealed that DF01 bacteriocin could potentially help control these pathogens in food processing and human health by reducing the biofilm formation of *E. coli* and *S. typhimurium* [131]. Research by Krishna [132] shows that *E. faecium* from milk produces bacteriocin ALC102, which inhibits *L. monocytogenes* biofilm formation. ALC102's performance is comparable to nisin and remains effective at both high and freezing temperatures, suggesting its potential use in the food industry.

The findings suggest that bacteriocins can effectively inhibit biofilm formation, but disrupting already-formed biofilms is difficult. Synergistic combination with other antimicrobials, incorporation into nanoconjugates, and bioengineering applications may help to potentiate their antibiofilm activity [112].

6. Effects of Bacteriocins on Human Health

Bacteriocins have long been known to be effective against a variety of pathogenic bacteria. Recent discoveries of antiviral and anticancer properties in certain bacteriocins (Figure 5) have heightened interest in utilizing bacteriocins and GRAS-status bacteriocin-producing bacteria in food applications [133]. In this context, it seems possible to contribute to human well-being through bacteriocins with a better understanding of their spectrum of action and toxicity.

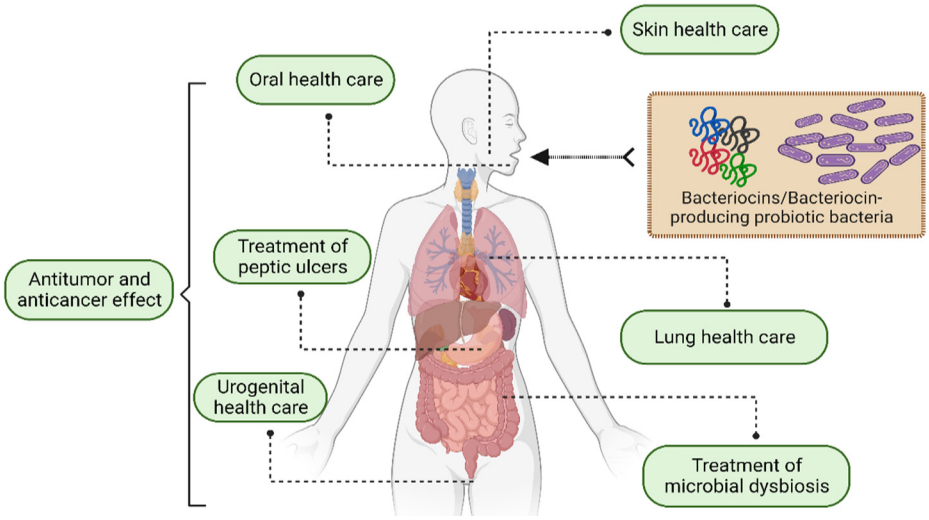


Figure 5. Schematic representation of the effects of bacteriocins on human health.

6.1. Use in the Treatment of Bacterial Infections

As is known, antibiotics have been used to combat pathogenic bacteria for almost a century, since the discovery of the first antibiotic. However, due to the long-term use of antibiotics incorrectly (overuse or misuse), the resistance developed by bacteria against antibiotics has reached alarming levels in recent years. Namely, if precautions are not taken, it is estimated that antimicrobial-resistant infections will cost the lives of up to 10 million people per year by 2050 [134]. Therefore, discovering/designing effective antibacterial compounds that can be alternatives to antibiotics is essential to protect public health. Among these alternatives, bacteriocins stand out due to their various advantages.

Compared to antibiotics, bacteriocins are more target-specific and, unlike antibiotics, are less likely to damage the intestinal microbiota [135]. As mentioned previously, the

mechanisms of action of bacteriocins differ from those of antibiotics, which generally affect target cells through pore formation and membrane disruption [136]. In addition, due to their peptide structure, bacteriocins are easily broken down by proteolytic enzymes, such as pepsin, trypsin, and chymotrypsin, and cannot remain stable in the human body and the environment for a long time [9]. These properties reduce the risk of bacteriocins interacting with bacterial cells and the risk of bacteria developing resistance and increase the potential for bacteriocins to be used as an alternative to conventional antibiotics [137].

Various in vitro and in vivo studies have determined that bacteriocins are effective for the inhibition of many foodborne and clinical pathogenic bacteria that can cause serious diseases and that they have a high potential to be used as an alternative to conventional antibiotics in the treatment of these diseases. In addition, there are narrow-spectrum bacteriocins as well as broad-spectrum bacteriocins, and, by using narrow-spectrum bacteriocins specific to the bacteria that cause bacterial infection, the risk of disruption of the host microbiota balance is reduced. In fact, bacteriocins may indirectly contribute to the treatment of microbial dysbiosis by contributing to the shaping of the host microbiota [138]. For example, the bacteriocin thuricin CD selectively targets *C. difficile*, which can often cause colon infections and can cause very serious diarrhea after antibiotic treatment, without affecting the commensals [139]. Various studies have shown that different bacteriocins can be used to protect intestinal health. For example, microcin J25 has been shown to significantly decrease *Salmonella* infection, which can cause gastroenteritis, in a mouse model [140]. In a study performed by Stern et al. [141], OR-7 bacteriocin synthesized by *L. salivarius* NRRL B-30514 reduced *Campylobacter jejuni* colonization in the chicken gastrointestinal tract by at least one millionfold compared to the control. These two results show that bacteriocins are not only effective against Gram-positive bacteria, but some bacteriocins are also effective against Gram-negative bacteria. In addition, understanding the existence of bacteriocins that are effective on *Salmonella* and *C. jejuni*, two of the most important culprits of foodborne infections, points to the importance of bacteriocins in ensuring food safety. Moreover, in a study conducted by van Kuijk et al. [142], it was determined that subtilosin was effective against another foodborne infection source bacterium, *L. monocytogenes* Scott A, which has a very high mortality rate, probably by disrupting the lipid bilayer of the cell membrane and causing intracellular damage. Additionally, Dabour et al. [143] reported that intragastric administration of pediocin PA-1 to *L. monocytogenes*-infected mice reduced the number of *Listeria* in feces without affecting mouse intestinal microbiota composition and that repeated doses of pediocin PA-1 led to the disappearance of *L. monocytogenes* infection in the liver and spleen within six days. Corr et al. [144] reported that the application of probiotic *L. salivarius* UCC118 reduced *L. monocytogenes* infection in mice and that this was due to the Abp118 bacteriocin produced by this strain. It has also been reported that some bacteriocins (such as lacticin A164 and lacticin BH5) are highly effective against *Helicobacter pylori*, which is found in significant amounts in patients with duodenal and/or stomach ulcers, and this may contribute significantly to ulcer treatment [145].

It has also been shown in various studies that some bacteriocins are effective against various pathogenic bacteria that cause respiratory infections. For example, nisin is effective against *Streptococcus pneumoniae*, which can cause diseases such as pneumonia and otitis media [146]. Nisin F was reported to exhibit inhibitory activity against *S. aureus* strains in the respiratory tract of immunocompromised rats [147]. Sosunov et al. [148] showed that four of the five bacteriocins tested were highly effective against *Mycobacterium tuberculosis*, the main cause of tuberculosis.

Bacteriocins may also contribute to the maintenance of oral health, urogenital health, and skin health. For example, it has been confirmed by many studies that [149,150] nisin is effective against *S. mutans*, one of the important responsible of dental caries, and, therefore,

nisin is used in some commercial oral care products. Another study showed that subtilosin was effective against *Gardnerella vaginalis*, which is associated with bacterial vaginosis [151]. It was reported by Oh et al. [152] that the bacteriocin synthesized by *Lactococcus* sp. HY 449 inhibited various bacteria (*S. epidermidis*, *S. aureus*, *S. pyogenes*, and *Propionibacterium acnes*) that cause skin infections. In a study where enterocin ESL5 was applied as a lotion to a patient with acne lesions caused by *P. acnes*, it was observed that the lotion with enterocin significantly reduced inflammatory lesions and pustules compared to placebo [153].

Many studies have shown that bacteriocins can also be used to combat infections caused by antibiotic-resistant bacteria. For example, a new bacteriocin called romsacin was determined to be effective against bacteria such as MRSA and VRE, which are identified as global priority pathogens by the World Health Organization [24]. Additionally, in the study conducted by Hanchi et al., it was shown that durancin 61A, a glycosylated bacteriocin produced by *Enterococcus durans*, was effective against drug-resistant *C. difficile* as well as MRSA and VRE [154]. Piper et al. [155] reported that nisin and lacticin 3147 are effective against both MRSA and VRE; however, nisin is more effective against MRSA with minimum inhibitory concentration values between 0.5 and 4.1 mg/L and lacticin 3147 is more effective against VRE with minimum inhibitory concentration values between 1.9 and 7.7 mg/L.

In summary, all data obtained from in vitro and in vivo studies indicate that bacteriocins and bacteriocin-producing bacteria can be very powerful tools in the treatment of both foodborne and clinical bacterial infections against antibiotic resistance, which has become a global problem.

6.2. Use in the Treatment of Viral Infections

In the treatment of viral infections, drugs that prevent the proliferation of the virus, such as inhibitors of DNA polymerase activity, are generally used. However, viruses can easily mutate and quickly develop resistance to these drugs. Therefore, the need for new antiviral drugs is increasing day by day [156]. Previous studies have reported that various bacteriocins, especially those synthesized by species of the *Enterococcus* genus, can inhibit various viruses by stopping glycoprotein synthesis at the late stage of virus replication [5].

Wachsman et al. showed that the CRL35 enterocin produced by the *E. faecium* CRL35 strain is effective against *Herpes simplex* virus type 1 (HSV-1) and type 2 (HSV-2), which cause intestinal ulcerative diseases in humans, by interfering with the final stage of viral replication [157]. In the study conducted by Todorov et al. [158], it was shown that the pediocin-like bacteriocin ST5Ha synthesized by *E. faecium* was effective against HSV-1. In this study, the EC_{50} value (50% of the effective concentration) of ST5Ha bacteriocin against HSV-1 was found to be 50 μg/mL and the selectivity index (CC_{50}/CE_{50} ratio) was 173. In a study conducted by Torres et al. [159], it was determined that subtilosin had antiviral and virucidal properties against HSV-1, and, in another study conducted by Quintana et al. [160], it was determined that subtilosin had antiviral and virucidal properties against HSV-2. Ermolenko et al. [161] reported that chemically synthesized enterocin B had anti-influenza effects at a concentration of 2.5–5 μg/mL, depending on the virus dose. Moreover, Cavicchioli et al. [162] showed that poliovirus (PV-1) was inhibited by bacteriocins GEn09, GEn12, and GEn17 synthesized by *E. durans*. However, Lange-Starke et al. [163] found that sakacin A and nisin were ineffective against murine norovirus S99, influenza A virus A/WSN/33 (H1N1), Newcastle disease virus Montana, and Feline Herpesvirus KS 285.

These results indicate that bacteriocins not only have antibacterial but also antiviral properties, especially against some enveloped viruses. Many bacteriocins are hydrophobic and tend to bind to the lipidic membranes of enveloped viruses, and, as a result, they can exert antiviral effects by interfering with the fusion of cellular and viral membranes [164].

However, the antiviral properties of bacteriocins should be confirmed with well-planned, in-depth in vivo tests, and how bacteriocins inactivate viruses should be thoroughly investigated. Bacteriocins have the potential to be used as alternatives to existing antiviral drugs after their antiviral action mechanisms are elucidated and bioavailability and safety tests are performed.

6.3. Effect on Cancer Cells

Traditional treatment methods used in cancer treatment have some important limitations and disadvantages, such as not being specific to cancer cells and, therefore, affecting normal cells and causing various side effects [165]. Although the focus has been on the antimicrobial properties of bacteriocins for many years, the number of pieces of research in this direction has increased in recent years with the understanding that some bacteriocins can selectively inhibit the proliferation of cancer cells.

Cancer cell membrane surfaces are negatively charged, while normal cells are neutral. Most of the bacteriocins are cationic because they contain many lysine and arginine amino acid residues and have a high affinity against the negative surface charge of cancer cells [166]. In addition, the cancer cell membrane has higher fluidity compared to normal cells, which makes it easier for the cell membrane to become unstable. In addition, microvilli on the surface of cancer cells facilitate the binding of bacteriocins. As a result of all this, bacteriocins can selectively target cancer cells without harming normal cells [167].

It has been reported in various studies that nisin has anticancer properties. In a study conducted by Joo et al. [168], nisin was reported to increase apoptosis and reduce cell proliferation in head and neck squamous cell carcinoma cells. Moreover, it was determined that nisin application in the in vivo mouse model system could inhibit tumor growth. Similarly, Kamarajan et al. [169] determined that nisin ZP significantly inhibited head and neck cancer tumorigenesis in an in vivo mouse model system, depending on time and dose, and long-term application prolonged survival. Ahmadi et al. [170] reported that 4000, 3000, 2500, and 2000 μg/mL nisin caused significant antiproliferative impact and increased apoptotic index at both mRNA and protein levels and their results suggested that nisin may induce apoptosis through intrinsic pathways and lead to cancer cell death.

Apart from nisin, various studies have shown that bacteriocins such as pediocin, microcin, colicin, and azurin have anticancer properties. For example, a bacteriocin similar to pediocin PA-1 was determined to be cytotoxic to human colon adenocarcinoma (HT29) and human cervical carcinoma (HeLa) cells in vitro [171]. Varas et al. [172] determined that the microcin E492 bacteriocin produced by *K. pneumoniae* has antitumorigenic properties against human colorectal cancer cells in vitro and in vivo. In a study investigating the cytotoxicity of colicin N in various human lung cancer cells (H460, H292, and H23), it was determined that colicin N selectively caused cytotoxicity and that this bacteriocin had an apoptosis-inducing effect [173]. Another study [174] reported that direct injection of colicin E3 into the subcutaneous nodes of solid HK adenocarcinoma resulted in an approximately 61% reduction in the mean tumor mass in mice. Punj et al. [175] determined that azurin bacteriocin synthesized by *P. aeruginosa* blocks breast cancer cell proliferation and induces apoptosis via the mitochondrial pathway both in vitro and in vivo.

The fact that some bacteriocins selectively affect cancer cells and cause cytotoxic effects indicates that bacteriocins have the potential to be used as promising agents in cancer treatment. However, bacteriocins may have low in vivo bioavailability and stability, which may reduce their effectiveness as an anticancer agent [176]. Therefore, more in-depth, in vivo studies are needed to confirm the anticancer properties of bacteriocins and to better understand their mechanisms of action. Although human trials are difficult to perform

due to ethical reasons, the anticancer properties of bacteriocins need to be validated with well-designed clinical studies.

7. Challenges and Limitations

Although bacteriocins have many advantages, some significant challenges limit their use in both food and medical fields. The first is that industrial-scale production is not economically feasible due to high process costs. Although it seems possible to reduce costs by improving fermentation parameters and using waste and by-products as fermentation media [177], extraction and purification processes still stand out as important cost items [178]. Since widespread use of bacteriocins will only be possible with low-cost bacteriocin production, future research should focus on improving production efficiency and developing easy, effective, and low-cost strategies for purifying bacteriocins from fermentation media. In fact, nisin has been marketed at a purity of 2.5% after being industrially produced.

As mentioned earlier, although it is difficult for any bacteria to develop resistance to bacteriocins compared to conventional antibiotics, there is a partial risk that target bacteria will develop resistance to bacteriocins due to increased use. Although the mechanisms by which bacteria develop resistance to bacteriocins have not yet been fully elucidated, bacteriocin resistance may occur through mechanisms such as cell wall thickening resulting in resistance to the lipid II-binding lasso peptide siamycin I or disruption of a protein target such as the mannose-PTS transporter, and high-level resistance may occur through the acquisition of specific resistance genes. In addition, some enzymes that target bacteriocins, such as the nisin resistance protein, which acts on nisin, can also inactivate bacteriocins [2]. Bacteriocin resistance may also be affected by environmental factors. Indeed, Inglis et al. [179] reported that resistance to the bacteriocin pyocin S2 produced by *P. aeruginosa* develops more easily when iron is present in the environment and less so when iron is limited. With the prediction that the development of resistance to bacteriocins will increase if the use of bacteriocins becomes widespread, more effective strategies can be developed in the use of bacteriocins or the design of bacteriocins through bioengineering by fully understanding the resistance mechanism that bacteria develop against bacteriocins.

Safety studies indicate that bacteriocins generally have low toxicity to mammals [180]. For instance, Thanjavur et al. [181] observed that nisin caused a negligible decrease in the number of healthy cells when applied at high concentrations. Similarly, Cox et al. [182] reported that cytolysin produced by some *E. faecalis* strains showed toxicity at high concentrations. However, there are not enough in vivo and clinical studies on the subject in sufficient number and scope. One of the important reasons why nisin is the only bacteriocin directly allowed for use by regulatory agencies, such as the EFSA (European Food Safety Authority) and FDA (Food and Drug Administration), despite the existence of many bacteriocins, is the lack of detailed data on the safety of other bacteriocins and their effects on human health when used. Therefore, the safety and toxicity of bacteriocins need to be demonstrated through well-designed clinical studies.

Legal regulations regarding the use of bacteriocin, bacteriocin-containing fermentates, or bacteriocin-producing cultures in foods vary depending on the purpose of use and the legislation of each country [183]. For example, although nisin is currently permitted as a food additive (E234) in more than 80 countries, the types of food products in which it can be used and the maximum dose vary between different countries [184]. Fermentates containing bacteriocins other than nisin are permitted for use in some countries. For example, the MicroGARD™ series and ALTA 2431, both containing pediocin PA-1, are approved by the FDA. The use of bacteriocin-producing cultures as starter or adjunct cultures may be preferred due to their lower cost and less regulatory control. For example, the Micocin® protective culture containing *Carnobacterium maltoaromaticum*, which produces

the bacteriocins carnobacterium BM1, piscicolin 126, and carnocyclin A, is approved for use in foods in Canada and the United States [185].

Bacteriocins, whose safety and efficacy have been demonstrated through sensitive and comprehensive evaluations, including preclinical and clinical tests, can also be used in human health applications. Briefly, the FDA considers a wide range of criteria in the safety assessment of bacteriocins, including in vitro and in vivo tests, bioavailability, exposure study, absorption, distribution, metabolism, excretion studies, and determination of acceptable daily intake doses [184]. Only those bacteriocins that are found to be safe at effective doses as a result of these comprehensive evaluations are allowed to be used in health applications.

8. Conclusions and Future Perspectives

Bacteriocins have demonstrated immense potential not only in food safety but also in various fields related to human health, including the treatment of clinically significant pathogens, biofilm inhibition, antiviral effects, and even anticancer applications. Their antibacterial properties against foodborne pathogens and spoilage organisms have long been used in food preservation. However, the increasing recognition of their broader applications opens up exciting new avenues for bacteriocin-based interventions beyond the food industry. Despite these promising benefits, several limitations in the traditional use of bacteriocins—such as low production rates, stability issues, regulatory concerns, and effectiveness in complex environments—remain challenges that hinder their widespread application.

Recent innovations, such as the use of bacteriocins in packaging materials, films, or in combination with nanoparticles, are paving the way for overcoming these challenges. These advancements suggest that bacteriocins can be utilized more effectively and efficiently, particularly in situations where the direct application of bacteriocins or bacteriocin-producing cultures is impractical. As such, research into improving the stability, delivery mechanisms, and synergistic effects of bacteriocins will be crucial to realizing their full potential in both the food and healthcare sectors.

Looking forward, it is important that future research continues to explore novel ways to enhance the versatility and functionality of bacteriocins. Specific areas of focus should include optimizing production processes, improving the integration of bacteriocins into non-food applications, and addressing safety and regulatory aspects for human health applications. For bacteriocins to be used for health purposes, well-planned, in-depth clinical studies must be conducted and the effects and mechanisms of action of bacteriocins on human health must be elucidated. As our understanding of bacteriocin mechanisms expands, interdisciplinary collaboration is needed to design innovative solutions that can integrate these antimicrobial agents into more complex systems, such as combination therapies for resistant infections or advanced biomaterials for medical applications. Ultimately, continued innovation and research will ensure that bacteriocins fulfill their potential as safe, sustainable, and highly effective tools in both food safety and human health.

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