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REVIEW

REVIEWS IN Aquaculture

Impact of bacteriocins on multidrug-resistant bacteria and their application in aquaculture disease prevention and control

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Abstract

Aquaculture plays an important role in meeting human demand for animal protein. Disease is a critical factor that restricts the green and healthy development of aquaculture. Intensive aquaculture practices can increase the susceptibility of aquatic animals to pathogens due to environmental stress. Antibiotics are commonly used for disease prevention and control, but their frequent use in aquaculture can increase the risk of antibiotic-resistant bacteria and resistance gene transmission, posing a threat to the health of aquatic animals and humans. Recent studies have shown that bacteriocins have inhibitory effects on different species of bacteria, fungi and viruses, and can even affect natural resistance structures such as bacterial biofilms, presenting promising prospects as antimicrobial agents. Bacteriocins have potential applications in various fields such as agriculture, food and medicine, but limited research has been conducted on their impact on aquaculture disease prevention and control, and the underlying mechanisms remain to be explored. Therefore, this review aims to summarise the classification, sources, preparation methods, antibacterial activity against multidrug-resistant bacteria and application of bacteriocins as antimicrobial agents in aquaculture disease prevention and control. In addition, limitations of bacteriocin application in aquaculture and future research directions are also discussed.

KEYWORDS
antibiotic-resistant bacteria, aquaculture, bacteriocins, pathogenic bacteria, resistance genes

1 | INTRODUCTION

In the past decade, global demand for animal protein has been increasing.[1] Aquatic products are an important source of high-quality protein, with aquaculture products accounting for a far greater proportion of aquatic products than captured products.[2] Modern intensive aquaculture practices are gradually replacing traditional extensive farming methods and are becoming increasingly common. Although this high-density farming method based on the reuse of water in aquaculture can achieve the sustainable use of natural resources and make important contributions to meeting human demand for aquatic products, it also has its drawbacks. Aquatic animals in intensive farming are stressed by various environmental factors such as overcrowding, poor water quality, poor nutrition and temperature changes, leading to physiological changes and increased susceptibility to various pathogens such as bacteria, fungi, viruses and parasites.[3] In addition, high stocking densities and a lack of sanitary barriers allow pathogens to spread rapidly, leading to high mortality rates.[4]

Antibiotics are widely used in aquaculture, not only for the treatment of pathogenic infections, but also for the prevention of diseases through immersion or feed mixing.[5,6] In addition, some antibiotics are used as growth promoters, such as oxytetracycline and florfenicol.[7] The frequent and large-scale use of antibiotics in aquaculture creates selection pressure on the natural microbial community, increasing the probability of producing antibiotic-resistant bacteria and genes. Antibiotic-resistant bacteria and genes have been detected in all major

aquaculture-producing countries worldwide. Common antibiotic-resistant bacteria in aquaculture include Vibrio, Aeromonas, Bacillus, Pseudomonas, Enterobacteriaceae, Streptococcus and Exiguobacterium sp. In addition, other resistant bacteria, including Flavobacterium, have been detected in aquaculture environments.[8] Common antibiotic resistance genes in aquaculture and their respective antibiotic classes include tetracyclines (tetA, tetB, tetK and tetM), quinolones (qnrA, qnrB and qnrS), sulphonamides (sull) and others. The existence and spread of resistant bacteria and genes pose a threat to both the health of aquatic animals and humans.[9–12]

There is an urgent need to develop new antibacterial substances as alternatives to antibiotics for the prevention and control of diseases in aquaculture. In recent years, the use of antimicrobial peptides in the prevention and treatment of aquatic animal diseases has received increasing attention.[13] Bacteriocins are antibacterial peptides produced by bacteria that can inhibit different species of bacteria, fungi and viruses, and even affect natural resistance structures such as bacterial biofilms.[14] Bacteriocins are widely present in bacterial species and are a type of bioactive peptide or protein substance produced during bacterial metabolism, showing potential as effective antibacterial agents.[15,16] The development and application of bacteriocins can not only increase the types of antibacterial drugs, but also prolong the lifespan of existing antibiotics through their combined use. By reducing the frequency of antibiotic use, the selection pressure intensity of resistant bacteria can be reduced, thus slowing down the frequency and speed of resistant bacteria, ultimately reducing the threat of multidrug-resistant bacteria.

Bacteriocins have been widely applied in various fields, including agriculture, food and medicine.[17,18] In the agricultural field, bacteriocins have been extensively studied in cattle, piglets and broilers, as they can inhibit important animal and plant pathogens, such as shiga toxin-producing Escherichia coli, enterotoxigenic E. coli, methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus and Agrobacterium.[19–21] In the food industry, nisin, a bacteriocin produced by Lactococcus lactis, has been approved by the European Union as a food preservative and is sold under the trade name Nisaplin.[22] Another commercially available bacteriocin is pediocin PA-1, which inhibits the growth of Listeria monocytogenes in meat products and is sold under the trade name Alta 2341.[23] In the medical field, some bacteriocins have shown activity against tumour cells, such as E. coli colicin A and E1, which inhibit the growth of a human standard fibroblast cell line (MRC5) and 11 human tumour cell lines.[24,25] However, the use of bacteriocins in aquaculture has received little attention. This review aims to discuss the potential application of bacteriocins as antimicrobial agents in the prevention and control of aquatic animal diseases, including their classification, sources, preparation methods, antimicrobial activity against multidrug-resistant bacteria, mode of action in preventing and controlling aquatic animal diseases, limitations of their application and future research directions. The exploration of bacteriocin application in the prevention and control of aquatic animal diseases is of great significance in reducing the incidence and spread of aquatic animal infections and multidrug-resistant bacteria.

2 | CLASSIFICATION OF BACTERIOCINS

Bacteriocins can be produced by both Gram-positive and Gram-negative bacteria, and a large number of bacteriocins have been reported to date. Compared to bacteriocins produced by Gram-positive bacteria, those produced by Gram-negative bacteria have a narrower spectrum of antimicrobial activity.[18] However, bacteriocins produced by both types of bacteria are important components of antimicrobial peptides.[14,26,27] Due to the diversity and partial overlap of different bacteriocins in terms of their chemical structure, molecular weight, thermal stability, synthesis mechanism, modification process, biological activity and genetic characteristics, there are currently various classification methods.[14,28–30] Bacteriocins are usually classified into four main categories.

2.1 | Class I bacteriocins

Class I bacteriocins include bacteriocins with molecular weights typically less than 5 kDa and post-translationally modified small peptides. These bacteriocins have a unique amino acid composition, such as lanthionine, dehydrated amino acids, 3-methyl-lanthionine, dehydroalanine, dehydrobutyrine and 2-amino isobutyric acid.[31,32] The presence of these unique amino acids results in the formation of multiple ring structures and structural stability against different temperature, pH and proteolytic enzymes.[33] These unique amino acids are a result of post-translational modifications that include dehydration and cyclisation of specific amino acid residues. This class of bacteriocins can affect the cell membrane of sensitive bacteria by forming pores, leading to depolarisation of the target cell membrane. Representative examples include nisin, epidermin, gallidermin and lacticin 3147.[34,35] In addition, certain bacteriocins can also exert their effects by targeting lipid II and interfering with peptidoglycan biosynthesis pathways, such as mersacidin.[36] Most Class I bacteriocins are produced by Gram-positive bacteria, but there are also a few produced by Gram-negative bacteria, such as microcins B17, C7, J25 and D93.[14] The target bacteria for Class I bacteriocins are usually Gram-positive bacteria, with nisin being the most studied and applied bacteriocin.[37]

2.2 | Class II bacteriocins

Class II bacteriocins are a group of heat-stable small molecule peptides with a molecular weight typically less than 10 kDa. They possess amphipathic helical structures that allow them to insert into the membrane of target bacteria, inducing destabilisation and permeabilisation of the bacterial membrane or causing the formation of membrane pores, leading to depolarisation and cell death.[35,38,39] Most Class II bacteriocins have very few unique amino acids in their structures, and post-translational modifications are limited to the formation of a conserved N-terminal disulphide bridge in only a few members, such as pediocin PA-1 and pediocin AcH.[40,41] This class of bacteriocins can be divided into four subclasses. The IIa subclass bacteriocins are monomeric peptides with a conserved

N-terminal amino acid sequence of tir-gly-asn-gly-val-xaa-cys and a disulphide bridge formed by two cysteine residues, with pediocin PA-1 being a typical representative that exhibits strong antibacterial activity against L. monocytogenes, also known as anti-listeriocin.[42,43] The IIb subclass bacteriocins are α and β peptide oligomers. Both peptide chains are essential for antibacterial activity, and their synergistic effect enhances antibacterial activity. Typical representatives include lactococcin G, lactation F, lactococcin Q and plantaricin NC8.[35,44] The IIc subclass bacteriocins typically have a leader sequence and may contain one or two cysteine residues in their structures. Bacteriocins with one cysteine residue are called cystibiotics, while those with two cysteine residues are called thiolbiotics. Typical representatives include lactococcin A, divergicin A and acidocin B.[29,39] Finally, Class II bacteriocins that do not belong to the above three subclasses can be classified as IId. Class II bacteriocins are mainly produced by Gram-positive bacteria, although some are also produced by Gram-negative bacteria, such as microcins E492 and H47. Microcins can interact with various different cellular targets, thus having multiple modes of action, including membrane disruption (e.g., microcin E492) or inhibition of critical enzymatic functions.[14] Among them, microcin J25 inhibits RNA polymerase, microcin B17 inhibits DNA gyrase and microcin C inhibits aspartyl-tRNA synthetase.[27]

2.3 | Class III bacteriocins

Class III bacteriocins are high molecular weight peptides and thermally unstable proteins, typically with a molecular weight greater than 30 kDa.[45–47] Class III bacteriocins can be divided into three subclasses. Subclass IIIa bacteriocins are bacteriolysins, which are large lytic peptides that target the peptidoglycan layer. The catalytic domain in their structure has three different biological activities, allowing them to hydrolyze peptidoglycan components. Typical examples include lysostaphin, zoocin A, millericin B and enterolysin A. Subclass IIIb bacteriocins are non-lytic bacteriocins, which are large non-lytic peptides that kill target cells by blocking glucose uptake and incorporation into macromolecules, leading to carbohydrate starvation. Typical examples include helveticin J and casecin 80. Subclass IIIc bacteriocins are tailocins, which are high molecular weight peptides produced by Gram-negative bacteria that have a structure highly similar to the tail structures of bacteriophages and are cylindrical in shape, hence their name as phage tail-like bacteriocins. Among them, bacteriocins diffocin and monocin can target lipopolysaccharides.[48–50] The most extensively studied bacteriocins in this group are the R- and F-pyocins produced by Pseudomonas aeruginosa, which can cause disruption of the bacterial membrane potential, leading to the formation of pores in the membrane and subsequent penetration of the bacterial cell membrane, ultimately resulting in cell death.[51]

2.4 | Class IV bacteriocins

Class IV bacteriocins are complex macromolecular complexes that contain both protein and carbohydrate or lipid components.[37] Their unique structural features make them sensitive to a variety of enzymes including glycolytic or lipolytic enzymes. Their antibacterial mechanism involves the disruption of bacterial cell membranes, with plantaricin S and leuconocin S being typical representatives.[52]

In addition to the above four classes, there are also bacteriocins that have nucleolytic activity and can exert antibacterial activity by degrading bacterial nucleic acids. For example, colicins produced by the Gram-negative bacterium E. coli, which are bacteriocins with a molecular weight greater than 10 kDa, have been used as a model for studying bacteriocin structure and functional evolution in recent decades. Colicins E2 to E9 have functions similar to DNA, RNA or tRNA enzymes and can degrade bacterial nucleic acids.[53–55] There are also other bacteriocins produced by Gram-negative bacteria that are structurally, sized and functionally similar to those produced by E. coli, such as klebicins produced by Klebsiella sp. and S-pyocins produced by P. aeruginosa.[51] It is worth noting that the same bacterium or strain can produce multiple bacteriocins with significant differences in antibacterial activity, such as microcins and colicins, which can both be produced by E. coli.[53]

3 | SOURCES OF NATURAL BACTERIOCIN ISOLATES AND PREPARATION METHODS OF BACTERIOCIN

3.1 | Sources of natural isolates of bacteriocins

Natural isolates refer to microorganisms that spontaneously inhabit certain ecological niches and have specific interactions with other organisms present in that environment. Bacteriocin-producing natural bacterial isolates can be obtained from various sources, including water, air, soil, faeces, animal and plant materials, silage, food and marine sediments.[48,56]

Bacteria from the microbial community in marine sediment exhibit high diversity, and about 10% of marine bacteria that form biofilms have antibacterial activity, making them an important source for developing bacteriocins that can be used in aquaculture.[57] The first identified bacteriocin from a marine source was harveycin, which was isolated from Vibrio harveyi after screening 795 strains of Vibrio species near Galveston Island, Texas, USA.[48,58] Chopra et al. isolated a strain of Bacillus sonorensis MT93 from marine soil capable of producing the bacteriocin Sonorensin.[59] Current research on marine-derived bacteriocins mostly focuses on the biochemical characterisation of new bacteriocins and bacteriocin-like compounds.[60] Bacteriocins with a wide range of molecular weights have been identified from marine bacteria, including small peptides of 5–10 kDa, such as microcins produced by Gram-negative bacteria, microgalocins of halobacteria and Class I and Class II bacteriocins produced by Gram-positive bacteria.[27,48] There are also larger compounds of 10–90 kDa, such as colicins produced by E. coli and colicin-like bacteriocins produced by Gram-negative bacteria.[61,62] Bacteriocin-producing marine bacteria belong to various genera, including Aeromonas, Burkholderia, Photobacterium, Bacillus, Pseudomonas, Serratia, Stenotrophomonas, Carnobacterium, Lactococcus, Streptomyces, Pseudoalteromonas,

Enterococcus, Pediococcus and some archaea.[63,64] It is worth noting that marine-derived bacteriocins exhibit high tolerance to extreme temperatures, osmotic stress, various proteolytic enzymes and organic solvents, presenting enormous potential for application and research.[48]

Bacteriocins from soil sources have been extensively studied, with most bacteriocins extracted from rhizosphere and soil bacteria synthesised by the Bacillus genus. They can be used as bioinsecticides, biopreservatives and growth promoters, and play an important role in plant protection.[65] For example, the putrid-smelling compound produced by the Pseudomonas putida strain BW11M1 isolated from the banana rhizosphere microbiome can target and inhibit the plant pathogen P. putida strain GR12-2R3.[66] Bacteriocin Bac 14B produced by Bacillus subtilis 14B has a preventive effect on the disease caused by the pathogen Agrobacter tumefaciens.[67] Bac GM17 produced by Bacillus clausii GM17 has broad-spectrum antibacterial and antifungal activities.[68] The bacterial strain Bacillus sp. TL12, isolated from soil by Liu et al., produces the antibiofilm-active bacteriocin bacin A2.[69] Additionally, bacteriocins from soil sources are also produced by non-Bacillus species, such as Stenocins produced by Stenotrophomonas, ST110LD produced by Leuconostoc citreum ST110LD and BAC-IB17 produced by S. aureus.[70–72]

Different types of fermentation or fresh foods prepared by traditional methods are rich sources of new bacterial strains capable of producing bacteriocins.[48,56] Karunakaramoorthy et al. isolated a Lactobacillus plantarum strain from local foods that produces the bacteriocin UL4, which exhibits inhibitory activity against Aeromonas hydrophila.[73] Baños et al. isolated Enterococcus faecalis UGRA10 from Spanish sheep's cheese, which produces the bacteriocin Enterocina AS-48 that inhibits Lactococcus garvieae.[74] Dubey et al. isolated L. garvieae KS1546 from cow milk, which produces the bacteriocin Garvicin KS that inhibits both L. garvieae and Streptococcus agalactiae.[75] Woraprayote et al. isolated Weissella hellenica BCC 7293 from Thai traditional fermented pork, which produces the bacteriocin 7293 that exhibits inhibitory activity against E. coli and P. aeruginosa.[76] Bashir and Ali isolated Lactobacillus acidophilus, Lactobacillus casei, L. plantarum, Lactobacillus reuteri and Lactobacillus sp. delbrukei from Pakistani dairy and fermented products, which produce bacteriocins that inhibit antibiotic-resistant S. aureus.[77]

Animal and plant materials are also important sources of bacteriocins. Most bacteria in the human and animal gut microbiota have the ability to produce bacteriocins, which can act on multiple pathogenic bacteria and help maintain microbial community balance.[78] For example, B. subtilis LR1 isolated from the intestine of Labeo rohita can produce bacteriocins that antagonize A. hydrophila, Aeromonas salmonicida, Bacillus mycoides and Pseudomonas fluorescens.[79] L. lactis isolated from the intestine of blacktip shark Carcharhinus limbatus can produce bacteriocins that antagonize Vibrio alginolyticus, Vibrio parahaemolyticus, E. coli, P. aeruginosa and Bacillus cereus.[80] L. plantarum FGC-12 and Enterococcus faecium MC13 isolated from the intestine of golden carp and Mugil cephalus can produce bacteriocins that inhibit V. parahaemolyticus.[81,82] Streptococcus phocae isolated from the intestine of Indian white shrimp can produce bacteriocins that inhibit Vibrio sp., called Phocaecin P180.[83] In addition, some plant pathogens can also produce antibacterial substances. For example, the plant pathogen strain Erwinia carotovora NA4 isolated from affected vegetables and fruits can produce euriniocin NA4, which can inhibit the growth of the pathogen Clavibacter michiganensis subsp. Sepedonicus that causes potato ring rot.[84]

3.2 | Preparation method of bacteriocin

Regardless of the source of the bacteriocin-producing strain, the preparation of bacteriocins usually involves steps such as screening for the bacteriocin-producing strain, expressing, purifying and identifying the bacteriocin (Figure 1).[85] Before isolating the bacteriocin, the antibacterial activity of the isolate needs to be tested. The most commonly used traditional methods for testing antibacterial activity include spot analysis on a lawn, disc diffusion and diffusion analyses. Specifically, the indicator strain is inoculated into an appropriate agar medium at the exponential growth phase or distributed in a cup with a dense culture medium. Indicator strains commonly used include E. coli, S. aureus, L. monocytogenes and Micrococcus luteus. The spot analysis on a lawn method requires at least 10 μL of test sample and is most suitable for substances with strong antibacterial activity, such as purified extracts. The agar diffusion analysis and the disc diffusion method require approximately 100 μL of sample to fill the well or soak the disc, and are thus suitable for low-activity supernatant samples that can be easily obtained by centrifugation. These methods evaluate antibacterial activity by measuring the lysis zone around the test spot. Although these methods are intuitive, they are time-consuming and require a large amount of screening work.[48]

Currently, there are several more effective and accurate methods available for screening bacteria that produce bacteriocins. For example, the presence of bacteriocin-encoding genes can be quickly identified using polymerase chain reaction analysis. This method allows for simultaneous detection of genes encoding multiple bacteriocins, such as nisin Q, lactococcin Q, lacticin Q and lactocyclicin Q.[86] In addition to the polymerase chain reaction method, there is also an in vivo screening method that involves using 96-well plates and fluorescent markers to identify bacteriocins from natural sources. Currently, this method is used to search for compounds that are active against S. aureus. Furthermore, the next-generation sequencing metagenomic analysis method can be used to screen bacteriocin-producing strains, and this method has already discovered eight new bacteriocins from Lactobacillus crustorum MN047.[87] Compared to traditional methods, these new screening methods are faster, more reliable and more cost-effective.

Bacteriocins can not only be expressed in the above-mentioned naturally isolated strains, but also through modern genetic engineering techniques, construct recombinant expression vectors to express in homologous or heterologous hosts, thereby obtaining recombinant bacteriocins. These recombinant expression vectors can be used for commercial production of bacteriocins by overexpressing the genes encoding them, which typically relies on the improvement or development of new expression vectors and

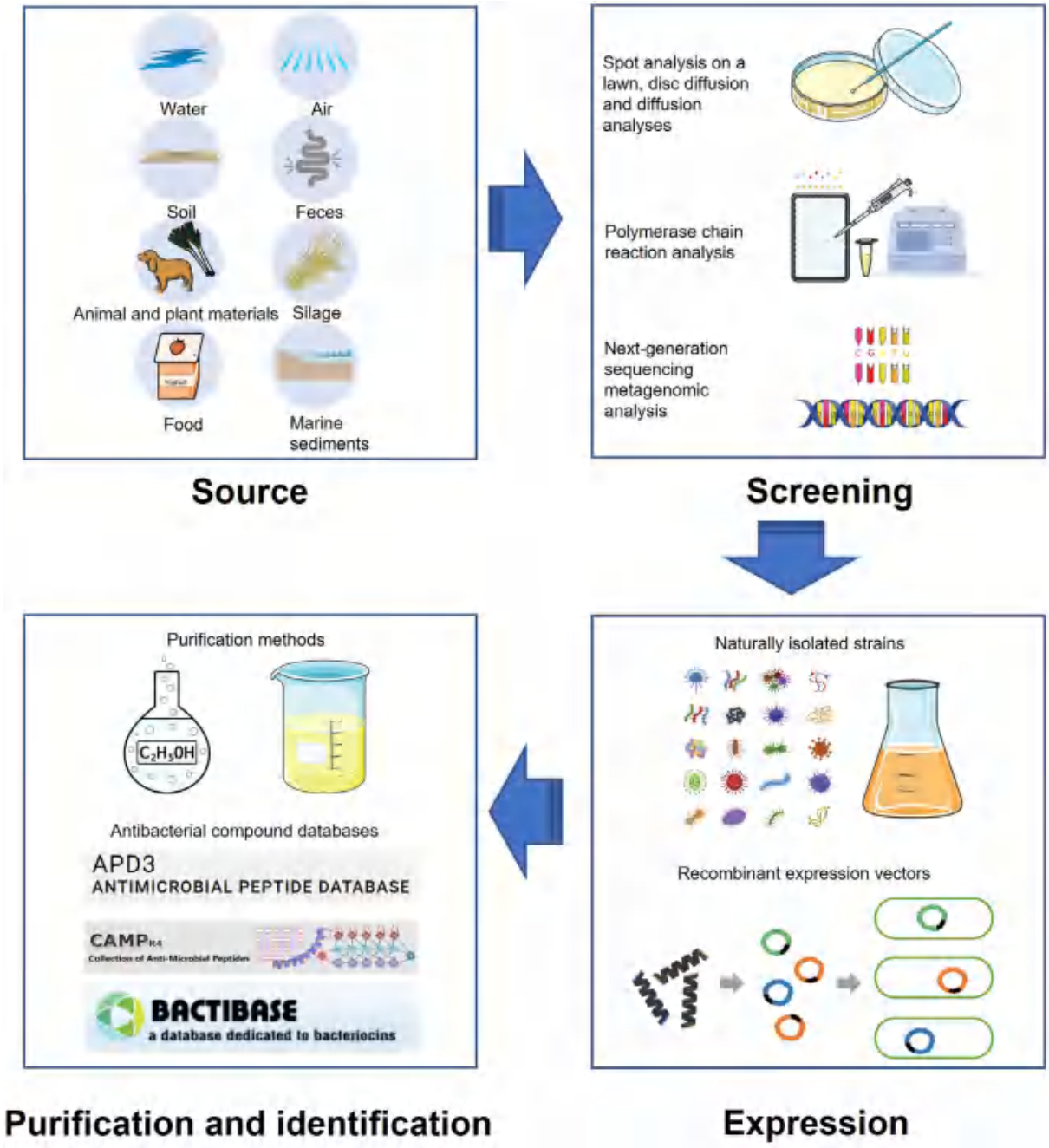

FIGURE 1 Preparation process of bacteriocins from different sources.

hosts.[88] The choice of bacteriocin purification method depends on characteristics such as molecular weight, charge and properties, and there is no universal method. Simple purification methods include ethanol extraction and cross-linked dextran chromatography, as in the case of enterocin L11. More complex purification methods include ammonium sulphate precipitation, cation exchange chromatography (IEC), gel filtration chromatography and reversed-phase high-performance liquid chromatography (RP-HPLC), among which ammonium sulphate precipitation, IEC and RP-HPLC are currently the most commonly used methods for obtaining most bacteriocins.[89]

Identification and annotation of bacteriocins or bacteriocin-like proteins can be facilitated with the help of several bioinformatics tools. There are several antibacterial compound databases available for reference, such as the antimicrobial peptides database (APD), the collection of antimicrobial peptides (CAMP), the BACTIBASE, the database of antimicrobial activity and structure of peptides (DBAASP) and the database of antimicrobial peptides.[90] The APD contains information on 2619 antibacterial compounds and 261 bacteriocins, including producer organism, peptide sequence, chemical modifications, structure and additional functions of the peptide, target organism, mode of action, discovery year and author. Additionally, the

APD Peptide Property Calculator allows researchers to calculate the molecular weight, molecular formula and molar extinction coefficient of bacteriocins. The CAMP is a database that provides information on the sequences and structures of antimicrobial peptides and links to other databases such as AMPer and CyBase, which focus on natural bacteriocins. BACTIBASE is the most commonly used database, providing various bacteriocin analysis tools, including homology search, multiple sequence alignment, Hidden Markov Model analysis, molecular modelling and taxonomic search.[91]

The above natural or recombinant expression methods all rely on fermentation of microorganisms, which is greatly influenced by fermentation efficiency. In addition to fermentation methods, a method using solid-phase peptide synthesis has been developed.[92] With the reduction in the price of peptide synthesis reagents and "building blocks" and the technological advances in post-translational modification catalysing the production of natural proteins, chemical synthesis methods have become attractive and competitive alternatives in biomedical applications. Bacteriocins that have already been successfully synthesised using this method include bacteriocin AS-48, uberolisin, garvicin ML and pediocin PA-1. The Word2vec bioinformatics programme can analyse peptide segments up to 20 amino acids in length based on their charge, conformation and hydrophobicity. By scanning 676 different bacteriocins for potential sequences, 16 artificially synthesised peptides with high antibacterial activity against E. coli and P. aeruginosa have been created. The disadvantage of this method is its low productivity, which requires further process optimisation to improve production capacity.[89]

4 | ANTIBACTERIAL ACTIVITY OF BACTERIOCINS AGAINST MULTIDRUG-RESISTANT BACTERIA

Currently, bacteriocins that display antibacterial activity against multidrug-resistant bacteria mostly come from lactic acid bacteria (LAB). Ibraheim et al. isolated LAB from cheese capable of producing bacteriocins. The crude bacteriocin extract exhibited inhibitory activity against biofilms produced by MRSA.[93] Yi et al. isolated a bacteriocin-producing strain of L. crustorum MN047 from fermented mare's milk and successfully identified the gene for a novel bacteriocin, BMP047, from its genome. Qiao et al. expressed BMP047 using an E. coli expression system and purified the recombinant bacteriocin, BMP32. Studies of its antibacterial properties showed that the recombinant bacteriocin BMP32 can promote wound healing by killing multidrug-resistant S. aureus without producing any adverse effects in experimental mice.[94] Bonhi et al. demonstrated that the cell-free supernatant (CFS) of L. acidophilus was effective in killing methicillin-resistant S. aureus, primarily through the action of its bacteriocin.[95] Hasan et al. identified a bacteriocin-like substance from a product of L. casei, which was able to inhibit various antibiotic-resistant pathogens, including S. aureus, Klebsiella pneumoniae and Proteus vulgaris. The production of this bacteriocin-like substance was highly influenced by the culture conditions of L. casei, including the nutrient medium, pH, temperature and incubation time. The highest inhibitory activity was observed in the CFS of L. casei grown in Man, Rogosa, and Sharpe broth at pH 4.0 and 37°C for 72 h.[96] Perales-Adán et al. demonstrated that the bacteriocins AS-48 and nisin from LAB were able to kill antibiotic-resistant S. aureus present in goat-milk cheese, and their combination showed superior antibacterial efficacy.[97] Allen-McFarlane et al. isolated Lactobacillus parafarraginis from yoghourt, which was able to inhibit 14 pathogenic bacteria, including multiple antibiotic-resistant strains. Their research suggested that a bacteriocin-like substance with a peptide band of approximately 75 kDa produced by this strain was closely related to the acidocin gene, one of the four bacteriocin structural genes identified from L. parafarraginis. Acidocin was considered the most likely candidate to produce this peptide, as it was reported to produce cyclic peptides and form oligomers, which could explain its resistance to proteases and the production of large peptide bands.[98] Prakash et al. investigated the bactericidal effects of bacteriocins produced by fermenting Lactobacillus fermentum and L. casei on antibiotic-resistant E. coli and Salmonella typhi. Their results showed that the bacteriocin LF60 produced by L. fermentum was able to inhibit both of the above two antibiotic-resistant pathogens.[99] Lü et al. isolated a bacteriocin-producing strain Lactobacillus coryniformis MXJ 32 from a traditional fermented vegetable (Jiangshui Cai) of Xixiang county, Shaanxi Province, China. The bacteriocin lactocin MXJ 32A produced by this strain effectively inhibits the growth of antibiotic-resistant pathogenic strains such as Salmonella, S. aureus and Sakazakii.[100] Abramov et al. isolated a strain Limosilactobacillus fermentum 3872 that produces a Class III bacteriocin from the milk of a healthy lactating and breast-feeding woman. The cell-free culture supernatant of this strain induces cell damage and ATP leakage in methicillin-resistant S. aureus.[101] Bucheli et al. isolated bacteriocins from different strains of LAB, which showed high specificity and good inhibitory effects against vancomycin-resistant enterococci.[102]

In addition to bacteriocins from LAB, a small number of bacteriocins from non-LAB have been found to exhibit antimicrobial activity against antibiotic-resistant bacteria. Ansari et al. investigated the bacteriocin BAC-IB17 produced by B. subtilis KIBGE-IB17 and found that it had inhibitory effects against various methicillin-resistant S. aureus strains. BAC-IB17 has an approximate molecular weight of 10.7 kDa, and is primarily composed of nonpolar and basic amino acids with a small amount of acidic amino acids. The N-terminal sequence of the first 17 amino acid residues obtained from BAC-IB17 is NKPEALVDYTGVXNS. BAC-IB17 exhibits high thermal and pH stability, as well as stability against various heavy metals, organic solvents, surfactants and proteolytic enzymes, indicating that it can maintain its activity in a range of extreme environments.[72] Chopra et al. showed that the bacteriocin Sonorensin effectively kills both Gram-positive and Gram-negative bacteria, as well as non-proliferating cells, and has significant inhibitory activity against the biofilms of S. aureus. Sonorensin can also effectively inhibit non-proliferating antibiotic-resistant bacteria and has the potential to be a substitute for preservatives/antibiotics in the food and medical industries.[59] The study conducted by Gutiérrez-Chávez et al. demonstrates that antibiotic-resistant bacteria, which

TABLE 1 Bacteriocins and their sources that can inhibit antibiotic-resistant bacteria.

Bacteriocin	Antibiotic-resistant bacteria	Producer organism	Source	References
Raw bacteriocin	Staphylococcus aureus	LAB	Cheeses	Ibraheim et al.[93]
Bacin A2	S. aureus	Bacillus sp. TL12	Soil samples	Liu et al.[69]
Stenocins	Stenotrophomonas maltophilia	Stenotrophomonas	Soil environment	Paškevičius et al.[70]
XJS01	S. aureus	Lactobacillus salivarius	Intestinal mucosa of Yunnan black-bone chicken (Gallus gallus)	Xiang et al.[106]
Bacteriocin-like inhibitory substances (BLIS)	Enterococcus	Enterococcus faecium E86	Meat pie	Farias et al.[107]
Enterocin OS13	Enterococcus faecalis, E. faecium	E. faecalis OS13	Food	El-Gendy et al.[108]
ST110LD	S. aureus	Leuconostoc citreum ST110LD	Soil samples from a Korean organic farm	Woo et al.[71]
Bacteriocins produced by Lactobacillus	S. aureus	Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus reuteri and Lactobacillus sp. delbrukei	Pakistani dairy and fermented products (raw milk, cheese, butter milk, pickle and yoghourt)	Bashir and Ali[77]
ST651ea, ST7119ea, ST7319ea	E. faecium VRE19	E. faecium ST651ea, E. faecium ST7119ea and E. faecium ST7319ea	Korean traditional fermented soybean paste	Fugaban et al.[109]
AS-48	S. aureus	E. faecalis UGRA10	Spanish sheep's cheese	Perales-Adán et al.[97]; Velázquez-Suárez et al.[110]
Cell-free neutralised supernatants	S. aureus	L. acidophillus	Dairy food waste	Bonhi and Imran[95]
CFS	Bacillus cereus, Klebsiella pneumonia, Salmonella typhimurium, S. aureus and Escherichia coli	Lactobacillus fermentum strain NBRC15885, L. fermentum strain CIP102980, L. plantarum strain JCM1149 and Lactobacillus natensis strain LP33	Fermented food samples (fufu, gari, kunu, nono, and ogi)	Imade et al.[111]
BMP32	S. aureus	Lactobacillus crustorum MN047	Koumiss	Qiao et al.[94]
Plantaricin GZ1-27	S. aureus	L. plantarum GZ1-27	Kipper	Du et al.[112]
Crude BLIS	S. aureus, Klebsiella pneumoniae and Proteus vulgaris	L. casei	Urinary catheters	Hasan et al.[96]
BAC-IB17	B. subtilis KIBGE-IB17	S. aureus	Soil	Ansari et al.[72]
LF60	E. coli	L. fermentum		Prakash et al.[99]
Pentocin JL-1	S. aureus	Lactobacillus pentosus	Intestinal tract of Chiloscyllium punctatum	Jiang et al.[113]
Enterocin DD28, DD93	S. aureus	E. faecalis strain 28, 93	Meconium	Al Atya et al.[114]
BM1029	S. aureus, C. sakazakii, Salmonella	L. crustorum MN047	Koumiss	Yi et al.[115]
Sonorensin	S. aureus, E. coli	Bacillus sonorensis MT93	Marine soil	Chopra et al.[59]
Plantaricin LpU4	S. aureus	L. plantarum LpU4	Raw sheep milk cheeses	Milioni et al.[116]
Plantaricin ZJ217	S. aureus	L. plantarum ZJ217	Raw milk	Zhu et al.[117]
Plantaricin ZJ008	S. aureus	L. plantarum ZJ008	Fresh milk	Zhu et al.[118]
Enterocin RM6	S. aureus	E. faecalis OSY-RM6	Raw milk	Huang et al.[119]
Bacteriocin KU24	S. aureus	Lactococcus lactis KU24	Homemade kimchi	Lee et al.[120]

(Continues)

TABLE 1 (Continued)

Bacteriocin	Antibiotic-resistant bacteria	Producer organism	Source	References
Paracaseicin A	S. aureus, E. coli, Citrobacter freundii, Citrobacter diversus, Klebsiella oxytoca, Enterobacter cloacae and Pseudomonas aeruginosa	Lacticaseibacillus paracasei subsp. paracasei BMK2005	Healthy baby faeces	Bendjeddou et al.[121]
Acidocin LCHV	S. aureus	L. acidophilus n.v. Er 317/402	Newborn baby faeces	Mkrtchyan et al.[122]
Nisin	S. aureus, Enterococcus	LAB	Fresh goat-milk cheeses	Perales-Adán et al.[97]; Piper et al.[123]
Nisin Z	S. aureus, Enterococcus	L. lactis subsp. lactis	Kimchi	Park et al.[124]
Lacticin 3147	S. aureus, Enterococci	L. lactis subsp. lactis DPC317	Kefir grain	Piper et al.[123]; Galvin et al.[125]
Bacteriocin KT11	Staphylococcus epidermidis, Staphylococcus warneri, Serratia marcescens and Enterococcus sp.	E. faecalis KT11	Traditional Kargı Tulum cheese	Abanoz and Kunduhoglu[126]
Lactocin MXJ 32A	Salmonella, S. aureus and Sakazakii	Lactobacillus coryniformis MXJ 32	Traditional fermented vegetable	Lü et al.[100]
Bacteriocin E 50–52	C. freundii, E. coli, K. pneumoniae, Acinetobacter baumannii, Proteus spp., S. aureus and P. aeruginosa	E. faecium 50–52	Russian broiler chicken cecum	Svetoch et al.[104]
Bacteriocin B 602	C. freundii, E. coli, K. pneumoniae, A. baumannii, Proteus spp., S. aureus and P. aeruginosa	Paenibacillus polymyxa B 602	Russian broiler chicken cecum	Svetoch et al.[104]
BLF3872	S. aureus	Limosilactobacillus fermentum 3872	Milk of a healthy lactating and breastfeeding woman	Abramov et al.[101]
CFS from strain K35	P. aeruginosa	Pediococcus inopinatus K35	Kimchi	Yi and Kim[127]
Semi-Purified bacteriocins	E. faecium	LAB	Dairy products	Bucheli et al.[102]
Bacteriocin-like substance	Vibrio alginolyticus, Vibrio parahaemolyticus and S. aureus	Paenibacillus ehimensis NPUST1	Water samples from local tilapia culture pools	Chen et al.[105]

Abbreviations: CFS, cell-free supernatant; LAB, lactic acid bacteria.

are commonly linked to subclinical mastitis in dairy goats from Guanajuato, Mexico, exhibit susceptibility to bacteriocins produced by Bacillus thuringiensis.[103] Svetoch et al. isolated a strain Paenibacillus polymyxa B 602 from the ceca of commercial broiler chickens in Russia, which produces the bacteriocin bacillocin B-602. It exhibits inhibitory effects against various multidrug-resistant strains including Citrobacter freundii, E. coli, K. pneumoniae, Acinetobacter baumannii, Proteus spp., S. aureus and P. aeruginosa.[104] Chen et al. isolated Paenibacillus ehimensis NPUST1 from tilapia farming ponds, and the bacteriocin-like substance produced by this strain exhibited broad-spectrum antibacterial activity against various aquatic pathogens, food spoilage bacteria, clinical pathogens and plant pathogens, including multidrug-resistant strains of V. alginolyticus, V. parahaemolyticus and S. aureus.[105]

It is important to highlight that in contemporary research pertaining to the inhibition of multidrug resistant bacteria by bacteriocins, the primary focus is on S. aureus and E. coli (Table 1). Further exploration is needed to investigate the inhibitory impact of bacteriocins on resistant pathogenic bacteria in various aquatic organisms, along with the underlying mechanisms involved.

5 | POTENTIAL APPLICATION OF BACTERIOCINS IN THE PREVENTION AND CONTROL OF AQUATIC ANIMAL DISEASES

Aquaculture satisfies nearly half of the global demand for fish and shellfish consumption. The green and healthy development of aquaculture is an important guarantee for food security, and is closely related to human health.[128] Intensive aquaculture practices such as overcrowding, water quality deterioration and temperature changes can induce stress responses in farmed animals, leading to disease outbreaks.[129] Common microbial diseases in aquaculture animals include furunculosis, vibriosis, columnaris disease, streptococcosis,

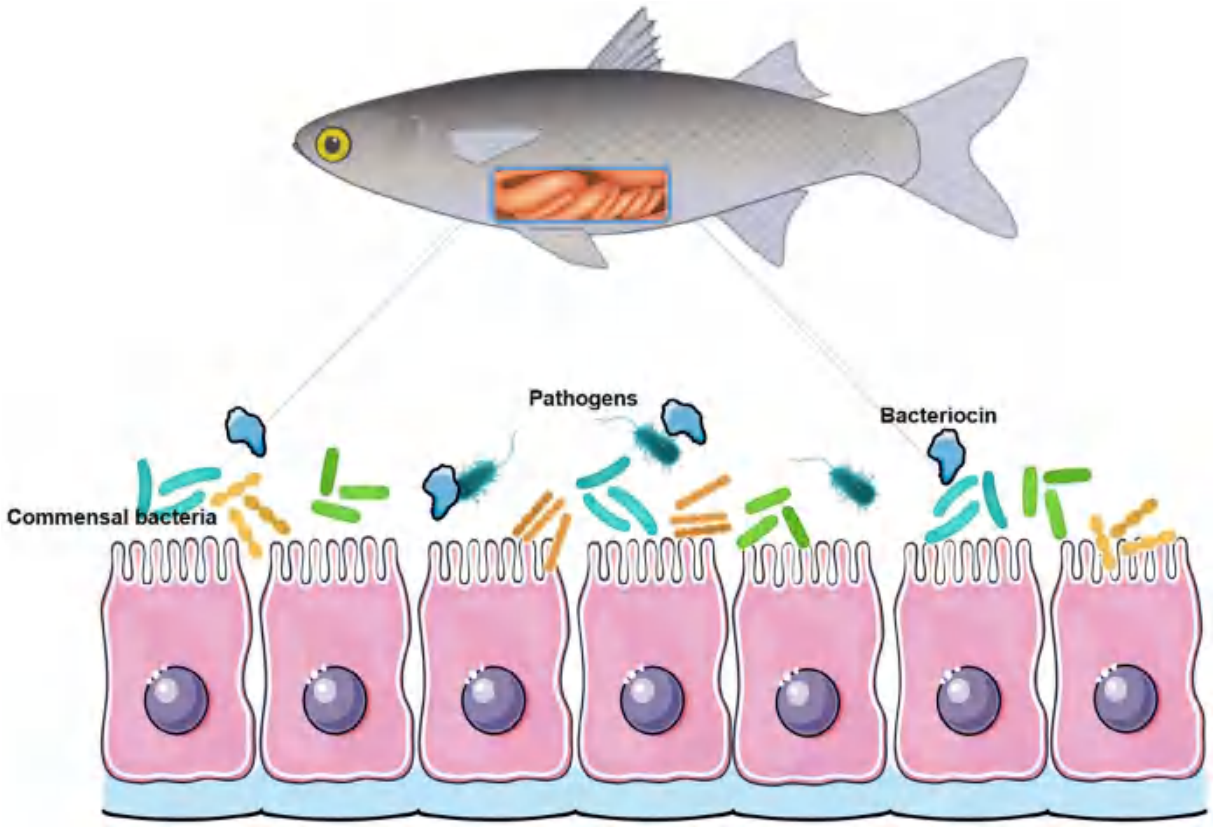

FIGURE 2 Potential regulation of aquatic animal gut microbiota by bacteriocins.

pasteurellosis, fish tuberculosis and enteric septicemia, mainly caused by pathogenic bacteria such as Aeromonas, Vibrio, Cytophaga, Streptococcus, Pasteurella, Mycobacterium and Edwardsiella genera.[129,130] Antibiotics are currently the most commonly used method for preventing and treating aquatic animal diseases. However, overuse of antibiotics can disrupt the microbial ecological balance in the aquatic environment, affect the development of the gut microbiota in aquatic animals, and facilitate the spread of antibiotic-resistant genes and bacteria in aquatic environments. The transfer of antibiotic resistance genes and bacteria from aquatic to terrestrial environments increases the risk of public health safety issues, and has adverse effects on human and animal health.[131,132]

Bacteriocins are bioactive antimicrobial peptides produced in bacterial ribosomes and released extracellularly, which have the ability to inhibit both Gram-positive and Gram-negative bacteria, and can be used as an alternative to antibiotics to combat pathogenic bacteria and antibiotic-resistant strains (Figure 2).[133–135] The use of bacteriocins in aquaculture is an important strategy for disease control and health improvement.[133,136] Dubey et al. investigated the protective effect of bacteriocin Garvicin KS against L. garvieae infection in zebrafish (Danio rerio) using the immersion method. The results showed that Garvicin KS has a broad spectrum of inhibition against both Gram-positive and Gram-negative bacteria, and can improve the survival rate of zebrafish.[75] Baños et al. studied the protective effect of Enterocina AS-48 produced by E. faecalis UGRA10 against L. garvieae infection in Oncorhynchus tshawytscha through intraperitoneal injection and immersion. Results showed that Enterocina AS-48 could improve the survival rate of O. tshawytscha after infection.[74] Karunakaramoorthy investigated the protective effect of bacteriocin UL4 produced by L. plantarum against A. hydrophila infection in Oreochromis niloticus through feed feeding. Results showed that bacteriocin UL4 could enhance the survival rate of O. niloticus after infection.[73] Ravindran et al. isolated five Bacillus species from the hydrothermal vent region. Among them, studies in zebrafish showed that the cell-free extracts of B. subtilis and Bacillus amyloliquefaciens, which produce bacteriocins, respectively exhibit in vivo and in vitro inhibitory effects against Vibrio cholerae and S. aureus, reducing the high rate of malformation and mortality caused by these pathogens.[137] Tseng et al. purified the heterologously expressed bacteriocin peocin and evaluated its in vivo antibacterial activity through injection administration. The results showed that treatment with peocin significantly increased the survival rate of zebrafish after infection with A. hydrophila.[138] In addition to their potential as antimicrobial agents, bacteriocins can also act as immunomodulators in aquaculture. Villamil et al. studied the effect of nisin on the non-specific immune response in turbot (Scophthalmus maximus L.) in vitro and in vivo. The results showed that nisin not only exhibited good in vitro antibacterial effects against the fish pathogen Carnobacterium piscicola (CECT 4020), but also increased the phagocytic activity of macrophages. In vivo studies demonstrated that intraperitoneal administration of nisin significantly

TABLE 2 Bacteriocins and their sources that can inhibit pathogenic bacteria in aquaculture.

Aquatic animal pathogens	Bacteriocin	Producer organism	Source	Predicted bacterial diseases or associated symptom prevention	References
Aeromonas hydrophila	Bacteriocin produced by Bacillus subtilis LR1	B. subtilis LR1	Intestine of Labeo rohita	Motile Aeromonas septicemia, haemorrhagic septicemia, ulcer disease, or red-sore disease	Banerjee et al.[79]
	Bacteriocin 99% homologous to that produced by Bacillus sp.	Uncultured Bacillus sp.	Tiger shrimp		Feliatra et al.[140]
	Bacteriocin 7293	Weissella hellenica BCC 7293	Thai traditional fermented pork		Woraprayote et al.[76,141]
	Bacteriocin UL4	Lactobacillus plantarum	Local foods		Karunakaramoorthy[73]
	BLIS	Lactobacillus casei AP8	Sturgeon fish		Ghanbari et al.[142]
	BLIS	L. plantarum H5	Sturgeon fish		Ghanbari et al.[142]
	BLIS	LAB	Intestine of Cherax quadricarinatus		Lim et al.[143]
	Peocin	Paenibacillus ehimensis NPUST1	Tilapia culture pond		Tseng et al.[138]
Aeromonas salmonicida	Bacteriocin produced by B. subtilis LR1	B. subtilis LR1	Intestine of L. rohita	Furunculosis	Banerjee et al.[79]
Aeromonas veronii	Bacteriocin-like substances	Enterococcus faecium MU8	Marine fish intestines	Skin ulceration or necrosis, organ haemorrhage and severe ascites	Promrug et al.[144]
Aeromonas jandaei	Bacteriocin-like substances	E. faecium MU8	Marine fish intestines	Anorexia, hepatic congestion and intestinal inflammation	Promrug et al.[144]
Vibrio alginolyticus	Bacteriocin 99% homologous to that produced by Bacillus sp.	Uncultured Bacillus sp.	Tiger shrimp	Decreased motor power, body surface ulcer, digestive tract congestion, etc.	Feliatra et al.[140]
	CFS	Lactococcus lactis	Intestine of Black tip shark Carcharhinus limbatus		Tengku Abdul Hamid et al.[80]
	Bacteriocin produced by fstm2	Pseudomonas putida strain fstm2	Shark skin		Ahmad et al.[145]
Vibrio parahaemolyticus	Bacteriocin produced by L. plantarum FGC-12	L. plantarum FGC-12	Golden carp intestine	Hepatopancreas enlargement, decreased appetite, etc.	Lv et al.[81]
	Enterocin MC13	E. faecium MC13	Mugil cephalus intestine		Satish Kumar et al.[82]
	CFS	L. lactis	Intestine of black tip shark C. limbatus		Tengku Abdul Hamid et al.[80]
	Bacteriocin produced by fstm2	P. putida strain fstm2	Shark skin		Ahmad et al.[145]

TABLE 2 (Continued)

Aquatic animal pathogens	Bacteriocin	Producer organism	Source	Predicted bacterial diseases or associated symptom prevention	References
	Bacteriocin CAMT2	Bacillus amyloliquefaciens	Marine fish Epinephelus areolatus		An et al.[146]
Vibrio vulnificus	Enterocin MC13	E. faecium MC13	M. cephalus intestine	Slow movement, loss of appetite, ulceration of the body surface	Satish Kumar et al.[82]
	Bacteriocin produced by fstm2	P. putida strain fstm2	Shark skin		Ahmad et al.[145]
Vibrio anguillarum	BLIS	L. casei AP8	Sturgeon fish	Vibrio septicaemia	Ghanbari et al.[142]
	BLIS	L. plantarum H5	Sturgeon fish		Ghanbari et al.[142]
	Bacteriocin produced by fstm2	P. putida strain fstm2	Shark skin		Ahmad et al.[145]
Vibrio cholerae	Cell-free extracts	B. subtilis subsp. spizizenii	Hydrothermal vent regions	Reduced food intake, decreased vitality and increased mortality	Ravindran et al.[137]
Vibrio sp.	BLIS	Vibrio anguilarrum AVP10	Catfish	Vibrio septicaemia	Zai et al.[147]
	Phocaecin P180	Streptococcus phocae	Indian white shrimp gut		Satish Kumar and Arul[83]
	Nisin Z	Bacteriocinogenic L. lactis subsp. lactis 3MT	Tilapia intestines		Kaktcham et al.[148]
	P-153	Pseudoalteromonas species strain x153	A pebble collected at St. Anne du Portzic (France)		Longeon et al.[149]
Streptococcus iniae	Bacl49	L. lactis L49	Oxyeleotris lineolatus	Septicemia, central nervous system damage and meningoencephalitis	Wright et al.[150]
	Bacteriocin SW1-1	Bacillus sp. SW1-1	Intestine of shrimp		Kim et al.[151]
Bacillus mycoides	Bacteriocin produced by B. subtilis LR1	B. subtilis LR1	Intestine of L. rohita	Eyeball ulcer	Banerjee et al.[79]
Pseudomonas fluorescens	Bacteriocin produced by B. subtilis LR1	B. subtilis LR1	Intestine of L. rohita	Body surface ulcer, mouth and nose congestion, liver, spleen and kidney enlargement	Banerjee et al.[79]
Lactococcus garvieae	Enterocina AS-48	Enterococcus faecalis UGRA10	Spanish sheep's cheese	Systemic hyperacute infection with the occurrence of widespread haemorrhaging	Baños et al.[74]
	Nisin Z	L. lactis TW34	Intestine of Odontesthes platensis(Berg)		Sequeiros et al.[152]
	Garvicin KS	L. garvieae KS1546	Cow milk		Dubey et al.[75]
	BLIS	Enterococcus thailandicus B3-22	Intestine of M. cephalus L.		Lin et al.[153]
Escherichia coli	Coagulina L1208	Bacillus coagulans L1208 (Bcoa)	Derived from B. coagulans LL1103	Body surface ulcer, bleeding	Fu et al.[154]
	Bacteriocin 7293	W. hellenica BCC 7293	Thai traditional fermented pork		Woraprayote et al.[76]

(Continues)

TABLE 2 (Continued)

Aquatic animal pathogens	Bacteriocin	Producer organism	Source	Predicted bacterial diseases or associated symptom prevention	References
	CFS	L. lactis	Intestine of black tip shark C. limbatus		Tengku Abdul Hamid et al.[80]
	BLIS	L. casei AP8	Sturgeon fish		Ghanbari et al.[142]
	BLIS	L. plantarum H5	Sturgeon fish		Ghanbari et al.[142]
	Bacteriocin CAMT2	B. amyloliquefaciens	Marine fish Epinephelus areolatus		An et al.[146]
Shewanella putrefaciens	Coagulina L1208	B. coagulans L1208 (Bcoa)	Derived from B. coagulans LL1103	Septicemia	Fu et al.[154]
	Mundticin KS	Enterococcus mundtii	O. platensis		Schelegueda et al.[155]
P. aeruginosa	Mundticin KS	E. mundtii	O. platensis	Loss of appetite, surface bleeding, back rot, abdominal bleeding	Schelegueda et al.[155]
	Bacteriocin 7293	W. hellenica BCC 7293	Thai traditional fermented pork		Woraprayote et al.[76]
	Nisin Z	Bacteriocinogenic L. lactis subsp. lactis 3MT	Tilapia intestines		Kaktcham et al.[148]
	CFS	L. lactis	Intestine of black tip shark C. limbatus		Tengku Abdul Hamid et al.[80]
	Bacteriocin produced by fstm2	P. putida strain fstm2	Shark skin		Ahmad et al.[145]
Streptococcus agalactiae	Garvicin KS	L. garvieae KS1546	Cow milk	Septicemia and meningitis	Dubey et al.[75]
Edwardsiella tarda	Bacteriocin SW1-1	Bacillus sp. SW1-1	Intestine of shrimp	Septicemia	Kim et al.[151]
Streptococcus parauberis	Bacteriocin SW1-1	Bacillus sp. SW1-1	Intestine of shrimp	Clinical symptoms resembling septic characteristics	Kim et al.[151]
B. cereus	BLIS	L. casei AP8	Sturgeon fish	Epidermal hyperemia and inflammation, scabies and skin rot	Ghanbari et al.[142]
	BLIS	L. plantarum H5	Sturgeon fish		Ghanbari et al.[142]
	CFS	L. lactis	Intestine of black tip shark C. limbatus		Tengku Abdul Hamid et al.[80]
Staphylococcus aureus	Cell-free extracts	Bacillus thuringiensis	Hydrothermal vent regions	Growth deformities	Ravindran et al.[137]

Abbreviations: BLIS, bacteriocin-like inhibitory substances; CFS, cell-free supernatant; LAB, lactic acid bacteria.

increased the serum lysozyme content in turbot, acting as an immune regulator.[139]

Additionally, numerous other bacteriocins have been shown to have the ability to inhibit aquatic animal pathogens, highlighting their potential for the prevention and control of aquaculture diseases, although some bacteriocins still require confirmation from in vivo research results (Table 2). Lin et al. found that bacteriocin-like inhibitory substances (BLIS) secreted by Enterococcus thailandicus could effectively control the pathogenic L. garvieae in aquaculture.[153] Sequeiros et al. isolated the bacteriocin-producing strain L. lactis TW34 from marine fish and found that it produced a type I bacteriocin, streptococcin Z, with a molecular weight of about 4.5 kDa. Streptococcin Z could inhibit the growth of the fish pathogen L. garvieae at a minimum inhibitory concentration of 5 AU/mL and had a minimum bactericidal concentration of 10 AU/mL.[152] Satish Kumar et al. isolated the bacteriocin-producing strain E. faecium MC13 from the intestine of M. cephalus and found that it produced a bacteriocin enterocin MC13 with a molecular weight of 2.148 kDa. Enterocin

MC13 was heat-resistant and sensitive to protein-hydrolyzing enzymes, but not sensitive to catalase and lipase. It exhibited inhibitory activity against aquatic animal pathogens such as V. parahaemolyticus and Vibrio vulnificus.[82] The study by Feliatra et al. demonstrated that the bacteriocin produced by Bacillus sp. isolated from tiger shrimp can effectively inhibit the growth of the opportunistic pathogen A. hydrophila.[140] Banerjee et al. isolated a bacteriocin-producing strain of B. subtilis LR1 from the gastrointestinal tract of L. rohita. The bacteriocin produced by the bacteria has a molecular weight of about 12 kDa, is not sensitive to surfactants, and shows inhibitory activity against four fish pathogens, including B. mycoides, A. salmonicida, P. fluorescens and A. hydrophila, with the highest activity observed at a temperature of 40°C and pH 7.0.[79] The study by Fu et al. demonstrated that the bacteriocin Coagulin L1208 produced by Bacillus coagulans L1208 effectively inhibited the growth of the aquatic animal pathogen E. coli.[154] Kaktcham et al. isolated bacteriocinogenic L. lactis subsp. lactis 3MT from the intestinal tract of tilapia, which produced the bacteriocin nisin Z with high tolerance to heat, pH and detergents. Nisin Z was able to antagonize multiple fish pathogens, including S. aureus, P. aeruginosa and Vibrio species.[148] Similarly, Kim et al. isolated a Bacillus strain SW1-1 from the intestinal tract of shrimp, which produced the bacteriocin SW1-1 that inhibited the growth of fish pathogens such as Streptococcus iniae, Edwardsiella tarda and Streptococcus parauberis.[151] Tengku et al. isolated four strains of L. lactis from the intestinal tract of blacktip shark C. limbatus that exhibited inhibitory activity against aquatic animal pathogens, including B. cereus, E. coli, P. aeruginosa, V. parahaemolyticus and V. alginolyticus. The crude CFS of these strains contained a bacteriocin-like substance with characteristics similar to nisin.[80] Lim et al. isolated LAB that secreted BLIS from the intestinal tract of Cherax quadricarinatus, which effectively antagonized the pathogen A. hydrophila.[143] Garces et al. isolated a strain of Carnobacterium sp. from the intestinal tract of Patagonian trout that produced a bacteriocin with antibacterial activity against Streptococcus chillis, which was heat stable.[156] Ghanbari et al. isolated L. casei AP8 and L. plantarum H5 from the gut microbiota of sturgeon, which produced BLIS that antagonized A. hydrophila, Vibrio anguillarum, E. coli and B. cereus.[142] Longeon et al. isolated a marine bacterium X153 from a pebble, which produced a novel antibacterial peptide (P-153) belonging to anionic proteins with a molecular weight of approximately 87 kDa, and effectively antagonized pathogenic Vibrio species.[149] Ahmad et al. isolated a P. putida strain FStm2 from shark skin that produced a bacteriocin with antibacterial activity against various pathogens, including V. parahaemolyticus, V. alginolyticus, V. vulnificus, Vibrio harvey and P. aeruginosa. The stability of the bacteriocin was maintained within a range of 30–70°C and pH 3–9, but the activity was greatly affected by the culture conditions of the strain.[145]

In addition to possessing antimicrobial properties, bacteriocins may also play a role in immune regulation. Bacteriocins can act as signalling peptides, regulating the host immune system by signalling through quorum sensing or signalling cells of the host immune system.[157] Research by Pablo et al. suggests that LAB peptides can modulate the immune system of mice by increasing CD4 and CD8 T lymphocytes and fundamentally increasing macrophage/monocyte populations isolated from peripheral blood.[158] The effects of nisin on immune cells are thought to be mediated through their regulatory activity on antigen-presenting cells. Additionally, nisin have been shown to act as immunomodulators in pigs.[159] However, further research is needed to investigate the immune modulation properties of bacteriocins, particularly in aquatic animals.

6 | LIMITATIONS AND FUTURE PROSPECTS

Bacteriocins have been widely studied as a potential alternative to antibiotics in aquaculture, but there are still some limitations that restrict their application in this field (Figure 3). Firstly, the high cost of commercial production of bacteriocins and the low yield of industrial purification methods limit the industrial application of bacteriocins, with the culture media and nutrient supplements for bacteriocin-producing microorganisms accounting for approximately 30% of the production cost.[160] The high cost of producing nisin presents a challenge to its widespread use.[161,162] Secondly, the efficacy of bacteriocins is easily affected by factors such as temperature, pH, processing conditions and environmental microbiota, as compared to antibiotic drugs.[25,163,164] Thirdly, orally ingested bacteriocins are rapidly degraded by proteolytic enzymes in the gastrointestinal tract, such as gastric protease, pancreatic protease and pancreatic trypsin, and their half-life is expected to be lower than that of antibiotics.[165–168] Additionally, administering bacteriocins through feed is an ineffective approach for treating diseased aquatic animals that refuse to eat.[169] Fourthly, there is currently a lack of approved bacteriocin products for use in aquaculture. Nisin, as a bacteriocin that is legally approved for use by regulatory agencies, plays an important role in food safety as a natural substitute for chemical preservatives.[170] Fifthly, most existing bacteriocins have a narrow spectrum of antimicrobial activity and are not suitable for treating multiple microbial infections in aquaculture.[171] Sixthly, crude extracts of bacteriocin-producing bacteria can disrupt the gut microbiota of aquatic animals and interfere with the levels of host bioactive compounds and cytokines.[172] Additionally, some bacteriocin-producing bacteria themselves are conditionally pathogenic to aquatic animals and cannot be used directly, such as A. hydrophila, which produces the toxic factor aerolysin.[173] Seventhly, while some bacteriocins have been shown to have beneficial effects similar to probiotics, some bacteriocins can reduce the abundance of beneficial bacteria in the gut microbiota, such as nisin A and nisin Z, which have been shown to significantly reduce the abundance of Bifidobacterium and Lactobacillus in the human gut microbiota, a result that has been confirmed in mice.[174,175] The impact of bacteriocins on the gut microbiota of aquatic animals remains to be further studied. Eighthly, exposure to bacteriocins can induce bacterial cells to develop resistance.[176] In addition, co-resistance and cross-resistance between bacteriocins or between antibiotics and bacteriocins have been observed.[177] Studies have reported cross-resistance of bacteriocin-resistant variants to several antimicrobials such as nisin,

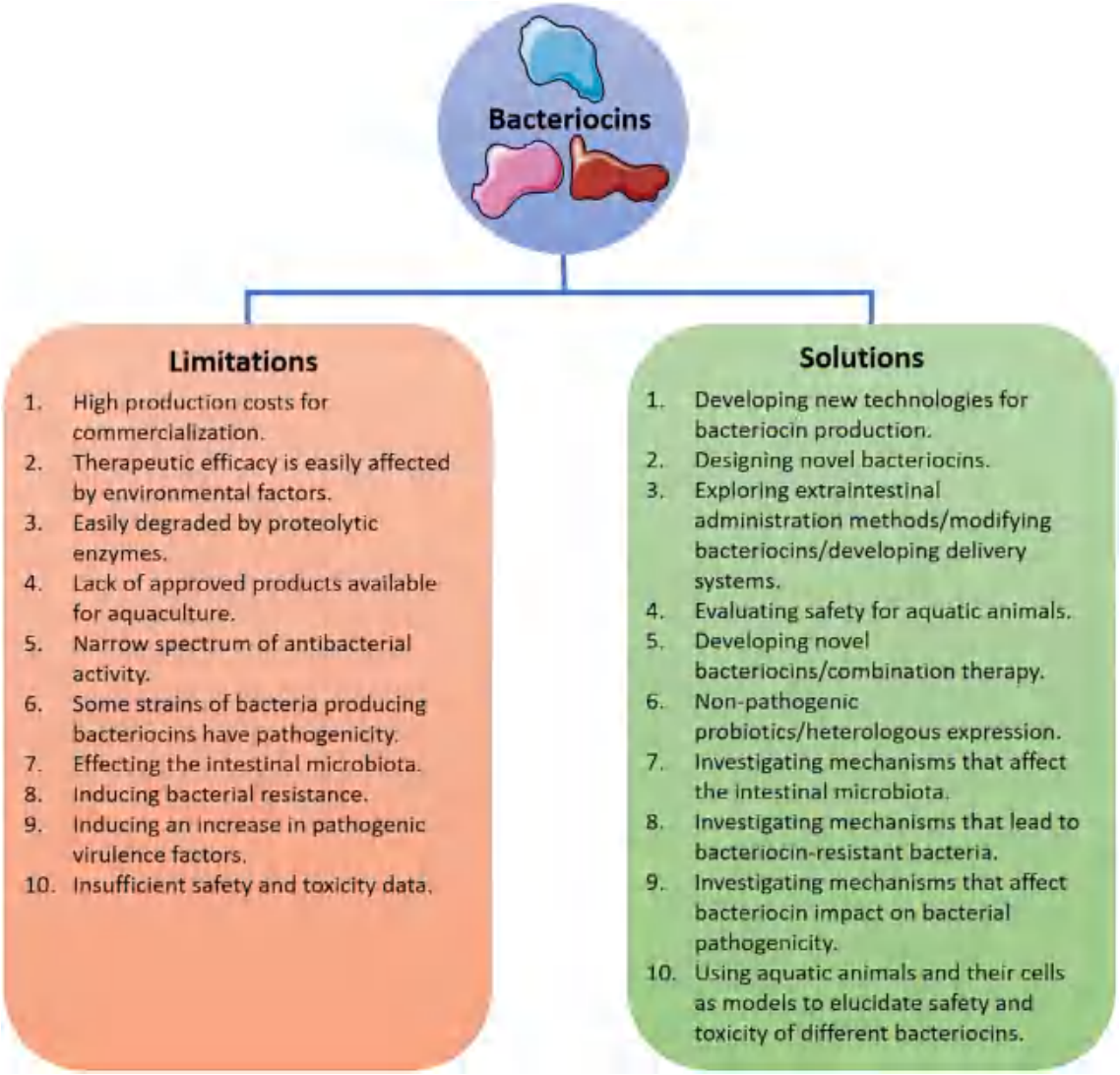

FIGURE 3 Limitations and possible solutions for the application of bacteriocins in aquaculture.

pediocin 34 and enterocin FH99.[178] Furthermore, bacteriocins can induce an increase in virulence factors of some Gram-positive bacteria, thereby enhancing their pathogenicity. For example, various bacteriocins produced by pathogenic streptococcal strains, including intermedilysin and streptolysin S, are associated with invasive Group A streptococcus infections.[179] Additionally, there is insufficient safety and toxicity data regarding the use of bacteriocins in aquaculture. Some bacteriocins have been shown to exhibit varying degrees of cytotoxicity when measured using cell-based assays.[170] The potential toxicity of bacteriocins to organisms depends on their bioavailability and absorption after oral administration. The potential systemic effects of bacteriocins can be studied by estimating the absorbed dose after administration. Oral administration of bacteriocin E50-52 in chickens has been shown to reduce Salmonella enteritidis in the liver and spleen, indicating that bacteriocins can be absorbed through the intestinal wall.[180,181] Moreover, Dreyer et al. demonstrated that nisin and plantaricin 423 can cross the intestinal-blood barrier and migrate across gastrointestinal epithelial and endothelial cells in vitro.[182] However, there is currently a lack of relevant data in aquaculture, and more research is needed to determine the safe dosages of each bacteriocin.

Despite the challenges mentioned above, bacteriocins still show promising prospects in preventing and controlling diseases in aquaculture (Figure 3). Firstly, the high cost of bacteriocin production can be reduced by using food-grade substrates (e.g., by-products of the food and dairy industry) as alternatives to culture media.[183] One way to control costs is to develop new methods for isolation that are cheaper and have shorter processing times to replace traditional chromatography-based techniques.[184] Additionally, screening for bacteriocin-producing microorganisms has been replaced by genome mining methods that rely on next-generation sequencing technology rather than culture-based screening methods, providing a way to reduce costs.[185] Yi et al. developed a rapid method using complete genome and peptidome to discover novel bacteriocins with or without low homology to known genes in the database.[87] In terms of bacteriocin expression, heterologous expression of newly discovered

bacteriocins in bacterial hosts (such as E. coli) obtained through database mining can be an attractive option for reducing production costs under conditions with fewer nutritional requirements and faster growth rates and wider genetic characteristics.[186] In addition, precise application of bacteriocins to susceptible populations, such as broodstocks or juvenile fish, can also achieve cost control in aquaculture. Secondly, to address the issue of the efficacy of bacteriocin use being easily affected, one can screen and characterise bacteriocins with more stable antibacterial activity, or obtain new bacteriocins by improving their physicochemical properties. Since the stability of bacteriocin activity is related to its various structures and post-translational modifications (cyclisation, disulphide bonding and unconventional amino acids), designing natural bacteriocin variants through genetic engineering is one way to address stability issues.[168] Studies have shown that engineered variants of nisins A and Z can exhibit different pharmacokinetic properties.[187] Thirdly, to address the issues of bacteriocin degradation in the digestive tract and refusal to eat feed in aquatic animals, one can explore extraintestinal administration methods, such as water application or injection, while testing bacteriocin immunogenicity.[188,189] Another approach is to modify bacteriocins using biotechnology to address proteolytic degradation issues, such as targeting protease recognition sites for mutation to enhance bacteriocin stability and activity.[190–192] Shea et al. obtained an anti-trypsin bacteriocin by changing the trypsin recognition site of salivaricin P.[193] Engineering modifications of nisin can overcome the proteolytic cleavage of the C-terminal region by nisin resistance protein while maintaining its activity.[190,192] Additionally, protecting and controlling bacteriocins can be achieved through the development of delivery systems, such as peptide engineering and encapsulation technology, which can maintain bacteriocin activity in the gastrointestinal tract.[194,195] Gough et al. demonstrated that incorporating nisin into two different starch substrates can protect them from degradation in the gastrointestinal tract.[196] Fourthly, regarding the issue of the lack of approved bacteriocin-related products applicable to aquaculture, bacteriocin safety for aquatic animals can be assessed based on compound identification, bioavailability, in vitro and in vivo testing, exposure research, ADME studies (absorption, distribution, metabolism and excretion studies), and establishing acceptable daily intake to determine a safe dose. Additionally, the intended use of the product must be determined before evaluation to determine if it should be classified as a feed component or a therapeutic drug.[170] Fifthly, to address the problem of narrow-spectrum antibacterial activity, bacteriocins with broad-spectrum antibacterial activity against fish pathogens can be developed through screening or bioengineering methods, or by exploring the combined effects of different bacteriocins and antibacterial agents to optimise combination strategies.[169] Sixthly, for the issue of application of bacteriocin-producing bacteria, non-pathogenic probiotics can be chosen for live applications.[135] For pathogenic bacteria producing bacteriocins, the bacteriocin gene can be heterologously expressed, purified and then applied. Seventhly, to address the unclear effect of bacteriocins on the gut microbiota of aquatic animals, future research can combine metagenomics and metabolomics methods to investigate the effects of different bacteriocins with different structures and mechanisms on the composition and balance of the gut microbiota of aquatic animals.[170] Eighthly, studying the exact mechanism of bacteriocin resistance will help solve the problem of bacteriocin resistance. Previous research has shown that bacteriocin-resistant mutants may be closely related to factors such as bacterial membrane fluidity, lipid composition, potential and charge, cell wall thickness and spontaneous mutations of related genes, which are the results of multiple factors.[170] Understanding the mechanism of bacteriocin resistance can help us develop engineered bacteriocins with unique target ranges and modes of action, such as preparing bacteriocins with enhanced potency and reduced bacteriocin resistance rates.[197] In addition, the use of combination therapy between different bacteriocins or between bacteriocins and other antibacterial agents can reduce the dosage and frequency of use of single bacteriocins, thereby reducing the emergence of bacteriocin-resistant bacteria. Ninthly, for the problem of bacteriocins increasing the virulence factors of pathogenic bacteria, the effects of bacteriocins on the virulence of target bacteria and their related mechanisms should be thoroughly explored before application. Tenthly, for the issue of insufficient safety and toxicity data for the use of bacteriocins in aquaculture, differences in the hydrophobicity of different types of cell surfaces may affect the interaction and binding of bacteriocins, thereby affecting their cytotoxicity. Therefore, relevant research needs to be conducted using aquatic animals and cells as models to clarify the safety and toxicity of different bacteriocins.[198] Additionally, the purity of bacteriocins may also affect their toxicity to different cells. Furthermore, the purity of bacteriocins may also affect their toxicity towards different cells. In summary, in order to perform comparative assessments of bacteriocin cytotoxicity towards different cells, it is necessary to specify the concentration and purity of the tested bacteriocin, the type and metabolic activity of eukaryotic cells, as well as the measured parameters.[199]

7 | CONCLUSION

With the frequent use of antibiotics in aquaculture, there is an urgent need to develop new antibacterial agents to combat the increasing drug-resistant bacteria and genes. New antibacterial agents should have different modes of action than antibiotics, to effectively combat existing resistant bacteria and resistance genes. Bacteriocins have shown great potential for application in aquaculture disease prevention and control, as they have a wide range of types and diverse modes of action, targeting the cell wall, cell membrane or genetic material of target cells. Naturally occurring bacterial strains capable of producing bacteriocins can be obtained from various sources, including water, air, soil, faeces, animal and plant materials, silage, food and marine sediments. Bacteriocins can be prepared using various methods, such as traditional fermentation and purification, genetic engineering to produce recombinant bacteriocins, or chemical synthesis. Bacteriocins can reduce the production and transmission of resistant bacteria through multiple pathways. On the one hand, bacteriocins have antibacterial activity against multidrug-resistant

bacteria. On the other hand, bacteriocins can be used alone or in combination with other antibacterial agents to reduce the use of antibiotics, thereby reducing the production of antibiotic-resistant bacteria and resistance genes. Bacteriocins can inhibit various aquatic animal pathogens, showing potential for aquaculture disease prevention and control. In addition, bacteriocins have immunomodulatory effects, although this needs further confirmation in aquatic animals. Currently, there are still some bottlenecks in the application of bacteriocins in aquaculture, including high production costs, susceptibility to environmental influences, oral administration susceptibility to protein hydrolysis or rejection by aquatic animals, lack of approved bacteriocin products for use in aquaculture, narrow antibacterial spectrum, adverse effects of crude extracts, interference with gut microbiota, development of resistance, increased pathogenicity of pathogens and insufficient safety and toxicity data. Future research can focus on breakthroughs in cultivation methods, biotechnology, administration methods, product development, combined applications, safety evaluation, gut microbiota multi-omics analysis, resistance mechanisms and toxicity mechanisms to overcome these bottlenecks. With the breakthroughs in these bottlenecks, bacteriocins will have a bright future in aquaculture disease prevention and control.

AUTHOR CONTRIBUTIONS

Xiaoli Chen: Conceptualization; investigation; writing – original draft; writing – review and editing; funding acquisition; methodology; software; formal analysis; visualization; data curation. Hong Liu: Writing – original draft; writing – review and editing; validation; software; methodology; formal analysis. Shuangping Liu: Writing – review and editing; supervision; resources; project administration; funding acquisition. Jian Mao: Supervision; funding acquisition; resources; project administration; writing – review and editing.

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DATA AVAILABILITY STATEMENT

Data will be made available on request.

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