Engineering 27 (2023) 222–233

Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

Research
Antimicrobial Resistance—Review

The Bioprospecting of Microbial-Derived Antimicrobial Peptides for Sustainable Agriculture

Shuhua Lin [a,b,#], Xuan Chen [a,b,#], Huimin Chen [b], Xixi Cai [b], Xu Chen [b], Shaoyun Wang [b,*]

[a] College of Chemical Engineering, Fuzhou University, Fuzhou 350108, China
[b] College of Biological Science and Engineering, Fuzhou University, Fuzhou 350108, China

ARTICLE INFO

Article history:
Received 19 May 2022
Revised 4 July 2022
Accepted 1 September 2022
Available online 30 September 2022

Keywords:
Antibiotic alternatives
Microbial-derived AMPs
Sustainable agricultural systems

ABSTRACT

Strategies aimed at defining, discovering, and developing alternatives to traditional antibiotics will underlie the development of sustainable agricultural systems. Among such strategies, antimicrobial peptides (AMPs) with broad-spectrum antimicrobial activity and multifaceted mechanisms of action are recognized as ideal alternatives in the post-antibiotic era. In particular, AMPs derived from microbes with active metabolisms that can adapt to a variety of extreme environments have long been sought after. Consequently, this review summarizes information on naturally occurring AMPs, including their biological activity, antimicrobial mechanisms, and the preparation of microbial-derived AMPs; it also outlines their applications and the challenges presented by their use in the agroindustry. By dissecting the research results on microbial-derived AMPs of previous generations, this study contributes valuable knowledge on the exploration and realization of the applications of AMPs in sustainable agriculture.

1. Introduction

Pathogenic microbes, which are the leading cause of disease in animals and plants, need to be controlled with the continuous use of traditional antibiotics to meet the huge global food consumption. Nevertheless, there are already indications that the emergence of antibiotic-resistant (ABR) and multidrug-resistant (MDR) strains due to an overdependence on antibiotics is a serious threat to the sustainable development of the agroindustry. For example, plasmid-mediated polymyxin-resistant *Escherichia coli* isolated from pigs can bypass many existing classes of conventional antibiotics. Frustratingly, these pathogens carrying drug-resistance genes can be transmitted to humans through the food chain and thus pose a safety risk to human life and health [1–3]. Overall, the dramatic spread of resistant isolates and the resulting negative long-term repercussions on human health have propelled a search for novel antimicrobials as substitutes for the traditional antibiotics currently in use [4].

Antimicrobial peptides (AMPs) with broad-spectrum antimicrobial activity and a multifaceted mechanism of action are regarded as promising novel antimicrobial agents in the post-antibiotic era. In general, as a class of immunomodulatory molecules secreted in a variety of organisms, AMPs can be obtained from the parent proteins of natural plants, animals, and microbes by means of fermentation or enzymatic hydrolysis. Microbial-derived AMPs differ from other sources in that microbes are able to secrete a wide range of immunomodulatory molecules that allow them to survive in extreme environments like volcanic craters, mines, and deserts, causing the isolation of AMPs with novel structures and superior properties that can, to a certain extent, avoid the rediscovery of existing molecules and enrich the existing AMP resource base. Moreover, microbial-derived AMPs have obtained dazzling achievements in transformation application. For example, antimicrobials including colistin, vancomycin, daptomycin, and ε-polylysine have been approved application by the US Food and Drug Administration (FDA) [5,6]. Most of the approved microbial-derived AMPs are non-ribosomal peptides (NRPs), which are produced by large multi-enzyme complexes called non-ribosomal peptide synthetases (NRPSs); the scope of activity of these peptides extends from antibiotics to immunosuppressants [7,8]. Other than a few NRPS-like enzymes reported in other organisms (e.g., ebony from the fruit fly), NRPSs are essentially exclusively identified in microbes [9]. Interestingly, NRPs come from far-ranging sources, including not only soil-derived microorganisms but also marine,

* Corresponding author.
E-mail address: shywang@fzu.edu.cn (S. Wang).
# These authors contributed equally to this work.

https://doi.org/10.1016/j.eng.2022.08.011

animal, plant, and human commensal microbes. Moreover, most extremophiles and endophytes have yet to be explored, rendering them prospective sources of NRPs for human, animal, and plant diseases.

This review summarizes information on naturally occurring AMPs, their biological activity, their antimicrobial mechanisms, and the production of microbial-derived AMPs, and outlines their applications and challenges in the agroindustry. This review paves the way for researchers to replace the application of traditional antibiotics in the agroindustry by utilizing microbial-derived AMPs.

2. AMPs occurring naturally in microorganisms

Since the introduction of the first NRP, penicillin, microbes have served as the predominant source of novel AMPs against ever-growing MDR strains [10]. Three main types of microbes are used to create AMPs: bacteria, fungi, and microalgae (Fig. 1). Thanks to their enormous diversity of microbes, extreme environments are an essential origin of AMP discovery. This is exemplified by ilamycins E1/E2, which are extracted from pelagic *Streptomyces atratus*: They exert potent antimicrobial activity against tuberculosis, with a low minimum inhibitory concentration (MIC) value ($9.8\ nmol{\cdot}L^{-1}$) [11]. Moreover, pedopeptins A–C, which are isolated from the *Pedobacter lusitanus* NL19 found in sludge, are novel inhibitors of lipopolysaccharides (LPSs) [12]. Meanwhile, coevolution between pathogens and endophytes of organisms provides strategies to withstand MDR pathogens, so endophytes of organisms are also important sources of antimicrobial peptides with novel structures and potent bioactivity. Lugdunin, a thiazolidine-containing peptide generated by nasal *Staphylococcus lugdunensis*, has an excellent bactericidal effect against a wide spectrum of MDR Gram-positive (G^+) pathogens and is unaffected by serum [13]. Although it is difficult to isolate novel chemicals (e.g., the existing molecules increasingly being rediscovered from soil microorganisms such as actinobacteria), microbes from other habitats may be vital sources of AMPs with intriguing structures and promising performance.

2.1. Bacterial AMPs

Bacteria offer humankind a profusion of prominent metabolites [14]. Nevertheless, high-throughput sequencing has indicated that bacterial metabolic capacity has been vastly underestimated, due to bacterial genomes comprising far more biosynthetic gene

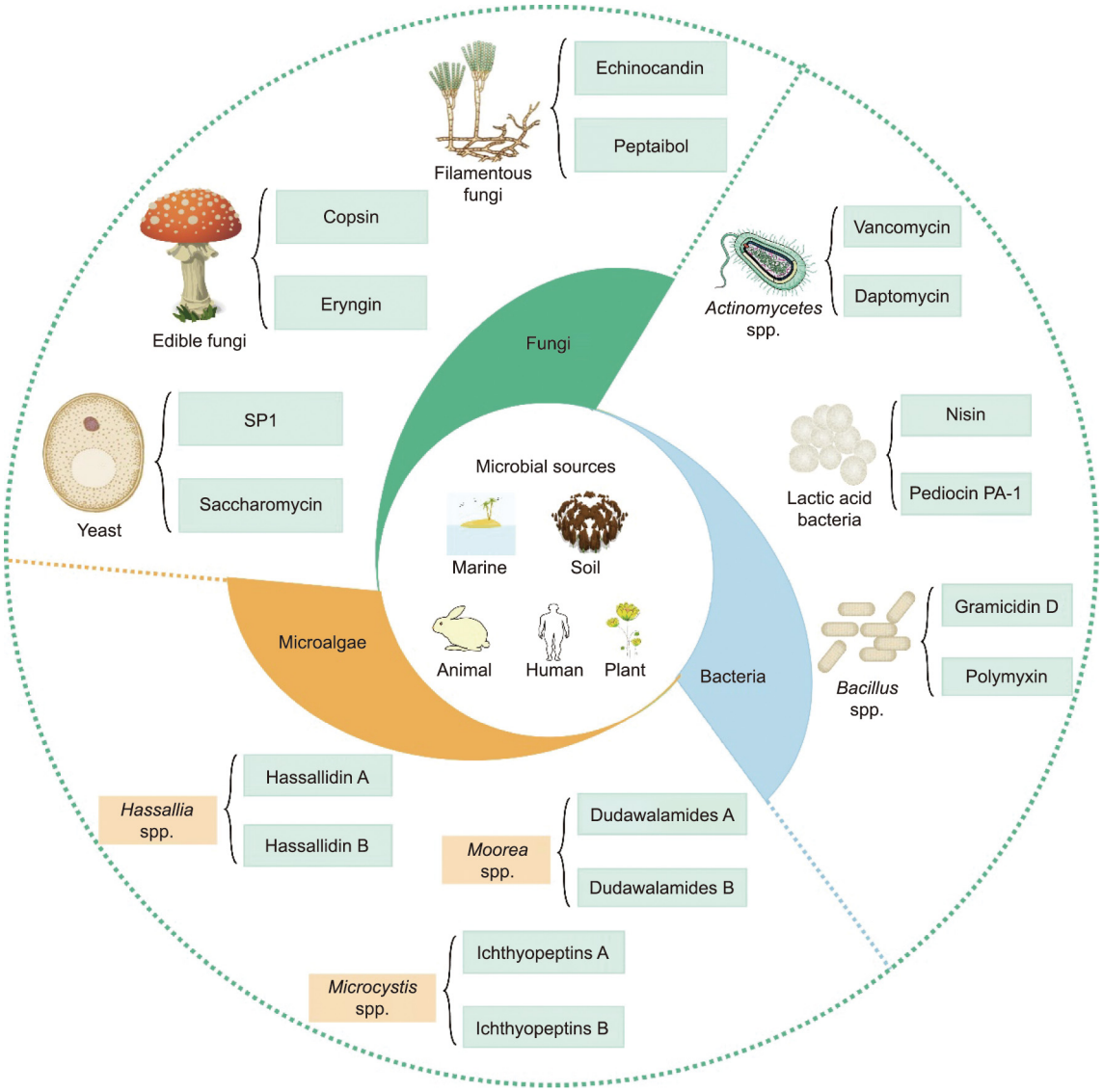

Fig. 1. AMPs occurring naturally in microbes. Producers are principally from soil, marine, animal, plant, and human microbes, including bacteria, fungi, and microalgae.

clusters (BGCs) than the currently isolated AMPs [15]. In artificial culture settings, this potentiality is either undeveloped or undetectable and is presumed to contain desirable compounds [16]. Accordingly, genomics-driven discovery strategies can be used to activate cryptic BGCs in order to obtain more novel AMPs [17]. Hexapeptides ulleungmycin A–B, which were isolated from *Streptomyces* sp. KCB13F003 by genomics-driven discovery methods, display antimicrobial action against MDR pathogens [18]. Similarly, cyclic octapeptides octaminomycins A–B, derived from the *Streptomyces* sp. RK85-270 metabolite fraction library, exhibit excellent anti-plasmodial activity and show no cytotoxicity in the range of 0−30 μmol·L^{-1} [19]. To develop specialized AMPs, researchers have recently concentrated on bacteria that interact with insects, fungi, and plants. For example, the lipopeptide viennamycins, which has a cysteine profile and is produced by the edelweiss rhizosphere bacterium *Streptomyces* sp. S4.7, shows an inhibitory effect against G^+ pathogens [20].

Apart from producing NRPs, bacteria can synthesize ribosomal peptides known as bacteriocins, which have the features of high efficiency, nontoxicity, thermal resistance, and no residue [21,22]. In general, bacteriocins are divided into two broad categories based on whether or not they have a post-translational modified motif. Class I (modified) bacteriocins can be sub-grouped into lanthipeptides, sactipeptides, circular peptides, and glycocins produced by G^+ bacteria; linear azole(ine)-containing peptides and lasso peptides produced by both G^+ and Gram-negative (G^-) strains; and nucleotide peptides and siderophore peptides secreted by G^- bacteria. The linaridins and thiopeptides isolated from *Actinobacteria* also belong to this class [23]. The bacteriocins isolated from lactic acid bacteria (LAB) are currently the most investigated due to their potential as preservatives in agricultural products; similarly, bacteriocins from the industrially crucial *Bacillus* species, which have a history of safe usage in pathogen control, are of interest [24]. Class II bacteriocins are largely unmodified AMPs of 6–10 kDa and include three categories: pediocin-like bacteriocins with the YGNGV peptide fragment, non-pediocin-like ones without this property fragment, and two-peptide bacteriocins.

2.2. Fungal AMPs

Lately, fungal AMPs have gained tremendous attention for their beneficial effects in promoting health and decreasing disease [25]. One outstanding instance involved the FDA-approved cyclic non-ribosomal hexapeptides echinocandins from *Glarea lozoyensis*, which were found to be resistant to invasive mycoses [26,27]. *Trichoderma* species is an essential biocontrol fungus that can synthesize linear peptide peptaibols with diverse activities, such as antimicrobial, anti-tumor, and anti-nematode activity [28]. Thus far, *Trichoderma* species are known to produce more than 440 peptaibols, including tricholongins, longibrachins, trichobrachins, and trichovirins [29].

In addition, fungal defensin-like peptides have emerged as a new class of anti-infection drugs with excellent antimicrobial properties, low cytotoxicity, and high stability [30]. A considerable number of defensin-like peptides exhibit strong antimicrobial potency, as exemplified by *Pseudoplectania nigrella*-derived plectasin, which acts with a potent bactericidal effect *in vitro* and *in vivo* against drug-resistant G^+ pathogens by suppressing peptidoglycan synthesis [31]. Copsin produced by *Coprinopsis cinerea* was found to exert a pronounced anti-*Listeria* effect, with MIC values of 0.25–0.5 μg·mL^{-1} [32]. *Eurotium amstelodam*-derived eurocin showed pronounced antibacterial activity against *Staphylococcus aureus* and *Streptococcus pneumonia*, with MIC values of 16 and 0.25 μg·mL^{-1}, respectively [33]. In addition, edible fungi and yeast are crucial sources of AMPs, due to their production of numerous molecules with therapeutic properties. SP1, an AMP derived from the budding yeast glyceraldehyde-3-phosphate dehydrogenase (GAPDH) protein, showed an antifungal effect against *Cryptococcus neoformans* and *Cryptococcus gattii* at micromolar levels [34]. Another typical yeast-derived peptide is saccharomycin, produced by *Saccharomyces cerevisiae*, which can suppress colonization of the putrefying microbes *Brettanomyces bruxellensis* in wines [35]. *Pleurotus eryngii*-derived eryngin exerts a potent anti-*Fusarium oxysporum* effect, with half maximal inhibitory concentration (IC_{50}) values of 1.35 mol·L^{-1} [36].

2.3. Microalgae AMPs

Microalgae are photosynthetic microorganisms with a variety of cellular tactics, physiological abilities, and adaptations that allow them to live widely in the natural world [37]. The term "microalgae" refers to the prokaryotic cyanobacteria and eukaryotic photosynthetic organisms primarily found within the taxa *Alveolata*, *Haptophyta*, *Chlorarachniophyta*, *Euglenophyta*, *Glaucocystophyta*, *Rhodophyta*, and *Chlorophyta* [38]. Microalgae from diverse ecosystems—especially marine cyanobacteria—have been used as a source of biological peptides with antimicrobial, anti-plasmodial, anti-allergic, and anti-fouling properties [39–41]. Accordingly, numerous AMPs have been isolated from different species of microalgae, such as glycolipopeptides (e.g., hassallidin A–B produced by *Hassallia* sp.), cyclodepsipeptides (e.g., dudawalamides A–D from *Moorea* sp.), lectins (e.g., cyanovirin-N produced by *Nostoc* sp.), and microginins (e.g., microginin FR3 from *Microcystis* sp.) [42–46].

Microalgae have been identified as a sustainable source of AMPs due to their rapid growth, genetic tractability, and culturability. Moreover, their extraordinary biological activities have attracted tremendous attention in a variety of fields, including pharmaceutical chemistry, animal science, and agronomy. For example, the family of β-hydroxy alkynyl acid-containing cyclic depsipeptides dudawalamides A–D, produced by *Moorea producens*, exert a wide spectrum of anti-parasitic effects with low mammalian cell toxicity [44]. Chlorinated lipopeptide barbamide isolated from the cyanobacterium *Lyngbya majuscule* shows potent molluscicidal activity (LC_{100} = 10 μg·mL^{-1}) against the invertebrate pests *Biomphalaria glabrata* [47].

3. Biological activity of microbial AMPs

Microbes can produce a variety of essential AMPs for survival that protect them from damage caused by harsh conditions, such as a lack of nutrients. These AMPs have a rich variety of biological activities and are deemed to be a resource bank as alternatives to traditional antibiotics in sustainable agricultural systems. The functions of AMPs commonly include anti-microbial activity and immunoregulation (Fig. 2). Here, we will conduct an in-depth analysis of such functions. It is notable that, in addition to these activities, microbial AMPs possess multiple other biological activities, such as antitumoral, antihypertensive, and antifouling activities [48]. For example, ieodoglucomides B showed cytotoxicity against lung and stomach cancer cell lines with 50% cell growth inhibition (GI_{50}) values of 25.18 and 17.78 g·mL^{-1}, respectively [49]. In terms of anti-oxidation, cordymin was reported to have a protective effect on focal cerebral ischemic/reperfusion injury in rats [50].

3.1. Antimicrobial activity

AMPs' function against pathogens has been the most intensely investigated thus far [51]. AMPs that show activity against pathogenic microorganisms include bacteriocin nisin (purified from *Lactococcus lactis*), pentacationic lipopeptides colistin (secreted by *Paenibacillus polymyxa*), cyclic oligopeptide thiostrepton (extracted

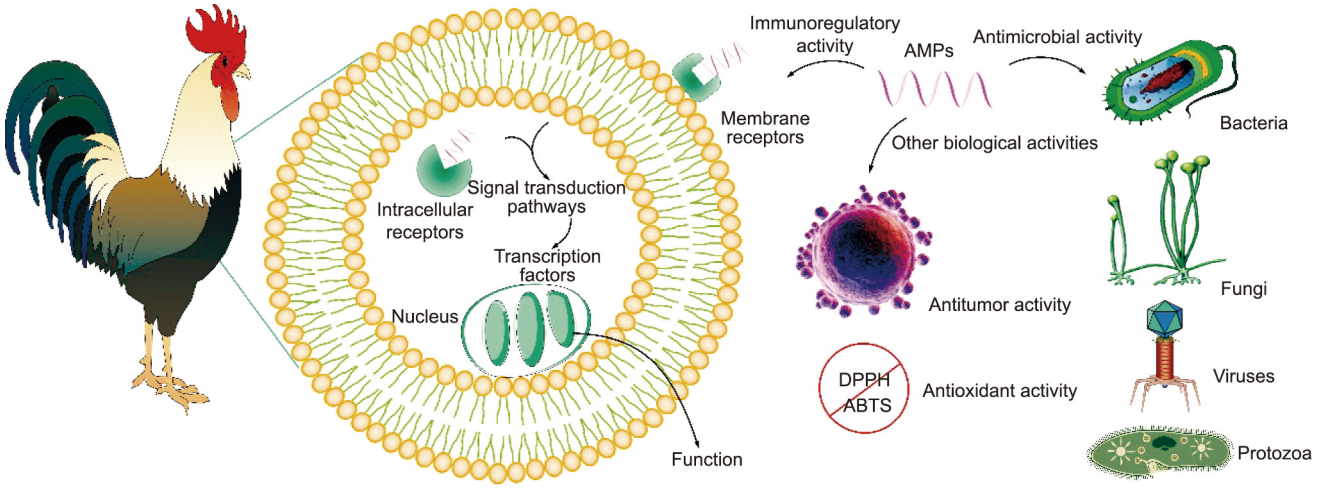

Fig. 2. Biological activity of microbial AMPs. DPPH: 1,1-diphenyl-2-picrylhydrazyl; ABTS: 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate).

from *Streptomyces azureus*), and cationic polymer ε-polylysine (produced by *Streptomyces albulus*), all of which are FDA-approved agents [52]. Among these approved AMPs, nisin has a wide spectrum of antibacterial action against a variety of spoilage organisms, including *Pediococcus* species, *Mycobacterium* species, and *Lactococcus* species, at very low concentrations (nmol•mL^{-1}) [53]. Colistin is the last-line agent against major MDR strains such as carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter* species [54]. ε-Polylysine is commonly used as an antimicrobial food additive due to its potent antimicrobial effect against a broad spectrum of G^+ and G^- bacteria, yeasts, molds, and bacteriophages [55,56]. Thiostrepton, a powerful agent belonging to the thiopeptide class, is used in veterinary medicine to treat bacterial or parasitic infections [57].

3.2. Immunomodulatory activity

Increasing evidence reveals that some AMPs exert their protective effect via an indirect mechanism rather than by simply eliminating microbes [58]. They can serve as powerful immune regulators to change host gene expression, thus acting suppress LPS-induced pro-inflammatory cytokine production, promote wound healing, and modulate the responses of the dendritic cells or T cells of the adaptive immune response [58]. In this way, AMPs can serve as a hub between innate immunity and acquired immunity. All of these functions aid in the resolution of infection and the reversal of potentially damaging inflammation, and complement the direct antimicrobial effect [59–61].

Surfactin, polymyxins, teicoplanins, and bacitracin are prominent immunomodulatory peptides [62]. For example, daptomycin exhibits immunomodulatory properties by causing inhibitory cytokine expression after methicillin-resistant *Staphylococcus aureus* (MRSA)-stimulated host immune response [63]. Surfactin inhibits the activation of nuclear factor-κB (NF-κB), which has been implicated in the NF-B cell signaling pathway, and hence reduces the pro-inflammatory cytokines generated by LPS in macrophages [64]. In *Yersinia pestis*-infected mice, the cell-penetrating peptides YopM suppressed the transcription of tumor necrosis factor (TNF) and interleukins (ILs)-12, -15, and -18 (pro-inflammatory cytokines) without affecting the anti-inflammatory cytokines [65]. Through the suppression of mitogen-activated protein kinase (MAPK) and NF-κB activation, Microcin J25 (MccJ25) improves the levels of anti-inflammatory cytokines IL-6 and IL-10 and modulates the amount of TNF-α, thereby relieving inflammation responses [66]. In bovine mammary epithelial cells, nisin stimulates the secretion of the antibacterial enzymes glucosaminidase and lysozyme, which are usually considered to be an indicator of dairy cow mammary inflammation and immune response activation [67]. In addition, some AMPs exhibit immune activities by binding protein molecules. For example, muramyl dipeptides (MDPs), which are found in microbial cell walls, are potent immunostimulators that work by binding to Y-box protein 1, a multifunctional transcription factor involved in innate immunity that modulates the expression of multiple cytokines, chemokines, and their receptors [68].

4. Antimicrobial mechanism of microbial AMPs

AMPs are first-line host defenses in a variety of living creatures against potentially hazardous contacts in their environment. The principal antimicrobial action is attributed to the membrane-lytic mechanism, which directly impairs the structural integrity of the microbial cytomembrane [69]. Many AMPs also self-aggregate or polymerize in the membrane, forming a transmembrane channel that allows cell contents to seep out, causing cell death [70]. Nevertheless, a growing stream of research suggests that microbial AMPs exert intracellular activities as the principal or supportive mechanisms to achieve effective elimination [71]. In this section, we discuss the primary mechanisms of microbial AMPs (Fig. 3).

4.1. Membrane dysfunction

4.1.1. Toroidal pore model

In the toroidal pore model of AMP action, the amphiphilicity of AMPs enables the hydrophilic and hydrophobic areas to respectively bind to the polar head and nonpolar tail of a pathogen's phospholipid molecules [72]. Microbial AMPs will embed into the phospholipid bilayer when the ratio of AMPs to phospholipid molecules reaches a certain threshold. The lipid membrane bends inward as a result of this displacement, causing membrane damage and allowing intracellular chemicals to leak out, which makes normal physiological metabolism impossible to maintain [73]. This mechanism has been widely demonstrated in multiple microbe-derived AMPs, such as lacticin Q [74], bifidocin A [75], and colicin E1 [76].

4.1.2. Barrel-stave model

Athough the mechanism of the barrel-stave model is similar to that of the toroidal-pore model, the difference between the barrel-stave model and the annular pore model is that the barrel-stave mechanism has nothing to do with the membrane polarity [77].

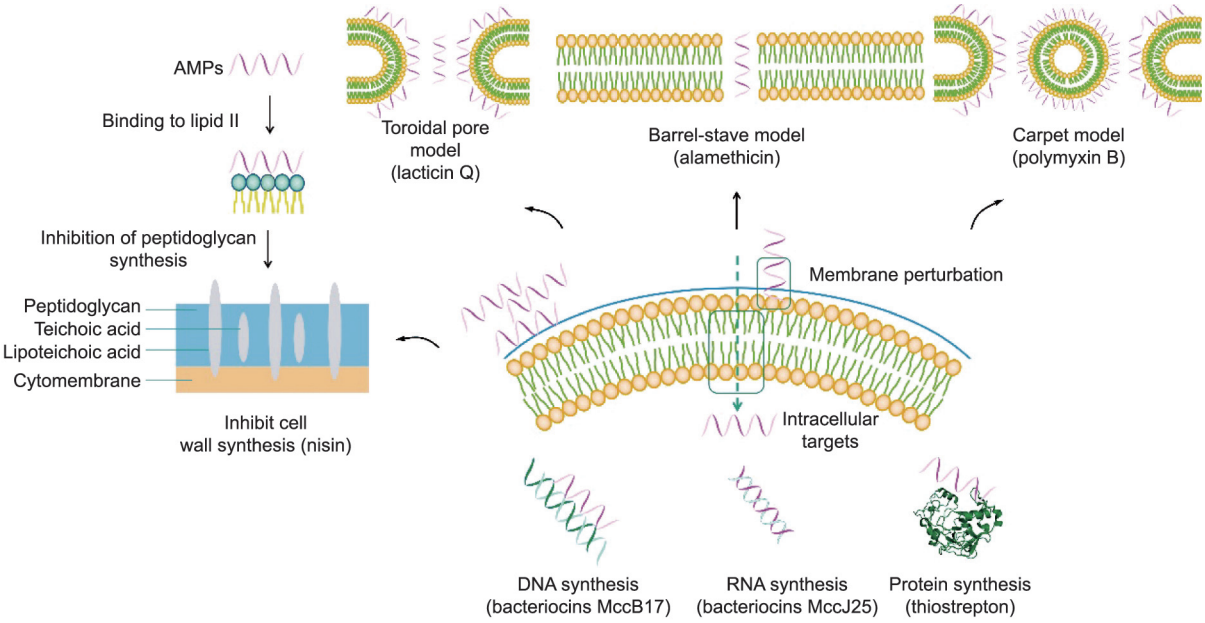

Fig. 3. Models of antimicrobial mechanisms of AMPs.

The barrel-stave mode is a state in which the binding of AMPs to the cytomembrane promotes more AMPs to aggregate onto the cytomembrane surface, and the AMPs will be embedded vertically into the lipid bilayer like a barrel plate, with each peptide monomer becoming a slat in the barrel-like cluster [78]. In the phospholipid layer, a barrel-shaped channel is formed and the raised peptide molecules expand the channel size, inducing cell death by causing leakage of cellular contents. Alamethicin, secreted by *Trichoderma viride*, was the first AMP discovered to kill pathogens by barrel mode. In this model, the alamethicin helix binds to the middle lumen to form a bundle, just like a barrel with a helical AMP as a barrel plate [79].

4.1.3. Carpet model

In the carpet model, the AMP covers the membrane surface in a carpet-like fashion and interacts with the cytomembrane in parallel, due to electrostatic interactions between the cytomembrane and the anionic phospholipid head group [78]. The lipid bilayer is disrupted by the generation of micelles at high AMP concentrations. Through this mechanism, lysate peptides can lyse the cells of diverse microbes as well as normal mammalian cells, resulting in marked cytotoxicity issues. Polymyxins, which are the last treatment resort for extensively drug-resistant G^+ microbial infections, are thought to act via this mechanism [80].

4.2. Non-membrane damage

Although the microbicidal actions of AMPs were originally reported to occur through membrane-target mechanisms, it has recently been found that some AMPs target critical cell components to induce microbial death. These AMPs traverse the cytomembrane without disrupting it and subsequently engage with important intracellular sites to impede key cellular activities. Many intracellular targeting mechanisms—such as the suppression of protein, nucleic acid, and cell wall formation—have been reported to date.

4.2.1. Inhibiting the biosynthesis of cell walls

The cell wall is a microbe's outermost barrier against various environmental pressures and is pivotal for microbial survival [81]. Lcn972 is a bacteriocin with an atypical 66-amino-acid sequence that suppresses septum production in *Lactococcus lactis* rather than creating cytoplasmic membrane holes [82]. Further works have demonstrated that Lcn972 blocks the incorporation of cell wall precursors in the septum area by binding to lipid II, a pivotal intermediate in peptidoglycan biosynthesis, and thereby suppressing cell division [83,84]. Lantibiotics are a well-known family of AMP that interferes with cell wall formation; they are post-translational-modified bacteriocins produced by G^+ bacteria [85]. L. A. Rogers discovered nisin, the best-characterized lantibiotic, in 1928 [86]. Nisin is made up of 34 amino acids and five (methyl-)lanthionine rings (rings A–E) (Fig. 4) [87]. It can bind to the pyrophosphate moiety of the cell wall precursor lipid II with its N-terminal rings A and B, prohibiting cell wall biosynthesis [88,89]. By binding to lipid II, the C-terminal portion of nisin can insert itself into the cytomembrane to form pores consisting of eight nisin and four lipid II molecules, which subsequently results in rapid cell death [90,91]. It was later found that the bacteriocins haloduracin and lacticin 3147 in the lantibiotic family can kill bacteria through the dual mechanisms of cell membrane attack and the inhibition of cell wall synthesis [92,93].

4.2.2. Inhibiting the biosynthesis of nucleic acids

Some AMPs enter cells through transmembrane action to perturb the cell's normal life functions [94,95]. Albicidin, a polyaromatic oligopeptide derived from *Xanthomonas albilineans*, exerts strong antibacterial effects versus G^+ and G^- pathogens by interfering with the catalytic DNA cleavage–religation cycle [96]. Griselimycin, a cyclic depsipeptide from *Streptomyces griseus*, exerts anti-*Mycobacterium* activity by acting on the DNA polymerase sliding clamp [97]. The colicin E series, a group of bacteriocins derived from *Escherichia coli*, enter the cytoplasm of sensitive pathogens in a Tol system-dependent manner (i.e., via the BtuB receptor), and then suppress the target pathogens by cleaving their DNA (colicins E2, E7, E8, and E9), 16S RNA (colicins E3, E4, and E6), or transfer RNA (tRNA; colicin E5) [98].

4.2.3. Inhibiting protein synthesis

Protein synthesis starts with the transcription of DNA to messenger RNA (mRNA), which is then translated to polypeptides by

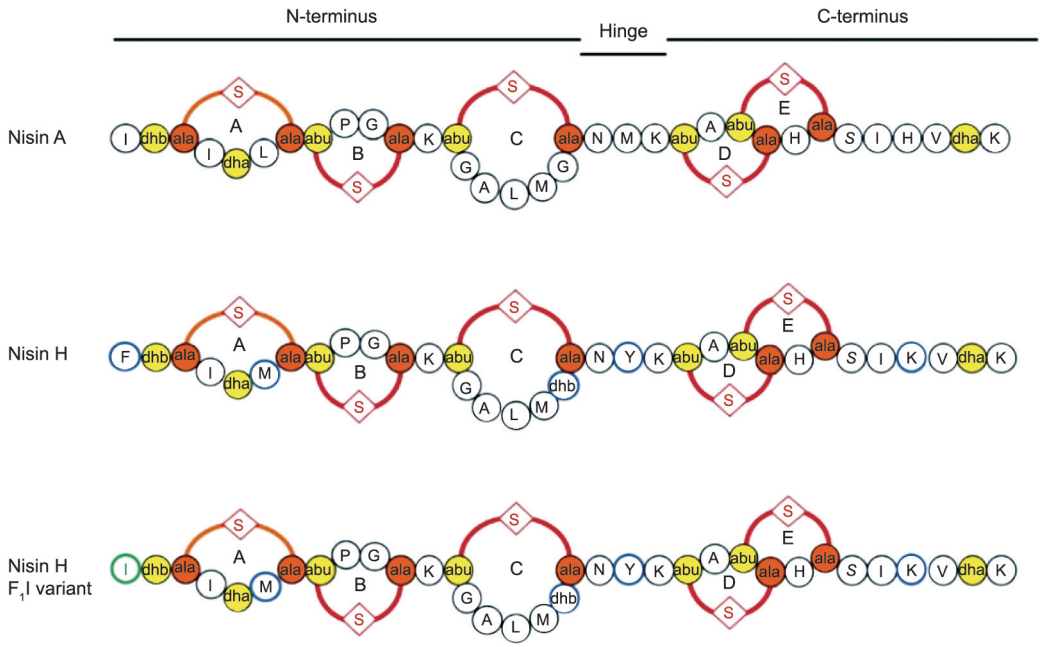

Fig. 4. Schematic overview of the used lantibiotics nisin A, nisin H, and the nisin H F_1I variant. Blue highlights point mutations in nisin H and nisin H F_1I compared to nisin A. Yellow and orange labels are used to identify cysteine residues and dehydrated amino acids that contribute to the synthesis of the (methyl-)lanthionine rings (rings A–E). The nisin H F_1I variant's mutation is highlighted in green. Reproduced from Ref. [1] with permission.

the 70S microbial ribosomal machinery. The polypeptides are then folded and assembled into functional proteins with the help of chaperones [99]. Protein synthesis stops when any of the related enzymes or effector molecules are disturbed. Notably, most characterized thiopeptides—such as nocathiacins, thiostrepton, and thiazomycin—display nanomolar potency toward G^+ pathogens by perturbing protein translation [100]. Bottromycins exert their antimicrobial effect by selectively hindering aminoacyl-tRNA binding to the site of microbial ribosomes [101]. Odilorhabdins, which are NRPs isolated from the nematode-symbiotic bacterium *Xenorhabdus nematophila*, display potent activity against MDR pathogens by targeting a small subunit of the microbial ribosome [102].

5. Production of microbial AMPs

There is an increasing demand for peptide production in sustainable agriculture [103]. However, the amounts of AMPs occurring naturally in microbes that are available for use are relatively limited. To date, enzymatic synthesis, recombinant expression, and chemical synthesis are the main methods that can be used to accomplish these goals (Fig. 5). These methods can be used independently or in combination, depending on the complexity and difficulty of manufacturing the molecules [104].

5.1. Enzymatic hydrolysis

The microbe-derived AMPs used in agricultural production can be produced by the enzymatic hydrolysis of parent proteins. Interestingly, some peptide fragments may be inactive in the parent protein molecules but exhibit activity when released by proteolytic enzymes *in vivo* or *in vitro*. The enzymes administered in the manufacturing of AMPs are acquirable from plants, microbes, and animals [105]. Pepsin, trypsin, bromelain, ficin, and so forth are frequently used enzymes from plant or animal sources, which are either used alone or in combination with other enzymes [106]. The proteases from microbes that are most broadly deployed are those obtainable from the *Bacillus* species, *Bifidobacterium*, and LAB [107]. Proteases from microbial sources are more attractive than proteases from other origins for the following reasons: First, microbes have low nutritional requirements and a short maturation period, resulting in cheaper cultivation costs. Second, most microbial proteases—especially those from LAB—are expressed on the cytomembrane, making separation and purification comparatively inexpensive and less laborious. With recent advancements in microbe cultivation and identification processes, microbiologists can analyze a wide variety of natural microbes and their products.

The primary critical factors that determine an AMP's characteristics (i.e., molecular size, amino acid sequence, hydrophobicity, and polar groups) are the protease's selectivity toward the substrate, the pH value, the temperature, and the hydrolysis time [108]. Accordingly, the functional characteristics of AMPs can be improved by enzymatic hydrolysis under controlled circumstances [109]. Agyei and Danquah [107] provided a short description of the process for preparing AMPs by this method (Fig. 5). The first step of this process involves the acquisition of starting materials: parent protein and proteases or microbes [110]. Byproducts from the bioenergy, food, and brewing industries—such as microalgae [111], mushrooms [112], yeast [113], and so forth—are appropriate inexpensive origins for AMPs. The second step relates to the proteolysis of the parent proteins. The final steps in the process of enzymatic hydrolysis are the fractionation and isolation of AMPs. Although ultrafiltration, solvent precipitation, and liquid chromatography technologies have been reported for the purification of AMPs, their current inherently high prices limit their use on a large scale. Electro-membrane filtration, which combines electrophoresis with traditional membrane filtration and is thus a more cost-effective option for purifying AMPs than the above technologies, is a well-established alternative.

5.2. Recombinant expression

In recent years, the recombinant expression of AMPs has attracted a great deal of attention for its comparatively low manufacturing cost and low ecological burden. Heterologous expression

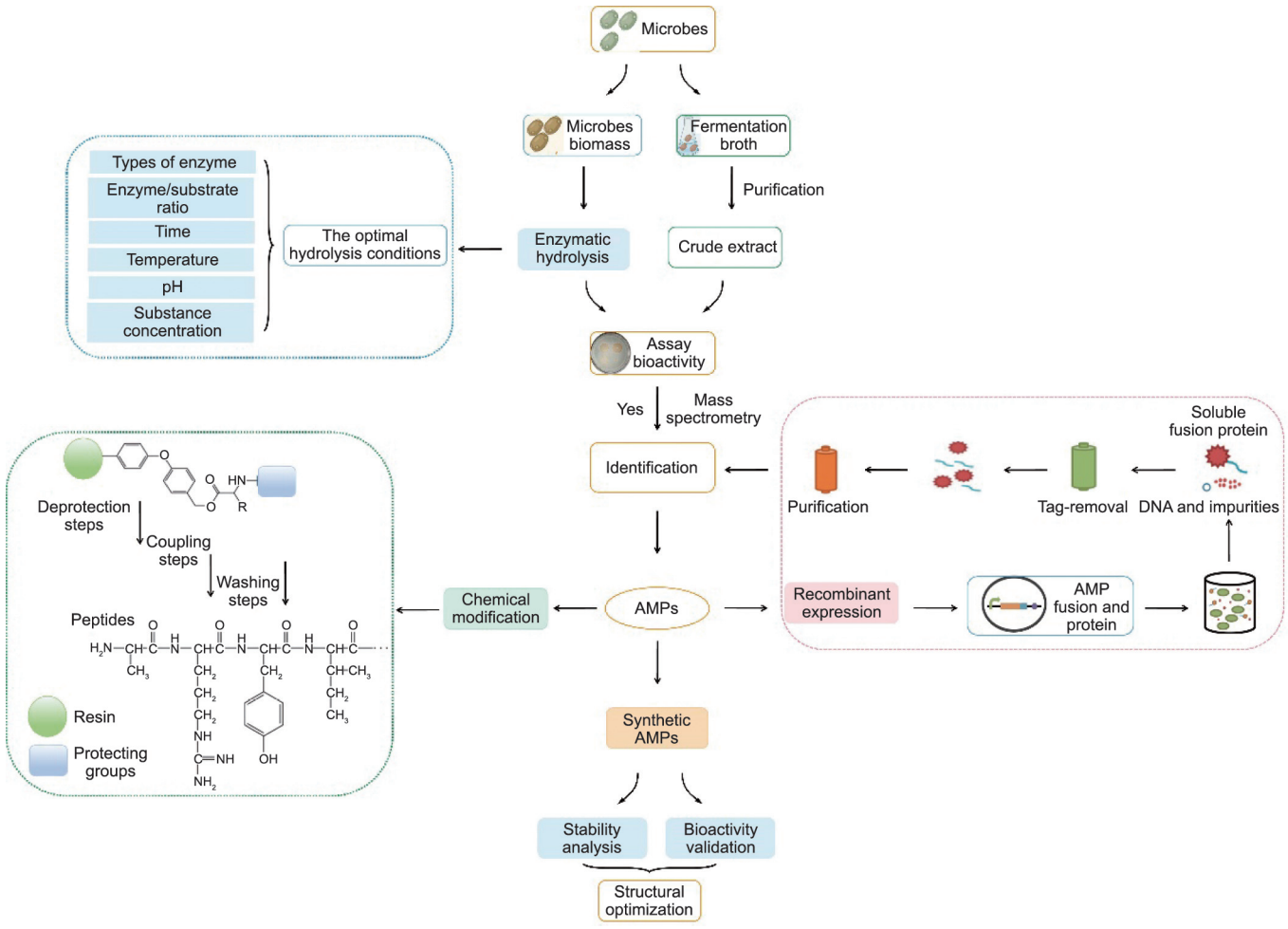

Fig. 5. General flowsheet for the preparation of AMPs.

strategies, such as the expression of the defensins Pvd1 in *Escherichia coli*, plectasin in *Bacillus subtilis*, and protegrin in *Pichia pastoris*, provide a viable option for making these peptides available in a cost-effective manner [114]. Genetically engineering strains not only facilitates the production and functional expression of desired bioactive compounds but—crucially—also allows for the production of bioengineered and encrypted peptides that cannot be produced by other methods [115]. Most microbial AMPs are still concealed in genomes, as only a portion of the microbes are cultivated in artificial settings, and a relatively small proportion of the peptides encoded by cultured microbes have been isolated in ideal fermentation tests [116]. Thus, modern sequencing techniques are used to mine microbial microbiomes and develop unexploited AMPs [116,117]. For example, Hover et al. [118] created a culture-independent development platform that incorporates the sequencing, bioinformatic analysis, and recombinant expression of BGCs captured on the DNA obtained from ambient specimens. The sequence-guided metagenomic development process also offers a way to parse sophisticated ambient metagenomes for such unidentified substances via tracing undiscovered BGCs. Novel calcium-dependent AMPs known as malacidins were extracted using this technique, and display powerful anti-MDR activity by targeting lipid II [118].

Nevertheless, the probability of successful heterologous expression may be highly varied due to a series of selective factors. The selection and design of hosts and expression systems are influenced by the composition and physicochemical characteristics of the desired AMPs. The selection of the host, codon bias, protein expression vector, plasmid copy number, and fusion proteins can all affect the synthesis, folding, and secretion of recombinant AMPs by the cell machinery. The most favored expression host for peptide manufacturing is *Escherichia coli*; however, the major constraint of peptide expression is its inherent lethality to the host [119]. Moreover, most AMPs have a positive net charge and are thus prone to digestion by proteases [120]. Accordingly, several methods for manufacturing fusion protein have been developed to address these issues, since fused proteins can disguise the toxicity of AMPs while affording protection from proteolytic digestion [121,122]. Nonetheless, these approaches result in low protein expression levels of about 10–30 $mg \cdot L^{-1}$ (fusion proteins) and 1–5 $mg \cdot L^{-1}$ (AMPs) [123]. Fungi are a potential substitute for bacteria as a host for the recombinant production of AMPs, because such microbes have the advantage of being tolerant to peptide-mediated killing. In addition, fungal species can effectively secrete AMPs into the culture broth to allow cost-effective manufacture scale-up [124,125].

5.3. Chemical synthesis

The early discovery of AMPs depended on isolating them from their original strains, which generally required enormous volumes of fermentation broth, even though only small yields of the pure compound could be isolated [126]. Chemical synthesis can now be used to harvest large quantities of pure peptides—particularly

peptide chains with less than 50 residues. There are two main types of chemical peptide synthesis: liquid-phase peptide synthesis (LPPS) and solid-phase peptide synthesis (SPPS). LPPS applies to the large-scale production of polypeptides. In LPPS, the α-carboxyl group of the acyl receptor is typically modified by esterification or amidation, leading to a longer sequence [127]. The main disadvantages of LPPS are its long synthesis cycle and heavy workload. SPPS is frequently applied to the small-scale production of AMPs, and entails linking the target compound's C-terminal amino acid to a polymeric solid support, normally via a cleavable chemical linker. This is followed by consecutive deprotections and the coupling of amino acid building blocks to elongate the peptide chain [126,128]. Once the desired fragment is formed, it can be separated from the resin to produce the target product in high yield and purity.

Notably, LPPS and SPPS can also be combined, with particular peptide fragments being synthesized by SPPS and then joined by means of LPPS. However, the high cost of the synthesis process markedly restricts its application, particularly for peptide fragments with long amino acid lengths or sophisticated structures [129]. Taking lactocin S as an example, its biosynthesis requires only two enzymatic steps (modification and cleavage) after the formation of a pro-peptide in the ribosome [130]. Utilizing SPPS, lactocin S production requires 71 steps (including all deprotections and couplings) [131] due to the intrinsic process complexity of SPPS, which requires numerous chemical protection–deprotection processes for each introduced residue.

6. Applications in sustainable agricultural systems

The extensive use of antibiotics for sustainable agricultural systems over the past several decades has caused the emergence of MDR strains and the dissemination of resistance genes among pathogens. The urgency to explore alternative drugs in order to control the breaking out of infectious diseases and decrease the selection pressure by antibiotics has been the main push in the development of AMPs. Interestingly, aside from their direct inhibitory or microbicidal actions, AMPs are multifunctional molecules with a variety of therapeutic characteristics such as being antioxidant and immunomodulatory and having anticancer activity, making them good candidates for sustainable agricultural systems. Thus far, nisin, ε-polylysine, and pediocin PA-1 have been commercialized as preservatives [114]. The use of other microbial AMPs for agricultural production has also been attempted. Based on this, in the next sections, we discuss some microbial AMPs that have been tested for applications in agriculture and list some with potential for use in the preservation of agricultural products.

6.1. Antibiotic alternatives in food-producing animals

Antibiotic-resistant infections in livestock are increasingly becoming a severe danger to public health and food security, due to the potential risk of antibiotic-resistance genes being passed from microbes to humans [132]. Accordingly, microbial AMPs have been put forward as a substitute for antibiotic feed additives for enhanced production performance, immunity, and the promotion of intestinal health (Table 1) [133–137]. For example, rabbits supplemented with nisin showed better growth performance, higher phagocytic activity, and lower fecal coagulase-negative pseudomonads [138]. Gassericin A, a bacteriocin that interacts with keratin 19 on intestinal epithelial cells to enhance fluid uptake, could therefore be utilized as an antibiotic substitute to avoid diarrhea in livestock [139]. Multiple investigations have demonstrated that adding AMPs to animal diets could beneficially impact hosts by strengthening immune function and reducing intestinal pathogens, such as gassericin A [140], colisin E1 [141], and albusin B [142]. In addition, five bacteriocins (i.e., morricin 269, kurstacin 287, kenyacin 404, entomocin 420, and tolworthcin 524) originating from *Bacillus thuringiensis* have exhibited bactericidal activity against the mastitis-causing pathogen *Streptococcus aureus* [143]. Moreover, lipopeptides from *Bacillus* species exhibit direct inactivation action against animal-infecting viruses such as porcine parvovirus, newcastle disease virus, and bursal disease virus [144].

Table 1
Antibiotic alternatives in food-producing animals.

Name	Source	Reference
Divercin AS7	*Carnobacterium divergens* AS7	[133]
Garvicin A	*Lactococcus garvieae* 21881	[134]
Surfactant	*Pseudomonas* H6	[135]
Sublancin	*Bacillus subtilis* 168	[136]
Albusin B	*Ruminococcus albus* 7	[137]

6.2. Pesticide alternatives in edible plants

Numerous pesticides and antibiotics—most notably, streptomycin—are used annually around the world to reduce the output losses caused by pests and phytopathogens during crop cultivation [145]. Nevertheless, the extended use of chemical pesticides and antibiotics in a field context is one of the fundamental reasons for environmental pollution and human health problems. Microbial AMPs are promising candidates to combat phytopathogens and pests (Table 2) [146–150]. Research has suggested that a considerable number of microbial AMPs are potential plant protectants; these are exemplified by the lipopeptide fengycin, which exerts a potent antimicrobial activity against various phytopathogens through pore formation [151–153]. Mycosubtilin exerts a potent antifungal effect, such that the germination rates of *Fusarium graminearum* and *Fusarium verticillioides* were only 17.52% and 29.03%, respectively, after treatment with 50 $\mu g \cdot mL^{-1}$ of mycosubtilin for 24 h [154]. Tailocins shows considerable antibacterial activity against the phytopathogen *Xanthomonas vesicatoria* Xcv Bv5-4a and has no cytotoxic effects on mammalian cells [155]. Cycloaspeptide E is a bioactive pentapeptide synthesized by various filamentous fungi, which has garnered interest from the agricultural industry due to excellent insecticidal activity against Lepidoptera [156].

6.3. Effective preservatives in agricultural products

Agricultural products—particularly aquatic products, vegetables, and fruits—are strongly favored by consumers for their delicious taste and abundant nutritional value. However, the nutrients in agricultural products can support the colonization and proliferation of pathogens, resulting in increased health risks for consumers and economic losses in agriculture [157,158]. AMPs are a reasonable choice to address this issue (Table 3) [159–163]. For example, amylolysin has an anti-listerial effect to defend poultry meat from *Listeria monocytogenes* [164]. With the addition of pentocin 31-1, pork exhibited good sensory characteristics under preservation at 4 °C for 15 days [165]. Bacteriocin DY4-2 exhibited good inhibitory activity against *Pseudomonas fluorescens*, *Pseudomonas aeruginosa*, *Vibrio parahaemolyticus*, and *Aeromonas sobria*, which can be devastating to aquatic products [166]. Bacteriocin GP1, which is produced by *Lactobacillus rhamnosus*, effectively inhibited many kinds of bacteria yet retained the total volatile base nitrogen (TVB-N) content and total methyl amine (TMA) level within the acceptable limit when added to grouper filets [167]. Lipopeptides isolated from *Bacillus* XT1 CECT 8661 acted as a highly efficient antagonist against *Botrytis cinerea*-caused grey

Table 2
Pesticide alternatives in edible plants.

Name	Source	Reference
Bacilysin	*Bacillus velezensis* FZB42	[146]
Orfamide A	*Pseudomonas*	[147]
Bacillomycin D	*Bacillus amyloliquefaciens* FZB42	[148]
Thuricin 17	*Bacillus* thuringiensis NEB17	[149]
Poaeamide	*Pseudomonas poae*	[150]

Table 3
Effective preservatives in agricultural products.

Name	Source	Reference
Plantaricin DL3	*Lactobacillus plantarum* DL3	[159]
Enterocin F4-9	*Enterococcus faecalis* F4-9	[160]
Pentocin JL-1	*Chiloscyllium punctatum*	[161]
Pediocin DT016	*Pediococcus pentosaceus* DT016	[162]
Sonorensin	*Bacillus sonorensis* MT93	[163]

mold rot on fruit and vegetables (including tomatoes, grapes, and strawberries) [168]. Similarly, Jia et al. [169] reported that, when fresh strawberries were aspersed with bacteriocin LF-1 at room temperature for six days, the spore germination of *Rhizopus* was suppressed, and the overall quality of the strawberries did not change markedly, while their shelf life was prolonged. To summarize, AMPs can be applied to the storage and preservation of agricultural products in the form of food preservatives.

7. Conclusions and outlook

Due to the growing number of antibiotic-resistant pathogens, there has been increased interest in AMPs as a potential substitute for traditional antibiotics. Microbial AMPs exhibit distinct advantages over traditional antibiotics against various animal pathogens and phytopathogens in sustainable agricultural systems. In particular, they exhibit extensive antimicrobial and immunoregulatory bioactivity with multi-hit unconventional mechanisms of action, which lead to the restricted development of resistance. Microbes secrete a wide variety of AMPs due to their extraordinary synthetic plasticity, which is endowed by their ability to synthesize both ribosomal AMPs and NRPs. In addition, their diversity allows them to grow in restricted spaces, require a low yield of nutrients, and produce different biomolecules under various conditions.

The challenges presented by AMPs in sustainable agricultural system applications include cytotoxicity, manufacturing costs, and issues associated with peptide bioavailability and stability. The focal point of future research should be to overcome the weaknesses outlined above and transform AMPs into useful medication candidates. The first step would be cost reduction through the implementation of more efficient and cost-effective synthesis methods, or the development of superior recombinant AMP manufacturing methods. For example, the design and synthesis of polymers may become a perfect alternative to reduce costs in the future, with the ongoing optimization of controlled polymerization techniques and the continuous development of polymers that imitate AMPs. A second step would be to increase AMP bioavailability using engineering tactics targeted at avoiding proteolytic destruction, such as the alteration of AMPs' primary sequence through unnatural amino acid substitution, the generation of peptide mimics, peptide cyclization, and hybrid construction [170]. Furthermore, the implementation of AMP nanocarriers would enhance the bioavailability of AMPs by targeting them to the correct cell sites, thereby reducing waste and off-target effects, and circumventing protease destruction. A greater reduction in the dose of AMPs entering the pipeline for biopeptide exploitation can be accomplished by the computer-aided option of up-to-date prediction tools for candidate screening on the basis of a desired higher activity or lower toxicity. Notably, cross-innovation is very important for the further optimization and development of peptide-based microbicidal medicines; the combined efforts of multidisciplinary experts such as microbiologists, pharmacologists, and computer scientists are required to achieve this goal. Although many barriers remain to the successful agricultural application of microbial AMPs, conceptual innovation combined with computer-aided techniques can undoubtedly speed this advancement.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (2020YFD0900905), Central Government Guided Local Science and Technology Development Projects of China (2020L3004), and Fujian Major Project of Provincial Science & Technology Hall, China (2020NZ010008).

Compliance with ethics guidelines

Shuhua Lin, Xuan Chen, Huimin Chen, Xixi Cai, Xu Chen, and Shaoyun Wang declare that they have no conflict of interest or financial conflicts to disclose.

References

[1] Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, et al. Characterization of a new metallo-beta-lactamase gene, *bla*$_{(NDM-1)}$, and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. Antimicrob Agents Chemother 2009;53(12):5046–54.
[2] Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 2016;16(2):161–8.
[3] Gu D, Dong N, Zheng Z, Lin D, Huang M, Wang L, et al. A fatal outbreak of ST11 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* in a Chinese hospital: a molecular epidemiological study. Lancet Infect Dis 2018;18(1):37–46.
[4] Ma B, Fang C, Lu L, Wang M, Xue X, Zhou Y, et al. The antimicrobial peptide thanatin disrupts the bacterial outer membrane and inactivates the NDM-1 metallo-β-lactamase. Nat Commun 2019;10(1):3517.
[5] Chen CH, Lu TK. Development and challenges of antimicrobial peptides for therapeutic applications. Antibiotics 2020;9(1):24.
[6] Chen CH, Bepler T, Pepper K, Fu D, Lu TK. Synthetic molecular evolution of antimicrobial peptides. Curr Opin Biotechnol 2022;75:102718.
[7] Awan AR, Blount BA, Bell DJ, Shaw WM, Ho JCH, McKiernan RM, et al. Biosynthesis of the antibiotic nonribosomal peptide penicillin in baker's yeast. Nat Commun 2017;8:15202.
[8] Inoue M. Total synthesis and functional analysis of non-ribosomal peptides. Chem Rec 2011;11(5):284–94.
[9] Süssmuth RD, Mainz A. Nonribosomal peptide synthesis-principles and prospects. Angew Chem Int Ed Engl 2017;56(14):3770–821.
[10] Travin DY, Watson ZL, Metelev M, Ward FR, Osterman IA, Khven IM, et al. Structure of ribosome-bound azole-modified peptide phazolicin rationalizes its species-specific mode of bacterial translation inhibition. Nat Commun 2019;10:4563.
[11] Ma J, Huang H, Xie Y, Liu Z, Zhao J, Zhang C, et al. Biosynthesis of ilamycins featuring unusual building blocks and engineered production of enhanced anti-tuberculosis agents. Nat Commun 2017;8:391.
[12] Covas C, Almeida B, Esteves AC, Lourenço J, Domingues P, Caetano T, et al. Peptone from casein, an antagonist of nonribosomal peptide synthesis: a case study of pedopeptins produced by *Pedobacter lusitanus* NL19. N Biotechnol 2021;60:62–71.
[13] Zipperer A, Konnerth MC, Laux C, Berscheid A, Janek D, Weidenmaier C, et al. Human commensals producing a novel antibiotic impair pathogen colonization. Nature 2016;535(7613):511–6.
[14] Kling A, Lukat P, Almeida DV, Bauer A, Fontaine E, Sordello S, et al. Targeting DnaN for tuberculosis therapy using novel griselimycins. Science 2015;348(6239):1106–12.
[15] Duncan KR, Crüsemann M, Lechner A, Sarkar A, Li J, Ziemert N, et al. Molecular networking and pattern-based genome mining improves discovery of biosynthetic gene clusters and their products from *Salinispora* species. Chem Biol 2015;22(4):460–71.
[16] Santos-Aberturas J, Chandra G, Frattaruolo L, Lacret R, Pham TH, Vior NM, et al. Uncovering the unexplored diversity of thioamidated ribosomal

peptides in *Actinobacteria* using the RiPPER genome mining tool. Nucleic Acids Res 2019;47(9):4624–37.
[17] Rutledge PJ, Challis GL. Discovery of microbial natural products by activation of silent biosynthetic gene clusters. Nat Rev Microbiol 2015;13(8):509–23.
[18] Son S, Hong YS, Jang M, Heo KT, Lee B, Jang JP, et al. Genomics-driven discovery of chlorinated cyclic hexapeptides ulleungmycins A and B from a *Streptomyces* species. J Nat Prod 2017;80(11):3025–31.
[19] Jang JP, Nogawa T, Futamura Y, Shimizu T, Hashizume D, Takahashi S, et al. Octaminomycins A and B, cyclic octadepsipeptides active against *Plasmodium falciparum*. J Nat Prod 2017;80(1):134–40.
[20] Bekiesch P, Zehl M, Domingo-Contreras E, Martín J, Pérez-Victoria I, Reyes F, et al. Viennamycins: lipopeptides produced by a *Streptomyces* sp. J Nat Prod 2020;83(8):2381–9.
[21] Drider D, Bendali F, Naghmouchi K, Chikindas ML. Bacteriocins: not only antibacterial agents. Probiotics Antimicrob Proteins 2016;8(4):177–82.
[22] Flaherty RA, Freed SD, Lee SW. The wide world of ribosomally encoded bacterial peptides. PLoS Pathog 2014;10(7):e1004221.
[23] Soltani S, Hammami R, Cotter PD, Rebuffat S, Said LB, Gaudreau H, et al. Bacteriocins as a new generation of antimicrobials: toxicity aspects and regulations. FEMS Microbiol Rev 2021;45(1):fuaa039.
[24] Pang X, Song X, Chen M, Tian S, Lu Z, Sun J, et al. Combating biofilms of foodborne pathogens with bacteriocins by lactic acid bacteria in the food industry. Compr Rev Food Sci Food Saf 2022;21(2):1657–76.
[25] Youssef FS, Ashour ML, Singab ANB, Wink M. A comprehensive review of bioactive peptides from marine fungi and their biological significance. Mar Drugs 2019;17(10):559.
[26] Hüttel W. Echinocandins: structural diversity, biosynthesis, and development of antimycotics. Appl Microbiol Biotechnol 2021;105(1):55–66.
[27] Mattay J, Houwaart S, Hüttel W. Cryptic production of *trans*-3-hydroxyproline in echinocandin B biosynthesis. Appl Environ Microbiol 2018;84(7):e02370-17.
[28] Shi WL, Chen XL, Wang LX, Gong ZT, Li S, Li CL, et al. Cellular and molecular insight into the inhibition of primary root growth of *Arabidopsis* induced by peptaibols, a class of linear peptide antibiotics mainly produced by *Trichoderma* spp. J Exp Bot 2016;67(8):2191–205.
[29] Grigoletto DF, Trivella DBB, Tempone AG, Rodrigues A, Correia AML, Lira SP. Antifungal compounds with anticancer potential from *Trichoderma* sp. P8BDA1F1, an endophytic fungus from *Begonia venosa*. Braz. J Microbiol 2020;51(3):989–97.
[30] Li Z, Wang X, Wang X, Teng D, Mao R, Hao Y, et al. Research advances on plectasin and its derivatives as new potential antimicrobial candidates. Process Biochem 2017;56:62–70.
[31] Schneider T, Kruse T, Wimmer R, Wiedemann I, Sass V, Pag U, et al. Plectasin, a fungal defensin, targets the bacterial cell wall precursor lipid II. Science 2010;328(5982):1168–72.
[32] Essig A, Hofmann D, Münch D, Gayathri S, Künzler M, Kallio PT, et al. Copsin, a novel peptide-based fungal antibiotic interfering with the peptidoglycan synthesis. J Biol Chem 2014;289(50):34953–64.
[33] Oeemig JS, Lynggaard C, Knudsen DH, Hansen FT, Nørgaard KD, Schneider T, et al. Eurocin, a new fungal defensin: structure, lipid binding, and its mode of action. J Biol Chem 2012;287(50):42361–72.
[34] Zhang Y, Zhou L, Liu Y, Zhao X, Lian X, Zhang J, et al. A peptide from budding yeast GAPDH serves as a promising antifungal against *Cryptococcus neoformans*. Microbiol Spectr 2022;10(1):e0082621.
[35] Branco P, Coutinho R, Malfeito-Ferreira M, Prista C, Albergaria H. Wine spoilage control: impact of saccharomycin on *Brettanomyces bruxellensis* and its conjugated effect with sulfur dioxide. Microorganisms 2021;9(12):2528.
[36] Landi N, Clemente A, Pedone PV, Ragucci S, DiMaro A. An updated review of bioactive peptides from mushrooms in a well-defined molecular weight range. Toxins 2022;14(2):84.
[37] Guzmán F, Wong G, Román T, Cárdenas C, Alvárez C, Schmitt P, et al. Identification of antimicrobial peptides from the microalgae *Tetraselmis suecica* (Kylin) butcher and bactericidal activity improvement. Mar Drugs 2019;17(8):453.
[38] Brasil BDAF, de Siqueira FG, Salum TFC, Zanette CM, Spier MR. Microalgae and cyanobacteria as enzyme biofactories. Algal Res 2017;25:76–89.
[39] MubarakAli D, MohamedSaalis J, Sathya R, Irfan N, Kim JW. An evidence of microalgal peptides to target spike protein of COVID-19: *in silico* approach. Microb Pathog 2021;160:160105189.
[40] Swain SS, Paidesetty SK, Padhy RN. Antibacterial, antifungal and antimycobacterial compounds from cyanobacteria. Biomed Pharmacother 2017;90:760–76.
[41] Mi Y, Zhang J, He S, Yan X. New peptides isolated from marine cyanobacteria, an overview over the past decade. Mar Drugs 2017;15(5):132.
[42] Hassan S, Meenatchi R, Pachillu K, Bansal S, Brindangnanam P, Arockiaraj J, et al. Identification and characterization of the novel bioactive compounds from microalgae and cyanobacteria for pharmaceutical and nutraceutical applications. J Basic Microbiol 2022;62(9):999–1029.
[43] Vestola J, Shishido TK, Jokela J, Fewer DP, Aitio O, Permi P, et al. Hassallidins, antifungal glycolipopeptides, are widespread among cyanobacteria and are the end-product of a nonribosomal pathway. Proc Natl Acad Sci USA 2014;111(18):E1909–17.
[44] Almaliti J, Malloy KL, Glukhov E, Spadafora C, Gutiérrez M, Gerwick WH. Dudawalamides A–D, antiparasitic cyclic depsipeptides from the marine cyanobacterium *Moorea producens*. J Nat Prod 2017;80(6):1827–36.
[45] Fidor A, Konkel R, Mazur-Marzec H. Bioactive peptides produced by cyanobacteria of the genus *Nostoc*: a review. Mar Drugs 2019;17(10):561.
[46] Ujvárosi AZ, Hercog K, Riba M, Gonda S, Filipič M, Vasas G, et al. The cyanobacterial oligopeptides microginins induce DNA damage in the human hepatocellular carcinoma (HepG2) cell line. Chemosphere 2020;240:124880.
[47] Essack M, Alzubaidy HS, Bajic VB, Archer JA. Chemical compounds toxic to invertebrates isolated from marine cyanobacteria of potential relevance to the agricultural industry. Toxins 2014;6(11):3058–76.
[48] Agrawal S, Acharya D, Adholeya A, Barrow CJ, Deshmukh SK. Nonribosomal peptides from marine microbes and their antimicrobial and anticancer potential. Front Pharmacol 2017;8:828.
[49] Tareq FS, Kim JH, Lee MA, Lee HS, Lee YJ, Lee JS, et al. Ieodoglucomides A and B from a marine-derived bacterium *Bacillus licheniformis*. Org Lett 2012;14(6):1464–7.
[50] Wang J, Liu YM, Cao W, Yao KW, Liu ZQ, Guo JY. Anti-inflammation and antioxidant effect of cordymin, a peptide purified from the medicinal mushroom *Cordyceps sinensis*, in middle cerebral artery occlusion-induced focal cerebral ischemia in rats. Metab Brain Dis 2012;27(2):159–65.
[51] Valero Y, Saraiva-Fraga M, Costas B, Guardiola FA. Antimicrobial peptides from fish: beyond the fight against pathogens. Rev Aquacult 2020;12(1):224–53.
[52] Kepp O, Kroemer G. Autophagy induction by thiostrepton for the improvement of anticancer therapy. Autophagy 2020;16(6):1166–7.
[53] Zhang J, Zhong J. The journey of nisin development in China, a natural-green food preservative. Protein Cell 2015;6(10):709–11.
[54] Cannatelli A, Principato S, Colavecchio OL, Pallecchi L, Rossolini GM. Synergistic activity of colistin in combination with resveratrol against colistin-resistant Gram-negative pathogens. Front Microbiol 2018;9:1808.
[55] Lopez-Pena CL, McClements DJ. Impact of a food-grade cationic biopolymer (ε-polylysine) on the digestion of emulsified lipids: *in vitro* study. Food Res Int 2015;75:34–40.
[56] Wang S, Zheng H, Zhou L, Cheng F, Liu Z, Zhang H, et al. Nanoenzyme-reinforced injectable hydrogel for healing diabetic wounds infected with multidrug resistant bacteria. Nano Lett 2020;20(7):5149–58.
[57] Nicolaou KC. How thiostrepton was made in the laboratory. Angew Chem Int Ed Engl 2012;51(50):12414–36.
[58] Lai Y, Gallo RL. AMPed up immunity: how antimicrobial peptides have multiple roles in immune defense. Trends Immunol 2009;30(3):131–41.
[59] Yeung ATY, Gellatly SL, Hancock RE. Multifunctional cationic host defence peptides and their clinical applications. Cell Mol Life Sci 2011;68(13):2161–76.
[60] Mahdi LH, Jabbar HS, Auda IG. Antibacterial immunomodulatory and antibiofilm triple effect of salivaricin LHM against *Pseudomonas aeruginosa* urinary tract infection model. Int J Biol Macromol 2019;134:1132–44.
[61] Hernández-González JC, Martínez-Tapia A, Lazcano-Hernández G, García-Pérez BE, Castrejón-Jiménez NS. Bacteriocins from lactic acid bacteria. A powerful alternative as antimicrobials, probiotics, and immunomodulators in veterinary medicine. Animals 2021;11(4):979.
[62] Der Torossian TM, de la Fuente-Nunez C. Reprogramming biological peptides to combat infectious diseases. Chem Commun 2019;55(100):15020–32.
[63] Jenab A, Roghanian R, Emtiazi G. Bacterial natural compounds with anti-inflammatory and immunomodulatory properties (mini review). Drug Des Devel Ther 2020;14:3787–801.
[64] Zhang Y, Liu C, Dong B, Ma X, Hou L, Cao X, et al. Anti-inflammatory activity and mechanism of surfactin in lipopolysaccharide-activated macrophages. Inflammation 2015;38(2):756–64.
[65] Rüter C, Buss C, Scharnert J, Heusipp G, Schmidt MA. A newly identified bacterial cell-penetrating peptide that reduces the transcription of pro-inflammatory cytokines. J Cell Sci 2010;123(13):2190–8.
[66] Yu H, Ding X, Shang L, Zeng X, Liu H, Li N, et al. Protective ability of biogenic antimicrobial peptide microcin J25 against enterotoxigenic *Escherichia coli*-induced intestinal epithelial dysfunction and inflammatory responses IPEC-J2 cells. Front Cell Infect Microbiol 2018;8:242.
[67] Malvisi M, Stuknytė M, Magro G, Minozzi G, Giardini A, De Noni I, et al. Antibacterial activity and immunomodulatory effects on a bovine mammary epithelial cell line exerted by nisin A-producing *Lactococcus lactis* strains. J Dairy Sci 2016;99(3):2288–96.
[68] Laman AG, Lathe R, Savinov GV, Shepelyakovskaya AO, Boziev KM, Baidakova LK, et al. Innate immunity: bacterial cell-wall muramyl peptide targets the conserved transcription factor YB-1. FEBS Lett 2015;589(15):1819–24.
[69] Dou X, Zhu X, Wang J, Dong N, Shan A. Novel design of heptad amphiphiles to enhance cell selectivity, salt resistance, antibiofilm properties and their membrane-disruptive mechanism. J Med Chem 2017;60(6):2257–70.
[70] Islam MS, Mohamed G, Polash SA, Hasan MA, Sultana R, Saiara N, et al. Antimicrobial peptides from plants: a cDNA-library based isolation, purification, characterization approach and elucidating their modes of action. Int J Mol Sci 2021;22(16):8712.
[71] Nguyen LT, Haney EF, Vogel HJ. The expanding scope of antimicrobial peptide structures and their modes of action. Trends Biotechnol 2011;29(9):464–72.
[72] Tuersuntuoheti T, Wang Z, Wang Z, Liang S, Li X, Zhang M. Review of the application of ε-poly-L-lysine in improving food quality and preservation. J Food Process Preserv 2019;43(10):e14153.
[73] Zhang Q, Yan Z, Meng Y, Hong X, Shao G, Ma J, et al. Antimicrobial peptides: mechanism of action, activity and clinical potential. Mil Med Res 2021;8(1):48.

[74] Yoneyama F, Imura Y, Ohno K, Zendo T, Nakayama J, Matsuzaki K, et al. Peptide-lipid huge toroidal pore, a new antimicrobial mechanism mediated by a lactococcal bacteriocin, lacticin Q. Antimicrob Agents Chemother 2009;53(8):3211–7.
[75] Liu G, Song Z, Yang X, Gao Y, Wang C, Sun B. Antibacterial mechanism of bifidocin A, a novel broad-spectrum bacteriocin produced by *Bifidobacterium animalis* BB04. Food Control 2016;62:62309–16.
[76] Sobko AA, Kotova EA, Antonenko YN, Zakharov SD, Cramer WA. Effect of lipids with different spontaneous curvature on the channel activity of colicin E1: evidence in favor of a toroidal pore. FEBS Lett 2004;576(1–2):205–10.
[77] Zhang S, Luo L, Sun X, Ma A. Bioactive peptides: a promising alternative to chemical preservatives for food preservation. J Agric Food Chem 2021;69 (42):12369–84.
[78] Yan Y, Li Y, Zhang Z, Wang X, Niu Y, Zhang S, et al. Advances of peptides for antibacterial applications. Colloids Surf B Biointerfaces 2021;202:111682.
[79] Su Z, Shodiev M, Leitch JJ, Abbasi F, Lipkowski J. Role of transmembrane potential and defects on the permeabilization of lipid bilayers by alamethicin, an ion-channel-forming peptide. Langmuir 2018;34(21):6249–60.
[80] Travkova OG, Moehwald H, Brezesinski G. The interaction of antimicrobial peptides with membranes. Adv Colloid Interface Sci 2017;247:521–32.
[81] Wang Y, Feng K, Yang H, Zhang Z, Yuan Y, Yue T. Effect of cinnamaldehyde and citral combination on transcriptional profile, growth, oxidative damage and patulin biosynthesis of *Penicillium expansum*. Front Microbiol 2018;9:597.
[82] Roces C, Courtin P, Kulakauskas S, Rodríguez A, Chapot-Chartier MP, Martínez B. Isolation of *Lactococcus lactis* mutants simultaneously resistant to the cell wall-active bacteriocin Lcn972, lysozyme, nisin, and bacteriophage c2. Appl Environ Microbiol 2012;78(12):4157–63.
[83] Madera C, García P, Rodríguez A, Suárez JE, Martínez B. Prophage induction in *Lactococcus* lactis by the bacteriocin lactococcin 972. Int J Food Microbiol 2009;129(1):99–102.
[84] Martínez B, Böttiger T, Schneider T, Rodríguez A, Sahl HG, Wiedemann I. Specific interaction of the unmodified bacteriocin lactococcin 972 with the cell wall precursor lipid II. Appl Environ Microbiol 2008;74(15):4666–70.
[85] Héchard Y, Sahl HG. Mode of action of modified and unmodified bacteriocins from Gram-positive bacteria. Biochimie 2002;84(5–6):545–57.
[86] Münch D, Müller A, Schneider T, Kohl B, Wenzel M, Bandow JE, et al. The lantibiotic NAI-107 binds to bactoprenol-bound cell wall precursors and impairs membrane functions. J Biol Chem 2014;289(17):12063–76.
[87] Reiners J, Lagedroste M, Gottstein J, Adeniyi ET, Kalscheuer R, Poschmann G, et al. Insights in the antimicrobial potential of the natural nisin variant nisin H. Front Microbiol 2020;11:573614.
[88] Sun Z, Zhong J, Liang X, Liu J, Chen X, Huan L. Novel mechanism for nisin resistance via proteolytic degradation of nisin by the nisin resistance protein NSR. Antimicrob Agents Chemother 2009;53(5):1964–73.
[89] Kawada-Matsuo M, Watanabe A, Arii K, Oogai Y, Noguchi K, Miyawaki S, et al. *Staphylococcus aureus* virulence affected by an alternative nisin a resistance mechanism. Appl Environ Microbiol 2020;86(8):e02923-19.
[90] Barbosa JC, Gonçalves S, Makowski M, Silva ÍC, Caetano T, Schneider T, et al. Insights into the mode of action of the two-peptide lantibiotic lichenicidin. Colloids Surf B Biointerfaces 2022;211:112308.
[91] Zaschke-Kriesche J, Behrmann LV, Reiners J, Lagedroste M, Gröner Y, Kalscheuer R, et al. Bypassing lantibiotic resistance by an effective nisin derivative. Bioorg Med Chem 2019;27(15):3454–62.
[92] Oman TJ, Lupoli TJ, Wang TSA, Kahne D, Walker S, van der Donk WA. Haloduracin α binds the peptidoglycan precursor lipid II with 2:1 stoichiometry. J Am Chem Soc 2011;133(44):17544–7.
[93] Bakhtiary A, Cochrane SA, Mercier P, McKay RT, Miskolzie M, Sit CS, et al. Insights into the mechanism of action of the two-peptide lantibiotic lacticin 3147. J Am Chem Soc 2017;139(49):17803–10.
[94] Cotter PD, Ross RP, Hill C. Bacteriocins—a viable alternative to antibiotics? Nat Rev Microbiol 2013;11(2):95–105.
[95] Metelev M, Serebryakova M, Ghilarov D, Zhao Y, Severinov K. Structure of microcin B-like compounds produced by *Pseudomonas syringae* and species specificity of their antibacterial action. J Bacteriol 2013;195(18):4129–37.
[96] Cociancich S, Pesic A, Petras D, Uhlmann S, Kretz J, Schubert V, et al. The gyrase inhibitor albicidin consists of p-aminobenzoic acids and cyanoalanine. Nat Chem Biol 2015;11(3):195–7.
[97] Fredersdorf M, Kurz M, Bauer A, Ebert MO, Rigling C, Lannes L, et al. Conformational analysis of an antibacterial cyclodepsipeptide active against *Mycobacterium tuberculosis* by a combined ROE and RDC analysis. Chemistry 2017;23(24):5729–35.
[98] Radaic A, de Jesus MB, Kapila YL. Bacterial anti-microbial peptides and nano-sized drug delivery systems: the state of the art toward improved bacteriocins. J Control Release 2020;321:100–18.
[99] Le CF, Fang CM, Sekaran SD. Intracellular targeting mechanisms by antimicrobial peptides. Antimicrob Agents Chemother 2017;61(4):e02340-16.
[100] Schwalen CJ, Hudson GA, Kille B, Mitchell DA. Bioinformatic expansion and discovery of thiopeptide antibiotics. J Am Chem Soc 2018;140(30):9494–501.
[101] Gomez-Escribano JP, Song L, Bibb MJ, Challis GL. Posttranslational β-methylation and macrolactamidination in the biosynthesis of the bottromycin complex of ribosomal peptide antibiotics. Chem Sci 2012;3 (12):3522–5.
[102] Pantel L, Florin T, Dobosz-Bartoszek M, Racine E, Sarciaux M, Serri M, et al. Odilorhabdins, antibacterial agents that cause miscoding by binding at a new ribosomal site. Mol Cell 2018;70(1):83–94.
[103] Espitia PJP, de Fátima Ferreira Soares N, dos Reis Coimbra JS, de Andrade NJ, Cruz RS, Medeiros EAA. Bioactive peptides: synthesis, properties, and applications in the packaging and preservation of food. Compr Rev Food Sci Food Saf 2012;11(2):187–204.
[104] Wang L, Wang N, Zhang W, Cheng X, Yan Z, Shao G, et al. Therapeutic peptides: current applications and future directions. Signal Transduct Target Ther 2022;7(1):48.
[105] Kim S, Wijesekara I. Development and biological activities of marine-derived bioactive peptides: a review. J Funct Foods 2010;2(1):1–9.
[106] Akalın AS. Dairy-derived antimicrobial peptides: action mechanisms, pharmaceutical uses and production proposals. Trends Food Sci Technol 2014;36(2):79–95.
[107] Agyei D, Danquah MK. Industrial-scale manufacturing of pharmaceutical-grade bioactive peptides. Biotechnol Adv 2011;29(3):272–7.
[108] Cunha SA, Pintado ME. Bioactive peptides derived from marine sources: biological and functional properties. Trends Food Sci Technol 2022;119:348–70.
[109] de Castro RJS, Sato HH. Biologically active peptides: processes for their generation, purification and identification and applications as natural additives in the food and pharmaceutical industries. Food Res Int 2015;74:185–98.
[110] Ryder K, AeD B, McConnell M, Carne A. Towards generation of bioactive peptides from meat industry waste proteins: generation of peptides using commercial microbial proteases. Food Chem 2016;208:42–50.
[111] Sun Y, Chang R, Li Q, Li B. Isolation and characterization of an antibacterial peptide from protein hydrolysates of *Spirulina platensis*. Eur Food Res Technol 2016;242(5):685–92.
[112] Ovando CA, Carvalho J, de Melo Pereira GV, Jacques P, Soccol VT, Soccol CR. Functional properties and health benefits of bioactive peptides derived from *Spirulina*: a review. Food Res Int 2018;34(1):34–51.
[113] Oliveira AS, Ferreira C, Pereira JO, Pintado ME, Carvalho AP. Spent brewer's yeast (*Saccharomyces cerevisiae*) as a potential source of bioactive peptides: an overview. Int J Biol Macromol 2022;208:1116–26.
[114] Cui Y, Luo L, Wang X, Lu Y, Yi Y, Shan Y, et al. Mining, heterologous expression, purification, antibactericidal mechanism, and application of bacteriocins: a review. Compr Rev Food Sci Food Saf 2021;20(1):863–99.
[115] Wibowo D, Zhao CX. Recent achievements and perspectives for large-scale recombinant production of antimicrobial peptides. Appl Microbiol Biotechnol 2019;103(2):659–71.
[116] Zhang C, Seyedsayamdost MR. Discovery of a cryptic depsipeptide from *Streptomyces ghanaensis* via MALDI-MS-guided high-throughput elicitor screening. Angew Chem Int Ed Engl 2020;59(51):23005–9.
[117] Tracanna V, de Jong A, Medema MH, Kuipers OP. Mining prokaryotes for antimicrobial compounds: from diversity to function. FEMS Microbiol Rev 2017;41(3):417–29.
[118] Hover BM, Kim SH, Katz M, Charlop-Powers Z, Owen JG, Ternei MA, et al. Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens. Nat Microbiol 2018;3(4):415–22.
[119] Kim K, Choe D, Lee DH, Cho BK. Engineering biology to construct microbial chassis for the production of difficult-to-express proteins. Int J Mol Sci 2020;21(3):990.
[120] Ishida H, Nguyen LT, Gopal R, Aizawa T, Vogel HJ. Overexpression of antimicrobial, anticancer, and transmembrane peptides in *Escherichia coli* through a calmodulin-peptide fusion system. J Am Chem Soc 2016;138 (35):11318–26.
[121] Pina AS, Lowe CR, Roque ACA. Challenges and opportunities in the purification of recombinant tagged proteins. Biotechnol Adv 2014;32 (2):366–81.
[122] Mejía-Pitta A, Broset E, de la Fuente-Nunez C. Probiotic engineering strategies for the heterologous production of antimicrobial peptides. Adv Drug Deliv Rev 2021;176:113863.
[123] Cao J, de la Fuente-Nunez C, Ou RW, Torres MT, Pande SG, Sinskey AJ, et al. Yeast-based synthetic biology platform for antimicrobial peptide production. ACS Synth Biol 2018;7(3):896–902.
[124] Ahmad M, Hirz M, Pichler H, Schwab H. Protein expression in *Pichia pastoris*: recent achievements and perspectives for heterologous protein production. Appl Microbiol Biotechnol 2014;98(12):5301–17.
[125] Deo S, Turton KL, Kainth T, Kumar A, Wieden HJ. Strategies for improving antimicrobial peptide production. Biotechnol Adv 2022;59:107968.
[126] Gan BH, Gaynord J, Rowe SM, Deingruber T, Spring DR. The multifaceted nature of antimicrobial peptides: current synthetic chemistry approaches and future directions. Chem Soc Rev 2021;50(13):7820–80.
[127] Santos JCP, Sousa RCS, Otoni CG, Moraes ARF, Souza VGL, Medeiros EAA, et al. Nisin and other antimicrobial peptides: production, mechanisms of action, and application in active food packaging. Innov Food Sci Emerg Technol 2018;48:48179–94.
[128] Liu Y, Sameen DE, Ahmed S, Dai J, Qin W. Antimicrobial peptides and their application in food packaging. Trends Food Sci Technol 2021;112:471–83.
[129] Rai M, Pandit R, Gaikwad S, Kövics G. Antimicrobial peptides as natural bio-preservative to enhance the shelf-life of food. J Food Sci Technol 2016;53 (9):3381–94.
[130] Wu Z, Li Y, Zhang L, Ding Z, Shi G. Microbial production of small peptide: pathway engineering and synthetic biology. Microb Biotechnol 2021;14 (6):2257–78.

[131] Ross AC, Liu H, Pattabiraman VR, Vederas JC. Synthesis of the lantibiotic lactocin S using peptide cyclizations on solid phase. J Am Chem Soc 2010;132(2):462–3.
[132] Erdem Büyükkiraz M, Kesmen Z. Antimicrobial peptides (AMPs): a promising class of antimicrobial compounds. J Appl Microbiol 2022;132(3):1573–96.
[133] Józefiak D, Sip A, Rutkowski A, Rawski M, Kaczmarek S, Wołuń-Cholewa M, et al. Lyophilized *Carnobacterium divergens* AS7 bacteriocin preparation improves performance of broiler chickens challenged with *Clostridium perfringens*. Poult Sci 2012;91(8):1899–907.
[134] Maldonado-Barragán A, Cárdenas N, Martínez B, Ruiz-Barba JL, Fernández-Garayzábal JF, Rodríguez JM, et al. Garvicin A, a novel class IId bacteriocin from *Lactococcus garvieae* that inhibits septum formation in *L. garvieae* strains. Appl Environ Microbiol 2013;79(14):4336–46.
[135] Li X, Jaafar R, He Y, Wu B, Kania P, Buchmann K. Effects of a *Pseudomonas* H6 surfactant on rainbow trout and I*chthyophthirius multifiliis: in vivo* exposure. Aquaculture 2022;547:737479.
[136] Wang S, Zeng XF, Wang QW, Zhu JL, Peng Q, Hou CL, et al. The antimicrobial peptide sublancin ameliorates necrotic enteritis induced by *Clostridium perfringens* in broilers. J Anim Sci 2015;93(10):4750–60.
[137] Wang HT, Yu C, Hsieh YH, Chen SW, Chen BJ, Chen CY. Effects of albusin B (a bacteriocin) of *Ruminococcus albus* 7 expressed by yeast on growth performance and intestinal absorption of broiler chickens—its potential role as an alternative to feed antibiotics. J Sci Food Agric 2011;91(13):2338–43.
[138] Huan Y, Kong Q, Mou H, Yi H. Antimicrobial peptides: classification, design, application and research progress in multiple fields. Front Microbiol 2020;11:582779.
[139] Lauková A, Chrastinová L, Plachá I, Kandričáková A, Szabóová R, Strompfová V, et al. Beneficial effect of lantibiotic nisin in rabbit husbandry. Probiotics Antimicrob Proteins 2014;6(1):41–6.
[140] Hu J, Ma L, Nie Y, Chen J, Zheng W, Wang X, et al. A microbiota-derived bacteriocin targets the host to confer diarrhea resistance in early-weaned piglets. Cell Host Microbe 2018;24(6):817–32.
[141] Cutler SA, Lonergan SM, Cornick N, Johnson AK, Stahl CH. Dietary inclusion of colicin E1 is effective in preventing postweaning diarrhea caused by F18-positive *Escherichia coli* in pigs. Antimicrob Agents Chemother 2007;51(11):3830–5.
[142] Wang HT, Li YH, Chou IP, Hsieh YH, Chen BJ, Chen CY. Albusin B modulates lipid metabolism andincreases antioxidant defense in broilerchickens by a proteomic approach. J Sci Food Agric 2013;93(2):284–92.
[143] Barboza-Corona JE, de la Fuente-Salcido N, Alva-Murillo N, Ochoa-Zarzosa A, López-Meza JE. Activity of bacteriocins synthesized by *Bacillus thuringiensis* against *Staphylococcus aureus* isolates associated to bovine mastitis. Vet Microbiol 2009;138(1–2):179–83.
[144] Zhao H, Shao D, Jiang C, Shi J, Li Q, Huang Q, et al. Biological activity of lipopeptides from *Bacillus*. Appl Microbiol Biotechnol 2017;101(15):5951–60.
[145] Rooney WM, Chai R, Milner JJ, Walker D. Bacteriocins targeting Gram-negative phytopathogenic bacteria: plantibiotics of the future. Front Microbiol 2020;11:575981.
[146] Han X, Shen D, Xiong Q, Bao B, Zhang W, Dai T, et al. The plant-beneficial rhizobacterium *Bacillus velezensis* FZB42 controls the soybean pathogen *Phytophthora sojae* due to bacilysin production. Appl Environ Microbiol 2021;87(23):e01601-21.
[147] Ma Z, Ongena M, Höfte M. The cyclic lipopeptide orfamide induces systemic resistance in rice to *Cochliobolus miyabeanus* but not to *Magnaporthe oryzae*. Plant Cell Rep 2017;36(11):1731–46.
[148] Gu Q, Yang Y, Yuan Q, Shi G, Wu L, Lou Z, et al. Bacillomycin D produced by *Bacillus amyloliquefaciens* is involved in the antagonistic interaction with the plant-pathogenic fungus *Fusarium graminearum*. Appl Environ Microbiol 2017;83(19):e01075-17.
[149] Jung WJ, Mabood F, Souleimanov A, Smith DL. Induction of defense-related enzymes in soybean leaves by class IId bacteriocins (thuricin 17 and bacthuricin F4) purified from *Bacillus* strains. Microbiol Res 2011;167(1):14–9.
[150] Zachow C, Jahanshah G, de Bruijn I, Song C, Ianni F, Pataj Z, et al. The novel lipopeptide poaeamide of the endophyte *Pseudomonas poae* RE*1-1-14 is involved in pathogen suppression and root colonization. Mol Plant Microbe Interact 2015;28(7):800–10.
[151] Lei S, Zhao H, Pang B, Qu R, Lian Z, Jiang C, et al. Capability of iturin from *Bacillus subtilis* to inhibit *Candida albicans in vitro* and *in vivo*. Appl Microbiol Biotechnol 2019;103(11):4377–92.
[152] Xiao J, Guo X, Qiao X, Zhang X, Chen X, Zhang D. Activity of fengycin and iturin a isolated from *Bacillus subtilis* Z-14 on *Gaeumannomyces graminis* var. *tritici* and soil microbial diversity. Front Microbiol 2021;12:682437.
[153] Medeot DB, Fernandez M, Morales GM, Jofré E. Fengycins from *Bacillus amyloliquefaciens* MEP(2)18 exhibit antibacterial activity by producing alterations on the cell surface of the pathogens *Xanthomonas axonopodis* pv. *vesicatoria* and *Pseudomonas aeruginosa* PA01. Front Microbiol 2019;10:103107.
[154] Yu C, Liu X, Zhang X, Zhang M, Gu Y, Ali Q, et al. Mycosubtilin produced by *Bacillus subtilis* ATCC6633 inhibits growth and mycotoxin biosynthesis of *Fusarium graminearum* and *Fusarium verticillioides*. Toxins 2021;13(11):791.
[155] Príncipe A, Fernandez M, Torasso M, Godino A, Fischer S. Effectiveness of tailocins produced by *Pseudomonas fluorescens* SF4c in controlling the bacterial-spot disease in tomatoes caused by *Xanthomonas vesicatoria*. Microbiol Res 2018;212–213:94–102.
[156] de Mattos-Shipley KMJ, Greco C, Heard DM, Hough G, Mulholland NP, Vincent JL, et al. The cycloaspeptides: uncovering a new model for methylated nonribosomal peptide biosynthesis. Chem Sci 2018;9(17):4109–17.
[157] Bi J, Tian C, Jiang J, Zhang G, Hao H, Hou H. Antibacterial activity and potential application in food packaging of peptides derived from turbot viscera hydrolysate. J Agric Food Chem 2020;68(37):9968–77.
[158] Fu L, Wang C, Ruan X, Li G, Zhao Y, Wang Y. Preservation of large yellow croaker (*Pseudosciaena crocea*) by coagulin L1208, a novel bacteriocin produced by *Bacillus coagulans* L1208. Int J Food Microbiol 2018;266:60–8.
[159] Lv X, Lin Y, Jie Y, Sun M, Zhang B, Bai F, et al. Purification, characterization, and action mechanism of plantaricin DL3, a novel bacteriocin against *Pseudomonas aeruginosa* produced by *Lactobacillus plantarum* DL3 from Chinese Suan-Tsai. Eur Food Res Technol 2018;244(2):323–31.
[160] Maky MA, Ishibashi N, Zendo T, Perez RH, Doud JR, Karmi M, et al. Enterocin F4-9, a novel O-linked glycosylated bacteriocin. Appl Environ Microbiol 2015;81(14):4819–26.
[161] Jiang H, Zou J, Cheng H, Fang J, Huang G. Purification, characterization, and mode of action of pentocin JL-1, a novel bacteriocin isolated from *Lactobacillus pentosus*, against drug-resistant *Staphylococcus aureus*. BioMed Res Int 2017;2017:7657190.
[162] Ramos B, Brandão TRS, Teixeira P, Silva CLM. Biopreservation approaches to reduce *Listeria monocytogenes* in fresh vegetables. Food Microbiol 2020;85:103282.
[163] Chopra L, Singh G, Jena KK, Sahoo DK. Sonorensin: a new bacteriocin with potential of an anti-biofilm agent and a food biopreservative. Sci Rep 2015;5(1):13412.
[164] Halimi B, Dortu C, Arguelles-Arias A, Thonart P, Joris B, Fickers P. Antilisterial activity on poultry meat of amylolysin, a bacteriocin from *Bacillus amyloliquefaciens* GA1. Probiotics Antimicrob Proteins 2010;2(2):120–5.
[165] Zhang J, Liu G, Li P, Qu Y. Pentocin 31–1, a novel meat-borne bacteriocin and its application as biopreservative in chill-stored tray-packaged pork meat. Food Control 2010;21(2):198–202.
[166] Lv X, Ma H, Sun M, Lin Y, Bai F, Li J, et al. A novel bacteriocin DY4-2 produced by *Lactobacillus plantarum* from cutlassfish and its application as bio-preservative for the control of *Pseudomonas fluorescens* in fresh turbot (*Scophthalmus maximus*) fillets. Food Control 2018;89:8922–31.
[167] Sarika AR, Lipton AP, Aishwarya MS. Biopreservative efficacy of bacteriocin GP1 of *Lactobacillus rhamnosus* GP1 on stored fish filets. Front Nutr 2019;6:29.
[168] Toral L, Rodríguez M, Béjar V, Sampedro I. Antifungal activity of lipopeptides from *Bacillus* XT1 CECT 8661 against *Botrytis cinerea*. Front Microbiol 2018;9:1315.
[169] Jia N, Xie Y, Zhang H, Liu H, Feng J, Zhu L, et al. Effect of bacteriocin treatment on storage and quality of postharvest strawberry fruit. Adv Mat Res 2012;554–556:1547–52.
[170] Tan P, Fu H, Ma X. Design, optimization, and nanotechnology of antimicrobial peptides: from exploration to applications. Nano Today 2021;39:101229.