Research
Antibiotics Alternatives—Review

The Bioprospecting of Microbial-Derived Antimicrobial Peptides for Sustainable Agriculture

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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,

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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·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
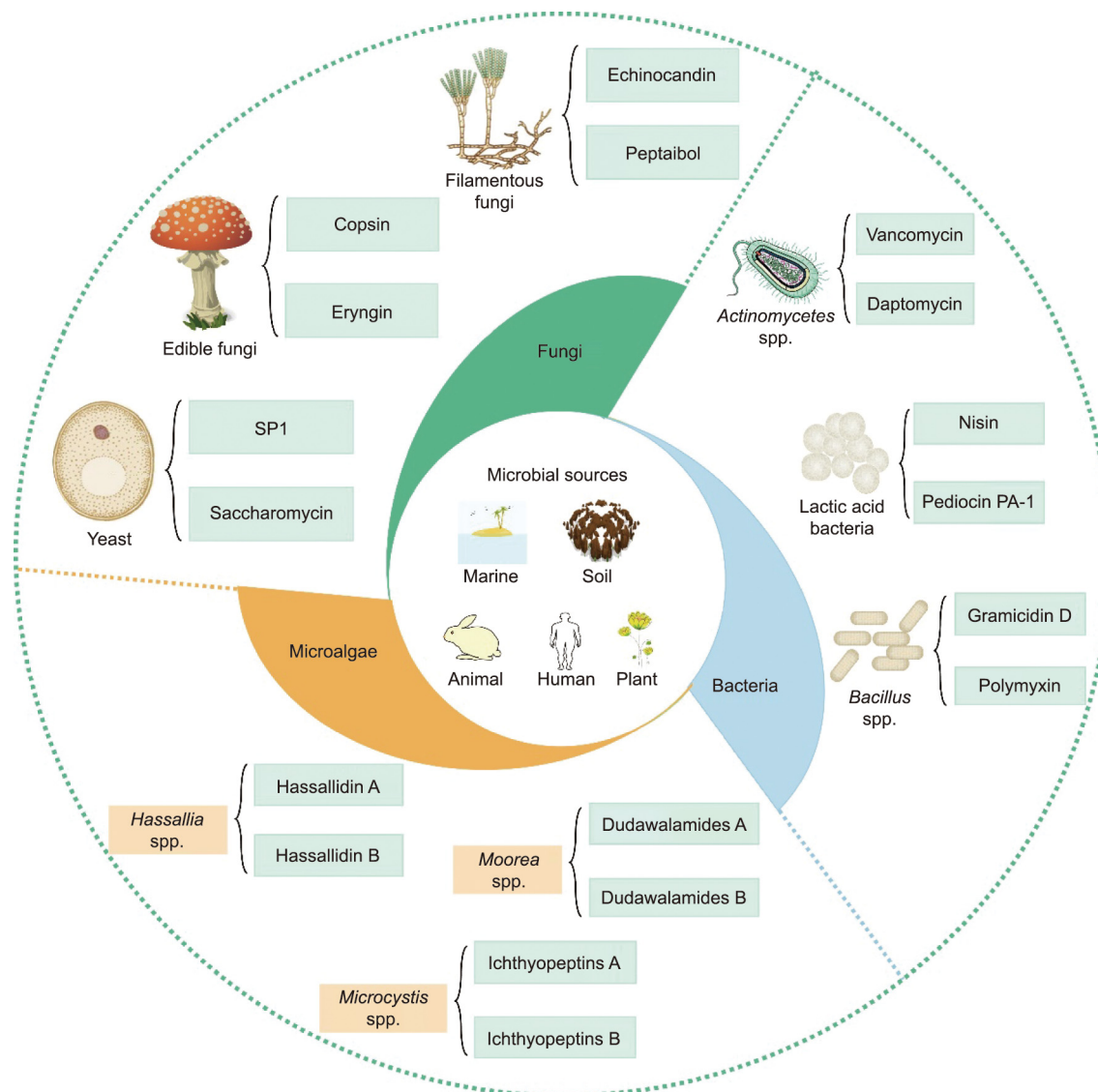

Fig. 1. AMPs occurring naturally in microbes. Producers are principally from soil, marine, animal, plant and human microbes, including bacteria, fungi and microalgae.

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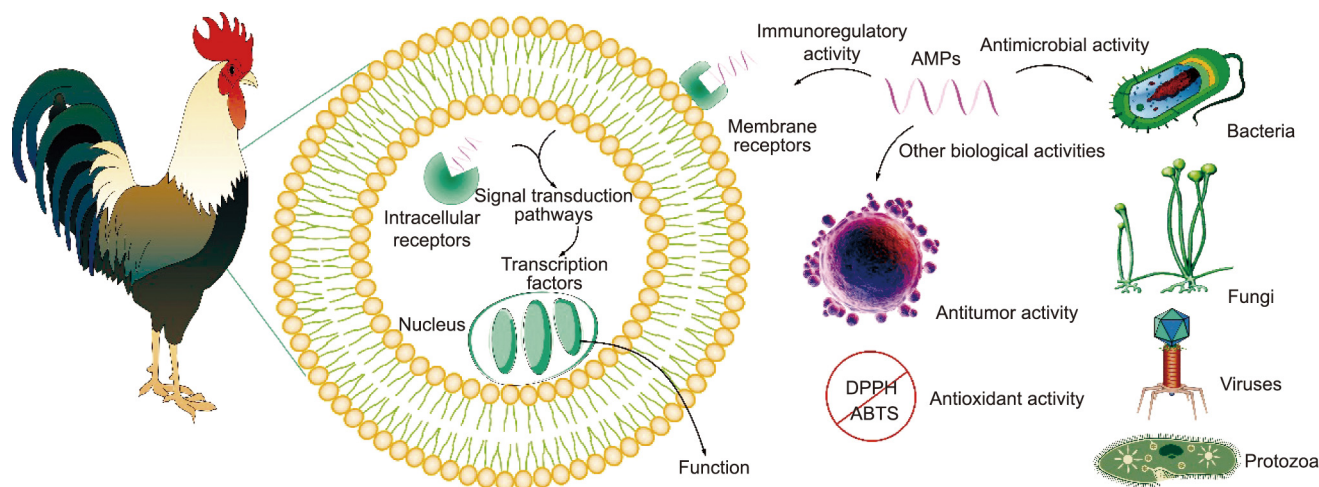
Fig. 2. Biological activity of microbial AMPs. DPPH: 1,1-diphenyl-2-picrylhydrazyl; ABTS: 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate).

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
Although 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].
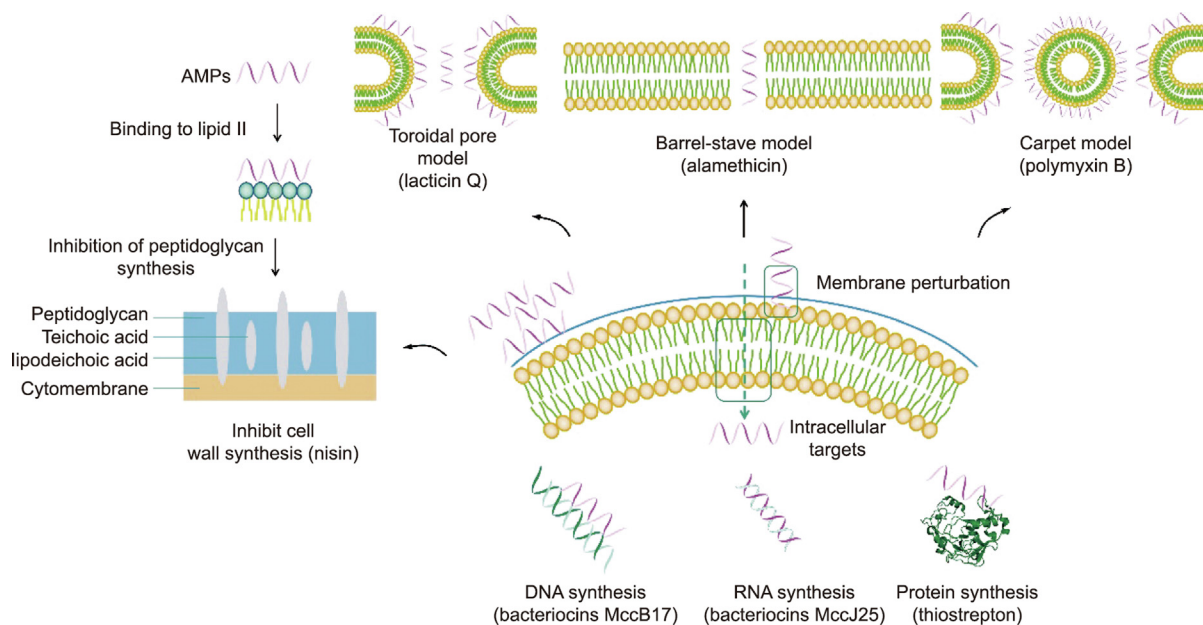
Fig. 3. Models of antimicrobial mechanisms of AMPs.

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
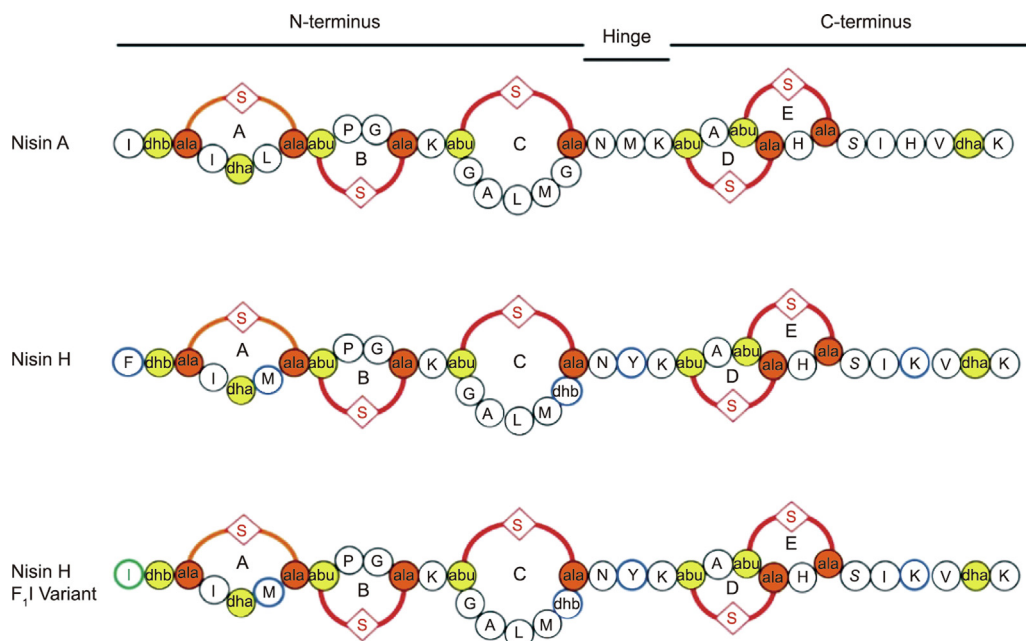
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Fig. 4. Schematic overview of the used lantibiotics nisin A, nisin H, and the nisin H F_1I variant. Blue highlights point mutations in nisin H and nisin H F_1I compared to nisin A. Yellow and orange labels are used to identify cysteine residues and 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, ©2020.

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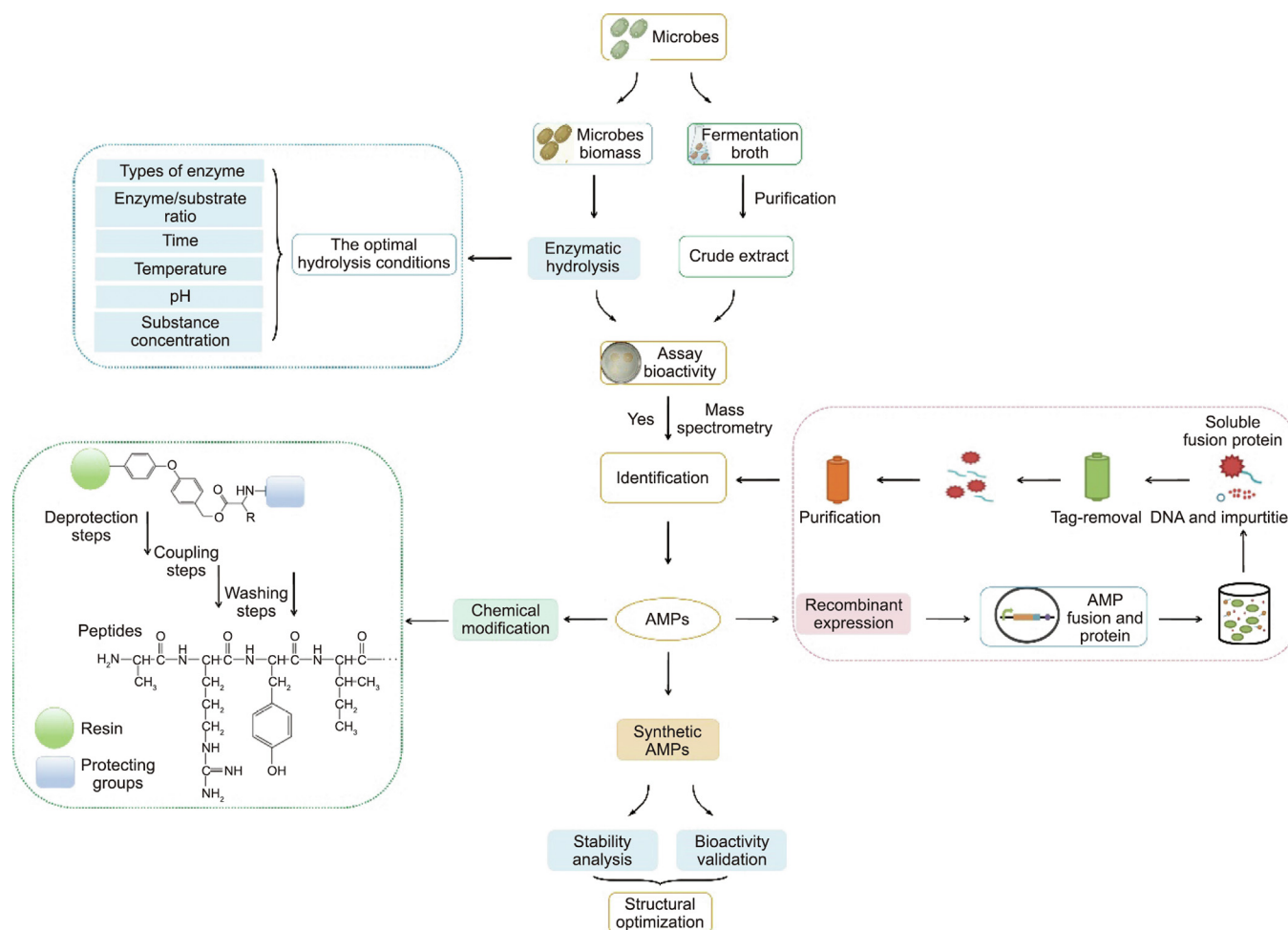
Fig. 5. General flowsheet for the preparation of AMPs.

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·L^{-1} (fusion proteins) and 1–5 mg·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 (LPSS) 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 SPSS, 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,

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]

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].

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 μg·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

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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.

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.

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