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Review article

Antimicrobial peptides: An alternative to traditional antibiotics

Shuaiqi Ji [a,c], Feiyu An [a,b], Taowei Zhang [a,c], Mengxue Lou [a,b], Jiawei Guo [a,c], Kexin Liu [a,c], Yi Zhu [a,b], Junrui Wu [a,b,c,*], Rina Wu [a,b,c,**]

[a] College of Food Science, Shenyang Agricultural University, Shenyang, 110866, PR China
[b] Liaoning Engineering Research Center of Food Fermentation Technology, Shenyang, 110866, PR China
[c] Shenyang Key Laboratory of Microbial Fermentation Technology Innovation, Shenyang, 110866, PR China

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ABSTRACT

As antibiotic-resistant bacteria and genes continue to emerge, the identification of effective alternatives to traditional antibiotics has become a pressing issue. Antimicrobial peptides are favored for their safety, low residue, and low resistance properties, and their unique antimicrobial mechanisms show significant potential in combating antibiotic resistance. However, the high production cost and weak activity of antimicrobial peptides limit their application. Moreover, traditional laboratory methods for identifying and designing new antimicrobial peptides are time-consuming and labor-intensive, hindering their development. Currently, novel technologies, such as artificial intelligence (AI) are being employed to develop and design new antimicrobial peptide resources, offering new opportunities for the advancement of antimicrobial peptides. This article summarizes the basic characteristics and antimicrobial mechanisms of antimicrobial peptides, as well as their advantages and limitations, and explores the application of AI in antimicrobial peptides prediction amd design. This highlights the crucial role of AI in enhancing the efficiency of antimicrobial peptide research and provides a reference for antimicrobial drug development.

1. Introduction

The introduction of antibiotics in the early 20th Century ended the era of human helplessness against bacterial infections. Since then, antibiotics have been widely used in clinical practice, saving tens of thousands of lives, and have been hailed as “an epoch-making new invention of medicine” [1]. However, irrational combinatorial use of antibiotics and unguided increases in antibiotic dosage have led to the emergence of many drug-resistant bacteria. This means that drugs used to treat infections are no longer as reliably effective, resulting in a serious threat to human health [2–5]. Drug-resistant bacteria have become a major public health threat in the 21st Century. For instance, the UK government stated in a review of antimicrobial resistance that antibiotic-resistant bacterial infections will cause approximately 10 million deaths per year by 2050 [6]. In addition, the misuse of antibiotics has caused a significant ecological damage to the environment. Animals cannot completely metabolize most antibiotics; as a result, they excrete excess antibiotics and metabolites into the environment through feces and urine, thereby impacting soil and aquatic organisms and insects and expanding drug resistance [7–9]. Therefore, there is an urgent need to identify alternatives to antibiotics.

In the field of antimicrobial research, various chemically synthesized antimicrobial compounds such as benzimidazole analogs, imidazole derivatives, hydrazone compounds, and fluorosulfonic aromatic analogs have shown significant antimicrobial potential owing to their unique chemical structures and mechanisms [10–15]. At the same time, Antimicrobial peptides have also received increasing attention owing to their unique antimicrobial mechanisms and broad-spectrum antimicrobial properties compared to those of traditional antibiotics. Antimicrobial peptides act on bacterial cell membranes, rapidly killing the bacteria by disrupting the cell membrane integrity [16]. Moreover, antimicrobial peptides have multitarget effects, enabling them to simultaneously act on multiple biological processes and cellular structures. Additionally, the diversity and modifiability of peptides means that they can be chemically linked to other molecular structures and designed to target specific bacterial types, thereby enhancing treatment specificity and effectiveness [17–19]. Although antimicrobial peptides have great antimicrobial properties, clinical investigations of

* Corresponding author. College of Food Science, Shenyang Agricultural University, PR China.
** Corresponding author. College of Food Science, Shenyang Agricultural University, PR China.
E-mail addresses: junruiwu@126.com (J. Wu), wrn6956@163.com (R. Wu).

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antimicrobial peptides have gradually revealed their limitations. The majority of antimicrobial peptides now developed and utilized are natural compounds taken from animals, plants, and microorganisms, which have a high cost, low biological activity, and may cause hemolytic and cytotoxic byproducts; these limitations have severely impeded their development [20]. With the development of computer technology, the intervention of AI technology has become a new direction in the study and application of antimicrobial peptides. Utilizing AI technology, researchers can predict the antimicrobial and hemolytic properties of peptides, enabling the design of antimicrobial peptide sequences with high antimicrobial activity and low cytotoxicity. These techniques have also helped establish structure-function relationships of antimicrobial peptides, optimize the production process, accelerate the mining of pharmacophores, predict the interactions of antimicrobial peptides with other drugs, and design novel antimicrobial peptides capable of combating multidrug-resistant pathogens. Combined with high-throughput screening techniques, AI can also rapidly select the most promising candidates from a large number of peptide sequences. In short, AI technology provides a great boost to the research, development and application of antimicrobial peptides, offering new possible solutions to the problem of antibiotic resistance [21,22].

In this article, we provide an overview of the fundamental characteristics of antimicrobial peptides and the mechanism of research into antimicrobial mechanisms, and summarize the application of AI techniques to antimicrobial peptide mining and design while discussing the advantages and disadvantages of antimicrobial peptides. We believe that continued research into the inhibitory mechanisms of antimicrobial peptides may accelerate the process of developing safer and more effective antimicrobial drugs as well as alternatives to antibiotics. In addition, we believe that the application of AI to antimicrobial peptides not only greatly improves the speed of discovery and optimization of novel antimicrobial peptides, but also mines unprecedented bioactive relationships through in-depth data analysis and pattern recognition, providing an innovative and efficient solution to face the challenge of antibiotic resistance in the future.

2. Properties of natural antimicrobial peptides

Many kinds of natural antimicrobial peptides with different amino acid sequences and structures have been described. They can further be classified according to origin, synthesis method, secondary structure, and biological function (Fig. 1).

2.1. Origins of natural antimicrobial peptides

2.1.1. Animal-derived antimicrobial peptides

Animal-derived antimicrobial peptides occur widely in nature, these include insects, mammals and amphibians, which can produce a large variety of antimicrobial peptides. According to the composition and structure of amino acids of insect antimicrobial peptides, they can be divided into 3 categories: linear α-helical peptides without cysteine residues, β-sheeted globular-structured peptides, and peptides containing specific amino acid residues, such as proline or glycine. Cecropins belong to the first category, do not possess disulfide bonds in their molecular structure, show resistance to gram-negative and -positive bacteria, and have a molecular weight of about 4 kDa [23]. Defensins, antimicrobial peptides widely distributed in different insect orders, have α-helix and β-folded structures, which are stabilized by intramolecular disulfide bonds in β-sheeted globular-structured peptides [24]. Proline-rich antimicrobial peptides contain 15–39 amino acids, of which

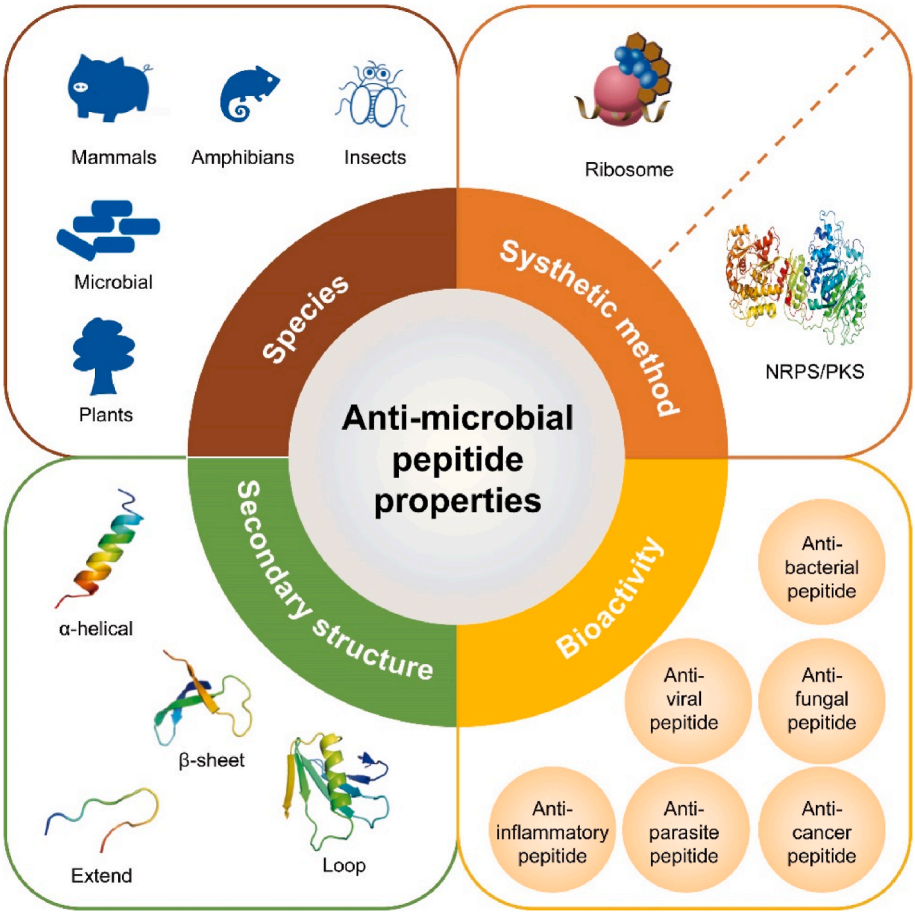

Fig. 1. Properties of antimicrobial peptides.

25 % are proline, have a molecular weight of 2 kDa, and are positively charged. Two structural domains have been described for proline-rich antimicrobial peptides, one of which is highly conserved and shows antimicrobial activity against both bacteria and fungi, while the other is less conserved and more specific in its antibiotic activity. Glycine-rich antimicrobial peptides have molecular weights of 10–30 kDa, and are highly specific for gram-negative groups of bacteria. Protegrins isolated from porcine leukocytes are characterized by their activity against gram-negative bacteria, gram-positive bacteria, and HIV [25]. Esculentin-2P and ranatuerin-2P, secreted by the skin of North American leopard frogs, and dermaseptin-1, secreted by the skin of the South American *Phyllomedusa bicolor*, can significantly reduce pathogen infectivity [26]. Because amphibian antimicrobial peptides are efficient, safe, and are infrequently associated with antibiotic-resistance, they have been extensively studied and have been successfully applied in clinical practice.

2.1.2. Plant-derived antimicrobial peptides

Throughout the lengthy evolutionary process of microbial invasion, plants have developed a distinct set of natural defenses, with plant-derived antimicrobial peptides playing the primary defense function. Plant-derived antimicrobial peptides, generally 20–60 amino acids with molecular weights of 2–7 kD and +2-+9 charges, are categorized into Thionins, Defensins, Heveins, Knottins, Lipid Transfer Proteins (LTPS), and Snakins. Thionins, found in graminaceous plant seeds, are basic proteins with antibacterial and antifungal properties [27]. Defensins are widespread in plant organs and inhibit fungi by altering the ion flow. Heveins present in lectin domains show potent antifungal activity. Knottins, which are the smallest, but functionally diverse, have hormone-like and antimicrobial activities. LTPS, binding various lipids, are termed "nonspecific LTPS". Snakins, which are structurally similar to thionins, prevent bacterial polymerization and show potent antimicrobial activities against diverse microorganisms [28].

2.1.3. Microbial-derived antimicrobial peptides

Microbial-derived antimicrobial peptides, including bacteriocins, cyclic peptides, lipopeptides, and glycopeptides, have notable antimicrobial properties but are less researched compared to plant and animal-derived peptides. Commonly used in food preservation, key peptides like nisin from *Streptococcus lactis*, ε-polylysine from *Streptomyces*, and pediocin PA-1 from *Pediococcus pentosaceus* are approved for use in the food industry [29]. Enterocin AS-48 from *Enterococcus* effectively reduces *Listeria* on strawberries [30], while a peptide derived from *Bacillus subtilis* ATCC 6633 fermentation broth effectively inhibits *Haemophilus parasius* [31].

2.2. Modes of natural antimicrobial peptide synthesis

2.2.1. Ribosomal synthesis

In 1925, Gratia discovered microcins in *Escherichia coli*, ribosomally synthesized antimicrobial peptides found in various microbial metabolites [32]. These peptides are categorized into three classes based on structure, amino acid content, enzyme sensitivity, size, and thermal stability.

Class I peptides are small (<5 kDa), consisting of 19–38 amino acids with lanthionine and β-methyllanthionine, subdivided into Ia, Ib, Ic, and Id. Ia includes amphiphilic cationic peptides, such as Pep5, epidermin, and nisin, with varying thioether bonds that bind non-specifically to bacterial surfaces; Ib, stable peptides with a spherical β-type structure, include mersacidin and actagardin; Ic, similar to haloduracin, has a two-component structure with antimicrobial action; and Id are linear, undergo post-translocation modification, and form cyclic structures such as subtiliosin A [33].

Class II peptides, 25–60 amino acids, <10 kDa, lack lanthionine and β-methyllanthionine, are thermally stable and membrane-active. IIa contains a conserved YGNGVX sequence that targets *Listeria monocytogenes*, including coagulin and SRCAM37 [34]. IIb, with its DWTXWSXL sequence, acts synergistically, similar to enterocins L50A/L50B [35]. IIc, which forms ring structures, includes enterocin AS-48, whereas IId consists of different linear peptides, including the non-pediocin-like peptide bacteriocin.

Class III consists of polypeptides with molecular weights >30 kDa, a broad-spectrum of bacterial inhibition, and a thermally unstable regional structure. These include lacticin B from *Lactobacillus acidophilus*, megacins A-216 and A-19213 from *Bacillus megaterium*, and helveticin J from *Lactobacillus helveticus* 481.

2.2.2. Non-ribosomal synthesis

Nonribosomal antimicrobial peptides, typically <3 kDa, include lipopeptides, glycopeptides, glycolipid peptides, and cyclic peptides synthesized via multifunctional enzyme systems, such as nonribosomal peptide synthetases (NRPs) and polyketide synthases (PKs). These enzymes modify peptides via acylation, heterocyclization, N-methylation, cyclization, and glycosylation to produce active antimicrobials. NRPs consist of multi-modular enzymes arranged in a line with each module containing adenylate (A), peptidyl carrier protein (PCP), and condensation (C) domains for substrate activation, transportation, and peptide formation [36]. The final NRPS module includes a thioesterase domain that facilitates peptide release via hydrolysis or cyclization, thereby enabling continuous synthesis [37]. PKs, similar to NRPs, have acyltransferase (AT), ketone synthase (KS), and acyl carrier protein (ACP) domains. Key non-ribosomal peptides include Bacillus surfactin, iturin, fengycin, polymyxin, rhizocticin, and amicoumacin [38].

2.3. Secondary structure of natural antimicrobial peptides

The primary structures of antimicrobial peptides vary widely, while the secondary structures include α-helical, β-folded, loop, and extended structures. The secondary structure, which is generally identified by circular dichroism, is related to inhibitory activity and is also a key factor of the inhibitory mechanism.

α-Helical antimicrobial peptides form near cell membranes, generally amphiphilic and positively charged, with key residues like lysine and arginine enhancing helicity and antimicrobial activity [39]. Proline or D-amino acids disrupt this structure, thereby reducing its effectiveness. Antimicrobial peptides featuring a β-sheet structure are common in plants and animals, effectively inhibiting bacteria and fungi. Based on cysteine content, they are categorized into pure β-sheet, triple, and mixed β-sheet/α-helical structures. Cysteine stabilizes these peptides and facilitates their crossing of cell membranes [40]. Circular dichroism chromatograms show characteristic peaks for α-helical and β-folded peptides. Loop structure peptides form ring structures with disulfide bonds and often coexist with α-helical and β-sheet peptides, showing broad-spectrum antimicrobial effects. These structural details were revealed using nuclear magnetic resonance (NMR) spectroscopy [41]. Extended structure peptides, cysteine-free but rich in glycine and proline, form disordered linear structures that interact with membrane lipids through hydrogen bonds or van der Waals forces [42]. Alanine substitution in these peptides alters their structure, enhancing membrane activity. An example is indolicidin from bovine leukocytes [43].

2.4. Biological functions of natural antimicrobial peptides

Natural antimicrobial peptides are highly specific, encompassing antibacterial, antifungal, antiviral, antiprotozoal, antiparasitic, anticancer, and anti-inflammatory properties. Antibacterial and antifungal peptides are widely used in medical, food, and agricultural sectors; antiviral peptides, like EK1C4, have shown effectiveness against COVID-19 S protein-mediated membrane fusion [44]. Antiprotozoal and antiparasitic peptides act on cell membranes to alter metabolic activities [45]. Anticancer peptides disrupt tumor cell membranes or inhibit cancer cell proliferation with low toxicity to normal cells [46].

Anti-inflammatory peptides work by inhibiting inflammatory factors and modulating related pathways, with promising applications in treating various inflammatory diseases despite dosage and in vivo efficacy challenges [47].

Currently, dozens of antimicrobial peptides are being evaluated as antimicrobial agents in clinical trials (Table 1). P-113 effectively inhibits Candida, has been used for the treatment of oral diseases, and has been applied in phase II clinical trials for HIV [48]. Iseganan, which is derived from the parent antimicrobial peptide protegrin-1, has successfully passed phase IV clinical trials and will be used to treat oral mucositis in patients with head and neck cancer treated with radiation therapy. Since antimicrobial peptides exert their bactericidal effect by inducing a host immune response, they have been widely studied as adjuvant anticancer agents [49]. Most clinical trials of antimicrobial peptides are still limited to local treatment. Therefore, further research is required for the basic and clinical application of antimicrobial peptides.

3. Inhibitory mechanisms of antimicrobial peptides

As the resistance of pathogens to existing antibiotics increases, a deeper understanding of the mechanisms of action of antimicrobial peptides is crucial for the design and synthesis of new drugs. This understanding can lead to more effective treatment options and optimized clinical applications, thereby increasing treatment efficiency while minimizing potential side effects. Currently, the mechanisms of action of antimicrobial peptides are primarily categorized into two types: membrane disruption and non-membrane disruption. Detailed research into these two mechanisms not only aids in the development of new antimicrobial strategies but also provides valuable insights into how antimicrobial peptides function within complex biological systems.

3.1. Mechanisms of membrane perturbation

The interaction between antimicrobial peptides and bacterial cell membranes is a complex and precise process that involves various molecular and mechanical forces. These forces collectively drive the initial binding between antimicrobial peptides and bacterial membranes [50]. Positively charged antimicrobial peptides interact electrostatically with negatively charged phospholipid groups on bacterial membranes, leading to the accumulation of peptides on the membrane surface. Upon reaching a certain threshold concentration, the hydrophobic groups insert into the lipid bilayer. During this process, peptide concentration, molecular structure, and lipid composition are key factors. At high concentrations, antimicrobial peptide molecules aggregate on the membrane surface, altering membrane fluidity and structure, and leading to membrane thinning or pore formation. This disruption not only affects the bacterial cell membrane barrier function but may also cause an imbalance in the exchange of materials inside and outside the cell, thereby affecting bacterial growth. Antimicrobial peptides can also cause cell death by reducing the proton gradient (loss of membrane potential), terminating ATP production, and disrupting cellular metabolism [51–53]. This process can be further studied and validated through molecular dynamics simulations. Molecular dynamics can be used to observe and analyze the interactions between antimicrobial peptides and cell membranes at the atomic level, revealing how the molecular dynamics of peptides affect the physical state of the membrane. For example, Wu et al. used molecular dynamics simulations to analyze the interaction between the natural antimicrobial peptide As-CATH4 and cell membranes and found that this peptide exerts strong antimicrobial activity through membrane permeation [54]. Similarly, Adelaide et al. explored the structural characteristics of the SAAP-148, derived from LL-37, and its mechanism of action on the phospholipid membranes of mammalian and bacterial cells using solid-state NMR spectroscopy and molecular dynamics simulations [55].

Based on the manner by which antimicrobial peptides disrupt the cell membrane, mechanisms of membrane perturbation can be divided into

Table 1
Antimicrobial peptides in clinical trials.

Name	Sources	Stage	Application
HB-50	Derivative of Cecropin analogue	Preclinical	Antimicrobial agents
HB-107	Derivative of Cecropin B	Preclinical	Treatment of wounds
HB1345	Synthetic lipohexapeptide	Preclinical	Treatment of acne
HB1275	Synthetic lipohexapeptide	Preclinical	Treatment of *Trichophyton* infections
AP138	Derivative of Plectasin	Preclinical	Treatment of MRSA implant infections
AP139	Derivative of Arenicin	Preclinical	Antimicrobial agents
Plectasin	Fungal defensin	Preclinical	Antimicrobial agents
Bac8c	Derivative of Bactenecin	Preclinical	Antimicrobial agents
MU1140	*Streptococcus mutans*	Preclinical	Inhibition of Gram-positive bacteria
Bacteriocin OR-7	*Lactobacillus salivarius*	Preclinical	Inhibition of Gram-positive bacteria
Buforin II	*Bufo bufo* gargarizans	Preclinical	Antimicrobial agents
Novarifyn (NP432)	Synthetic antimicrobial	Preclinical	Antimicrobial agents
CA(1–7)M (2–9)	Derivative of Cecropin A/melittin splice	Preclinical	Antimicrobial agents
Colicin E1	*Escherichia coli*	Preclinical	Antimicrobial agents
IMXC001	Derivative of natural antimicrobial peptide fragment	Preclinical	Treatment of sepsis
ETD151	Derivative of Heliomycin analogue	Preclinical	Antifungal agents
SB006	Derivative of Cecropin analogs	Preclinical	Treatment of wounds
IDR-1002	Derivative of Bactenecin	Preclinical	Inhibition of *Staphylococcus aureus* biofilms
Lactocin 160	*Lactobacillus rhamnosus*	Preclinical	Antifungal agents
lactoferricin-B	Milk lactoferrin hydrolysate	Preclinical	Antifungal agents
Nisin A	*Lactococcus lactis*	Preclinica	Antimicrobial agents, birth control pills
Demegel (D2A21)	Derivative of Cecropin analogue	Preclinical	Antifungal agents, Antimicrobial agents
Planosporicin	*Actinomycetes*	Preclinical	Inhibition of Gram-positive bacteria
Pediocin PA-1	*Pediococcus acidilactici*	Preclinical	Antimicrobial agents
Syphaxin (SPX1-22)	Leptodactylus syphax	Preclinical	Antimicrobial agents
Ruminococcin C	*Ruminococcus gnavus*	Preclinical	Anti-clostridial
Temporin10a	Pelophylax nigromaculatus	Preclinical	Regulate the immune system, Antimicrobial agents
WLBU2 (PLG0206)	Derivative of LL37 based design	I	Antimicrobial agents, antiviral agents
Surotomycin (CB-183315)	Cyclic lipopeptide	II	Treatment of *Clostridium difficile* infection
P-113	Human saliva	II	Treatment of oral mucositis
XMP.629	From the BPI	II	Treatment of acne
MX-594AN	Derivative of Indolicidin	IIb	Treatment of acne
SGX942	A synthetic, 5-amino acid peptide and innate defense regulator (IDR)	II	Treatment of oral mucositis
Brilacidin (PMX-30063)	Derivative of Defensin analogue	II	Antimicrobial agents, Treatment acute bacterial skinand skin structure infections (ABSSSI)
POL7080	Productin of *Pseudomonas aeruginosa*	II	Antimicrobial agents

(*continued on next page*)

Table 1 (*continued*)

Name	Sources	Stage	Application
C16G2	Derivative of Novispirin analogue	II	Remove plaque, inhibit the demineralization of *Streptococcus mutans* and enamel in saliva
DPK 060 (GKH17-WWW)	Derivative of human protein kininogen	II	Antimicrobial agents
LTX-109	Optimization of lactoferrin	II	Antimicrobial agents
EA-230	Derivative of humanchorionic gonadotrophinhormone	II	Immune regulation, enhance immunity
CZEN-002	From alpha melanocyte stimulant	II	Resistance of candida albicans infection and anti-inflammatory
Exeporfinium chloride (XF-73)	Derivative of Dicationic porphyrin	II	Antimicrobial agents
Hlf1-11	From the first 11 amino acid residues of human lactoferrin	II	Antimicrobial agents
LL-37	In mammals	II	Antimicrobial agents, antibiofilm Treatment of metastatic melanoma
PAC-113	Saliva in the tissue protein in nature	II	Treatment of oral candidiasis
Melimine	Derivative of Melittin/ protamine splice	II	Antimicrobial agents
Novexatin (NP213)	Derivative of Human α-defensin and human β-defensin design	II	Antifungal agents
OP-145	Derivative of Human Cathelicidin LL-37	II	Antimicrobial agents
Lytixar	Synthetic analogue tripeptide	II	Antimicrobial agents
PAC113 (Nal-P-113)	Derivative of Histatin analogue	II	Antimicrobial agents
Opebacan	Human recombinantendotoxin-binding protein	II	Inhibit gram-negative bacteria and promote wound healing
XMP-629 (XOMA-629)	Derivative of Human Recombinant endotoxin-bindingprotein	II	Treatment cream acne, inhibition of gram-negative bacteria
Pexiganan (MSI-78)	Derivative of Magainin	III	Treatment of infectious foot ulcers in diabetic patients
Iseganan (IB-367)	Derivative of Protegrins	III	Treatment of oral lotion ulcerative oral mucositis
Iseganan	Endogenous antimicrobial peptides in pigs	III	Treatment of oral mucositis
MBI 594AN	An indolicidin analogue derived from the cathelicidin structure	III	Treatment of acne
MX-226	Antimicrobial peptide derivatives of bovine indoliridine	III b	Reduce catheter infection
Dalbavancin	lipoglycopeptide antibiotic	III	Antimicrobial agents
Enfuvirtide	By Hlv 1 gp41 protein derivative HRZ area	III	Treatment of HIV
p2TA (AB103)	Synthetic deca-peptide containing d-amino acids	III	Treatment of necrotizing soft tissue infection
Mel4	Derivative of Methylimine analogue	III	Antimicrobial agents
PG-1 protegrin	Cathelicidin family	III	Antimicrobial agents
Murepavadin	Protegrin-1 synthetic mimic	III	Treatment of bacterial infections
Omiganan (CLS001)	Derivatives similar to xenopus xenopus antimicrobial peptides	III	Having anti-inflammatory effects on rosacea
Talactoferrin	Derivative of Lactoferrin analogue	III	Promote the maturation and proliferation of anti-tumor CD^{8+}T cells and NK cells
Neuprex	From the BPI	III	Treatment for meningitis

four categories: a barrel-stave, carpet, aggregate, and toroidal pore models (Fig. 2) [56]. (1) In the barrel wall model, when the number of antimicrobial peptide molecules reaches a threshold, they combine to form a polypeptide, which enters the hydrophobic core region of the cell membrane vertically. The hydrophobic side of the polypeptide combines with the non-polar lipid acyl side of the lipid bilayer to form a barrel-shaped pore. SK84, Hf-1, and Ctx-Ha are characterized in their mechanism of action by the barrel-stave model. (2) In the carpet model, the aggregation of antimicrobial peptides is a change in the curvature of the cell membrane, and the cell membrane disintegrates inward. Cell membrane dissolution occurs in a dispersive manner without involving channel formation, where peptides are not necessarily inserted into the hydrophobic membrane core [57]. (3) In the aggregation model, positively charged antimicrobial peptide molecules combine with bacterial outer membrane LPS or peptidoglycans to form micellar complexes, which compete with divalent metal ions (i.e., Mg^{2+} and Ca^{2+}) for binding sites; this induces the surrounding bacteria to agglomerate and prevent the release of bacterial endotoxins, thus disrupting the assembly of macromolecules on the membrane surface to achieve the antimicrobial effect. After entering the cell membrane, antimicrobial peptides change their internal conformation to form a colloidal complex with the cell membrane lipid molecules; this complex extends as a cohesive material across the cell membrane into the cell. Lin et al. conducted N-terminal lipidation of antimicrobial peptides MSI-78 (4–20) and pardaxin (1-22) and observed a significant enhancement in their antimicrobial activity. Their research indicated that these peptides disrupt and leak cell membranes by inserting into the lipid bilayer via an aggregate model [58]. (4) In the toroidal pore model, after binding to the cell membrane, the hydrophobic group of antimicrobial peptides is inserted vertically into the phospholipid bilayer and forms a transmembrane channel by binding to the phospholipid head. This transmembrane channel disrupts the hydrophobic center and, thus, the integrity of the cell membrane. As the ratio of antimicrobial peptides to lipids increases, the antimicrobial peptides begin to self-aggregate and orient vertically to the cell membrane to form supramolecular polymers, which form circular pores in the cell membrane, causing a leakage of intracellular small molecules and leading to bacterial apoptosis. Won et al. designed MSI-78 and VG16KRKP peptides, which employ carpet and toroidal pore mechanisms to lyse cell membranes [59]. Jin et al. developed derivative peptides that showed stronger antibacterial activity against *Staphylococcus aureus* than the parent peptide GHb, functioning by forming toroidal pores on the cell membrane [60].

3.2. Mechanisms of non-membrane perturbation

3.2.1. Cell wall-targeting peptides

Antimicrobial peptides that target the cell wall do not disrupt the integrity of the cytoplasmic membrane, but instead, they enter the cell through transmembrane transport. These peptides inhibit the formation of bacterial cell walls by suppressing the synthesis of cell wall precursor molecules, such as lipid II. Lipid II, a key cell wall synthesis precursor, is

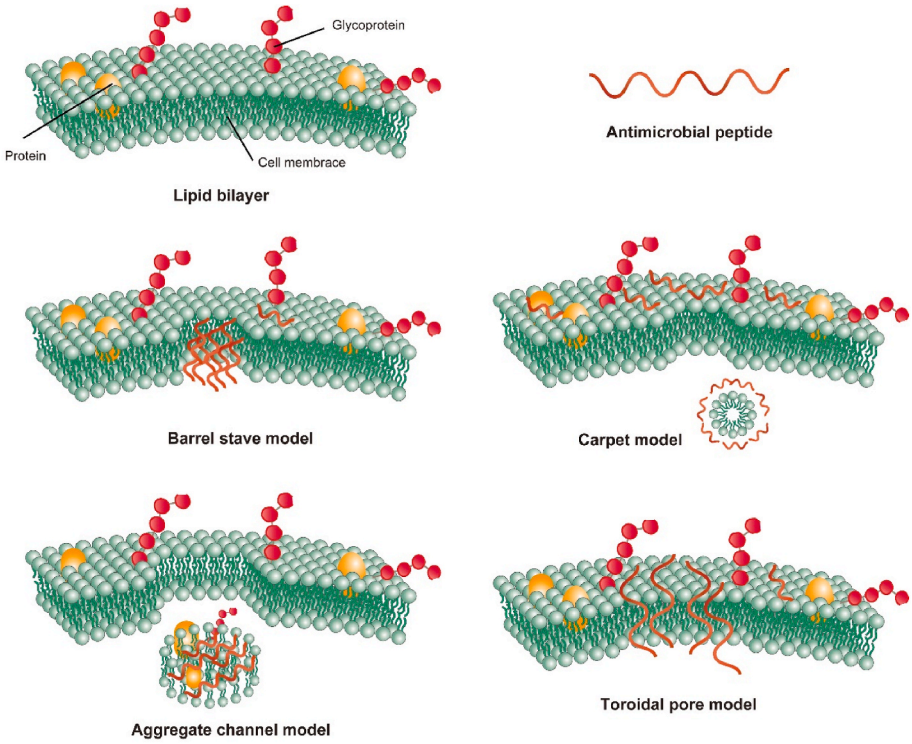

Fig. 2. Model of antimicrobial peptides membrane disturbance.

composed of a peptidoglycan component consisting of N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), along with an attached peptide chain and a lipid molecule. This structure not only plays a connecting role in cell wall synthesis but is also essential for the transmembrane transport of peptidoglycans and cell wall cross-linking. Antimicrobial peptides, by affecting lipid II synthesis, can further inhibit peptidoglycan transport and cell wall stability, exerting an inhibitory effect. For example, gallidermin targets lipid II by binding its first and second thioether rings to the lipid II pyrophosphate [61]. Cochrane et al. found that the lipopeptide Tridecaptin A(1) exerts its bactericidal effect by binding to the cell wall precursor, lipid II, on the bacterial cell membrane, thereby disrupting the proton motive force [62]. Zhao et al. created a novel antimicrobial peptide called TL19, which shows stronger antimicrobial activity than peptides with only one lipid II binding site by binding to two different lipid II binding sites [63]. In addition to targeting lipid II, some antimicrobial peptides can directly act on peptidoglycan chains, affecting the cell wall structure and function by degrading or disrupting peptidoglycan chains [64].

Antimicrobial peptides targeting the cell wall also influence the stability and integrity of the cell wall by activating specific enzymes and signaling pathways within the cell. They increase the cell wall permeability and affect it from inside the cell membrane by inducing the release of lysosomes and activating autolysins, thereby hindering cell wall growth. Studies have shown that TriTonX-100 activates autolysins and increases the permeability of the cell wall [65]. Yasir et al. discovered the cationic antimicrobial peptide Mel4, which induces the release of autolysins, leading to *Staphylococcus aureus* cell death [66].

In gram-negative bacteria, antimicrobial peptides can interact with special cell wall components, such as the outer membrane, thereby increasing its permeability. This weakens the barrier function of the bacteria, making them more susceptible to external attacks. Magainin peptides from the skin of African clawed frogs enhance the outer membrane permeability of gram-negative bacteria, inducing the loss of intracellular potassium ions and the formation of vesicular structures on the cell surface, thereby exerting an inhibitory effect. Antimicrobial peptides can interfere with the synthesis of wall teichoic acid (WTA) in gram-positive bacteria, thus inhibiting their growth [67].

The action of antimicrobial peptides on cells can also involve inhibiting bacterial cell wall synthesis by restricting bacterial cell respiration. Cell wall synthesis is an energy-intensive process, and when antimicrobial peptides disrupt bacterial respiration and reduce ATP production, they affect cell wall synthesis [68]. Xia et al. found that a synthetic cationic peptide, D11, enhances attachment to lipopolysaccharides and membrane phospholipids, increasing membrane permeability, facilitating antibiotic uptake, and subsequently disrupting the proton motive force (PMF), affecting the respiratory chain, promoting reactive oxygen species (ROS) production, and ultimately leading to cell death [69].

3.2.2. *Intracellular-targeting peptides*

Some antimicrobial peptides' transmembrane processes are not completely known. In addition to the receptor-mediated translocation transmembrane pathway, it has been demonstrated that some antimicrobial peptides can enter the cell directly through defects in the membrane boundary and pass the cell membrane directly by producing a circular breach. The intracellular inhibitory activities of these peptides include: inhibiting the synthesis of DNA, RNA, or other biomolecules, disrupting key metabolic enzymes and cellular respiration processes, damaging nucleic acid repair pathways, and inhibiting cell division (Fig. 3).

Antimicrobial peptides inhibit DNA and RNA synthesis, thereby disrupting the transfer of genetic information in bacterial cells and affecting the replication of bacterial genetic material and protein expression. Proteins are key components of cellular structures and functions including metabolism, cell repair, and defense mechanisms. Therefore, the action of antimicrobial peptides not only inhibits bacterial growth but may also lead to metabolic imbalances and physiological dysfunctions within the cell. For example, buforin II penetrates the bacterial cell membrane to inhibit the replication of genetic material (i.e., DNA and RNA), which is highly dependent on the complementarity of the N-terminal region of histone H2A [70]. TO17 acts on *Staphylococcus aureus* by entering the cell through the cell membrane and inducing DNA

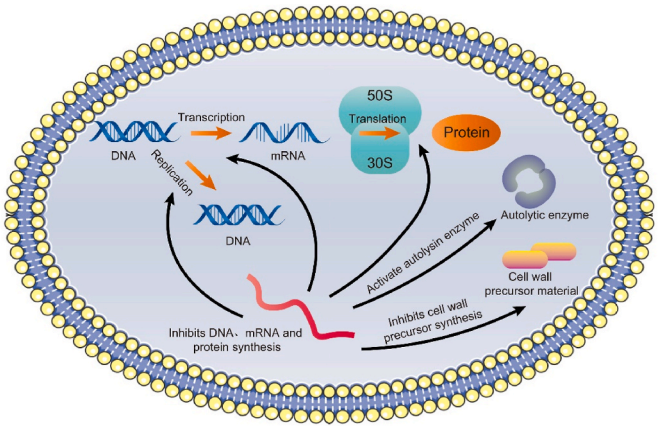

Fig. 3. Model of non-membrane perturbation in the cell membrane of antimicrobial peptides.

and RNA degradation, leading to rapid cell death [71]. Bac binds to the intracellular protein transporter SbmA and undergoes internalization to inhibit the synthesis of the 70S ribosome, resulting in the inhibition of bacterial reproduction. Bac5 and Bac7 inhibit protein and RNA synthesis as well as respiration in *Escherichia coli* and *Klebsiella pneumoniae*, leading to a decrease in ATP content [72].

After cell entry, antimicrobial peptides may affect the activity of enzymes responsible for energy production and cellular metabolism. Some antimicrobial peptides may bind directly to key enzymes in the respiratory chain, thereby blocking electron transfer and ATP production. A reduction in ATP levels can significantly reduce bacterial activity. Antimicrobial peptides may also interfere with enzymatic activity in other metabolic pathways, including the synthesis and breakdown of carbohydrates, lipids, and proteins, thereby affecting cell growth. Additionally, antimicrobial peptides can cause metabolic imbalances and physiological dysfunctions within the cell, leading to the accumulation of toxic intermediates and further damage to the cell's physiological state [73]. The action of gramicidin Son *Bacillus subtilis* causes the shedding of phospholipid synthase and cytochrome in bacterial cells, resulting in impaired ATP synthesis, which in turn affects bacterial respiration [74].

Antimicrobial peptides can also exert their inhibitory effects by disrupting bacterial nucleic acid damage repair pathways. These peptides may directly bind to DNA repair enzymes, inhibit their function, or interfere with the signal transduction pathways related to DNA repair. This interference can block the bacterial response to DNA damage, leading to genetic instability and cell death. The antimicrobial peptide BTP-001 was recently shown to reduce the activation of several enzymes in the TCA cycle, thereby inhibiting DNA repair [75].

In addition, antimicrobial peptides inhibited cell division and blocked the cell cycle. Temporin L blocked *Escherichia coli* cell division by interacting with the tubulin FtsZ, which has GTPase activity [76]. Lcn972 blocked cell division by specifically binding to Lipid II in numerous cell wall precursors, thereby affecting septum formation [77].

3.2.3. Targeted biofilms

Scholars domestically and internationally are paying increasing attention to antimicrobial peptide as a new anti-biofilm agent that has been applied to clinical therapy. It is regarded as a safe and effective anti-biofilm medicine. The mechanism of anti-biofilm activity of antimicrobial peptides is primarily comprised of prevention of initial adhesion of bacterial cells to attached surfaces, interference with the expression of signaling molecules involved in biofilm formation, and removal of extracellular matrix in bacterial biofilms [78].

In investigations on cell surface adhesion disruption, it was discovered that the Cathelicidin family member LL-37 inhibits *Pseudomonas aeruginosa* biofilm formation by upregulating the expression of genes linked to type I bacterial hair production, increasing the rubbing motion of bacteria, and decreasing their adhesion to plastic film surfaces [79]. Research indicates that Temporin-GHa, extracted from the frog Hylarana guentheri, along with its derivative peptides GHaR and GHa11R, are capable of reducing the adhesiveness of *Streptococci* [80].

Antimicrobial peptides primarily interfere with the regulation of the bacterial biofilm population sensing system and the prevention of severe bacterial response as signaling molecules involved in biofilm formation. Studies have demonstrated that the QS system is strongly connected with pathways such as bacterial biofilm formation, pathogenicity-related virulence factor expression, and numerous drug resistance metabolic pathways [81]. The Las system and the Rh1 system are two distinctive QS systems found in *Pseudomonas aeruginosa* it was found that LL-37 prevented *Pseudomonas aeruginosa* biofilm formation by inhibiting the expression of key signaling molecules within the *Pseudomonas aeruginosa las I* and *rhlR* QS systems and drastically downregulating more than 50 genes involved in biofilm formation [82]. In addition, antimicrobial peptides exert anti-biofilm activity via influencing the severe stress response prominent in bacteria. IDR1018, DJK-5 and DJK-6 inhibit biofilm formation by blocking the biosynthesis of (p)ppGpp, an important intracellular signaling molecule that mediates the stress response of bacterial cells to environmental stress. By reducing *spoT* promoter activity, DJK-5 and IDR-1018 also have a response on bacterial stress responses and prevent *Pseudomonas aeruginosa* biofilm formation [83].

The dense structure of the extracellular matrix (EPS), which is made up of extracellular polysaccharides, nucleic acids, proteins, and lipids, creates a physiological barrier to the penetration of antibacterial drugs. EPS can also capture and store antibacterial drugs, which significantly lessens their inhibitory effect on bacteria in biofilms [84]. By eliminating or degrading EPS components, the antimicrobial peptide can exert anti-biofilm activity. An anti-biofilm peptide produced by maggots of the red-headed fly Calliphora vicina was able to degrade biofilm substrates produced by drug-resistant *Escherichia coli*, *Staphylococcus aureus*, and *Acinetobacter baumannii* [85]. On the other hand, the fish antimicrobial peptide Piscidin-3 has the ability to operate as a nuclease by creating covalent connections with Cu^{2+} through its N-terminal amino acid, disrupting the extracellular DNA of *Pseudomonas aeruginosa* and removing the extracellular matrix [86].

3.2.4. Immunomodulatory mechanisms

Antimicrobial peptides serve multifaceted roles within the immune system, their functions extending well beyond mere pathogen neutralization. These small proteinaceous entities are critically important due to their immunomodulatory capabilities, playing pivotal roles in both innate and adaptive immune responses. Investigating these roles offers insights into the broad-ranging impact of antimicrobial peptides on the immune system (Fig. 4).

Antimicrobial peptides can recruit immune and epithelial cells to sites of inflammation or infection by releasing chemotactic factors, thus promoting wound healing and angiogenesis. An example is LL-37, which plays a role in both nonspecific and specific immune responses, capable of chemotaxing various immune cells [87].

Antimicrobial peptides contribute to modulating inflammatory responses, either by inducing or regulating these mechanisms, aiding the body in its defense against pathogen invasion [88]. Furthermore, antimicrobial peptides are vital in maintaining the balance of the immune system, influencing the apoptotic pathways of immune cells. This regulatory ability is key to modulating the intensity and duration of immune responses, thus ensuring an effective defense against infections while preventing excessive tissue damage due to immune overreaction [89].

Additionally, certain antimicrobial peptides like magainin have the ability to target cancer cells and induce their apoptosis, while being less toxic to normal cells. These peptides not only activate adaptive immune

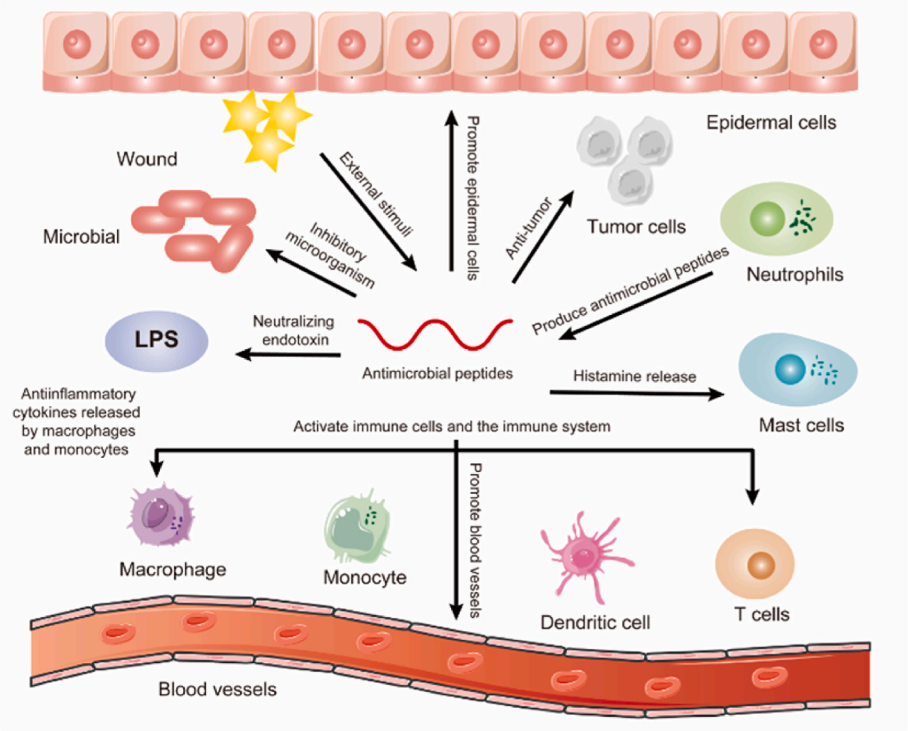

Fig. 4. Antimicrobial peptides modulate immune model.

system responses but also enhance overall immunity. Magainin targets cell membranes through a non-receptor pathway, dissolving hematopoietic and solid tumor cells with minimal toxicity to normal blood lymphocytes. It inhibits the production of pro-inflammatory cytokines induced by lipopolysaccharides (LPS), activates adaptive immune system responses, and strengthens immunity [90].

4. Advantages and limitations of antimicrobial peptides

4.1. Advantages

4.1.1. Natural antimicrobial peptides are relatively safe

The chemical nature of natural antimicrobial peptides as a biologically endogenous active molecule allows their degradation by proteases of the human digestive system. Compared to the low degradability of traditional antibiotics, antimicrobial peptides are also more easily degradable in the environment and do not cause secondary issues related to pollution, bacterial resistance, or ecosystem disruption. In addition, as the synthesis and secretion of natural antimicrobial peptides occur in response to cues from the environment, they can be used as a signal for immune mediation to enhance the immunity of the body. For instance, one of the functions of intestinal epithelial cells is to prevent the entry of microorganisms; thus, human intestinal epithelial cells secrete a variety of antimicrobial peptides that are well targeted to intestinal pathogenic bacteria to avoid over-stimulating immune cells in the intestine or inflammation [91].

4.1.2. Natural antimicrobial peptides are less susceptible to microbial resistance

Antibiotics target specific sites inside and outside the bacterial cell membrane to exert their effects. Bacterial resistance can arise from alterations to these target sites. For instance, β-lactam antibiotics, like penicillin, lose effectiveness when their extracellular membrane targets in bacteria mutate, preventing bindin [92]. The mechanism of action of quinolone antibiotics is mainly related to DNA topoisomerases. These enzymes can be classified into different types, among which topoisomerases II and IV play an important regulatory role in bacterial growth, and inhibition of one of them leads to bacterial death [93]. Resistance to quinolone antibiotics occurs due to mutations in one or more loci of genes encoding DNA gyrase or topoisomerase located on the chromosomes of gram-negative bacteria, where the antibiotic agent loses affinity to the target site and thus loses its effect. Other mechanisms of bacterial resistance include efflux pump systems, degradation of antibiotic agents, and altered cell membrane permeability. Whenever the corresponding gene is activated or mutated, it may cause the loss of antibiotic action and promote antibiotic resistance [94].

Compared to antibiotics, antimicrobial peptides are safer and more efficient (Table 2). Antimicrobial peptides act on structurally conserved components of cell membranes and induce changes in cell membranes, which require prolonged mutagenesis for complete recovery of cell membrane structure, greatly reducing the probability of bacteria developing resistance. With regard to methicillin-resistant *Staphylococcus aureus*, antimicrobial peptides target the cell membrane, thus avoiding the mechanism of resistance and maintaining their inhibitory effect [95]. Apart from disrupting the integrity of cell membranes, antimicrobial peptides can exert their biological activities by interfering with cell metabolism and interacting with intracellular substances. The combination of multiple mechanisms not only increases their antimicrobial efficacy, but also reduces the opportunities for bacteria to develop resistance.

In contrast to antibiotics, which disrupt the body's immune system, antimicrobial peptides can complement immunomodulatory mechanisms. In higher eukaryotes, a class of antimicrobial peptides called host defense peptides act as leukocyte chemoattractants that enhance the activity of leukocytes and pro-inflammatory cytokines in the immune system [96]. Human keratinocytes are immune cells that produce the antimicrobial peptide calprotectin, which modulates the host immune response against viral infections [97]. Furthermore, antimicrobial peptides act synergistically with the immune system through the modulation of cell membrane adhesion, transfer, and respiratory burst activities [98]. For example, adding cecropin to the diet of weaning piglets increases the spleen and thymus indexes, which in turn strengthens their

Table 2
Comparison of antimicrobial peptides and antibiotics.

Characteristics	Antimicrobial Peptides	Antibiotics
Chemical Essence	Peptides and peptide complexes	Mostly consisting of aromatic hydrocarbons and their derivatives
Generation Method	Genes encode products related to innate immunity synthesized on ribosomes are small peptide proteins with some nutritional value	Enzyme-mediated synthesis of secondary metabolites
Action Mechanism	Combining the physical action of anions and cations to act on cell membranes or targets, multiple modes of action are thus less likely to produce antibiotic-resistant	Bacteria can easily develop antibiotic-resistant through mutation by binding to specific receptors on the bacterial cell membrane or intracellular, with receptors of a limited type
Immunomodulation	Engaging in the immune regulation of the body and enhancing the immunity of the body	Long-term use impairs vital organs such as the liver and heart, and destroy the immune system of the body
Action Speed	Rapid action	Slow action
Antibacterial Spectrum	Broad-spectrum of bacterial inhibition is effective against bacteria, fungi, pathogens, and parasites	Inhibition of bacteria only
Biodegradation	Completely decomposable	Unable to decompose completely
Pollution of the environment	No pollution	Damage to the ecological environment
Toxicity	Unknown	Known

immune system. Human β-defensins and cathelicidins also induce the secretion of cytokines and chemokines and enhance the innate immune response [98,99].

Some evidence exists for the development of resistance against the mechanisms of action of antimicrobial peptides. Although it is widely believed that antimicrobial peptides do not cause serious resistance as they target the conserved regions of cell membranes, genetic mutation induced by some antimicrobial peptides in specific cell targets may allow the development of resistance in bacteria. The mechanisms of resistance to antimicrobial peptides are divided into intrinsic and inducible tolerance mechanisms. Bacteria, such as *Serratia*, *Proteus*, and *Providencia*, are inherently resistant to inhibition by cationic antimicrobial peptides. Inducible tolerance mechanisms refer to the development of resistance by bacteria previously sensitive to antimicrobial agents through genetic mutations, acquisition of resistance genes, or spontaneous development of resistance mutations. Inducible resistance mechanisms can be manifested through the hydrolysis of antimicrobial peptides by proteases, modifications in the target of action of antimicrobial peptides, and efflux pumps. The highly expressed outer membrane protease OmpT of enterohemorrhagic *Escherichia coli* degrades LL-37 and deactivates its function [100]. Mutation in the *gyrB* gene of *Escherichia coli* impairs the inhibitory effect of microcin B17 on DNA synthesis [101]. Although antimicrobial peptide resistance has been reported, a combination of several antimicrobial peptides or antibiotic–antimicrobial peptide therapy significantly reduces the occurrence of resistance and improves the safety of clinical antibiotics. For instance, DP7–antibiotic combination therapy eliminated vancomycin and azithromycin resistance in *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* [102]. Chen et al. linked the antimicrobial peptide UBI21-49 (TGRAKRRMQYNRR) to the antibiotic CAP via glutaric anhydride acylation [103]; Although research on combination therapies are only in the exploratory stage, their development provides a novel opportunity for the application of antimicrobial peptides. However, complete replacement of antibiotics with antimicrobial peptides would require a more in-depth understanding of 1) the mechanisms that promote resistance to antimicrobial peptides, 2) the diverse mechanisms of action between different pathogens, and 3) their bioactivity and safety between different hosts and developmental stages.

4.2. Issues in the application of natural antimicrobial peptides

Despite their advantages, natural antimicrobial peptides are not a panacea and have many inherent limitations to their application, including high production cost, unstable activity, sensitivity to proteases and extreme pH, and incomplete toxicological safety data.

4.2.1. High production costs

Although natural antimicrobial peptides are present in most organisms, their levels are relatively low. Additionally, their extraction is affected by degradation reactions and can only be achieved by complex chromatographic techniques, such as gel-, ion exchange-, and reversed-phase chromatography [104]. Peptides are also lost in each step of the extraction and purification processes, resulting in a relatively low yield. Moreover, antimicrobial peptides originating from protected species cannot be sustainably produced.

4.2.2. Unstable activity

Natural antimicrobial peptides are susceptible to protease digestion, which limits their application in vivo. Additionally, maganin and tensin, for example, are sensitive to other environmental conditions, such as salinity and acidity, greatly limiting their use in clinical practice [105].

The instability of natural antimicrobial peptide activity is influenced by several factors. Gruden and Ulrih suggested that sequence length, hydrophobicity, charge number, amphipathicity, secondary structure, and specific amino acids are related to antimicrobial peptide activity, though no clear quantitative relationship existed between these factors and biological activity [106]. Moreover, these factors are interdependent; thus, it is difficult to improve the stability of natural antimicrobial peptide activity by altering only one or some of these factors. However, the factors affecting activity will prove important in the design and synthesis of artificial antimicrobial peptides.

4.2.3. Concerns of toxicological safety

Experiments determining the toxicological safety of natural antimicrobial peptides are not yet comprehensive or systematic, and our knowledge of the mechanisms of action is largely model-based. Natural antimicrobial peptides are not completely non-toxic, as they have many characteristics similar to those of eukaryotic-localized signal peptides and can be translated into cells, thus causing toxicity. Potential side effects include induction of apoptosis, mast cell degranulation, or extracellular DNA transfer. The hemolytic nature of antimicrobial peptides, caused by their selective action on erythrocyte membranes, is also an important obstacle to their safe application [107]. Antimicrobial peptides alter the biochemical properties of erythrocyte membranes, enhancing their fluidity or causing them to rupture. Whether an antimicrobial peptide has hemolytic activity depends on the structural organization of the N-terminal domain. The hemolytic activity of an antimicrobial peptide can be eliminated with site-specific mutations, which is currently the main approach used in synthetic antimicrobial peptides [108]. Changing the sequence structure of amino acids to form different peptide secondary structures has different degrees of effect on hemolytic and antimicrobial activities.

In summary, the defects of antimicrobial peptides limit the development of antimicrobial peptides, especially in terms of production cost, even if the chemical synthesis method is used, the antimicrobial peptides activity will be reduced and the cost still cannot be reduced to meet the demand of mass production. Therefore, there is an urgent need to design new safe and non-toxic antimicrobial peptides to promote the development of antimicrobial peptides.

5. Application of AI to antimicrobial peptides

5.1. Prediction of novel antimicrobial peptide resources using AI

The traditional method of mining antimicrobial peptide resources is experimentation, such as isolation and purification, to verify their antimicrobial activity and mechanism of action. Using the traditional method ensures high identification rates; however, given the number and diversity of antimicrobial peptides, this method becomes particularly complicated and costly in terms of time, resources, and expertise. Therefore, the amount of resources gained is sparse compared to the investment, and the degree of optimization that this allows is unacceptable [109]. Along with the rapid development of life- and computer sciences, new antimicrobial peptide mining methods have become available, including AI and bioinformatics, which have become the basis for discovery, prediction, and optimization of antimicrobial peptide structures using mined resources [110]. AI is an important branch of computer science that involves the research and development of machines that learn, solve problems, and mimic reasoning, similar to conscious intelligence [111]. It is worth noting that while AI provides powerful tools for antimicrobial peptide prediction, they are not a solution that completely replaces laboratory work. Instead, they are viewed more as a complement to laboratory studies that can help researchers quickly screen the most promising candidates, thus saving time and resources (Fig. 5).

5.1.1. Prediction of novel antimicrobial peptides based on machine learning

Machine learning is a higher-order prediction method for complex models that can process large amounts of data in a short period of time [112]. Machine learning-based antimicrobial peptide prediction methods apply statistics, induction, and inference and can identify nonlinear associations between samples. The general process of predicting and designing antimicrobial peptides using AI includes data collection and feature extraction, model selection, as well as model training and evaluation (Fig. 6).

In the data collection and preprocessing stage, firstly, a large amount of antimicrobial peptide and non-antimicrobial peptide sequence data need to be collected and the dataset is divided into a training set and a test set [113]. The preprocessing includes data cleaning, redundancy removal, and data normalization to ensure the quality and applicability of the data. In the feature extraction and selection stage, feature selection and extraction is a key step in determining the effectiveness of the

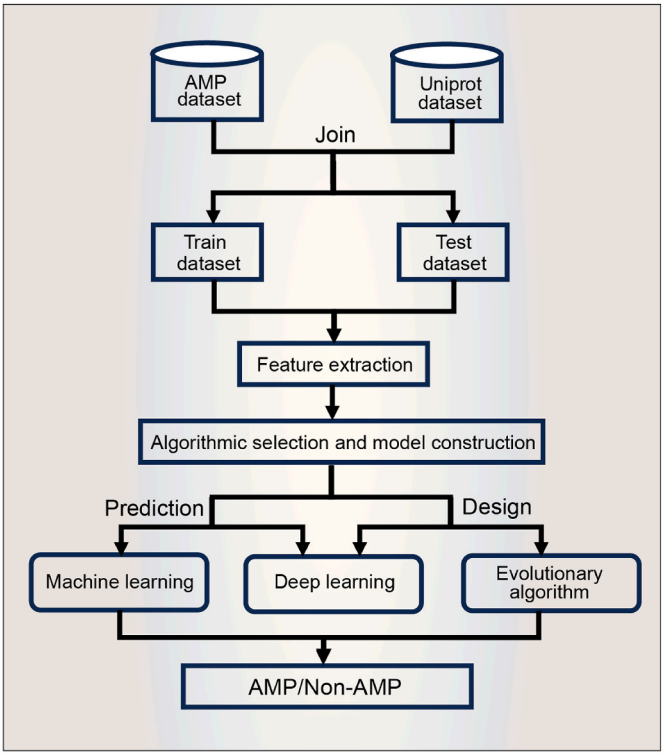

Fig. 6. AI-based antimicrobial peptide prediction and design workflow.

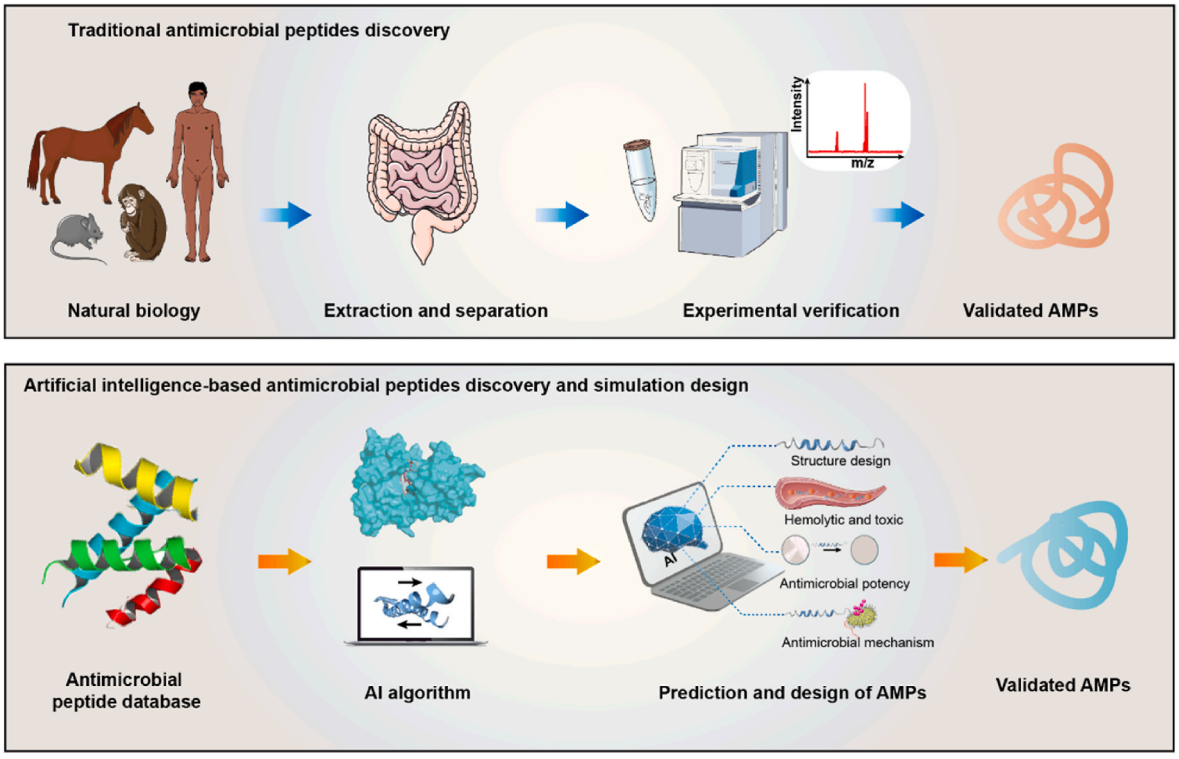

Fig. 5. Traditional antimicrobial peptides discovery and AI-based antimicrobial peptides discovery and simulation design.

model, the amino acid sequence of the antimicrobial peptide, its spatial structure, and its physicochemical properties can be used as potential features, and the study shows the correlation between specific amino acid combinations or patterns and antimicrobial activity. These features can be extracted by various bioinformatics tools, such as amino acid composition analysis, PSSM (Position-Specific Scoring Matrix), hydrogen bond distribution and pattern recognition [114].

Appropriate algorithmic model selection is crucial for accurate antimicrobial peptide prediction. Traditional algorithms in machine learning, including Support Vector Machines (SVM), random forests (RF), K-nearest neighbors (KNN), and logistic regression, have unique advantages and have achieved varying degrees of success in antimicrobial peptide prediction. SVM is adept at handling high-dimensional data and effectively determining decision boundaries in complex feature spaces. Lee et al. developed an SVM-based classifier to analyze and identify α-helical antimicrobial peptides, successfully revealing their functional commonalities and sequence homologies [115]. Wan et al. selected features such as amino acid composition, N5C5, k-space, and PSSM. Using the SVM algorithm model, they built a predictive model for anticancer peptides, which is important for anticancer drug discovery [116]. RF improves prediction accuracy and stability by constructing multiple decision trees. Wani et al. used a large and diverse dataset to explore various machine learning prediction models applied to antimicrobial peptide classification [117]. Testing revealed that models based on RF had the best predictive performance and identified key features. Bhadra et al. studied an antimicrobial peptide prediction method based on the RF algorithm, which accurately predicted the distribution patterns of amino acid properties in sequences. Tests on benchmark datasets showed that this model outperformed existing methods in terms of accuracy, including Matthew's correlation coefficient (MCC) and the area under the receiver operating characteristic curve (AUC-ROC) [118]. The KNN is an instance-based learning method that classifies or regresses by finding the closest K neighbors of a test sample in the feature space. This algorithm is simple and intuitive but may be computationally intensive for large datasets and sensitive to feature scaling. Jan et al. used a PSSM, pseudo-amino acid composition, dipeptide composition, and their combinations to extract significant features from antimicrobial peptide sequences. They employed algorithms such as KNN, random forest, and SVM, and the model demonstrated high accuracy on both independent and training datasets [119]. Logistic regression is a widely used statistical model for binary classification problems and is predicted by estimating the probability of an event's occurrence. Lv et al. established the ensemble model AMPpred-EL based on ensemble learning, LightGBM, and logistic regression and showed that the model predictions on the benchmark datasets were superior to those of other algorithms [120].

Model training and evaluation involve the use of a test set to validate the performance of the model, further ensuring prediction accuracy and reliability. This step not only assesses the model's performance in handling unknown data but also ensures its effectiveness in practical applications. Evaluation metrics such as accuracy, recall, precision, and F1 score not only measure the model's capability to correctly predict antimicrobial peptides but also reflect its sensitivity and accuracy in differentiating between positive and negative class samples. These comprehensive evaluation results can guide researchers in making the necessary model adjustments and optimizations, thereby enhancing the overall performance of antimicrobial peptide prediction.

5.1.2. Prediction of novel antimicrobial peptides based on deep learning

Deep learning technology has emerged as a powerful tool for predicting novel antimicrobial peptides. It processes and analyzes biological data using complex neural network models to identify potential antimicrobial peptide sequences. The core advantage of deep learning is its ability to automatically learn and extract high-level features from data without manual intervention, enabling it to handle more complex and abstract data patterns. Additionally, the automatic feature extraction capability of deep learning reduces the dependence on prior biological knowledge, offering new directions and methodologies for antimicrobial peptide discovery and development. Similar to machine learning, deep learning requires a substantial amount of data during the data collection and preprocessing stages. These datasets typically include known antimicrobial peptide sequences and their biological characteristics. Preprocessing involves standardization, noise reduction, and data consistency. However, compared to traditional machine learning, deep learning can process raw data more effectively, thereby reducing the dependency on complex feature engineering. Deep learning differs from machine learning in that it employs more complex multilayered neural network models to process data. Deep learning models typically consist of multilayer neural networks, such as Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs) and their variants, Graph Convolutional Networks (GCNs), and hybrid models [121,122].

CNNs extract local features in data through convolutional layers [123]. Each convolutional layer consists of multiple convolutional kernels that slide over the input data to extract features and reduce their spatial dimensions through pooling layers. CNNs can effectively extract local patterns and features of antimicrobial peptide sequences, such as local combinations and spatial arrangements of amino acids. Hussain et al. developed a method for predicting short antimicrobial peptides (sAMPs) based on two deep convolutional models, RESNET-50 and VGG-16. This method outperforms previous technologies in terms of accuracy and efficiency and is significant for assisting computer-aided drug design and virtual screening [124]. Su et al. designed a predictive model using a multiscale convolutional network that contained convolutional layers with multiple filter lengths capable of utilizing all potential features captured by multiple convolutional layers [125]. Yan et al. developed MBC-attention, a model that combines a multibranch CNN architecture with an attention mechanism to predict the experimental minimum inhibitory concentration of antimicrobial peptides against *Escherichia coli*. This model significantly outperformed traditional machine learning methods in terms of the average Pearson correlation coefficient and root mean square error [126].

RNNs are neural networks designed to process sequential data and are capable of handling dependencies between data points over time. Long Short-Term Memory (LSTM), an improved version of the RNN, addresses the issue of vanishing gradients encountered by traditional RNNs with long sequences. RNNs and LSTMs are particularly suited for processing sequence data, making them highly effective for predicting the types of amino acids at specific positions in a sequence and their biological activities, and efficiently capturing long-distance dependencies within sequences [127]. Youmans et al. utilized a bidirectional LSTM recurrent neural network to extract features from the amino acid sequences of antimicrobial peptides. By iteratively processing the peptide sequences in both directions using a bidirectional LSTM network, they obtained a finite-length feature vector for classification, thus enhancing the efficiency of antimicrobial peptide classification [128]. Ma et al. combined various natural language processing neural network models, including LSTM, attention mechanisms, and BERT, to identify candidate antimicrobial peptides from human gut microbiome data and successfully discovered new peptides that remain effective against drug-resistant gram-negative pathogens [129].

GCNs are specialized neural networks that process graph-structured data. In GCNs, data are represented as graphs, where nodes represent amino acids and edges indicate interactions or chemical bonds between them. GCNs can be used in antimicrobial peptide prediction to analyze and understand the complex interactions between amino acids and their impact on antimicrobial activity [130]. Sun et al. designed a framework based on GCNs to identify lactic acid bacteria antimicrobial peptides (LABAMPs). By constructing a heterogeneous graph based on amino acids and tripeptides and their relationships, and learning the weights of GCNs, they achieved a higher identification accuracy than other machine learning algorithms [131]. Puentes et al. developed a deep

learning model, AMPs-Net, based on GCNs, which improved the average precision by 8.8 % compared to existing state-of-the-art methods, and was able to predict the antimicrobial and antiviral capabilities of numerous antimicrobial peptides with high accuracy. In addition, researchers have identified multifunctional peptides with potential therapeutic effects by combining deep learning with molecular dynamics simulations [132].

Hybrid models also play a crucial role in antimicrobial peptide prediction by merging the advantages of CNNs and RNNs for comprehensive analysis of antimicrobial peptide characteristics [133,134]. In these models, CNN layers are used to extract the local features of the sequence data, enabling the model to capture key local patterns in antimicrobial peptide sequences. RNN layers, particularly variants such as LSTMs, were used to process the contextual relationships of these local features throughout the sequence. Through this synergistic action, hybrid models not only enhance the capability of recognizing data features but also improve the overall predictive performance. Yao et al. established a deep learning-based framework, DeepAFP, to identify antifungal peptides (AFPs) efficiently. It combines multiple CNN branches with bidirectional LSTM layers and transfer learning strategies, demonstrating a strong predictive capability for AFPs and accelerating AFP development and fungal infection treatment [135]. Tang et al. designed an MLBP bioactive peptide prediction model, a multi-label deep learning approach that can simultaneously predict multiple functions such as anticancer, antidiabetic, antihypertensive, anti-inflammatory, and antimicrobial activities. The MLBP model uses peptide sequence vectors as input and extracts features through embedding, CNNs, and bidirectional gated recurrent unit layers, thereby exhibiting outstanding predictive performance in identifying multifunctional peptides [136].

Training deep learning models involves substantial computation, often requiring high-performance computing resources such as GPUs. During the training process, the models adjust the network parameters to reduce prediction errors using optimization methods, such as the backpropagation algorithm and gradient descent. Similar to machine learning methods, deep learning models require validation using independent test sets. Moreover, owing to their complexity, deep learning models must address the issue of overfitting and adopt appropriate strategies such as dropout and regularization.

5.2. Design of antimicrobial peptides using AI simulation

Traditional methods of optimizing antimicrobial peptides involve the use of amino acid sequence modification techniques [137]. However, because sequence modification cannot compensate for all influencing factors and has a relatively low design turnover rate, the introduction of AI technology has opened new possibilities for the design and optimization of antimicrobial peptides. AI plays a crucial role in antimicrobial peptide design, not only improving traditional amino acid sequence modification techniques but also expanding researchers' horizons in exploring new types of antimicrobial peptides. By utilizing templates from antimicrobial peptide databases, researchers can more efficiently design new antimicrobial peptides with specific spatial structures and functions (Table 3). These databases provide a wealth of information, allowing AI technologies to perform precise and complex molecular designs in three-dimensional space, thereby generating antimicrobial peptides with potentially high biological activity [138,139]. In the AI design of antimicrobial peptides, there are two main approaches: designs based on evolutionary algorithms and *de novo* designs based on deep learning. Each method has its own characteristics and, together, contributes to the forefront of antimicrobial peptides research and new drug discovery.

5.2.1. Design of antimicrobial peptides based on evolutionary algorithms

Recently, antimicrobial peptides design based on evolutionary algorithms has become an important research topic. This method is derived from the process of natural selection and genetic variation in

Table 3
Antimicrobial peptides databas

Database name	Web Address	Application	Reference
DRAMP	http://dramp.cpu-bioinfor.org/	Data repository of antimicrobial peptides	[157]
SAPD	http://oma.terkko.helsinki.fi:8080/~SAPD	Synthetic antibiotic peptides database	[158]
APD	http://aps.unmc.edu/AP/	A tool for research and education the antimicrobial peptides	[159]
PenBase	http://www.penbase.immunaqua.com	The shrimp antimicrobial peptides	[160]
AMPer	http://www.cnbi2.com/cgi-bin/amp.pl	A database and an automated discovery tool for gene-coded antimicrobial peptides	[161]
Defensins	http://defensins.bii.a-star.edu.sg/	A manually curated database and information source devoted to the defensin family of antimicrobial peptides	[162]
AntiBP2	http://www.imtech.res.in/raghava/antibp2	Prediction of improved antimicrobial peptides	[163]
Bactibase	http://bactibase.pfba-lab-tun.org/	Bacteriocin characterization	[164]
RAPD	http://faculty.ist.unomaha.edu/chen/rapd/index.php.	Data resources for synthesis and recombinant antimicrobial peptides	[165]
BAGEL	http://bioinformatics.biol.rug.nl/websoftware/bagel	Mining bacteriocin genome information	[166]
CAMP	http://www.camp.bicnirrh.res.in/	Collection of anti-microbial peptides,a useful resource for study of antimicrobial peptides	[167]
PhytAMP	http://phytamp.pfba-lab.org	The antimicrobial plant peptides	[168]
NORINE	http://bioinfo.lifl.fr/norine/	Nonribosomal synthesis of peptides	[169]
DAMPD	http://apps.sanbi.ac.za/dampd	Antibacterial peptide database of artificial management;	[170]
PepBank	http://pepbank.mgh.harvard.edu	A database of peptides based on sequence text mining and public peptide data sources	[171]
LAMP	http://biotechlab.fudan.edu.cn/database/lamp	Linking antimicrobial peptides database	[172]
ANTIMIC	http://research.i2r.a-star.edu.sg/Templar/DB/ANTIMIC/	Institute of infocomm research, Singapore - database of antimicrobial peptides	[173]
ACD	http://amdr.amu.ac.in/acd	Antimicrobial chemotherapeutics database	[174]
InverPep	http://ciencias.medellin.unal.edu.co/gruposdeinvestigacion/prospeccionydisenobiomoleculas/InverPep/public/home_en	A invertebrate antimicrobial peptides	[175]
DBAASP	http://dbaasp.org	Database of antimicrobial activity and structure of peptides, development of antibacterial compounds with high therapeutic index database	[176]
YADAMP	http://www.yadamp.unisa.it	Primarily antimicrobial peptides targeting bacteria	[177]

(*continued on next page*)

Table 3 (*continued*)

Database name	Web Address	Application	Reference
BaAMPs	http://www.baamps.it	Collect data on effective antimicrobial peptides for microbial biofilm	[178]
AMAP	http://faculty.pieas.edu.pk/fayyaz/software.html#AMAP	Prediction of bioactivity of antimicrobial peptide sequences	[179]
AniAMPpred	https://aniamppred.anvil.app/	AI predicts new animal antimicrobial peptides	[180]
dbAMP	http://csb.cse.yzu.edu.tw/dbAMP/	Explore the function of antibacterial peptide activity and the physical and chemical properties	[181]
dPABBs	http://ab-openlab.csir.res.in/abp/antibiofilm/	Prediction and design of anti–biofilm peptides	[182]

biological evolution, optimizing and creating new antimicrobial peptide sequences by simulating this evolutionary process. Among these methods, genetic algorithms are particularly prominent because they generate new antimicrobial peptides with improved characteristics while retaining the original biological activity features. Genetic algorithms usually start with a known antimicrobial peptide template sequence and produce a series of new variants by simulating natural selection and genetic mutations. These variants are then "screened" in a simulated biological environment based on their predicted antimicrobial activities or other biological properties. During this process, the algorithm iteratively improves these sequences and gradually optimizes them for improved antimicrobial activity or lower cytotoxicity toward human cells [140]. In addition to genetic algorithms, other types of evolutionary algorithms such as Random Model of Sequence Evolution (ROSE), Simulation Protein Evolution (SIMPROT), and Insertions and Deletions Simulator (INDELible) have also been applied in the design of antimicrobial peptides. The ROSE algorithm is used to generate offspring sequences derived from a parent sequence, simulating the diversified evolution of peptides. This algorithm allows the use of user-defined evolutionary trees, known topologies, and branch lengths to guide probabilistic mutations, insertions, and deletions in peptide sequences. SIMPROT and INDELible offer similar functionalities, being utilized to assess relationships between peptide sequences and to create peptide libraries that simulate biological diversity. These algorithms provide potential avenues for discovering peptides with novel antimicrobial properties [141].

This design method, which combines evolutionary algorithms with machine learning techniques, allows for a more effective prediction and evaluation of the potential biological activity of newly generated sequences. In this process, machine learning serves not only as an assessment tool to determine which sequences may have stronger biological activity but also guides the algorithm to iterate towards more efficient antimicrobial peptide designs. It simulates the natural evolution of antimicrobial peptide sequences by selecting sequences with higher predicted antimicrobial activity in each generation, thereby generating new and potentially more effective antimicrobial peptide sequences that enhance biological activity, while reducing toxicity to human cells. Boone et al. utilized evolutionary algorithms and rough set theory combined with a codon-based peptide-encoding method to successfully design a customized antimicrobial peptide with good inhibitory activity against *Staphylococcus epidermidis* [142]. Yoshida et al. combined genetic algorithms, machine learning, and a closed-loop approach with in vitro evaluation to optimize the potency of antimicrobial peptides and enhance their antimicrobial activity against *Escherichia coli*. This strategy not only demonstrated the potential of using genetic algorithm systems for in vitro molecular evolution but also accelerated the discovery of antimicrobial peptides and other functional molecules [143].

Overall, the design method of antimicrobial peptides based on evolutionary algorithms has the potential to discover and optimize novel antimicrobial peptides. However, this method mainly focuses on the amino acid composition and does not comprehensively consider the interactions between residues. Moreover, this design approach focuses primarily on optimizing existing sequences rather than exploring entirely new sequence spaces, which may limit its accuracy in predicting antimicrobial peptide structure and function.

5.2.2. *De novo* design of antimicrobial peptides based on deep learning

Natural antimicrobial peptide sequences are long and complex. The strategy for *de novo* antimicrobial peptide design is based on structural minimization, which combines amino acids, such as arginine, lysin, and histidine that can interact with negatively charged cell membranes and non-polar amino acids, such as alanine, valine, leucine, phenylalanine, tyrosine, and tryptophane that can mediate the insertion of antimicrobial peptides into the phospholipid bilayer of cell membranes. Structural minimization allows rapid identification and determination of the smallest motif or pharmacophore that acts as an antimicrobial peptide, reducing production costs and providing an efficient basis for the development of shorter antimicrobial peptides [144].

Deep learning is not only used for prediction in antimicrobial peptide research, but also enables the *de novo* design of new antimicrobial peptides. These methods utilize complex neural network models capable of analyzing existing antimicrobial peptide sequences and generating entirely new antimicrobial peptide candidates. For example, RNN and their variants, such as LSTM, are widely used to generate sequence data. Similar to the task of antimicrobial peptide prediction, these networks can recognize and learn the complex dependencies of existing sequences, thereby producing new antimicrobial peptide sequences with specific biological activities [145]. Wang et al. established a generative model based on LSTM and a bidirectional LSTM classification model to design novel sAMPs with potential antimicrobial activity against *Escherichia coli*. They trained and optimized multiple versions of generative and classification models through Bayesian hyperparameter optimization and identified antimicrobial peptides with good activity and short sequences [146]. Bolatchiev et al. used an LSTM generative model to obtain the amino acid sequences of 198 new antimicrobial peptides and synthesized five of these for antimicrobial efficacy evaluation. The results showed that two of the peptides exhibited in vitro activity against carbapenem-resistant *Klebsiella* spp [147]. Mao et al. developed an AMPTrans-lstm antimicrobial peptide *de novo* design model, combining submodels of LSTM samplers and transformer converters, effectively generating novel and diverse functional antimicrobial peptides, making it an efficient tool for antimicrobial drug design [148].

Variational Autoencoders (VAEs) are powerful deep learning tools used to generate new chemical spaces. VAEs operate through an encoding-decoding process, transforming molecular structures into representations in a latent vector space, and then reconstructing the original molecular structures [149,150]. By generating random variables, this method enhances the network's ability to generalize, enabling the creation of entirely new antimicrobial peptides with structures different from known sequences. Das et al. developed a design approach based on deep generative autoencoder modeling. They introduced conditional latent-space sampling guided by an attribute classifier trained on the latent space of the system of interest. They used a rejection sampling scheme to generate molecules with the desired attributes, and employed deep learning classifiers and molecular dynamics simulations to predict the physicochemical characteristics of the peptides. Finally, antimicrobial peptides with low toxicity and broad-spectrum antimicrobial properties were designed [151].

In addition, a new path for antimicrobial peptide design has been opened by deep generative adversarial networks (GANs), neural network algorithms that provide a completely new, computer-assisted framework for antimicrobial peptide discovery and optimization. GANs consist of two main components: a generator and a discriminator,

which compete with each other during training [152]. The purpose of the generator is to produce new antimicrobial peptide sequences, while the goal of the discriminator is to distinguish these generated sequences from real antimicrobial peptide sequences. Through multiple rounds of training, the generator is able to produce sequences that are closer and closer to real antimicrobial peptides, thus providing researchers with new, potentially active antimicrobial peptide candidates. Tucs et al. proposed PepGAN, a generative model for designing peptides. PepGAN is an approach that utilizes a generative adversarial network to generate new possible antimicrobial peptide sequences, which not only adapts the generation pattern of the generated sequences based on their similarity to known antimicrobial peptides, but also integrates an activity predictor to evaluate the activity of the generated sequences in order to further guide the generation process [153]. Gupta et al. proposed a new feedback loop mechanism that uses a GAN to generate the DNA sequences and an independent predictor called Function Analyzer to optimize these sequences. The sequences are optimized using an independent predictor called "function analyzer" to obtain the desired properties. This feedback mechanism is primarily used to train the GAN to generate sequences that encode proteins, such as antimicrobial peptides and alpha-helical peptides [154].

In summary, in the prediction and design of antimicrobial peptides, methods based on deep learning have shown significant potential but still face several challenges. These challenges include the difficulty in obtaining high-quality, complete datasets and issues with the interpretability of deep learning models. Nonetheless, with the continuous advancement of algorithms and computational capabilities, deep learning not only can effectively predict and generate peptide sequences with potential antimicrobial activity but also can delve deeper into the structure and function exploration during the design process, offering new perspectives and solutions for the research and development of the next generation of antimicrobial drugs.

6. Conclusion and prospects

As the development of traditional antibiotics has stagnated, antimicrobial peptides are increasingly showing tremendous potential to replace them as efficient antimicrobial strategies. These natural or synthetic peptide compounds not only surpass traditional antibiotics in several aspects but also demonstrate significant effects against drug-resistant bacteria. Despite the advantages of antimicrobial peptides, their inherent drawbacks cannot be overlooked and require further improvement. In this regard, AI technology can analyze a vast amount of antimicrobial peptide data and predict the relationship between their structure and function to optimize antimicrobial activity, reduce side effects, and enhance stability. In short, the development of antimicrobial peptides combined with AI technology not only opens a new chapter in the fight against multidrug-resistant bacteria but also heralds potential revolutions in the field of anti-infective treatments.

Furthermore, antimicrobial peptides are not entirely immune to resistance development. Joo et al. research found that *Staphylococci*, including through changes in cell wall and membrane surface charge, repel antimicrobial peptides [155]. Abdi et al. outlined direct resistance strategies of bacteria against various antimicrobial peptides, including bacterial cell envelope modification, antimicrobial peptide degradation, sequestration, expelling, and capsulation [156]. Therefore, continuous monitoring and proper use of antimicrobial peptides are particularly important to ensure their effectiveness and safety and to avoid the development of resistance due to uncontrolled use. In summary, resistance issues are an unavoidable challenge in antimicrobial peptide development but should not cause unnecessary panic. Moreover, AI can help identify potential drug resistance mechanisms, guide researchers to design safe and effective antimicrobial peptides, and provide opportunities for further optimization to address potential resistance challenges in the future. It is believed that with their continued exploration using new technologies, antimicrobial peptides are expected to replace antibiotics and provide yet unimagined benefits to mankind.

CRediT authorship contribution statement

Shuaiqi Ji: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **Feiyu An:** Conceptualization, Data curation, Investigation, Methodology, Project administration. **Taowei Zhang:** Conceptualization, Project administration, Resources, Software, Visualization. **Mengxue Lou:** Conceptualization, Formal analysis, Methodology, Project administration. **Jiawei Guo:** Conceptualization, Data curation, Methodology, Project administration. **Kexin Liu:** Investigation, Methodology, Project administration, Resources. **Yi Zhu:** Conceptualization, Data curation, Resources, Software. **Junrui Wu:** Data curation, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Rina Wu:** Data curation, Funding acquisition, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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