

Review

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Review

# A Comprehensive Overview of Antimicrobial Peptides: Broad-Spectrum Activity, Computational Tools, and Applications

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## Abstract

Among bioactive peptides, those with antimicrobial activity have attracted increasing attention due to their potential as alternatives to traditional antibiotics. Antimicrobial peptides (AMPs) are small molecules, typically composed of 5 to 40 amino acid residues, with low cytotoxicity and minimal side effects. They act through multiple mechanisms and interact with the immune system, offering broad-spectrum activity against bacteria, viruses, fungi, and parasites. This review presents the main aspects of AMPs, including their biochemical characteristics, sources, mechanisms of action, and computational tools used for their analysis and discovery. It also examines recent progress in clinical trials and the current limitations that restrict the development and commercialization of AMPs. The review discusses the application of AMPs beyond human medicine, including their use in food preservation to prevent microbial contamination and in veterinary medicine to control infections in livestock and reduce dependence on conventional antibiotics. AMPs are versatile antimicrobial agents, but they require multidisciplinary strategies to ensure their effective implementation in the health, food, and veterinary sectors.

**Keywords:** application; bioactive peptide; characteristic; peptide database

## 1. Introduction

Bioactive peptides (BAPs) are small molecules that usually contain 2-20 amino acid residues and have molecular masses less than 6000 Da [1]. However, BAPs with longer chains, ranging up to 40 amino acids have also been reported, likely due to improvements in peptide synthesis and manufacturing technologies [2]. The biological activity of peptides depends on their amino acid characteristics and sequences, which determine their physiological actions. BAPs have been gaining increasing attention in biomedical, food, and pharmaceutical sciences because of their specific functional properties, such as antimicrobial, antioxidant, immunomodulatory, and antitumor activities [3, 4]. These amino acid oligomers are present in a wide variety of organisms and play key roles in cellular communication, immune defense, and metabolic regulation [4]. Although numerous studies have reported various potential biological activities of peptides, their antimicrobial potential remains highly promising [5].

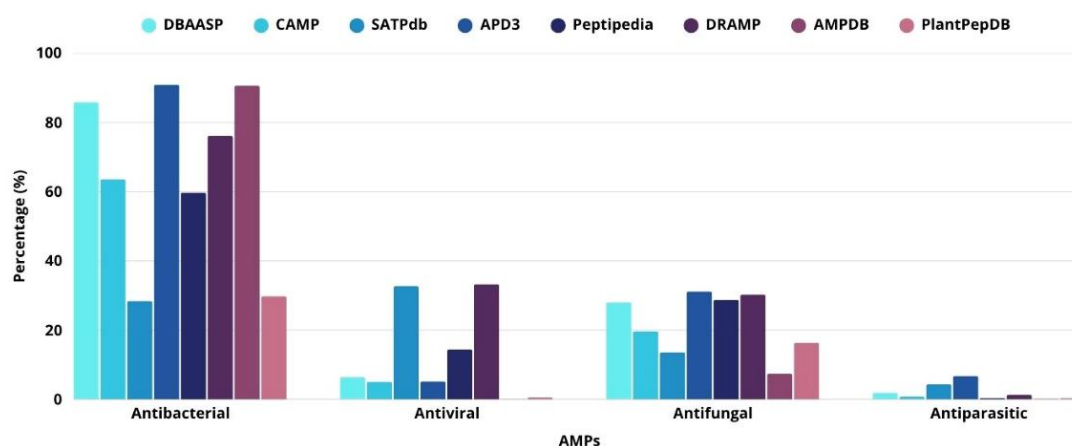
Antimicrobial peptides (AMPs) are molecules capable of combating disease-causing microorganisms such as bacteria, viruses, fungi, and parasites through different mechanisms. The first report on the identification of AMPs was published in 1939 by René Dubos, who isolated a compound (gramicidin) from a *Bacillus* lineage that could protect mice against pneumococcal

infections [6]. Subsequently, a series of AMPs have been identified in a wide range of organisms, which employ them in defense strategies against pathogens [7]. The Antimicrobial Peptide Database 3 (APD3), which was updated in September 2025, contains data for 5,680 peptides. This includes 3,351 natural AMPs, 1,733 synthetic AMPs, and 329 predicted AMPs. Among them, 4,865 have antibacterial activity, 270 antiviral, 1,664 antifungal and 348 antiparasitic [8].

AMPs typically have 5 to 40 amino acid residues, with a positive net charge and cationic features. Unlike conventional antibiotics, AMPs kill microbial cells by disruption of membrane integrity or the ionic gradient, through interactions with the negatively charged cellular membrane. They can also inhibit protein, DNA, and RNA synthesis or interact with specific intracellular targets [9, 10].

## 2. Broad-Spectrum Activity of Peptides

Antimicrobial peptides can act against different microorganisms, and several databases compiling various aspects related to AMPs have been established. **Figure 1** shows the types of activities associated with AMPs: antibacterial, antiviral, antifungal, and antiparasitic activities.



**Figure 1.** Distribution of AMPs according to their specific activities in different databases. Information obtained from databases available at: DBAASP (<https://dbaasp.org/home>) [11]; CAMP (<https://camp.bicnirrh.res.in/>) [12]; SATPdb (<http://crdd.osdd.net/raghava/satpdb/>) [13]; APD3 (<https://aps.unmc.edu/AP/>) [8]; Peptipedia (<https://app.peptipedia.cl/>) [14]; DRAMP (<http://dramp.cpu-bioinfor.org>) [15]; AMPDB (<https://bblserver.org.in/ampdb/>) [16]; PlantPepDB (<http://www.nipgr.ac.in/PlantPepDB/>) [17](accessed on August 24).

Antimicrobial peptides share common characteristics but exhibit specific properties. Moreover, they can act through multiple mechanisms, thereby affecting various biological processes of the infectious agent and/or enhancing the host immune response [7].

### 2.1. Antibacterial Activity

Most AMPs have been reported to show antibacterial effects; this may be related to the large number of studies seeking approaches to combat antibiotic resistance (AMR), a major challenge to global public health that has resulted in hard-to-treat infections and a shortage of effective therapies [18, 19]. Moreover, the lack of effective actions to control these microorganisms can have devastating consequences, claiming millions of lives and increasing treatment costs to over USD 100 trillion annually [20]. The organization of pathogenic microorganisms into biofilms prevents antibiotics from interacting with the bacterial cells [21]. Peptides have also been explored as potential solutions to counteract the aggravating factors in AMR [22].

### 2.2. Antiviral Activity

Despite the predominance of AMPs combating bacterial infections, AMPs targeting viral infections have gained importance because of the high number of deaths caused by these infections. This has led the World Health Organization (WHO) to develop a list of priority diseases to accelerate research and development. In July 2024, the list included 28 viral families, and the priority diseases, which are associated with a higher risk of epidemics or pandemics, included Ebola virus disease, Marburg virus disease, Lassa fever, Crimean-Congo hemorrhagic fever, Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), other known viral diseases, and the still-unknown "Disease X." Concerns regarding the risks associated with these diseases are reported monthly by the WHO, with records showing that they affect various regions of the world [23].

In addition to mortality rates, the emergence of new viruses, viral resistance mechanisms, delays in vaccine development, and the severe adverse effects of antiviral drugs have contributed to the complexity of this problem. In this context, natural and synthetic antiviral peptides (AVPs) have emerged as a new class of antiviral agents offering several advantages [24].

### 2.3. Antifungal Activity

The growing incidence of fungal infections has become a topic of concern since millions of individuals are estimated to die annually as a result of such infections. Some of the main human fungal pathogens include *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and the emerging multidrug-resistant *Candida auris*. The increase in fungal infections is associated with several factors. When considering the currently available treatment options, the limited number of antifungal drug classes combined with the development of resistance across different genera has driven the search for integrated and effective strategies [25].

Another factor that favors fungal infections is the growing number of vulnerable individuals resulting from various treatments involving immunosuppressive and chemotherapeutic drugs. In this context, antifungal peptides (AFPs) possess properties that could help overcome the limitations imposed by current therapies and can be applied to the control of fungal contamination in food products [26].

### 2.4. Antiparasitic Activity

Among the AMPs identified in various databases, those with antiparasitic activity were the least frequently represented. Parasitism is a biological interaction that can lead to disease and, in severe cases, result in host death. Among the most relevant human parasites are protozoans (e.g., *Toxoplasma gondii*, *Plasmodium* species, and *Trypanosoma cruzi*), which cause infections classified by the WHO as neglected diseases and, consequently, receive little investment for the development of new treatments. For some groups, the available drugs are toxic and only partially effective, and the emergence of resistant strains has driven the search for alternative strategies [27]. In this scenario, recent advances research on antiparasitic peptides has demonstrated that these molecules can act through specific mechanisms and targets and may, therefore, represent innovative solutions for combating these pathogens [28].

## 3. Approaches for Obtaining AMPs

With advances in biotechnology and protein engineering, the demand for efficient, scalable, and selective peptide production methods has substantially increased. Different routes are employed to produce peptides of interest, including chemical synthesis, enzymatic hydrolysis of proteins, extraction from natural sources, and expression through recombinant technologies. Each method shows specific advantages and limitations in terms of cost, purity, yield, scalability, and the possibility of structural modifications (**Table 1**) [29, 30].

**Table 1.** Comparative summary of the main characteristics of peptide production methods.

Criterion	Chemical Synthesis	Enzymatic	Natural	Recombinant
Cost	High	Moderate	Variable	Low
Yield	Medium	Low	Very Low	High
Scalability	High	Moderate	Low	Very High
Technical Complexity	High	Low	Medium	High
Application Versatility	Very High	Moderate	Low	High

3.1. Peptide Production via Chemical Synthesis

Chemical peptide synthesis is one of the most widely used approaches for producing specific peptide chains, enabling the precise modification of amino acid sequences with high reproducibility and structural control. This method is particularly important in the industrial and pharmaceutical contexts, where the production of peptides with well-defined characteristics (such as stability, enzymatic resistance, or optimized biological activity) is essential [3]. One of the major advantages of this approach is the possibility of incorporating non-natural amino acids or artificial post-translational modifications such as cyclization, glycosylation, and even fluorescent or radioactive labeling, which significantly broadens the applications of the peptides in pharmacokinetic and therapeutic studies [29].

The classic solid-phase peptide synthesis (SPPS) method introduced by Merrifield remains the most widely adopted method, primarily because of its compatibility with automated and scalable processes. In this process, peptide assembly begins at the carboxyl end, which is anchored to a solid resin. Protected amino acids are added individually in alternating steps of coupling and deprotection until the full peptide chain is built [31].

The choice of coupling reagents, such as O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate (HBTU), O-(7-azabenzotriazol-1-yl)-N,N,N,N'-tetramethyluronium hexafluorophosphate (HATU), or N,N'-diisopropylcarbodiimide (DIC), as well as protection systems (e.g., Fmoc-9-fluorenylmethyloxycarbonyl and Boc-tert-butyloxycarbonyl) directly influences the reaction efficiency, final purity, and failure rates during synthesis [4].

In certain situations, hybrid approaches combining solid- and liquid-phase syntheses are used to produce larger peptides or peptides with more complex cyclic structures. A well-known example is cyclotide kalata B1, a cysteine-rich peptide found in plants and characterized by a cyclic cystine knot (CCK) motif. Kalata B1 shows strong antimicrobial properties and is being studied as a structural framework for the development of therapeutic peptides, including receptor agonists and enzyme inhibitors [29].

Despite its versatility, chemical synthesis faces major challenges in scaling up the production of long or structurally intricate peptides in a cost-effective manner. Additionally, traces of leftover organic solvents and toxic reagents, such as dimethylformamide (DMF) and carbodiimide-based activators, require thorough purification, which can substantially increase production costs [3].

3.2. Peptide Production via Enzymatic Pathways

The production of peptides through enzymatic hydrolysis is a widely explored alternative, especially when seeking a more sustainable process with lower environmental impact and greater cleavage selectivity. This approach is based on the controlled action of proteases on natural proteins derived from milk, algae, eggs, fish, or plants, generating BAP fragments with various functions such as antioxidants, antihypertensive, antimicrobial, and other activities [3, 31].

In many cases, these peptides remain inactive while embedded in the native structure of their parent proteins and are only released through specific enzymatic cleavage. These bioactive fragments are typically hidden within full-length proteins and become active under controlled hydrolytic conditions, allowing the generation of peptides with targeted biological functions [31, 32]. This

process supports the idea that proteins serve as reservoirs for latent peptides with distinct physiological effects. The choice of enzymes, such as trypsin, chymotrypsin, pepsin, alcalase, flavourzyme, or microbial proteases, depends on the desired cleavage pattern and the nature of the protein source [3].

Recent technological developments have facilitated the combination of physical techniques with enzymatic hydrolysis to boost both the yield and specificity of peptides. Pretreatments such as ultrasound-assisted extraction (UAE), pulsed electric fields (PEF), and high hydrostatic pressure (HHP) can help improve enzyme access to the inner regions of the protein, increase the efficiency of hydrolysis, and enable the production of peptides with specific bioactivities [31].

For instance, enzymatic hydrolysis of marine microalgae such as *Tetraselmis suecica* has been shown to produce peptides with strong antimicrobial properties. One variant, AQ-1766, demonstrated significant efficacy against a wide range of pathogenic bacteria, including *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Listeria monocytogenes*, and *Pseudomonas aeruginosa*. These peptides typically disrupt microbial membranes, highlighting their potential in food preservation and therapeutic applications [32].

Enzymatic processes offer several advantages, including high specificity, environmental compatibility, and production of peptides that are generally considered safe, often eliminating the need for further chemical modifications. Nonetheless, this approach presents challenges such as variability in raw materials, high enzyme costs, and the need for additional purification steps, such as ultrafiltration, chromatography, and lyophilization [3, 32].

In this context, the use of artificial intelligence (AI) and machine learning (ML) to predict the bioactivity of enzymatically generated peptides has gained importance. These computational tools can help optimize peptide sequences, predict therapeutic potential, and identify the most effective fermentation or hydrolysis conditions [3].

### 3.3. Peptide Extraction from Natural Sources

Direct extraction of peptides from natural sources is one of the oldest methods still in use today, especially for AMPs and immunomodulatory compounds. A wide range of organisms, including plants, marine animals, bacteria, and fungi, naturally produce BAPs with important biological roles in pathogen defense, cell signaling, and metabolic regulation [4, 29].

In plants, many of these defense-related peptides are rich in cysteine and are stabilized by disulfide bonds, which help maintain their three-dimensional structures. Well-known peptide families exhibiting potent antifungal and antibacterial activities, such as defensins, cyclotides, and thionins, can be isolated from plant tissues such as leaves, seeds, and roots using conventional extraction methods such as maceration, solvent precipitation, chromatography, and ultrafiltration. The antimicrobial activity of these molecules is generally associated with their cationic nature and their interactions with anionically charged membranes of microorganisms [29].

Antimicrobial peptides have been extensively described in marine organisms such as sponges, mollusks, echinoderms, and fish. These molecules include arenicins, piscidins, and holothuroidins, which inhibit the growth of multidrug-resistant bacteria, fungi, and viruses even in extreme environments. Extraction of these molecules involves isolation from tissues or fluids (such as mucus, hemolymph, or pseudocoelom), followed by purification using reversed-phase HPLC, size-exclusion or ion-exchange chromatography and subsequent structural analysis by mass spectrometry and NMR imaging [4].

Despite the high therapeutic potential and natural diversity of these peptides, direct extraction from natural sources faces major limitations such as low yields, seasonality, and complexity of the extracts; these factors limit the ability to obtain such compounds on an industrial scale. Therefore, many natural peptides are cloned or synthesized using recombinant or chemical methods once their sequences have been identified [32].

### 3.4. Peptide Production via Recombinant Technology

Recombinant DNA technology is widely used for large-scale peptide production, especially for peptides that cannot be feasibly obtained using natural extraction or traditional chemical synthesis. In this approach, genes encoding the peptides of interest are inserted into plasmid vectors and expressed in hosts, such as bacteria, yeast, filamentous fungi, or even mammalian cells [33].

Recombinant production is particularly advantageous for producing peptides with specific post-translational modifications or when utilizing cellular systems for proper folding and disulfide bridge formation, as in the case of cyclotides and defensins. For small peptides, techniques such as fusion expression with carrier proteins (e.g., glutathione S-transferase [GST] or maltose-binding protein [MBP]) are used to increase solubility and facilitate purification [29].

A relevant example is the recombinant production of bacteriocins by genetically modified *Lactobacillus* strains, which allows the use of generally recognized as safe (GRAS) systems for producing bioactive compounds with applications in functional or therapeutic foods. Other strategies, such as the use of strong promoters, directed mutagenesis, and codon optimization, have also been explored to increase [33].

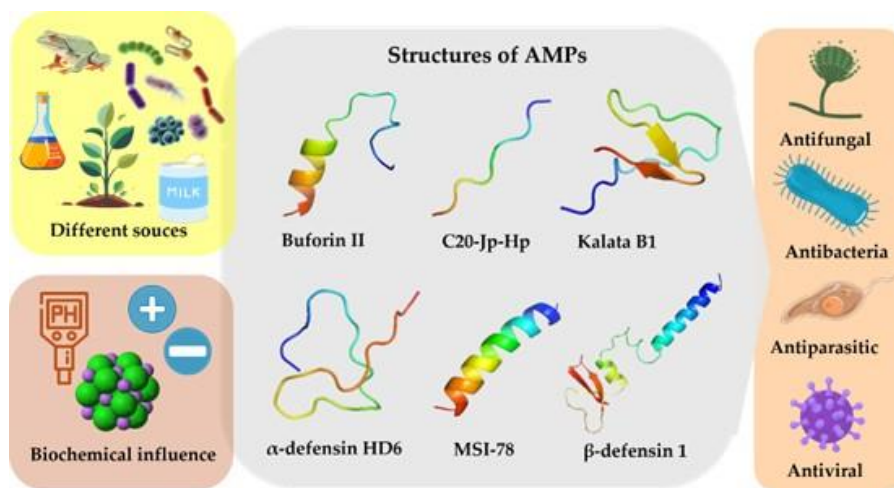
The main challenges of this approach include peptide toxicity to the host organism, the formation of inclusion bodies, and the need for additional purification steps, typically involving chromatographic techniques. Despite these challenges, recombinant methods are considered one of the most promising methods for producing BAPs with high purity and relatively low cost, particularly for pharmaceutical and industrial applications [29, 33].

## 4. Biochemical Characteristics of AMPs

### 4.1. Structure

The most common secondary structures in AMPs are  $\alpha$ -helices and  $\beta$  chains. Other types of structures include spirals, linear peptides, and cyclic peptides stabilized by disulfide bridges (**Figure 2**) [34]. Cyclotides, which show a three-dimensional structure containing loops and disulfide bridges, exhibit favorable biological activity and show resistance to proteolytic enzymes [35]. The combination of  $\alpha$ -helix and  $\beta$  chains is a critical condition for antimicrobial activity. The  $\alpha$ -helix structure favors membrane ruptures and  $\beta$  chains and cyclical structures undergo internalization into the cell [36]. Other tryptophan-rich AMPs can show transmembrane effects that favor the formation of ion channels and cell rupture [37].

Specific peptides from plants show specific conformations because they are rich in specific amino acids such as thionine and cysteine, favoring conformations with antifungal and antimicrobial activities. In addition, they can induce ribosome inactivation and trypsin inhibitor activity [38].



**Figure 2.** The scheme represents the different sources of production, biological activities and biochemical influences of AMPs. The central part shows examples of structures described for AMPs. Information obtained

from DRAMP (<http://dramp.cpu-bioinform.org/>) [15] and predicted by PEP-FOLD3 (<https://bioserv.rpbs.univ-paris-diderot.fr/index.html>) [39] (accessed August 25, 2025) and figures constructed with clean png (<https://www.cleanpng.com/>).

#### 4.2. Charge, pH, saline concentration

For antimicrobial function, the best peptides are those with a positive charge under physiological conditions and amphipathic chains containing between 5 and 100 amino acids. The positive charge interacts better with the anionic membranes of pathogens, promoting better interactions and efficiency in the destruction and lysis capacity. Charges between +14 and +16 are the most common found among AMPs [40, 41].

However, excess positive charges can affect active structures and decrease the antimicrobial capacity [42]. According to APD3, 87% of active peptides are cationic, 7% are neutral, and 6% are negative, and most contain chains rich in arginine and lysine [8]. Some anionic AMPs identified in invertebrates and plants play important roles in innate immune signaling [43].

Furthermore, the pH and saline concentration can also affect the antimicrobial potential of highly active structures. High salinity is a determinant of peptide activity. Most structures are stable in the pH range of 4 to 6 because an acidic pH favors the protonation of some amino acids and the action of positive charges against the bacterial cell wall [44].

#### 4.3. Hydrophobicity

The hydrophobicity of AMPs modulates their efficiency and specificity. Most AMPs contain approximately 50% hydrophobic residues. This favors the entry of these peptides into the lipid bilayer of pathogens [41].

There is no perfect combination of positive charge and hydrophobic chain length that can maximize activity and reduce cytotoxicity, instead the balance between positive charges and hydrophobicity modulates the interaction of the peptide with microorganisms. Higher hydrophobicity at a given charge has been shown to increase the antimicrobial effect, whereas lower hydrophobicity decreases this effect [40]. However, this relationship is not always proportional, and reports have shown that increments in hydrophobicity can reduce antimicrobial activity and toxic effects in mammals [41]. Therefore, the ratio of charge to hydrophobicity is a key factor in the development of AMPs. Brogden [45] proposed that ratios ranging from 1:1 to 2:1 between the hydrophobic and basic residues may be an efficient combination. Thus, amphipathic chain characteristics and positive charges can improve the efficiency of antimicrobial activity [46].

#### 4.4. Size

The size of a peptide with antimicrobial activity can vary from six to 60 amino acid residues [45]. This size is primarily correlated with toxicity in mammals. However, to achieve amphipathic characteristics, at least seven to eight amino acids are required [40]. APD3 shows that 90% of AMPs have less than 50 amino acids, and functional peptides have chains of 22 to 30 amino acids [8].

### 5. Antimicrobial Peptide Action Mechanism

The amino acid sequence, hydrophobicity, charge, and three-dimensional structure are essential for understanding the mode of action of AMPs [47]. Variations in these aspects across AMP classes ensure specific interactions with their respective targets [48]. AMPs can interact directly with the target microorganism (cell surface or intracellular components), leading to its death, or act indirectly by modulating the host immune system to combat the infection [49]. In addition, many AMPs possess the ability to act on multiple targets and, consequently, exert more than one convergent mechanism of action contributing to their antimicrobial activity.

#### 5.1. Extracellular Target AMPs

Several factors influence the ability of AMPs to permeate and destabilize microbial membranes, such as amino acid sequence, membrane lipids, and peptide concentration. Bacterial membranes are negatively charged due to the presence of phospholipid head groups such as phosphatidylglycerol (PG), cardiolipin (CL), or phosphatidylserine (PS). Additionally, the presence of lipopolysaccharides (LPS) in Gram-negative bacteria and teichoic acids in Gram-positive bacteria contributes to this negative charge [50, 51].

Membrane-active AMPs are typically amphipathic and positively charged (rich in lysine and arginine residues) at physiological pH 7.4. Due to their net positive charge and hydrophobicity, AMPs interact with negatively charged bacterial membranes, where the negative charge arises from lipid head groups and other anionic membrane components. This interaction is mediated by electrostatic forces on the bacterial surface, altering the cell's electrochemical potential, disrupting lipid organization, and leading to leakage of intracellular contents [52, 53].

In general, AMPs follow two major types of membrane action: pore formation, which includes two models: barrel-stave and toroidal pore and non-pore mechanisms, including: the carpet model and detergent-like action [49]. Barrel-stave model: AMPs insert perpendicularly into the lipid bilayer, forming oligomers that generate a transmembrane pore with a hydrophilic interior. Hydrophobic residues interact with the fatty acid chains within the membrane, stabilizing pore formation [51]. The peptide Mo-CBP3-Pep-CPAIQRCC and magainin2-GIGKFLHAS KKFGKAFVGEIMNS are examples of peptides that act via this model due to their hydrophobicity and  $\alpha$ -helical structure [54, 55]. Toroidal pore model: Peptides interact with the polar head groups of membrane lipids to form pores, causing the lipid bilayer to bend around the peptide and form a continuous curvature, resulting in stable channels that allow the passage of ions and other molecules [50, 56, 57].

Peptides such as YK5-NKVKEWIKYLKSLFK and MSI-78-GIGKFLKKAKKFGKA FVKILKK exemplify this mechanism by forming toroidal pores in membranes [58, 59]. Carpet model: Peptides accumulate on the membrane surface at high concentrations, aligning parallel to the membrane to form a dense layer resembling a carpet. When a threshold concentration is reached, this layer disrupts and lyses the membrane without forming pores [51, 60]. Cecropin P1-SWLSKTAKKLENSAKKRISGIAIAIQGGPR acts via this model, coating the lipid bilayer and inducing membrane rupture [61]. Detergent-like model: Similar to the carpet model, but with lipid solubilization leading to micelle formation and complete bilayer disintegration. This results in dissipation of the electrochemical gradient. Although structurally predisposed to pore formation, the peptide PepD2M-Myr-WKKLKKLLKKLKKL-NH<sub>2</sub> acts via a detergent-like mechanism, collapsing the membrane into lipid aggregates [62].

Some AMPs act via alternative or combined mechanisms. The S-thanatin-GSKKPVIYCNRRSGKCQRM peptide exerts multiple actions, combining membrane depolarization and interference with the bacterial respiratory chain, while maintaining low toxicity to mammalian cells due to its selectivity for lipid composition [63]. Melimine-TLISWIKNKRKQRPRVSRRRRRRGRRRR and Mel4-KNKRKRRRRRG GRRRR peptides, acting against *Pseudomonas aeruginosa*, follow a sequence of events including LPS neutralization, membrane depolarization, intracellular material release, and ultimately cell lysis [64]. The hRNase 7 peptide directly interacts with the OprI lipoprotein of *P. aeruginosa*, promoting increased membrane permeability and cellular content leakage [65]. Unlike the previously mentioned peptides,  $\alpha$ -defensin HD6-CLL QGRCNCNLKLGCKSGFCGGCVNLP acts by forming nanonets on the bacterial surface without directly inducing cell death. This physical net traps bacteria and prevents adhesion and invasion, protecting the intestinal epithelium [66]. The F6-KGGDLGLFEPTL peptide fraction derived from egg yolk also demonstrates that cationic and anionic peptides can act synergistically, while cationic peptides destabilize the membrane via direct interaction, anionic peptides use metal ions to facilitate penetration [52].

Antifungal peptides have emerged as a promising alternative in combating fungal infections, especially in light of the global rise in resistance to conventional antifungals such as azoles, polyenes, and echinocandins [67]. The mechanism of action of AFPs involves the destabilization of the

microbial cell membrane, a process mediated by electrostatic interactions between the cationic residues of the peptides and the anionic phospholipids of the membrane, such as phosphatidylglycerol. These peptides can create pores or disrupting membrane permeability, which compromises cellular structural integrity, therefore the result is cell death. Some examples include Mo-CBP3-Pep-CPAIQRCC and RcAlb-Pep-AKLPIPTIAL, which facilitate pore formation in fungal membranes and induce oxidative stress, thereby contributing to hyphal damage [68]. The AFP, derived from *Aspergillus giganteus*, interacts with the fungal membrane without forming pores but alters local membrane fluidity and compromises structural integrity, ultimately resulting in fungal cell destruction. Some antifungal peptides, such as CAADIVGQCPAKLK—derived from thaumatin—act through receptor-dependent mechanisms. This peptide interacts with the PHO36 receptor, found in *Saccharomyces cerevisiae* and *Candida albicans*, triggering apoptotic pathways mediated by oxidative stress [69].

The AVPs are strongly related to their physicochemical structure, which enables specific interactions with viral components or essential cellular elements involved in the viral replication cycle. Among these interactions, those with viral membranes, cellular receptors, or viral enzymes are particularly noteworthy [70]. Inhibition of viral entry is one of the most common mechanisms, especially for enveloped viruses. Membrane active peptides display broad-spectrum antiviral properties by disrupting the stability of the viral envelope. According to Hoffmann et al. [71], these molecules interact directly with the viral lipid bilayer, hindering endosomal fusion and inducing virion aggregation, effects reported for pathogens such as influenza, dengue, and herpes simplex viruses. Their specificity is linked to the pronounced curvature of viral membranes and to the lack of repair or homeostatic mechanisms in these structures. *In vitro* studies, the peptide p5(coil)-GGGYSKGGKG GKGKGKGGKGGKGGKGGKGGK prevents viral attachment to host cells by binding to a heparan sulfate proteoglycan (HSPG) located on the cell surface, thereby blocking the entry of human and murine cytomegaloviruses (HCMV and MCMV) [72]. Another example is Enfuvirtide (T20)-Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH<sub>2</sub>, which interferes with the formation of the six-helix bundle (6-HB) required for membrane fusion, while peptide C60 reinforces the pre-formed 6-HB, preventing further fusion events, particularly in endocytic pathways, with demonstrated efficacy against HIV [73]. In influenza A, inhibitory activity has also been observed for peptides such as C18-ARLPR and C12-Hp-KKWK, which target hemagglutinin subunits HA1 and HA2, respectively, blocking membrane fusion. Another peptide with a similar mode of action is C20-Jp-Hp-ARLPRKKWK, which blocks the conformational rearrangement of HA2 and interferes with endosomal acidification crucial step for viral activation [74]. Peptides such as cecropin B-(NH<sub>2</sub>)-KWKVFKKIEKMGRNIRNGIVKAGPAIAVLGEAKAL-(CONH<sub>2</sub>), and CAP37-NQGRHFCGGALIHARFVMTAASCFCQ have shown efficacy against non-enveloped viruses like adenovirus and rotavirus by promoting capsid disintegration or preventing viral entry through particle aggregation [57].

## 5.2. Intracellular target AMPs

By crossing the cell membrane without the need to induce lysis, AMPs interact with intracellular components such as DNA, RNA, enzymes, and metabolic systems, ultimately leading to cell death. Peptides such as KT2-NGVQPKYKWWK WWKKWW-NH<sub>2</sub>, RT2-NGVQPKYRWWRRWW-NH<sub>2</sub>, and PR-39-RRRPRPPYLPRPRPPFF PPRLPPRIPPGFPPRFPPRF-NH<sub>2</sub> exemplify cell entry without pore formation or membrane lysis, a process facilitated by interactions with lipopolysaccharides and exploitation of the bacterial electrochemical gradient. Once inside the cell, they bind to DNA, thereby inhibiting transcription and translation [75, 76]. Buforin II-TRSSRAGLQFPVGRVHRLLRK, NDEELNKLM, and RSSKRRQ are also capable of translocating across the membrane without causing lysis and accumulate in the cytoplasm, where they strongly bind to bacterial DNA and RNA, resulting in inhibition of their functions [77, 78]. Similarly, the AMP Oct-P2-MFLVVKVLKYVV interacts directly with plasmid DNA, promoting its aggregation and thereby impairing its functionality [79].

Some AMPs directly interfere with bacterial enzymatic activity. The peptide APKHKEMPFPKYP acts against *Staphylococcus aureus* by inhibiting critical enzymes such as DNA gyrase and dihydrofolate reductase (DHFR) through hydrogen bonding, hydrophobic interactions, and  $\pi$ - $\pi$  stacking. This interaction blocks DNA replication and cellular metabolism, ultimately leading to bacterial death [80]. The induction of reactive oxygen species (ROS) is a mechanism observed in several AMPs. The peptide LTX-315-KKWWKKW-Dip-K-NH<sub>2</sub> (Dip =  $\beta$ -difenilalanina) induces oxidative stress by increasing the production of nitric oxide and hypochlorite, disrupting NAD<sup>+</sup> metabolism and ATP production, and thereby compromising bacterial viability [81]. Peptides such as CM15-KWKLFFKKIGAVLKVL and MM63:CHx37 also induce oxidative stress by generating superoxide, hydroxyl radicals, and hydrogen peroxide, especially under aerobic conditions, while LL-37-LLGDFFRKSFKKLGKRLRRFFLSKSA causes oxidative stress by interfering with the cytochrome oxidase-bd complex in the periplasm [82]. The peptide [K4K15]-CZS-1-GFLKIVKGVGKVALKAVSKLF not only permeabilizes membranes but also disrupts bacterial metabolism by inhibiting essential pathways such as fatty acid biosynthesis, phospholipid metabolism, and the tricarboxylic acid (TCA) cycle, thereby hindering cellular recovery and enhancing bacterial death [83].

In addition to cell membrane action of AFPs, many antifungal peptides target essential intracellular components related to fungal metabolism. AMPs such as histatin5 (Hst5)-DSHAKRHHGYKRFHEKHSHRGY can interfere with genomic DNA without forming pores in the fungal membrane. As a result, these peptides cause morphogenetic defects, such as irregular chitin distribution, abnormal hyphal branching, and eventual cell lysis [84]. Metchnikowin (Mtk)-MQLNLGAIFLALLGVMATATSVLAEPHRHQG PIFDTRPSPFNPNQPRPGPIY, for example, derived from *Drosophila melanogaster*, acts specifically against *Fusarium graminearum* by inhibiting succinate-coenzyme Q reductase (SQR), an enzyme essential for mitochondrial energy production. Furthermore, Mtk interferes with fungal cell wall synthesis by inhibiting  $\beta$  (1,3)-glucanoyltransferase Gell1, a crucial enzyme for cell wall formation in *Fusarium* [85].

The peptide IJ4-Ac-KW $\Delta$ FWK $\Delta$ FAK $\Delta$ FAKNH<sub>2</sub> exhibits antifungal activity against various *Candida* species and other filamentous fungi by oxidative stress and stimulating the production of reactive oxygen species (ROS), which compromise fungal cellular components [86]. Similarly, the peptide AMT-RRWRF acts interacting with fungal membranes and causing structural disruption, while also targeting intracellular processes. This peptide can inhibit lanosterol demethylase, an important enzyme for ergosterol biosynthesis, a major constituent of the fungal cell membrane [87].

The AVPs may also function through diverse pathways beyond extracellular binding. For example, WL-1-GWKRIKQRIKDKLRNL combats herpes simplex virus type 1 (HSV-1) by blocking viral attachment, suppressing replication, and downregulating pro-inflammatory cytokine production [57]. Direct inhibition of viral enzymes, such as influenza polymerase or essential replication proteases, has been observed for P9 -NGAICWGPCPTAFRQIGNCGHFKVRCKIR and LVLQTM [57].

### 5.3. Immunomodulatory AMPs

The AMPs that do not exert their effects primarily through microbial killing can modulate the host immune system, thereby assisting in the clearance of pathogens. The human peptide LL-37-LLGDFFRKSFKKLGKRLRRFFLSKSA is a well-studied example of an immune regulator. Its activity involves binding to bacterial components such as LPS, which prevents excessive macrophage stimulation and decreases TNF- $\alpha$  production. Furthermore, LL-37 disrupts the interaction between LPS and LBP (binding protein), reducing TLR4 activation and limiting the development of sepsis. The LL-37 peptide promotes the recruitment of immune cells by inducing chemokines such as IL-8 and MCP-1 and increasing the expression of chemokine receptors such as IL-8RB, CXCR-4, and CCR2 [88]. The peptide's activity is dose dependent, so at low concentrations it functions as an "immune sentinel," while at higher levels it promotes cell migration. According to Fjell et al. [89], LL-37's antimicrobial action is strengthened by its ability to directly penetrate bacterial membranes without

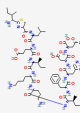
the need for active endocytosis, whereas its immunomodulatory effects rely on its translocation into eukaryotic cells.

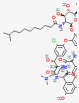


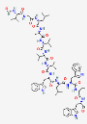
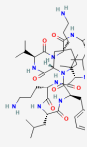
The peptides HV2-RRVHVHVDPGVHVHVRR-NH2 and PA-13-KIAKRIWKI LRRR also exhibit immunomodulatory activity. Their mechanism involves neutralizing LPS from Gram-negative bacteria, thereby inhibiting TNF- $\alpha$  production in RAW264.7 macrophage cells. This action is essential for protecting the host against endotoxic shock, which can result from severe Gram-negative [90]. Another immunomodulatory peptide is equine  $\beta$ -defensin 1 – MRTSYLLLF~~T~~LCLLLSEMASGGNFLTGLGHRSDHYNCVSSG GQCLYSACPIFTKI~~Q~~GTCYRGKAKCCK- (eBD-1), which acts on macrophages infected by *Staphylococcus aureus* by activating the PI3K-AKT-NF- $\kappa$ B signaling pathway. Activation of this cascade leads to increased expression of proinflammatory cytokines such as TNF- $\alpha$ , IL-6, CXCL10, CD40, and RANTES. Inhibition of this pathway significantly reduces cytokine expression, underscoring its importance in the immune response. Moreover, eBD-1 stimulates the expression of phagocytosis-related proteins such as CD16 and paxillin, thereby promoting efficient pathogen clearance [91].



6. Clinical trial of AMPs


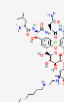
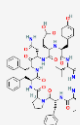
Over 5,000 antimicrobial peptides have been described, yet only 31 have reached preclinical trials (Supplementary 1), 38 are in phases I-III (Supplementary 2), and 17 have been FDA-approved and are currently on the market (Table 2). This scenario is primarily attributable to the pharmacokinetic and regulatory challenges associated with the use of AMPs *in vivo*, such as selective toxicity, low bioavailability, proteolytic degradation, and a lack of standardization in establishing specific legislative guidelines [92–94]. Nevertheless, AMPs remain promising alternatives for treating antibiotic resistance because they offer rapid antimicrobial activity, fewer adverse reactions, and broad therapeutic applications. This has led to a growing search for peptides with desirable characteristics as well as for peptide-engineering techniques and delivery systems that optimize their pharmacological profile [92, 93].

Table 2. AMPs approved for FDA and in market.

Pep tide Name	Sequence	Struc ture	Sourc e	Biolo gical Activ ity	Medical use	Tar get site	Deli very pat h	Comp any	Ref ere nce
Bacitra cin	Leu-D-Glu Ile-Lys-D-Orn-Ile-D-Phe-His-D-Asp-Asn		<i>Bacill us licheni formis</i>	Antiba cterial	Prevent wound infections, pneumonia and empyema in infants, skin and eye infections.	Cell wall	Top ical	Various companies	[95]

Dalbavancin Xydalba	Not available		Semi synthetic	Antibacterial	Acute bacterial skin infections, Osteomyelitis and septic arthritis Complicated skin infections	Cell wall	IV	DALVANCE®	[96]
Daptomycin Cubicin	decanoyl-Trp-Asn-Asp-Thr-Gly-Orn-Asp-D-Ala-Asp-Gly-D-Ser-Glu(3R-Me)-Asp (Ph(2-NH2))		Streptomyces roseosporus	Antibacterial	ns (cSSSI) and bloodstream infections (bacteremia) Human Immunodeficiency Virus (HIV) Infections; AIDS Skin lesions, surface wounds and eye infections	Cell membrane	IV	CUBICIN®	[97]
Enfuvirtide Fuzeon T20	YTSLIHSLEESQNQQEKNEQELLELDKWASLWNWF		Synthetic	Anti-HIV	ncy Virus (HIV) Infections; AIDS Skin lesions, surface wounds and eye infections	Fusion protein gp41	SC	FUZEON®	[98]
Gramicidin D	VGALAVVVWLWLWLW-ethanolamine		Bacillus brevis	Antibacterial	ns	Cell membrane	Topical	Various companies	[99]
Gramicidin S	cyclo[Leu-D-Phe-Pro-Val-Orn-Leu-D-Phe-Pro-Val-Orn]		Bacillus brevis	Antibacterial	Against bacteria and	Cell membrane	Topical	Various companies	[100]

					fungi restricte d use as spermic ide and to treat genital ulcers Treatm ent and prevent ion of inhalati onal anthrax	Antito xin IV	ANTHI M®	[101 ]
Obiltox aximab	Not available	Not avail able	monoc lonal antibo dy	Antiba cterial	Acute bacteria l skin	Cell wall IV	KIMYRS A™ ORBACT IV®	[102 ]
Oritava ncin	Not available	Not avail able	Semi synth etic	Antiba cterial	Prevent serious lung infectio ns (such as pneum onia) that are caused by respirat ory syncyti al virus- RSV Infect ions of the urinar y tract, meni	Blocki ng viral replic ation	IM	SYNAGI S® [103 ]
Paliviz umab	Not available		monoc lonal antibo dy	Antivi ral	Cell memb rane IV	Various compani es		[104 ]
Polym yxin B	Not available		<i>Bacill us polym yxa</i>	Antiba cterial				

					nges, and blood strea m Acute or chronic				
Polymyxin E Colistin	6-mh-DabTDab [Î³DabILDabDabT]		Bacillus polymyxa	Antibacterial	infections due to gram-negative bacilli	Cell membrane	Oral	Various companies	[105]
Raxibacumab	Not available	Not available	monoclonal antibody	Antibacterial	prevention of inhalational anthrax	Antitoxin	IV	RAXIBA CUMAB®	[106]
Telavancin TD-6424	Not available		Semisynthetic	Antibacterial	Osteomyelitis and bacterial infections	Cell membrane	IV	VIBATIV®	[107]
Tyrothricin	Not available		Brevibacillus parabrevis	Antibacterial Antifungal	Infected skin and infected oropharyngeal mucous membranes	Cell membrane	Topical/Oral	Various companies	[108, 109]

Peptides exhibit low bioavailability owing to their instability at acidic pH, enzymatic action, and poor intestinal mucosal absorption, which is why most AMPs are administered via injection [94]. However, this characteristic can be advantageous depending on the type of treatment, as observed for surotomycin, an antibacterial peptide in phase III clinical trials (NCT01598311). This peptide is minimally absorbed, making it ideal for treating *Clostridium difficile*-associated diarrhea and achieving the required high drug concentrations in the colon. Additionally, Surotomycin is a cyclic lipopeptide, ensuring greater stability and proteolytic resistance [114, 115].



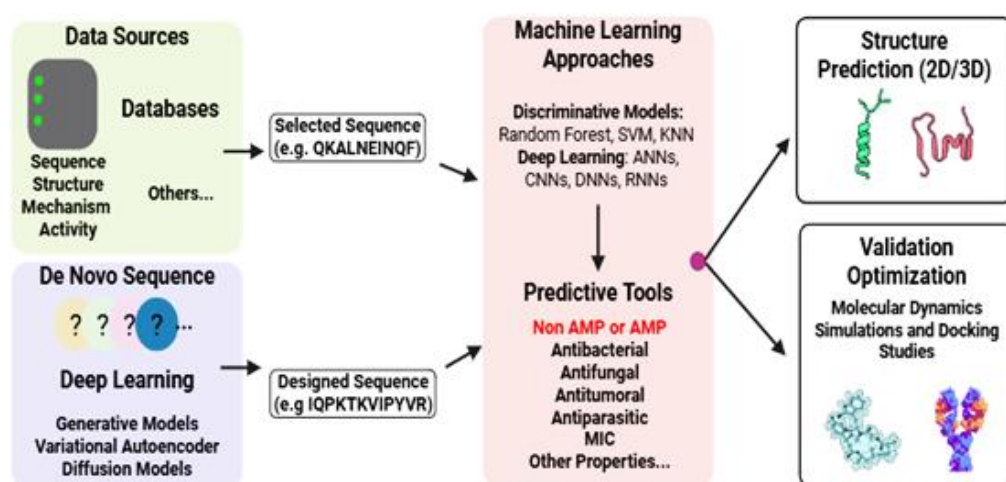
selecting appropriate *in vivo* and *in vitro* models, particularly for erythrocyte-based assays, since interspecies differences can affect the dose dependence of peptides [117]. Murepavadin is an example of an unsuccessful molecule that reached a phase III trial (NCT03582007) for the oral treatment of resistant *Pseudomonas aeruginosa* infections but exhibited dose-dependent nephrotoxicity [118, 119].

To improve the success of clinical trials, certain strategies are employed, such as topical or inhalable administration, which minimize systemic exposure. Examples such as XOMA-629, Omiganan, and PL-5 are applied topically as sprays or creams and are in phase III clinical trials. Meanwhile, nanotechnology-based systems using metallic nanomaterials (e.g., gold and silver nanoparticles) or polymeric materials (e.g., chitosan and lipid-based formulations), particularly with techniques like oil-in-water nanoemulsions, liposomes, and micelles, can optimize AMP delivery, absorption, and half-life [120, 121]. Nisin A, an oral AMP used in preclinical testing, demonstrated greater stability and antimicrobial activity against *Staphylococcus aureus* strains when formulated in chitosan/sodium alginate (CS/SA) microspheres [122].

Additionally, chemical modifications, such as substituting L-amino acids with their D-enantiomers, N-methylation, PEGylation, glycosylation, cyclization, and lipidation, can enhance AMP performance. These structural changes can improve solubility and stability in aqueous solutions, reduce renal clearance, extend antimicrobial function, and influence peptide activity through multiple mechanisms [123–125]. For example, oritavancin, a semisynthetic lipoglycopeptide antibiotic derived from vancomycin, is used to treat Gram-positive bacteria, including resistant strains. Its spectrum of activity and half-life are extended by its cyclic structure, lipophilic aromatic side chain, and amino acid d-enantiomers [125, 126].

## 7. Computational Approaches for AMPs Discovery and Design

Recent studies have shown notable advancements in computational methods for the discovery and optimization of AMPs. The existing research typically follows two complementary strategies: (1) bioinformatics-based mining of natural sequences to identify novel AMPs and (2) rational design of synthetic AMPs, either by modifying known templates through structure-based approaches or by employing de novo computational methods [127]. These strategies are summarized in **Figure 3**.



**Figure 3.** Two complementary strategies guide the discovery of antimicrobial peptides (AMPs): the identification of novel candidates from natural sources and the computationally guided design of synthetic AMPs. Protein images used in this figure were obtained from the freely accessible BioArt resource (<https://bioart.niaid.nih.gov/>).

Quantitative structure-activity relationship (QSAR) modeling is one of the longest-standing computational approaches in AMP research. This method predicts biological activity on the basis of the molecular structure, operating under the principle that structurally similar compounds exhibit similar functions [128]. Traditional QSAR employs linear regression models, in which biological activity is calculated as the weighted sum of molecular descriptors. More advanced ML-based QSAR

utilizes nonlinear algorithms, including random forest, artificial neural networks, K-nearest neighbor, and support vector machines, to capture complex structure-activity relationships through hierarchical feature interactions rather than simple weighted sums [129, 130]. Overall, the previously cited ML strategies and other approaches (e.g., hidden Markov models, logistic regression, fuzzy K-nearest neighbor, discriminant analysis), have substantially enhanced AMP classification accuracy within a hierarchical multilevel description [131, 132].

Discriminative models such as convolutional neural networks (CNNs), deep neural networks (DNNs), and recurrent neural networks (RNNs) are often integrated into pipelines for tasks such as AMP classification, property prediction, and bioactivity categorization [132, 133]. Building on these advances, Brizuela et al. [134] identified five hierarchical levels of tool functionality: (1) distinguishing AMPs from non-AMPs, (2) categorizing inputs by bioactivity, (3) target classification and prediction, (4) predicting AMP properties, and (5) estimating minimum inhibitory concentrations (MICs).

With the emergence of new methods, researchers are employing approaches combining evolutionary algorithms, codon-based optimization, and AI to design AMPs with enhanced antimicrobial activity and reduced host toxicity [127]. For de novo AMP design, deep learning-based generative models, such as variational autoencoders (VAEs), diffusion models, and generative adversarial networks (GANs), have shown notable success when trained on large datasets of known AMPs. These models generate novel peptide sequences while optimizing desired properties [135].

Computational tools such as AlphaFold [136], RoseTTAFold [137, 138] and PEP-FOLD [39] can be employed to predict AMP secondary and tertiary structures. Once structural models are available, molecular docking approaches, using platforms such as AutoDock [139] HADDOCK [140] and CABS-dock [141] allow the evaluation of potential interactions with target membranes or proteins. Subsequently, molecular dynamics simulations with packages such as GROMACS [142], CHARMM36 [143] or the coarse-grained MARTINI force field [144] provide insights into AMP stability, binding mechanisms, and dynamic behavior in biological environments. **Table 3** shows the common tools for AMP analysis, supporting researchers in the identification of AMPs and the generation of novel peptide sequences.

Table 3. AMPs tools for analysis.

Databa se Name	Functionality	Additional Information	URL	Refer ence
ACEP	Identification of AMPs.	The classification method is based on deep learning (DL).	<a href="https://github.com/Fuhaoyi/ACEP">https://github.com/Fuhaoyi/ACEP</a>	[145]
ADAPT ABLE	Designing novel peptides, predicting their activities, and identifying functional motifs.	Webserver and data-miner of antimicrobial peptides.	<a href="http://gec.upicardie.fr/adaptable/">http://gec.upicardie.fr/adaptable/</a>	[146]
AFP- MFL	A novel deep learning model that can predict antifungal peptides.	It only needs the peptide sequence to run.	<a href="https://inner.weigroup.net/AFPMFL/#/">https://inner.weigroup.net/AFPMFL/#/</a>	[147]
AlphaFo ld	To predict a protein/peptide's 3D structure based on amino acid sequence.	AI system developed by Google DeepMind.	<a href="https://colab.research.google.com/github/sokrypton/ColabFold/blob/main/AlphaFold2.ipynb">https://colab.research.google.com/github/sokrypton/ColabFold/blob/main/AlphaFold2.ipynb</a>	[148, 149]

<b>AntiBP 3.0</b>	A web-tool for predicting, scanning and designing AMPs.	Based on machine learning techniques.	<a href="https://webs.iitd.edu.in/raghava/anti-bp3/">https://webs.iitd.edu.in/raghava/anti-bp3/</a>	[150]
<b>AMP-Scanner</b>	A web server tool for predicting if it is an AMP based on amino acid sequence.	Only includes bacteria targets.	<a href="https://www.dveltari.com/ascan/">https://www.dveltari.com/ascan/</a>	[151]
<b>AMPA</b>	A web server tool for identifying active regions in antimicrobial proteins.	The algorithm uses an antimicrobial propensity scale to generate an antimicrobial profile.	<a href="https://tcoffee.crg.eu/apps/ampa/do">https://tcoffee.crg.eu/apps/ampa/do</a>	[152, 153]
<b>AMPDeep</b>	Deep learning approach to predict hemolytic activity of AMPs.	It was built on Python.	<a href="https://github.com/milad73s/AMPDeep">https://github.com/milad73s/AMPDeep</a>	[154]
<b>amPEPpy</b>	A python application for predicting antimicrobial peptide sequences.	The classification method is based on random forest.	<a href="https://github.com/tlawrence3/amPEPpy">https://github.com/tlawrence3/amPEPpy</a>	[155]
<b>AmpGram</b>	A web server tool for identification of AMPs.	The classification method is based on random forest and n-gram analysis.	<a href="http://biongram.biotech.uni.wroc.pl/AmpGram/">http://biongram.biotech.uni.wroc.pl/AmpGram/</a>	[156]
<b>AutoDock k</b>	A tool to predict how small molecules bind to a receptor of known 3D structure.	It has two options: AutoDock-GPU and AutoDock Vina.	<a href="https://autodock.scripps.edu/">https://autodock.scripps.edu/</a>	[139]
<b>AxPEP</b>	It is a collection of sequence-based machine learning methods for AMPs prediction.	The classification method is based on random forest.	<a href="https://app.cbbio.online/ampep/home">https://app.cbbio.online/ampep/home</a>	[157]
<b>CABS-dock</b>	A web server tool for flexible protein-peptide docking.	It requires the sequence of a protein receptor and a peptide sequence.	<a href="https://biocompchem.uw.edu.pl/CABSdock">https://biocompchem.uw.edu.pl/CABSdock</a>	[141]
<b>CHARM M36</b>	Broad-scope molecular simulation software for complex environments.	There is no cost to academic students.	<a href="https://academiccharmm.org/">https://academiccharmm.org/</a>	[143]
<b>CS-AMPPredict</b>	An SVM-based (support vector machines) tool to predict antimicrobial activity in cysteine-knotted proteins.	Were based on 310 AMPs and 310 non-antimicrobial peptide sequences.	<a href="https://sourceforge.net/projects/csamppred/">https://sourceforge.net/projects/csamppred/</a>	[158]
<b>Cysmotif Searcher</b>	A Perl package for revealing peptide sequences possessing cysteine motifs.	Cysteine motifs are common to various families of AMPs and others cysteine-rich peptides.	<a href="https://github.com/fallandar/cysmotifsearcher">https://github.com/fallandar/cysmotifsearcher</a>	[159]

<b>deepAMP</b>	A tool for predicting protein AMPylation sites from binary profile representation.	The classification method is based on a convolutional neural network.	<a href="https://github.com/MehediAzim/DeepAMP">https://github.com/MehediAzim/DeepAMP</a>	[160]
<b>GROMACS</b>	Powerful open-source suite for molecular dynamics simulation and analysis.	Broad spectrum of calculation types, preparation and analysis tools.	<a href="https://manual.gromacs.org/archive/4.6.7/online/speptide.html">https://manual.gromacs.org/archive/4.6.7/online/speptide.html</a>	[142]
<b>HADDOCK</b>	A web platform for biomolecular docking simulations.	A data-driven docking approach guided by ambiguous interaction restraints (AIRs).	<a href="https://rascar.science.uu.nl/haddock2.4/">https://rascar.science.uu.nl/haddock2.4/</a>	[140]
<b>iAMPCN</b>	DL approach to identifying antimicrobial peptides and their functional activities.	It was built on Python.	<a href="https://github.com/joy50706/iAMPCN">https://github.com/joy50706/iAMPCN</a>	[161]
<b>iTASSER</b>	DL approach to identifying antimicrobial peptides and their functional activities.	It was built on Python.	<a href="https://zhanggroup.org/I-TASSER/">https://zhanggroup.org/I-TASSER/</a>	[162]
<b>Joker</b>	A web tool to predict structure of a protein.	It also predicts the function.	<a href="https://github.com/williamfp7/Joker">https://github.com/williamfp7/Joker</a>	[163]
<b>MARTINI</b>	Coarse-grained force field for biomolecular simulations, parameterized using experimental data and atomistic simulations.	Based on a four-to-one mapping scheme.	<a href="https://cgmartini.nl/">https://cgmartini.nl/</a>	[144]
<b>MLBP</b>	Multi-label DL approach to identifying multi-functional bioactive peptide functions.	It was built on Python.	<a href="https://github.com/tangwending/MLBP">https://github.com/tangwending/MLBP</a>	[164]
<b>ModLAMP</b>	A Python package for working with any sequence of natural amino acids.	It includes the following modules: sequence generation, sequence library analysis and description calculation.	<a href="https://modlamp.org/">https://modlamp.org/</a>	[165]
<b>NAMD</b>	A highly scalable software for parallel molecular dynamics simulations of large biomolecules.	It uses the program VMD for simulation setup and trajectory analysis.	<a href="https://www.ks.uiuc.edu/Research/namd/">https://www.ks.uiuc.edu/Research/namd/</a>	[166]
<b>PEP2D</b>	A web tool for predicting secondary structure of peptides.	The model was trained and tested based on 3100 peptide structures.	<a href="https://webs.iitd.edu.in/raghava/pep2d/">https://webs.iitd.edu.in/raghava/pep2d/</a>	[167]

PEP-FOLD 4	A de novo approach to predict peptide structure from amino acid sequences.	The peptides should have 5 to 50 amino acids.	<a href="https://bioserv.rpb.s.univparisdiderot.fr/services/PEP-FOLD4/#overview">https://bioserv.rpb.s.univparisdiderot.fr/services/PEP-FOLD4/#overview</a>	[39]
RoseTTAFold	A Python-based AI tool for protein/peptide structure prediction.	The structure prediction method is based on DL.	<a href="https://github.com/RosettaCommons/RoseTTAFold?tab=readme-ov-file">https://github.com/RosettaCommons/RoseTTAFold?tab=readme-ov-file</a>	[137]
sAMPpred-GAT	A web tool for identification of AMPs.	The program uses graphs constructed based on predicted peptide structures.	<a href="http://bliulab.net/sAMPpred-GAT/server">http://bliulab.net/sAMPpred-GAT/server</a>	[168]
SWISS-MODEL	A web tool for protein structure prediction and modeling.	It supports interactive modeling for both simple and complex needs.	<a href="http://wissmodel.expasy.org">wissmodel.expasy.org</a>	[169]
VMD	A program to display, animate and analyze large biomolecules systems.	It has 3-D graphics	<a href="https://www.ks.uiuc.edu/Research/vmd/">https://www.ks.uiuc.edu/Research/vmd/</a>	[169]

\* All information was collected and reviewed on August 17.

Regardless of how the models are constructed, tool performance improves proportionally with database accuracy and proper structural organization [129, 170]. **Supplementary Table 3** presents the widely used databases containing AMP data. These databases typically provide comprehensive annotations on AMPs, including details such as amino acid sequence (composition and length), source organisms (bacteria, fungi, plants, or animals), biological activity (e.g., antibacterial, antiviral, or antifungal effects), physicochemical properties (hydrophobicity and charge), secondary structures ( $\alpha$ -helices,  $\beta$ -sheets, mixed  $\alpha/\beta$ , or non- $\alpha/\beta$  folds), mechanisms of action (molecular targets), and additional data [127].

8. AMPs and their Use in the Food Industry

Antimicrobial peptides can be potentially used for food preservation, mainly because they are considered ecological, safe, and economically viable in comparison with chemical preservatives [171]. Moreover, plant- and animal-based foods can be enzymatically hydrolyzed to generate peptides with antimicrobial activity [172]. Research has highlighted the challenges in applying AMPs in food systems, such as the use of nanotechnology through nanoencapsulation, which can enhance the stability, antimicrobial spectrum, and efficacy.

Microbial fermentation can generate BAPs from proteins of plant or animal origin. These peptides exhibit antimicrobial, antioxidant, antihypertensive, and anti-inflammatory properties, and show the potential for disease prevention and health promotion. Various microorganisms, including lactic acid bacteria, *Bacillus* spp., and fungi (*Aspergillus*, *Rhizopus*, *Saccharomyces*), can contribute to the release of these compounds during the fermentation of foods such as milk, meat, cereals, legumes, and seafood [173]. Bacteriocins are AMPs derived from probiotics and produced by lactic acid bacteria in traditional fermented foods. They have emerged as sustainable alternatives to antimicrobials and a means of food biopreservation [171, 174]. These bacteriocins act by forming pores and interfering with vital cellular processes and are selective, which preserve the body's beneficial microbiota [175].

The concept of "Clean Label" foods (foods produced with natural compounds) has gained prominence due to consumers' demand for healthier diets. This growing demand has pressured the food industry to replace synthetic preservatives with sustainable alternatives [176]. In this context, the use of bacteriocins and protective cultures has emerged as a promising approach for food preservation. These active cultures release antimicrobial substances directly into food, thereby increasing microbiological safety through a comprehensive effect against harmful bacteria, and are compatible with food systems [177, 178]. Despite these benefits, issues related to transparency, regulation, and social acceptance persist [179].

The combined use of probiotics and antimicrobials has been investigated as a novel approach to improve food safety and extend the shelf life of products. Probiotics can modulate microbiota, block pathogens, and simultaneously enhance the efficacy of AMPs. Synergistic approaches include the local production of antimicrobials through probiotic cultures and the strengthening of host immune defenses [180]. Analyses of toxicological risks, potential negative effects on beneficial microbiota, and mechanisms of bacterial resistance are important before these compounds can be used commercially [181]. Although these compounds have great potential as natural alternatives to artificial preservatives, information on their safety on a large scale is currently lacking. Obstacles include standardizing toxicological testing, investigating the effects on gut microbiota, and monitoring bacterial resistance [182]. From this perspective, integrating ethical principles into the development and application of food biotechnology is essential. Innovation should be guided not only by technological efficiency but also by environmental sustainability, social justice, and public health protection [172].

## 9. AMPs and Their Use in Veterinary Medicine

The abuse and inappropriate use of antibiotics has caused AMR to become a major public health concern. One aspect of AMR has been discussed in Swann's report published in 1969, which highlights the influence of AMR in animals and the latent concern that this may negatively affect humans [183].

In livestock animals, antibiotics are prophylactically used to promote growth. This approach employs sub-therapeutic doses, which are known to select for resistant organisms [184, 185]. Moreover, contrary to popular belief, domestic animals can influence this phenomenon. The indiscriminate use of antibiotics to prevent and treat diseases generates selective pressure that could lead to the transfer of AMR microorganisms to humans as a result of the close relationship between the two [186]. Wild animals may also aggravate this problem, since they could function as an ecological pool of resistant organisms however, the transmission routes involving wild animals are difficult to untangle [187]. In this scenario, the application of AMPs in the veterinary field may substantially contribute to resolving the issue at hand, facilitating the treatment of pathologies and the modulation of the immune system [188].

Antimicrobial peptides can be directly applied as growth-promoting agents. A recombinantly expressed piscidin from *Epinephelus lanceolatus* was used to supplement chicken feed. Animals fed 1.5%, 3%, and 6% recombinant *E. lanceolatus* peptide showed better growth than those in the control groups, with an increase of approximately 15%, 20%, and 16% in weight gain, respectively [189]. Another study on piglets performed with recombinant bovine lactoferrampin–lactoferricin as a dietary supplement suggested that it may improve the digestive microbiome in weaned piglets [190]. Similarly, dietary supplementation of weaning pig feed with 60 mg/kg of the antimicrobial peptide P5 (KWKKLLKKPLKLLKLL-NH<sub>2</sub>) improved nutrient digestibility and growth performance [191].

Antimicrobial peptides also have potential therapeutic applications. In a previous study, MPX (H-INWKGIAAMAKKLL-NH<sub>2</sub>), a peptide found in wasp venom, was found to counteract biofilm formation *in vivo* in a mouse model infected with *Actinobacillus pleuropneumoniae*, a highly infectious and relevant pathogen in the pig industry. This peptide destroyed the bacterial cell membrane and significantly reduced biofilm formation. MPX also prevented the death of mice infected with a lethal

dose of *A. pleuropneumoniae* [192]. In a study conducted on chickens, the peptide HJH-3 (VNFKLLSHSLLVTLRSHL) showed good antibacterial activity against *Salmonella pullorum*, with low hemolysis and no cytotoxicity, and prevented death in chickens infected with a lethal dose of *S. Pullorum* [193].

Furthermore, animals can be rich sources of AMPs, since these amino acid sequences are ubiquitous in the host defense system. Horses, for example, may be an interesting source of these substances, which encompass a wide range of peptides subdivided into several classes, including lysozymes, cathelicidins, defensins, and NK lysins [194]. Recently, a study integrating deep learning and bioinformatics attempted to describe new AMPs from the ruminant gastrointestinal microbiome, and the authors identified a peptide that can inhibit methicillin-resistant *Staphylococcus aureus* (MRSA). Fish are also a promising source of antimicrobial substances, since they are constantly exposed to pathogens [195]. Fish gills, spleen, skin, intestines, and other organs are rich with AMPs [196, 197].

Two recent reviews have focused on marine organisms and their application in aquaculture. García-Beltrán et al. [198] called attention to algae and cyanobacteria as sources of AMPs. Their study identified a wide range of activities, including antibacterial, antiparasitic, antifungal, antioxidant, and anti-inflammatory activities. Rodrigues et al. [199], on the other hand, focused on the AMPs derived from marine invertebrates. Their study identified approximately 350 peptides from 10 different invertebrate *phyla*, some of which showed broad-spectrum *in vitro* activities against pathogens, including fungi, Gram-positive bacteria, Gram-negative bacteria, and viruses. The only caveat described in their paper was the lack of *in vivo* studies reported in literature, highlighting a research gap that should be addressed [199].

Based on the aforementioned scenarios, the application of AMPs in veterinary medicine can be safely assumed to yield positive results. Nevertheless, more research is needed to draw definite conclusions about the efficacy and viability of the application of these compounds. However, these peptides offer concrete alternatives to antibiotics, since they are abundant in a wide range of sources, and therefore constitute a strong contender for antibiotic use.

10. Conclusions

Considering the potential advantages of using BAPs as therapeutic agents, along with their market appeal, studies that refine the mode of action of these biomolecules have gained relevance and require advanced and clinical practice. The diversity of sources and methods to obtain BAPs make them a rich and inexhaustible source of possibilities for the promotion of human and veterinary health.

The application of omics techniques, which combine the results of bioinformatics analyses, has led to the identification of several peptide sequences with biological activities, allowing the generation of these peptides through chemical synthesis or gene expression. Several servers and databases are available for researching biological activities and designing peptide amino acid sequences. These bioinformatics tools, combined with AI, can predict the biological activity of a given amino acid sequence and the possible changes and modifications that can optimize the biological activity of AMPs.

Abbreviations

BAP	Bioactive Peptide
AMP	Antimicrobial Peptide
APD3	Antimicrobial Peptide Database 3
AMR	Antibiotic Resistance
WHO	World Health Organization
MERS	Middle East respiratory syndrome
SARS	Severe acute respiratory syndrome

AVP	Antiviral peptides
AFP	Antifungal peptides
SPPS	Solid-phase Peptide Synthesis
HBTU	O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosph
DIC	N,N'-diisopropylcarbodiimide
CCK	Cyclic Cystine Knot
DMF	Dimethylformamide
UAE	Ultrasound-assisted extraction
PEF	Pulsed electric fields
HHP	High hydrostatic pressure
AI	Artificial Intelligence
ML	Machine Learning
GST	Gglutathione S-transferase
MBP	Maltose-binding protein
GRAS	Generally recognized as safe
PG	Phosphatidylglycerol
CL	Cardiolipin
PS	Phosphatidylserine
LPS	Lipopolysaccharides
HSPG	Heparan sulfate proteoglycan
HCMV	Human cytomegaloviruses
MCMV	Murine cytomegaloviruses
DHFR	Dihydrofolate reductase
TCA	Tricarboxylic acid
SQR	Succinate-coenzyme Q reductase
ROS	Reactive oxygen species
HSV-1	Simplex virus type 1
LBP	Binding protein
FDA	Food and Drug Administration
IV	Intravenous injections
IM	Intramuscular injections
SC	Subcutaneous injections
CS/SA	Chitosan/sodium alginate
QSAR	Quantitative Structure-Activity Relationship
CNNs	Convolutional Neural Networks
DNNs	Deep Neural Networks
RNNs	Recurrent Neural Networks
VAEs	Variational Autoencoders
GANs	Generative Adversarial Networks
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
DL	Deep learning
SVM	Support vector machines
AIR	Ambiguous interaction restraints (AIRs).

**Supplementary Materials:** The following supporting information can be downloaded at: X [199-266]. **Table S1:** AMPs in pre-clinical. All information was collected and reviewed in the DRAMP database (<http://dramp.cpu-bioinfor.org/>) [15] (accessed August 15, 2025). **Table S2:** AMPs in clinical trial. Data was collected and reviewed in the DRAMP database (<http://dramp.cpu-bioinfor.org/>), Chinese Clinical Trial Registry [ChiCTR] (<https://www.chictr.org.cn/indexEN.html>), European Union Clinical Trials Register (<https://www.clinicaltrialsregister.eu/ctr-search/search>), and

ClinicalTrials.gov (<https://www.clinicaltrials.gov/>) (accessed August 28, 2025). Table S3: AMPs databases. Data collected on September 5.

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