Review

Unveiling the Armory: A Comprehensive Review on Antimicrobial Peptides - Classification and Diverse Applications across Disease Landscapes

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Unveiling the Armory: A Comprehensive Review on Antimicrobial Peptides - Classification and Diverse Applications across Disease Landscapes

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Abstract: Antimicrobial peptides (AMPs) are essential components of the innate immune system, present across a spectrum of organisms. Their versatility lies in their ability to effectively inhibit a wide range of pathogens including bacteria, fungi, parasites, and viruses. As the challenge of antibiotic resistance escalates and concerns surrounding antibiotic use grow, AMPs have emerged as promising alternatives. Their applications span diverse domains such as medicine, agriculture, food production, animal husbandry, and aquaculture, primarily due to their efficacy against resistant pathogens, signifying their crucial role in combating infections. Beyond their antimicrobial properties, research illuminates their intricate involvement in the immune response network. These peptides impact crucial processes including cytokine release, chemotaxis, wound healing, angiogenesis and the activation of the adaptive immune system. This comprehensive review delves into the multifaceted realm of AMPs, encompassing their classification, varied applications across industries and notably, their significance in diverse disease conditions like infections, skin diseases, cancer, oral diseases, lung diseases and cardiovascular ailments. Special attention is directed towards current advancements in clinical applications of peptide-based therapeutics, offering invaluable insights into their potential future integration within clinical settings.

Keywords: antimicrobial peptides; classification; disease conditions; therapeutic action and clinical advancements

1. Introduction

Every member of the Animalia kingdom possesses inherent defense mechanisms against various disease-causing microorganisms such as bacteria, fungi, protozoa, and viruses. The human immune system comprises two key types: innate immunity, which is present from birth and provides natural protection against diseases; and acquired immunity, which develops after exposure to disease-causing agents. Notably, innate immunity is inherent in all multicellular organisms, necessitating no prior exposure to foreign pathogens and often being genetically predetermined. Among the integral components of this innate immune system are antimicrobial peptides, protein molecules with relatively small molecular weights that exhibit protective antimicrobial actions against a wide range of microbes including bacteria, fungi, and viruses. These evolutionarily conserved defense molecules are produced by various species such as plants, bacteria, insects and vertebrates and they are notably preserved in mammals [1]. Antimicrobial peptides function as naturally synthesized host organism defenses, akin to endogenous antibiotics, against invading pathogens. The discovery of lysozyme by Alexander Fleming in 1922 catalyzed further research and exploration into antimicrobial peptides. As per the antimicrobial peptide database (APD3), approximately 3,240 AMPs have been identified to date, and ongoing studies suggest the likelihood of discovering many more in the future [2].

Antimicrobial peptides typically manifest as small cationic molecules, ranging from 1-5 kDa in size, carrying an average positive charge of 3.32 and spanning 10-60 amino acid residues. However, there exists another category—negative charge-bearing anionic antimicrobial peptides—which

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possess notable quantities of glutamic acid and aspartic acid residues within their chemical structure [3,4]. These AMPs are predominantly expressed on primary barriers like the skin and mucosal epithelium of the respiratory, urinary, and gastrointestinal systems (including Paneth cells in the crypts of Lieberkühn in the small intestine), as well as on immune cells. Positioned as the first line of defense against infections, they effectively impede the colonization of pathogens within the host organism's body [5,6]. Antimicrobial peptides are stored in the granules of macrophages and other phagocytic cells, functioning to neutralize engulfed foreign pathogens by degrading their cell membranes and inducing cell death [7,8] . The majority of these peptides are characterized by their amphipathic nature, constituting small molecules with fewer than 50 amino acid units, often referred to as host defense peptides [9]. Presently, over 130 AMPs have been investigated within the human body.

Antimicrobial peptides exhibit diverse functions within the body, with their primary role being defense against invading microorganisms like bacteria, fungi, and enveloped viruses [10–12] . The various biological functions of AMPs are largely influenced by factors such as their molecular size, net charge, secondary or three-dimensional structure, and hydrophobicity[13,14]. Aside from their defensive actions, these peptides play crucial roles in wound healing, angiogenesis, neutralizing lipopolysaccharides and endotoxins, exhibiting chemotactic activity, and modulating the immune response [15–18]. Antimicrobial peptides engage with and penetrate bilayer lipid membranes using various mechanisms such as barrel-stave, carpet, or toroidal pore methods.

Antimicrobial peptides have emerged as alternative options to conventional antibiotics for combating various infectious diseases, showcasing broad-spectrum antimicrobial activity against both gram-positive and gram-negative bacterial species. Their bactericidal action primarily occurs through two mechanisms: direct disruption of the bacterial cell membrane or interference with intracellular biochemical processes. The positive charge of AMPs plays a pivotal role in selectively interacting with the anionic cell membrane of bacteria, while their hydrophobic segments effectively engage with the hydrophobic interior of the bacterial membrane [19–21]. Many AMPs not only perturb the synthesis of proteins and nucleic acids within bacteria but also hinder enzymatic reactions and generate reactive oxygen species (ROS) such as NK-18, buferin II, and lactoferricin B, initiating apoptosis in bacterial species [22–24].

Antimicrobial peptides play a pivotal role in preventing pathogen proliferation and biofilm development in skin lesions, thereby facilitating wound healing by modulating cellular migration, chemotaxis, angiogenesis, and cytokine release [25,26]. They serve as promising therapeutics for both infectious and non-infectious wounds [27,28]. Within the respiratory system, AMPs produced by neutrophils and airway epithelial cells aid in averting infectious conditions like pneumonia [29] . Moreover, AMPs demonstrate beneficial effects in healing corneal ulcers[30] and preventing peptic ulcers in the gastrointestinal tract while maintaining a balanced and healthy intestinal microbiota [31]. Certain AMPs exhibit potent antimicrobial properties against bacteria causing bone and joint infections without causing harm to osteoblasts [32]. In the oral cavity, AMPs synthesized by gingival epithelium act as the first line of defense against pathogens responsible for oral infections like mucositis and candidiasis [33]. Furthermore, AMPs possess the ability to internalize cells and interact with intracellular components, such as mitochondria, inducing natural cell death, thus holding promise in controlling tumor growth and preventing oncogenesis in various organs [34].

Within the human body, cathelicidins and defensins stand as extensively researched antimicrobial peptide groups. Their roles span diverse disease modulation, including gastrointestinal disorders, skin ailments, respiratory tract infections, oral diseases, cancer, and other epithelial infections. These peptides contribute significantly to bolster our immune system while providing protection against external invasive microorganisms. This review focuses on elucidating their classifications, applications across different fields, and the potential of antimicrobial peptides in preventing various diseases.

2. Classification Antimicrobial peptides (AMPs)

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Owing to their natural diversity, Antimicrobial Peptides (AMPs) are classified into different categories based on source, activity, structural characteristics and amino acid rich species (Figure 1).

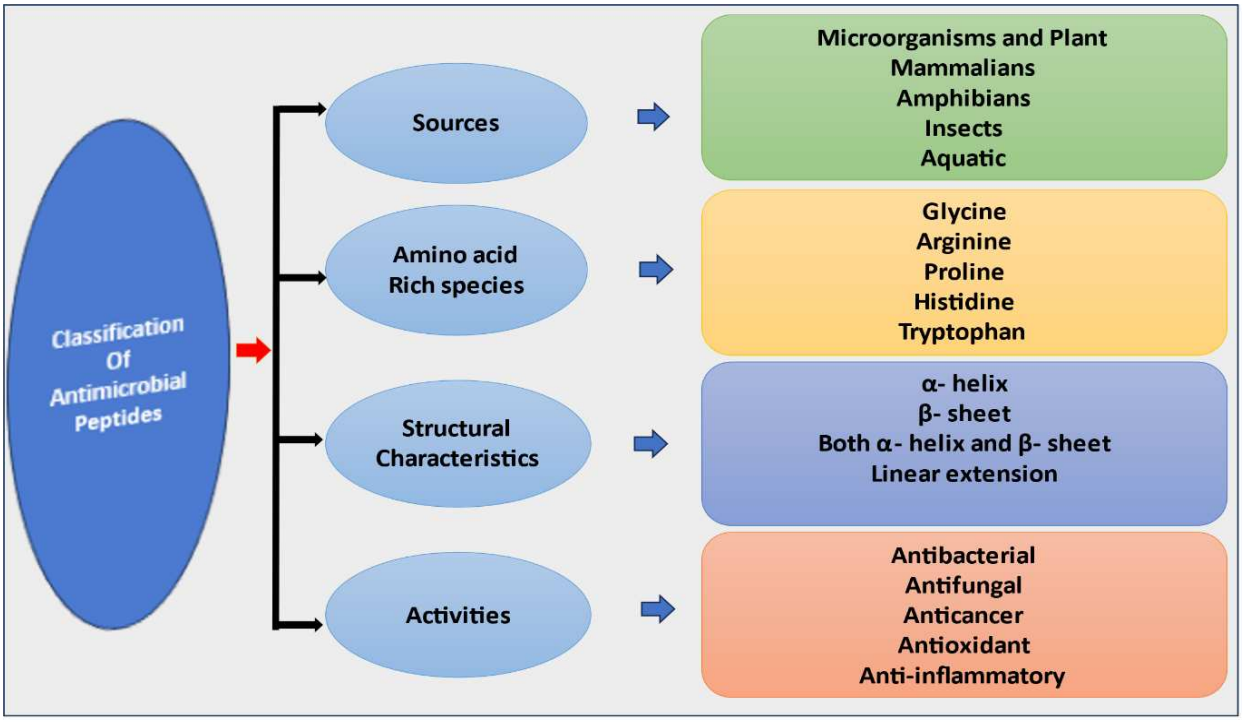

Figure 1. Classification of Antimicrobial Peptides.

2.1. Classification of AMPs Based on Sources

AMPs are categorized into different types based on organisms from various phyla or classes, spanning mammals, insects, birds, amphibians, and microorganisms. Additionally, numerous AMPs have been sourced from marine animals found in the ocean.

2.1.1. Antimicrobial Peptides Derived from Mammals

Antimicrobial peptides (AMPs) are abundant across various mammals, including humans, cattle, and vertebrates. Enzymatic hydrolysis of milk and its products serves as a promising source for these peptides, often isolated from components like α-lactalbumin, β-lactoglobulin, lactoferrin, and casein. Among these, lactoferricin B (Lfcin B) stands out as a prominent AMP derived from milk [35]. In humans, AMPs are primarily classified into cathelicidins and defensins. Defensins, categorized by the arrangement of disulfide bonds, encompass α-, β-, and θ-defensins [36]. Human host defense peptides (HDPs), pivotal in guarding against microbial infections, exhibit varied expressions at different life stages. For instance, cathelicidin LL-37 is prevalent in newborns' skin, while human β defensin 2 is predominantly found in older individuals [37]. AMPs are observed in multiple bodily locations including the skin, ears, eyes, mouth, lungs, respiratory tract, intestines, and urethra. Notably, AMPs present in breast milk play a crucial role in reducing morbidity and mortality rates in newborn infants [38]. Beyond their antimicrobial role, AMPs also regulate processes such as apoptosis, wound healing, and immune activity [39].

2.1.2. Antimicrobial Peptides Derived from Amphibians

Amphibians rely on antimicrobial peptides derived from their skin secretions as a defense against pathogenic threats, potentially contributing to the preservation of their population [40]. Notably, amphibians like frogs from genera *Xenopus, Silurana, Hymenochirus,* and *Pserdhymenochirus* offer sources for AMPs such as Magainin and others found in their skin secretions [41] . Additionally,

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the discovery of Cancrin, the first AMP extracted from the sea amphibian *Rana cancrivora*, underscores the broader spectrum of AMP sources within the amphibian community [42].

2.1.3. Antimicrobial Peptides Derived from Insects

Antimicrobial peptides in insects are synthesized within blood cells and fat bodies, providing them with remarkable adaptability for survival [43]. Among these peptides, cecropin stands out as one of the most well-known families and is found in various insects like the guppy silkworm, *Drosophila*, and bees. Notably, cecropin A exhibits protective properties against a range of inflammatory diseases and cancers [44]. The number of AMPs varies across different insect species; for instance, invasive harlequin ladybirds (*Harmonia axyridis*) and black soldier flies (*Hermetia illucens*) possess approximately 50 AMPs, whereas the pea aphid (*Acyrthosiphon pisum*) lacks AMPs altogether [45]. Royal jelly produced by bees contains a peptide called jellein, displaying antimicrobial activity against numerous bacteria and fungi. Additionally, its lauric acid-conjugated form effectively regulates the growth of the kalajar parasite *Leishmania major* [46].

2.1.4. Antimicrobial Peptides Derived from Microorganisms

Antimicrobial peptides find their origins in microorganisms such as bacteria and fungi, with nisin and gramicidin being well-known examples obtained from species like *Lactococcus lactis*, *Bacillus subtilis*, and *Bacillus brevis* [47]. Biological expression systems for AMPs encompass various yeast species like *Pichia pastoris, Saccharomyces cerevisiae*, bacteria including *E. coli* and *B. subtilis*, as well as plants [48]. In addition to these primary sources, an increasing number of AMPs are being isolated from different parts of plants—seeds, stems, and leaves—grouped into categories like defensins, thionins, and snakins [49]. Extracting immune-related AMPs from organisms like *Mytilus coruscus* provides alternatives to antibiotics; for instance, myticusin beta serves as an immune-related AMP derived from this source [50]. Originating from marine sources, AMPs like pardaxin (GE33) have been used in vaccines, enhancing antitumor capabilities in mice [51].

2.2. Classification of AMPs Based on Activity

The ADP3 database categorizes antimicrobial peptides into 18 distinct groups, where antibacterial peptides constitute 60 percent, antifungal peptides account for 26 percent, antitumor peptides make up 5 percent, antiviral peptides contribute 4 percent, antiparasitic peptides encompass 3 percent, and anti-HIV peptides represent 2 percent.

2.2.1. Antibacterial Peptides

Antibacterial peptides play a crucial role in inhibiting various pathogenic bacteria found in clinical settings, food production, and aquatic products manufacturing. They effectively target bacteria such as *Acinetobacter baumannii*, VRE, MRSA, *S. aureus, L. monocytogenes, E. coli, Salmonella*, and *Vibrio parahaemolyticus*. Peptides like nisin, defensins, and cecropins exhibit the ability to halt the growth of both gram-positive and gram-negative bacteria. Specific antimicrobial peptides like P5 and P9 demonstrate efficacy against MRSA while also reducing cellular toxicity levels [52].

2.2.2. Antifungal Peptides

Antifungal peptides serve as a defense against various fungi and enhance the body's resilience against organisms like Aspergillus, Candida albicans, yeast, filamentous fungi, and molds in clinical, food, and agricultural contexts. Peptides such as ranatuerin, cecropins, aurein, and synthetic antifungal variants are employed to hinder the growth of *Candida albicans* and *Aspergillus flavus*, known for producing aflatoxins [53]. Notably, approximately 37 antifungal peptides have been extracted from *Lactobacillus plantarum* TE10, and their combination has shown a reduction in the sporulation of Aspergillus flavus in maize [54].

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2.2.3. Antiviral Peptides

Antiviral peptides exhibit diverse mechanisms by hindering virus attachment, cell membrane fusion, and disrupting viral membranes, consequently impeding viral replication [55]. Within the antiviral peptide category, there exists a subgroup focused on combating HIV. Commonly used and commercialized anti-HIV peptides encompass alpha and beta defensins, LL-37, gramicidin D, caerin 1, maximin 3, maginin 2, dermaseptin-S1, dermaseptin-S4, siamycin-I, siamycin-II, RP71955, and FuzeonTM [56]. Specific AMPs like epinecidin-1 demonstrate inhibition against the virus responsible for foot-and-mouth disease [57]. Additionally, swine intestinal AMP (SIAMP)-IBV has shown effectiveness in reducing the occurrence of infectious bronchitis virus in chicken embryos [58]. Fusion inhibitor peptides like peptide HR2, its lipid binding counterpart, temporin, and rhesus theta defensin 1 collectively act against SARS-CoV and MERS-[59,60].

2.2.4. Anti-parasitic Peptides

Anti-parasitic peptides play a crucial role in thwarting the growth and reproduction of parasites responsible for various diseases such as kalazar and malaria, impacting both humans and other organisms [61,62]. Peptides like temporins-SHD and cathelicidin impede biological processes, effectively preventing the invasion of parasitic organisms [63]. A synthetic marine AMP, epinecidin 1, disrupts the membrane of *Trichomonas vaginalis* [64]. Furthermore, jellein from royal jelly, along with the amino acid AMP KDEL (lysine, aspartic acid, glutamic acid, and leucine), inhibits *Trichomonas vaginalis* and *the Leishmania donovani* parasite [65] . Notably, the antiparasitic action of cyanobacterial AMPs relies on specific protein targets, differing from those of higher eukaryotic AMPs.

2.2.5. Anticancer Peptides

Anticancer peptides display multifaceted functions including the ability to eliminate tumour cells through immune or dendritic cell activation, trigger apoptosis in cancerous cells, inhibit angiogenesis, impede metastasis, and activate regulatory proteins that disrupt the transcription and translation of tumour cells [66,67]. Peptides like tritripticin, inolicidin, and puroindoline A showcase anticancer properties and contribute to countering carcinogenesis [68]. These Anticancer Peptides (ACPs) operate by balancing net charge and hydrophobicity, thereby harnessing their anticancer benefits.

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2.3. Classification of AMPs Based on Amino Acid Rich Species

Antimicrobial peptides fall into four distinct categories:

(a) Proline-rich peptides function by targeting the bacterial inner membrane using the SbmA transporter. They gain entry into the cytoplasm, affecting ribosomes and disrupting the termination process of translation. This disturbance ultimately hampers protein synthesis in bacteria [69].

(b) Tryptophan and arginine-rich peptides impact the cell membrane by disrupting the lipid bilayer interface. They influence peptide charge and hydrogen bond interactions. Examples like tritripticin and indolicidin showcase effectiveness against gram-negative bacteria such as *E. coli* and *Pseudomonas aeruginosa*, as well as gram-positive *Staphylococcus aureus*.

(c) Histidine-rich peptides like HV2 enhance cell membrane permeation, leading to rupture and subsequent bacterial cell membrane death. They also exhibit anti-inflammatory properties by inhibiting the synthesis of tumour necrosis factor [70].

(d) Glycine-rich peptides like attacins and diptericins demonstrate efficacy against gram-negative bacteria, effectively eliminating them [71].

2.4. Classification of AMPs Based on Antimicrobial Peptide Structure

Antimicrobial peptides are grouped based on their structures into four classes: linear α-helical, β-sheet, linear extension, and peptides that combine both α-helix and β-sheet structures [72].

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Additionally, researchers have examined various cyclic peptides and antimicrobial peptides with more intricate configurations, including lasso peptides and thioether bridged structures [73].

3. Application of Antimicrobial Peptides in Different Fields

Antimicrobial peptides (AMPs) have gained extensive applications across diverse fields like medicine, food, agriculture, animal husbandry, aquaculture etc (Figure 2). In medicine, AMPs play roles in addressing infections, wound healing, skin diseases, gastrointestinal issues, dental problems, surgical injuries, cancer treatment, respiratory tract disorders, and ophthalmology. Notably, the FDA has approved three AMPs—gramicidin, daptomycin, and colistin—for specific medical uses. Innovations include pheromone-labelled and locally triggered AMPs that exhibit improved targeting mechanisms.

In the food industry, AMPs effectively inhibit the growth of bacteria, fungi, and other microorganisms, thereby preventing food spoilage. Their resilience against acids, alkalis, and temperature fluctuations positions them as alternatives to conventional food preservatives. Examples like nisin, plylysine, and Lactic acid bacteria in dairy products showcase this efficacy. Specific AMPs such as pedocin combat Listeria monocytogenes, a common cause of meat spoilage, while enterocin aids in preserving cider, fruit and vegetable juices, and soy milk.

Additionally, AMPs prove valuable in agriculture by inhibiting plant pathogens like *Aspergillus flavus* in corn and peanuts, *Penicillium digitatum*, and *Geotrichum citriaurantii* in citrus, and *Botrytis cinerea* in strawberries. In animal farming, AMPs like SIAMP and NKLPs help prevent various diseases and infections in poultry, swine, ruminants, and fish farming. They find applications in coating implants, contact lenses, and biomedical devices. Moreover, AMPs play a role in biosensors' detection and are utilized in water purifiers [74].

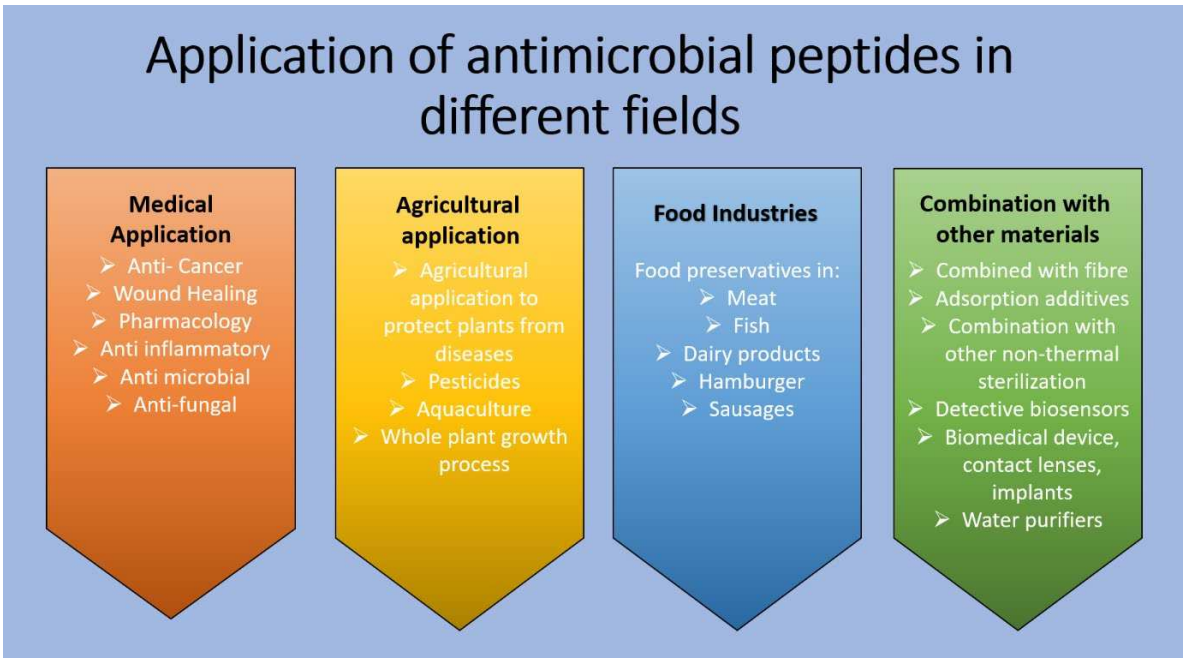

Figure 2. Application of antimicrobial peptides in different fields.

4. Application of Antimicrobial Peptides in Different Diseased Conditions

Antimicrobial peptides prove valuable in treating and preventing numerous diseases in humans and other organisms. They serve as an alternative to antibiotics in combating bacterial, viral, and fungal infections. These versatile compounds are utilized in addressing a wide array of infectious disorders, including skin infections, AIDS, lung diseases, gastrointestinal tract disturbances, oral and dental diseases, cancers, iron disorders, autoimmune diseases, and Alzheimer's disease, both in natural and synthetic forms within clinical settings.

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4.1. Role of AMPs in Infectious Diseases

Most antimicrobial peptides (AMPs) exhibit a unique ability to eliminate invasive microorganisms while causing minimal harm to host organisms. This effectiveness arises from the distinction in cell membrane structure between prokaryotes and eukaryotes. The outer membrane of gram-positive bacteria contains teichoic and lipoteichoic acid, while gram-negative bacteria possess lipopolysaccharide and phosphatidyl-glycerol, resulting in a negative charge. Positively charged AMPs interact electrostatically with this negative charge, affecting the surface structure of these bacteria. Notably, there is no interaction between AMPs and mammalian cell membranes due to the neutral net charge of mammalian membranes [75]. AMPs don't just impact the bacterial cell membrane; they also penetrate the cytoplasm, leading to alterations in numerous cellular processes such as cell wall formation, protein synthesis, nucleic acid synthesis, and enzyme activity [76].

AMPs have demonstrated a synergistic effect when combined with traditional antibiotics, enhancing the prevention of microbial infection [77]. Studies involving magainin II and cecropin A, administered either independently or with rifampicin against multi-drug-resistant *Pseudomonas aeruginosa*, both in vivo and in vitro, have shown significant reductions in bacterial multiplication, LPS and TNF-α secretion, as well as infection rates and mortality [78]. P5 peptide's collaboration with isepamicin in cholelithiatic patients effectively combats Pseudomonas aeruginosa [79].

AMPs also target bacterial biofilms linked to dental plaque, endocarditis, lung infections, and infections related to medical devices. For instance, Kappcin, a non-glycosylated κ-casein, has demonstrated a substantial reduction in *Streptococcus mutans* biofilms in the presence of zinc chloride [80]. Melimine, a non-hemolytic hybrid peptide derived from melittin and protamine, diminishes bacterial adhesion to covalently linked contact lenses [81]. Citropin 1.1, derived from the green tree frog *Litoria citropa*, in combination with rifampin and minocycline, exhibits increased anti-biofilm activity against *S. aureus* [82].

A multitude of AMPs, including magainins, temporins, defensins, cathelicidins, bacteriocins, bombinins, protonectins, abaecin, among others, effectively hinder the growth and formation of biofilms associated with various gram-positive and gram-negative bacterial infectious diseases. In conjunction with antifungal drugs like fluconazole, caspofungin, amphotericin B, clotrimazole, and flucytosine, antifungal peptides combat various fungal infections caused by *Candida spp.*, *Aspergillus, Histoplasma, Blastomyces*, and *Coccidioides* [83].

4.2. Role of AMPs in Skin Diseases

The skin acts as the initial defense line against various microorganisms in organisms, with the epidermis forming a physical barrier providing immediate protection against infections. Within the skin, low molecular weight antimicrobial peptides (AMPs) such as α- and β-defensins, cathelicidins, S100 proteins, and ribonucleases are present in cells like mast cells, keratinocytes, eccrine and sebaceous glands, and phagocytic cells [84,85]. Several AMPs play roles in chronic inflammatory skin conditions like atopic dermatitis and psoriasis vulgaris [86]. Defensins, including α-, β-, and θ-defensins, are small cystine-rich molecules with a β-hairpin structure stabilized by three conserved disulfide bonds [87,88]. Human α-defensins -1 to -4, known as human neutrophil peptides (HNP1 to HNP4), found in neutrophils, and enteric peptides like HD-5 and HD-6 expressed in Paneth cells are among these [89].

Human defensins exhibit antibacterial effects against various gram-negative bacteria like *Escherichia coli, Candida albicans,* and *Pseudomonas aeruginosa*. For instance, hBD-3 targets multidrug-resistant gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pyogenes*, and vancomycin-resistant *Enterococcus faecium* .hBD-3 contributes to wound healing, dendritic cell activation, migration, and polarization [90]. Another peptide, hBD-2, induced by the human papillomavirus, combats gram-negative bacteria like *E. coli, E. faecalis, Propionibacterium acnes*, and *P. aeruginosa* while aiding in wound repair. Dermcidin exhibits antibacterial activity against various pathogens such as *E. coli, S. aureus, C. albicans*, and *E. faecalis* [91]. RNase 7 displays antimicrobial activity against both gram-negative and gram-positive bacteria like *E. coli, S. aureus, E. faecium, P. aeruginosa*, MRSA, and yeast *C. albicans* [92].

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Human cathelicidin LL-37, a versatile antimicrobial peptide, disrupts bacterial cell membranes, viral envelopes, and fungal pathogens like yeast. LL-37 also exhibits pro-apoptotic activity in airway epithelial cells and promotes angiogenesis, contributing to the wound healing process [93]. Psoriasin (S100A7), a Ca2+ binding protein found in psoriatic lesions characterized by keratinocyte differentiation and tumor formation, demonstrates antibacterial activity against *E. coli* and chemotactic activity for CD4+ T lymphocytes and neutrophils [94,95]. Calprotectin provides protection against *E. coli, S. aureus, Staphylococcus epidermis, Klebsiella* spp., and *Candida albicans* [96].

4.3. Role of AMPs in Oral Diseases

Different oral diseases, including dental caries, periodontal issues, mucosal infections, and oral cancer, stem from various causes and microbes. Dental caries result from localized demineralization due to acid accumulation during bacterial fermentation of leftover food particles [97]. Secondary conditions like pulp and periapical diseases often involve bacteria like *Enterococcus faecalis,* which forms biofilms in root canals leading to apical periodontitis [98]. Natural and synthetic antimicrobial peptides (AMPs) play roles in inhibiting pathogenic microbes, aiding enamel remineralization, and pulp tissue healing. They also act as biomarkers indicating caries risk. Human β-defensins 1, 2, and 3 expressed in pulp and odontoblasts combat *Streptococcus mutans* and *E. faecalis* by preventing their association with host cells [99,100]. Histatin-5 and cathelicidin LL37 also exhibit antibacterial activities against *Streptococcus mutans* [101,102]. Synthetic AMPs derived from hBD-3, such as HBD3-C15 and D1-23, inhibit *Streptococcus gordonii* and *S. mutans*, preventing their biofilm formation [103,104]. Peptides like VSL2, DGL13K, PR39, DJK-5, IDR-1002, and C16G2 show efficacy against harmful effects of *E. faecalis* and *S. mutans* [71,105,106].

Periodontal diseases often involve bacteria like *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Prevotella intermedia*. hBD-2 displays inhibitory action against these pathogens, curbing periodontal inflammation similar to minocycline at comparable concentrations [107]. Cathelicidin LL37 helps suppress inflammation caused by *P. gingivalis* [108]. AMPs derived from humans, cattle, sheep, and pigs—such as P-113, hBD3-C15, BMAP28, PMAP23, SMAP28, SMAP29, and Nal-P-113—show broad-spectrum antimicrobial effects [109].

Oral mucosal diseases like oral candidiasis often stem from autoimmune inflammatory conditions and fungal attacks. AMPs like Histatin 5, HNP-1, hBD-2, hBD-3, LL37, and Lactoferricin B safeguard the oral environment against *Candida albicans* fungal infections. Salivary LL37 displays antiviral activity against Kaposi's sarcoma-associated herpes virus [110]. hBD-1 is effective in suppressing oral squamous cell cancer and benign tumors in salivary glands [111].

4.4. Role of AMPs in Lung Diseases

The respiratory pathway, being directly exposed to external air during inhalation, remains consistently vulnerable to microbial exposure. The innate immune system of the lungs comprises epithelial and myeloid cells like alveolar epithelial cells, neutrophils, and dendritic cells, which actively combat microbial colonization. These cells express primary antimicrobial peptides (AMPs) of the respiratory tract, particularly defensins and cathelicidins. Epithelial cells, monocytes, macrophages, and dendritic cells express hBD-1 and hBD-2 [112,113]. During microbial infections, hBD-2, hBD-3, and hBD-4 are significantly induced and abundantly expressed [114]. Bacterial exposure, such as to *Pseudomonas aeruginosa, Haemophilus influenza, Legionella pneumophila*, and *Streptococcus pneumoniae*, activates hBD-2 and hBD-3 in respiratory epithelium [115]. Various mycobacterial strains facilitate the expression of hBD-2 [116]. LL37 demonstrates antimicrobial activity against both gram-negative and gram-positive bacteria. α-defensins HNP-1 and HNP-2, along with LL-37, exhibit heightened levels in chronic obstructive pulmonary disease [117]. The antimicrobial efficacy of defensins is sensitive to salt, and excessive mucus production in the respiratory airways can affect the potency of LL-37 [118].

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4.5. Role of AMPs in Gastrointestinal Diseases

Antimicrobial peptides function as internal antibiotics, combating the health effects instigated by fungi, protozoa, viruses, and bacteria within the gastrointestinal (GI) tract from the oral cavity to the anal region. *Helicobacter pylori*-induced peptic ulcers trigger the production of hBD-2 and cathelicidin LL-37 by the GI tract's epithelial cells [119,120]. Chemokines CCL14 and CCL15, expressed in the intestinal lining, display potent antibacterial actions [121].

In liver, gallbladder, and bile duct issues like hepatolithiasis or biliary obstruction, cholangitis activates the induction and dominant expression of AMPs hBD-2 and hBD-1 [122]. α-defensins HD-5 and HD-6 are notably present in the human small intestine [123]. HD-5 expression decreases during Salmonella typhimurium infections [124]. Proteins like ATG16L1 aid in invading bacteria degradation, while X-box binding protein 1 poses a risk factor for Crohn's disease and ulcerative colitis [125]. Bacteria such as *E. coli* and *Campylobacter jejuni*, along with cytokines, stimulate hBD-2 [126]. Cathelicidin impedes the growth and colonization of *Citrobacter rodentium* [127]. Polymorphonuclear cells secrete lysozyme in high concentrations in ulcerative colitis [128]. Lactoferritin in milk binds to the lipopolysaccharide layer of the bacterial cell wall, rupturing the cell, depriving microbial pathogens of iron needed for their growth, and forming toxic peroxide inside the cell, ultimately killing it [129]. Hepcidin, significantly elevated in ulcerative colitis and Crohn's disease, inhibits the growth of *Salmonella* and *Mycobacteria* by restricting iron availability to them, showcasing antimicrobial properties [130]. Coprisin from the Korean dung beetle helps in curbing the mucosal inflammation caused by *C. difficile*. Synthetic glycopeptides like telavancin and dalbavancin exert antibacterial action against *C. difficile* and colitis associated with its contamination [131].

4.6. Role of AMPs in Autoimmune Disorders

Autoimmune diseases like psoriasis, type 1 diabetes, and rheumatoid arthritis often exhibit elevated levels of various antimicrobial peptides. In psoriasis, LL-37 directly activates T cells as an autoantigen [132]. Human α-defensin and LL-37 are significantly expressed in the synovial fluid of joints under the influence of TNF-α and interleukin 6. The macrocyclic peptide RTD-1 aids in alleviating painful symptoms and joint discomfort in arthritis patients [133]. Mouse β-defensin-14 diminishes inflammation in the central nervous system (CNS) and curbs cytokines and cytotoxic T cells, the causative agents in encephalomyelitis.

4.7. Role of AMPs in Alzheimer's Disease

Alzheimer's disease can stem from various causes, among which microbial infections in the central nervous system leading to sepsis and meningitis are considered significant factors. Microorganisms like *Chlamydia, Helicobacter pylori, Borrelia spirochetes*, herpes simplex virus, and human immuno-deficiency virus have been linked to infections affecting both outer and inner brain regions [133,134]. Some microorganisms like *E. coli*, herpes simplex virus, *Cryptococcus neoformans*, and *Chlamydia pneumoniae* contribute to the formation of amyloid plaques, a hallmark of Alzheimer's disease [135]. Certain antimicrobial peptides, when in their β-sheet configuration, disrupt cell membranes by aggregating on the membrane surface, causing leakage of cell contents [136]. AMPs exhibit immunostimulatory effects by neutralizing lipopolysaccharides, boosting TNF-α and interleukin-8 levels, and aiding in brain tissue wound healing [137]. The Aβ1-42 peptide, when self-aggregated into β-sheet structures, can act as pore-forming agents with antimicrobial properties [138].

4.8. Role of AMPs in Cardiovascular diseases

Cardiovascular diseases, particularly characterized by arterial wall thickening called atherosclerosis, arise due to various risk factors that trigger inflammation and oxidative stress within the vessel walls. The progression of atherosclerosis and coronary heart disease (CHD) often correlates with alterations in the expression of numerous proteins. Certain antimicrobial peptides, like CRAMP and cathelicidin LL-37, serve as biomarkers linked to the risk of cardiovascular disease. LL-37 levels

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have been observed to decrease at thrombosis sites. CRAMP plays a role in activating Akt and ERK1/2, facilitating FoxO3a phosphorylation and nuclear export. This action aids in safeguarding the heart by reducing cardiomyocyte apoptosis, thereby potentially decreasing the risk of myocardial infarction. Notably, the serum levels of LL-37 appear to be lower in individuals affected by cardiovascular conditions [139].

4.9. Role of AMPs in Cancer

Anticancer peptides differentiate between malignant and normal cells due to variations in cell membrane composition. Malignant cells possess a higher negative charge on their membranes, owing to the presence of anionic molecules like sialylated gangliosides, phosphatidylserine (PS), heparin sulfate, and O-glycosylated mucins. Anticancer peptides selectively target tumor cell membranes, causing pore formation, rapid disruption, altering ion channels, and enhancing permeation [140].

Various antimicrobial peptides exhibit anticancer properties, such as Na-D1, Polybia-MP1, Parasporin, m2386, and LTX-315. Na-D1, derived from ornamental tobacco Nicotiana alata, is a cationic peptide that interacts with phosphatidylinositol 4,5-bisphosphate on the plasma membrane of cancer cells, leading to their destruction. MP1 modifies tumor cell membranes by creating pores. These AMPs internalize within cells and engage with intracellular organelles like mitochondria, triggering programmed cell death. Peptide m2386, extracted from the lactic acid bacterium *Lactobacillus casei* ATCC334, induces tumor cell apoptosis. Parasporin, derived from *Bacillus thuringiensis*, and peptides from hexokinase-II expedite cell apoptosis as well [141].

Table 1. Expression level and proposed functions of antimicrobial peptides/proteins in various human inflammatory diseases.

Disease state	Peptides	Expression levels and potential functions	References
Skin inflammatory diseases			
Psoriasis	LL-37, defensins	Overexpressed, absence of *S. aureus*	[142]
Atopic dermatitis	LL-37, defensins	Downregulated, presence of *S. aureus*	[142]
Lupus, erythrematous, and contact dermatitis	LL-37	Increased	[143]
Acne vulgaris	MX-594 AN	Inhibits *P. acne*	[144]
	Granulysin	Kills *P. acne*, anti-inflammatory action	[145]
Respiratory diseases			
Cystic fibrosis	LL-37, β-defensins	Reduced antimicrobial activity due to salt accumulation	[146]
Periodontal disease	Defensins	Reduced in saliva of patients with oral candidiasis	[147]
	LL-37	Absent in patients with congenital neutropenia	[148]
	Histatin 5	Protects periodontium from bacterial infection and prevents biofilm formation	[149,150]
Inflammatory bowel disease			
Crohn's disease	HD5 and HD6	Deficient expression in Paneth cells	[151]
	HD5 and HD6	Reduced in CD patients with Nod2 mutation	[151]
	LL-37	Expression is altered	[151]
Ulcerative colitis	HD5, 6; hBD2–4	Upregulated in patients with UC	[152]
Cancer Magainin	II Toxic	effect against canc er cell lines melanoma, breast and lung cancer, lymphoma, and leukemia	[153,154]
	Insect cecropins	Lyse tumour cells	[155]
	Bovine lactoferrin	Inhibits lung and liver metastasis of murine melanomas and lymphomas and cytotoxic toward neuroblastoma cells	[156,157]

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Atherosclerosis	Defensins	Involved in lipoprotein metabolism, exhibit anti-fibrolytic activity and regulate angiogenesis	[158–160]
	LL-37	Increased expression in human lesions	[161]
Inflammatory articular joints	hBD-3, LL-37	Upregulated in osteoarthritis	[162]

5. Clinical development of antimicrobial peptides

The current focus lies in leveraging the knowledge of antimicrobial peptides (AMPs) to craft and advance beneficial drugs. Biotechnology firms have embarked on the development of new peptide-based compounds, showcasing distinct and potentially enhanced resistance profiles compared to earlier antibiotics. A recent comprehensive review detailing AMP-based therapeutics showcased various peptides in preclinical or clinical trials. Here are some noteworthy examples:

Plectasin (Novozymes), a defensin peptide, exhibits potent microbicidal activity against antibiotic-resistant bacteria linked to diseases like pneumonia [163]. Unlike other AMPs in clinical trials, plectasin displays tolerance at high doses and effectiveness in treating systemic infections. Its development as a therapeutic agent is progressing into the preclinical phase, with expectations for clinical approval within 8–10 years.

P-113 (Dermegen), a 12-amino acid fragment derived from histatin 5, demonstrates anti-candidal activity comparable to its parent form. Currently in phase I/II clinical trials, it's used as a mouth rinse for treating plaques and gingivitis. Human model data highlight P-113's efficacy against gingivitis and plaques [164]. MBI-226 (Migenix), an Idolicidin analogue in phase III clinical trials, aims to treat catheter-related bloodstream infections [165]. MX-594AN (Migenix), an antimicrobial cationic peptide, is developed as a topical treatment for mild to moderate acne vulgaris. Clinical trials demonstrate its efficacy against various acne lesions, and it's also being tested for topical treatment of rosacea. Phase II trials are projected for completion in 2007.PG-1 protegrin (Intrabiotics) is in phase III clinical trials for treating peritoneal infections caused by *P. aeruginosa*, *S. aureus*, and methicillin-resistant *S. aureus*. rBPI-21 (Xoma), a recombinant form of human bactericidal/permeability-increasing (BPI) protein, is in phase II/III clinical trials for treating meningococcaemia and Crohn's disease. Heliomycin (EntoMed), a peptide derived from insects with antifungal activity, is undergoing preclinical trials.

While numerous clinical trials have underscored the broad therapeutic potential of AMP-based drugs, these agents are still in early stages of technological refinement, with several challenges ahead to overcome.

6. Conclusion and Future perspectives

Pharmaceutical companies are eagerly exploring the development of novel peptides as a promising new avenue for medications. However, these antimicrobial peptides (AMPs) face inherent challenges due to their peptidic nature. These hurdles include the high costs associated with manufacturing, their short half-lives within the body, the potential loss of activity under physiological conditions, application-related issues, risks of unwanted systemic reactions like aggregation or immunoreactivity, and the possibility of disrupting normal bacterial flora. Moreover, several unresolved matters remain, such as the absence of standardized assessment techniques, incomplete understanding of molecular regulation mechanisms, difficulties in targeted delivery to specific sites, concerns regarding tolerance and toxicity, and the necessity for ideal peptide characteristics such as high tolerance, resistance to degradation, and suitability for various administration methods.

Despite these obstacles, ongoing research aims to shed light on the broader roles of AMPs beyond their antimicrobial activities. This exploration includes understanding their functions in complex diseases, which could potentially position these peptides as prototypes for innovative drugs, sensors, or biomarkers for early disease detection and prevention. Comprehensive knowledge of AMPs may eventually enable researchers to create drugs that modulate the expression of specific AMPs, effectively ameliorating particular disease conditions. Gene therapy involving AMPs could

revolutionize treatments for various inflammatory and infectious diseases if strategies for efficient gene delivery are optimized. However, these aspirations face significant challenges related to the properties of AMPs that need to be addressed, such as their cationic nature, which may lead to interactions with anionic components of host cells. An ideal peptide drug would be one that is well-tolerated at high doses, resistant to degradation, and suitable for administration via various routes, including topical and intravenous methods. In conclusion, focused research on these issues is poised to provide crucial insights into the roles AMPs play in complex diseases, potentially laying the groundwork for their effective use in innovative drug development, disease management, and early disease detection strategies.

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