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MINI-REVIEW ARTICLE

Biological Functions and Applications of Antimicrobial Peptides

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Abstract: Despite antimicrobial resistance, which is attributed to the misuse of broad-spectrum antibiotics, antibiotics can indiscriminately kill pathogenic and beneficial microorganisms. These events disrupt the delicate microbial balance in both humans and animals, leading to secondary infections and other negative effects. Antimicrobial peptides (AMPs) are functional natural biopolymers in plants and animals. Due to their excellent antimicrobial activities and absence of microbial resistance, AMPs have attracted enormous research attention. We reviewed the antibacterial, antifungal, antiviral, antiparasitic, as well as antitumor properties of AMPs and research progress on AMPs. In addition, we highlighted various recommendations and potential research areas for their progress and challenges in practical applications.

Keywords: Antimicrobial peptides, microbial resistance, antimicrobial activity, action mechanism, achievement transformation, clinical application.

1. INTRODUCTION

Antibiotics are mainly used to treat bacteria, parasitic mycoplasmas, and chlamydia. However, long-term antibiotic use may trigger microbial resistance, reducing their efficacy. In the past 25 years, no new class of antibiotics has been developed. Most of the currently used therapeutic approaches involve a combination of antibiotics to reduce the emergence of antibiotic resistance [1]. According to the World Health Organization, antibiotic resistance is one of the three major threats to human health [2]. A recent study by Britain's Commission on Antimicrobial Resistance estimated that if no new drugs are developed, antibiotic-resistant bacterial infections may kill 10 million people a year by 2050 [3]. Various efforts are aimed at developing alternatives to antibiotics to protect humans from "superbugs". Antimicrobial peptides (AMPs), which include peptide proteins that kill bacteria and other microorganisms, such as viruses and fungi, are potential alternatives. Compared to traditional antibiotics, AMPs have a wide spectrum of activity, a short bactericidal time, and do not elicit resistance.

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The favorable physicochemical properties of AMPs and their advantages over traditional antibiotics have been reported [4]. AMPs are active immune molecules produced by organisms and evolve to help organisms adapt to the environment. As important mediators of natural immunity, AMPs play an essential role in host immune defenses against pathogenic invasions. They can "mobilize" the host's immune system to destroy invading microbes [5]. They are present in eukaryotic cells and participate in immune responses. In prokaryotes, AMPs usually act against the bacteria, related to the producing strains. Although AMPs differ in amino acid content, length and structure, most of them are generally amphiphilic and have a high isoelectric point (pI, 8.9-10.7), high thermal stability (100 °C, 15min), do not affect eukaryotic cells and have no cross-resistance [6]. AMPs are diverse short peptides (10-100 aa) and are found in various life forms, including animals, plants, and microorganisms.They exhibit a natural structure with α-Helical, β-Sheet, extended construction, and mixed constructions (Fig. **1**) [7,8]. However, due to the presence of α-helical and β-sheet domains, some AMPs do not fit into any specific class [9]. Nearly half of known AMPs can be classified based on their structures, however, some AMPs have unclassified structures, and only a few hundred AMPs exhibit three-dimensional (3D) structures. More 3D structures of AMPs will be determined by nuclear magnetic resonance (NMR) and X-ray diffraction tools.

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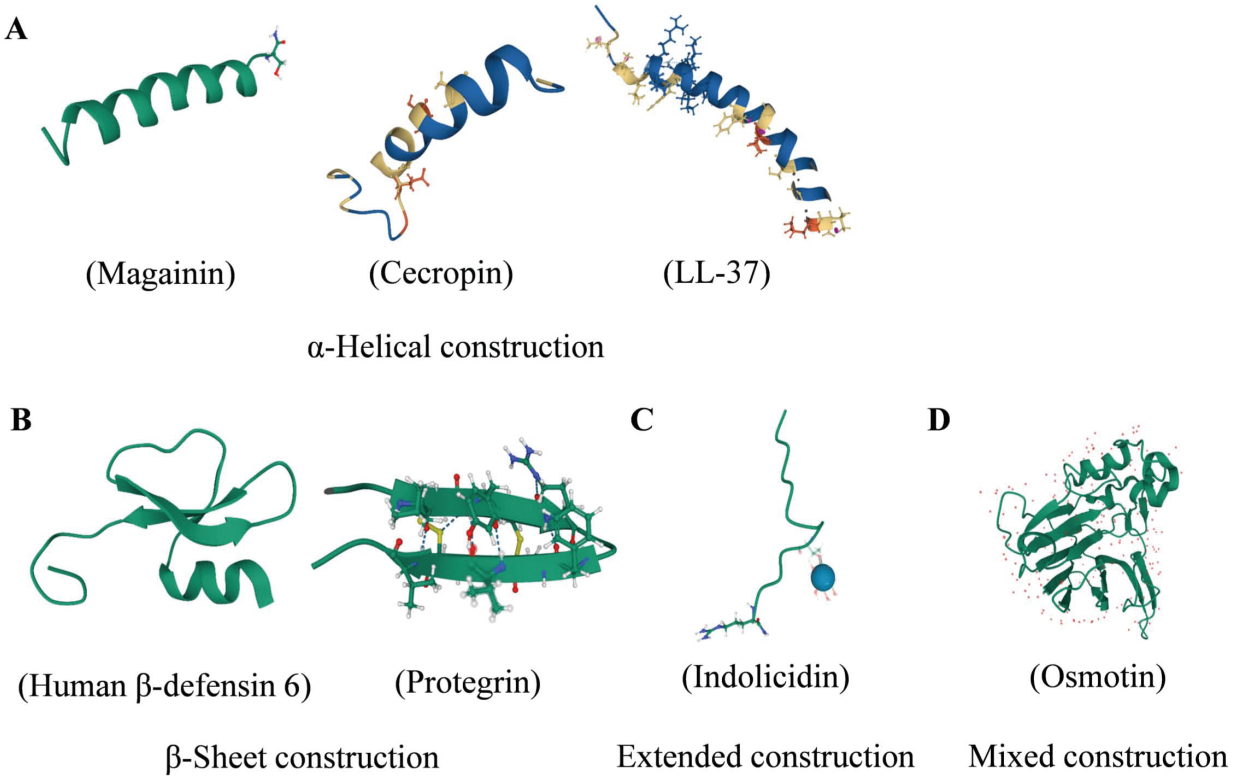

Fig. (1). Structure of AMPs. (**A**) Cysteine free, which is now the most common type of AMPs; (**B**) Structure containing two or more disulfide bonds in the molecule and some helical structures in the secondary structure. These AMPs mainly originate from insect, plant, mammalian defensins and proline-rich AMPs; (**C**) Lacking secondary structure, primary structure containing one or more amino acids, no cysteine, usually being linear. Some proline-rich AMPs also have o-glycosylated structures on specific amino acid residues. (**D**) Mixed secondary structure, also contains α helix or β rotation structure. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Bioinformatics and high-throughput proteomic techniques have aided the identification of many protein as well as polypeptide sequences and the development of several AMP databases (Table **1**). Some databases are built using design strategies such as ADP3 [10], DAMPD [11], FARME DB (database built on 'LAMP') [12], CAMPR3 [13], AMPer [14], and LAMP [15], whereas others are based on structural characteristics of AMPs in different functions or applications. For instance, the MilkAMP database [16] contains AMPs from milk; DADP [17] is a database of Anuran Defense Peptides; PhytAMP [18], BACTIBASE [19], and PenBase [20] are databases dedicated to AMPs from plants, bacterial sources, defensins and penaeidin families; PD [21], HIPdb [22], AVPdb [23], and Bagel4 [24] are databases of peptaibols (unusual class of peptides), bacteriocins, experimentally validated HIV-inhibiting peptides, antiviral peptides, as well as bacteriocins while DBAASP [25] is the manually-curated database for antimicrobial compounds with a high therapeutic index. In addition, a novel fish antimicrobial peptide [26] exhibiting non-redundant candidate AMP sequences has been identified from genomes of fish such as *Hippocampus erectus, Epinephelus lanceolatus, Oreochromis niloticus,* and *Oreochromis aureus*. These databases have expanded and facilitated the investigation of AMPs. However, to assess antibacterial activities of AMPs, several preprocessing steps are required. These steps involve complicated protocols, are labor intensive, costly, and time consuming, which makes it challenging to predict the activities of AMPs. There is a need to upstream and downstream the processes of AMPs by constructing a classification system to help in screening potential AMPs from a pool of peptides [27,28].

2. BIOLOGICAL FUNCTIONS OF AMPs

2.1. Anti-bacterial Properties

AMPs have broad-spectrum antibacterial activities. They inhibit gram-negative and gram-positive bacteria as well as bacteria with resistant phenotypes. Gram-negative bacteria can be inhibited by AMPs containing arginine and proline, while gram-positive bacteria can be inhibited by AMPs containing tryptophane and cysteine [29,30].

Most AMPs destroy bacteria by attacking cell membranes, while some act by inhibiting intracellular pathways such as those involved in DNA replication and protein synthesis (Fig. **2**). In the former mechanism, AMPs selectively bind the outer membrane, resulting in formation of holes in the cell membrane, leading to secretion of cell contents and bacterial death. Many AMPs, such as Jelleine-I, SCAP-29, BAM-27, and BAM-28 have amphipathic structures, which allows them to selectively combine components of target cell membranes or cell walls. This creates pores in these structures and disrupts osmotic pressure balance between inside and outside of cells, resulting in infiltration and loss of internal cellular contents [31-33]. The Wasp toxin, a cationic

Table 1. Working database of AMPs.

No.	Name	Website
1	Antimicrobial Peptide Database (APD3)	https://aps.unmc.edu/home
2	Fish Antimicrobial Peptide Database	http://www.bgimarine.com/data/amp
3	Database of Antimicrobial Activity and Structure of Peptides (DBAASP)	https://dbaasp.org/home
4	Functional Antibiotic Resistant Metagenomic Element Database (FARME DB)	http://staff.washington.edu/jwallace/farme.
5	Penaeidin Database（PenBase）	http://www.penbase.immunaqua.com
6	A Database and an Automated Discovery Tool for Gene-Coded Antimicrobial Peptides（AMPer）	http://www.cnbi2.com/cgi-bin/amp
7	Peptaibol Database（PD）	http://www.cryst.bbk.ac.uk/peptaibol
8	Collection of antimicrobial peptides (CAMPR3)	http://www.camp.bicnirrh.res.in
9	A Database Linking Antimicrobial Peptides（LAMP）	http://biotechlab.fudan.edu.cn/database/lamp
10	BACTIBASE	http://bactibase.pfba-lab-tun.org.
11	Bagel4	http://bagel4.molgenrug.nl/.
12	Database of anuran defense peptides（DADP）	http://split4.pmfst.hr/dadp/
13	Dragon Antimicrobial Peptide Database（DAMPD）	http://apps.sanbi.ac.za/dampd)
14	Database of HIV inhibiting peptides（HIPdb）	http://crdd.osdd.net/servers/hipdb.
15	MilkAMP	http://milkampdb.org/
16	PhytAMP	http://phytamp.pfba-lab-tun.org/main.php
17	Database of Antiviral Peptides（AVPdb）	http://crdd.osdd.net/servers/avpdb

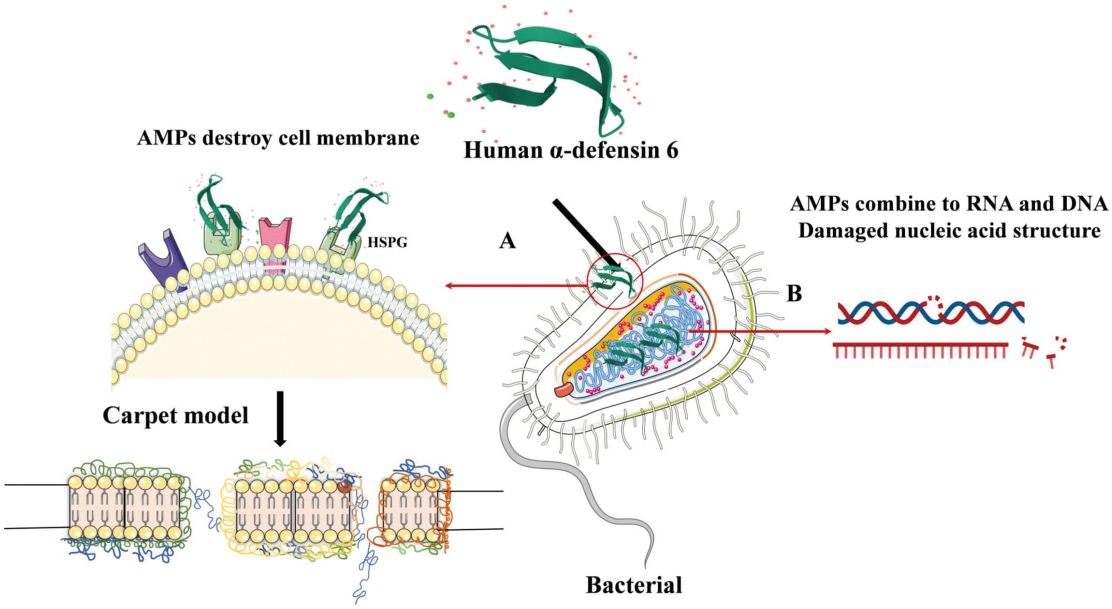

Fig. (2). Anti-bacterial mechanism of AMPs. (**A**) Destroy cell membrane by combining phospholipid bilayer and intracellular substances: AMPs binds to HSPG on the target cell membrane to restructure cell membrane, then exposing the gap and inside the cell, there are three basic pore formation mechanism: a. Carpet model, b. Barrel-stave, c. Toroidal; (**B**) Combine to genetic materials and damage the structure of nucleic acid. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

helical AMP, is highly effective against gram-negative bacteria after modification (composed of L1G, L7A, and L1GA5K). These polypeptides damage microbial cell membranes. For instance, L1GA5K exhibits strong antibacterial activities against rifampicin-resistant Escherichia coli (*E. coli*) [34].

In intracellular bacteriostasis, AMPs do not destroy target cell membranes but penetrate cell-protective barriers and accumulate in cytoplasms. Then, they combine and impair the functions of several cell molecules such as DNA, RNA, and other substances, leading to cell death. These AMPs are proline-rich (PrAMPs) and enter cytoplasms through transporters on bacterial membranes. PrAMPs bind ribosomes to inhibit protein synthesis. They are not toxic to host cells and have a narrow antibacterial spectrum. For instance, FP-CATH is structurally spiral and can bind and damage lipopolysaccharides (LPS) as well as bacterial DNA [35]. Through genome alignment analyses, Mario *et al.* identified PrAMPs (Tur1A and Tur1B) in dolphins. *E. coli* contains a transporter protein that facilitates the entry of Tur1A into the cytoplasm, which binds ribosomes to inhibit bacterial growth [36].

AMPs with β-folded structures usually kill bacteria by suppressing energy production and lysing bacterial cells [37-39]. For instance, Thanatin-GFP-HBsAg (TGH) is a hybrid protein that results from fusion of Thanatin and Hepatitis B virus surface antigens. TGH can penetrate the bacterial cell membrane and can kill multidrug-resistant *E. coli* [40]. Specifically, AMPs directly inhibit nucleotide synthesis [41], synthesis and folding of proteins [42,43], damage the cell membrane, and block the formation of new cell walls [43]. Furthermore, AMPs activate hydrolases in the cell membrane to inhibit cell division [44]. Mourtada *et al.* analyzed 58 stapled AMPs that are based on magainin II. They applied the structure-function-toxicity measurement method to obtain AMPs, Mag (i + 4) 1, 15 (A9K, B21A, N22K, S23K). This method was effectively used in a murine peritonitis model of mucin-resistant Acinetobacter baumannii (A. baumannii)-sepsis. There was no hemolysis or renal damage in mouse toxicity studies [45]. Spohn *et al.* analyzed the tolerance of *E. coli* to 14 AMPs (Blue) and 12 antibiotics (Red) (Fig. **3**) [6]. They found that AMPs such as polyphemusin II were associated with low levels bacterial resistance while antibiotic-resistant bacteria had no cross-resistance to these AMPs. Bacteria with low tolerance to AMPs share common physicochemical properties, including fewer polar and positively charged amino acids, and high hydrophilicity.

To improve the fight against superbugs, scientists are developing new antibiotics and are also modifying traditional antibiotics to enhance their activities or to exert their antimicrobial activities by targeting different targets. ZY4 was designed based on the reported peptide (cathelicidin-BF-15) with an *in vivo* half-life of 1.8 h. ZY4 inhibits biofilm formation and kills bacteria by penetrating bacterial membranes. In a mouse model of sepsis infection, ZY4 reduced the risk of Pseudomonas aeruginosa (P. aeruginosa) infection in the lungs and also inhibited P. aeruginosa and A. baumannii infections in other organs. These findings show that ZY4 is effective against multidrug-resistant bacteria [46]. Breij *et al.* used LL-37 in humans to generate a new AMP against methicillin-resistant Staphylococcus aureus (S. aureus) and A. baumannii, referred to as SAAP-148, which showed 100% activity against the two resistant bacteria in just 4 h. Besides, they found that the ointment supported with ASSP-148 achieved almost 100% sterilization of bacterial infected wounds. Even after more than 24 h of infection, a 67% antibacterial efficacy was achieved [47].

It is essential to maintain the antibacterial activities of AMPs, reduce their toxicity, increase their stability, and shorten the length of the peptide chain to improve their effects. However, the activity and specificity of AMPs depend on properties of natural AMPs and on the nature of target bacteria.

2.2. Antiviral Properties

Currently, 193 known AMPs inhibit viral pathogens [48]. In mammals, the human AMP (LL-37) has immunomodulatory effects. It also acts against HIV-1 virus [49], influenza A virus (IAV) [50], respiratory syncytial virus [51], rhinovirus [52], vaccinia virus [53], hepatitis C virus [54], herpes simplex virus, aichi virus [55] and dengue virus [56]. In fish, 254 AMPs have been identified in the genome of Epinephelus giganteus (E. giganteus), and some have exhibited the potential to prevent and treat viral diseases of E. giganteus [57]. They exert their antiviral properties by: (1) Interacting with phospholipids on viral surfaces or heparan sulfate proteoglycan (HSPG) on host cell surfaces. As shown in (Fig. **4A**), these interactions prevent fusion between the virus and host cells. For example, lactoferrin with an α-helical structure interferes with herpes simplex virus invasion by binding heparin molecules and blocking virus-receptor interactions [58]. Mammalian α- and β-defensins have antiviral effects against enveloped and unenveloped viruses [59]. Subtoxic concentrations of Melittin and Cecropin inhibited HIV-1 proliferation by repressing gene expressions [60,61]. These AMPs directly exert their effects on the viral envelope (Fig. **4B**). (2) AMPs also inhibit viral gene expressions and, thus, block viral replication (Fig. **4B**). For example, the recombinant SPIPm5 inhibits the replication of the shrimp white spot virus [62]. Melittin and Cecropin disrupts the proliferation of the HIV-1 virus [63]. Telaprevir acts on NS3/4, a protease inhibitor in Hepatitis C virus (HCV), to interfere with viral replication [64]. (3) AMPs, such as Temporin-1, interfere with viral infection processes (Fig. **4C**). Amino acid sequences of some AMPs are similar to those of virus-cell membrane proteins that participate in synthesis of other viral proteins. As such, AMPs bind viral RNAs, resulting in structural changes of RNA, loss of conditions for binding affinity to normal proteins, and failure to generate viral proteins.

2.3. Antifungal Properties

Fungal resistance is a major problem in microbial resistance. Therefore, elucidation of antifungal mechanisms of AMPs may provide new insights for developing strategies to prevent fungal resistance. AMPs inhibit fungal growth and are rich in histones or bacterial lipopeptides [65]. More than 1,100 antifungal AMPs have been reported in CAMP [66]. AMPs target some basic properties of fungal cells, such as the negative charge of cell membranes, which results in a low resistance rate of fungi to AMPs [67].

There are three main mechanisms of antifungal peptides. First, AMPs exert their antifungal properties by penetrating fungal membranes (Fig. **5**). The penetration is mediated by proteins such as osmotin, which combines with cell wall adenosine monophosphate, promoting cell wall diffusion and damage [68]. The raphanussativus antifungal protein (Rs AFP2) inhibits the growth of filamentous fungi by increasing

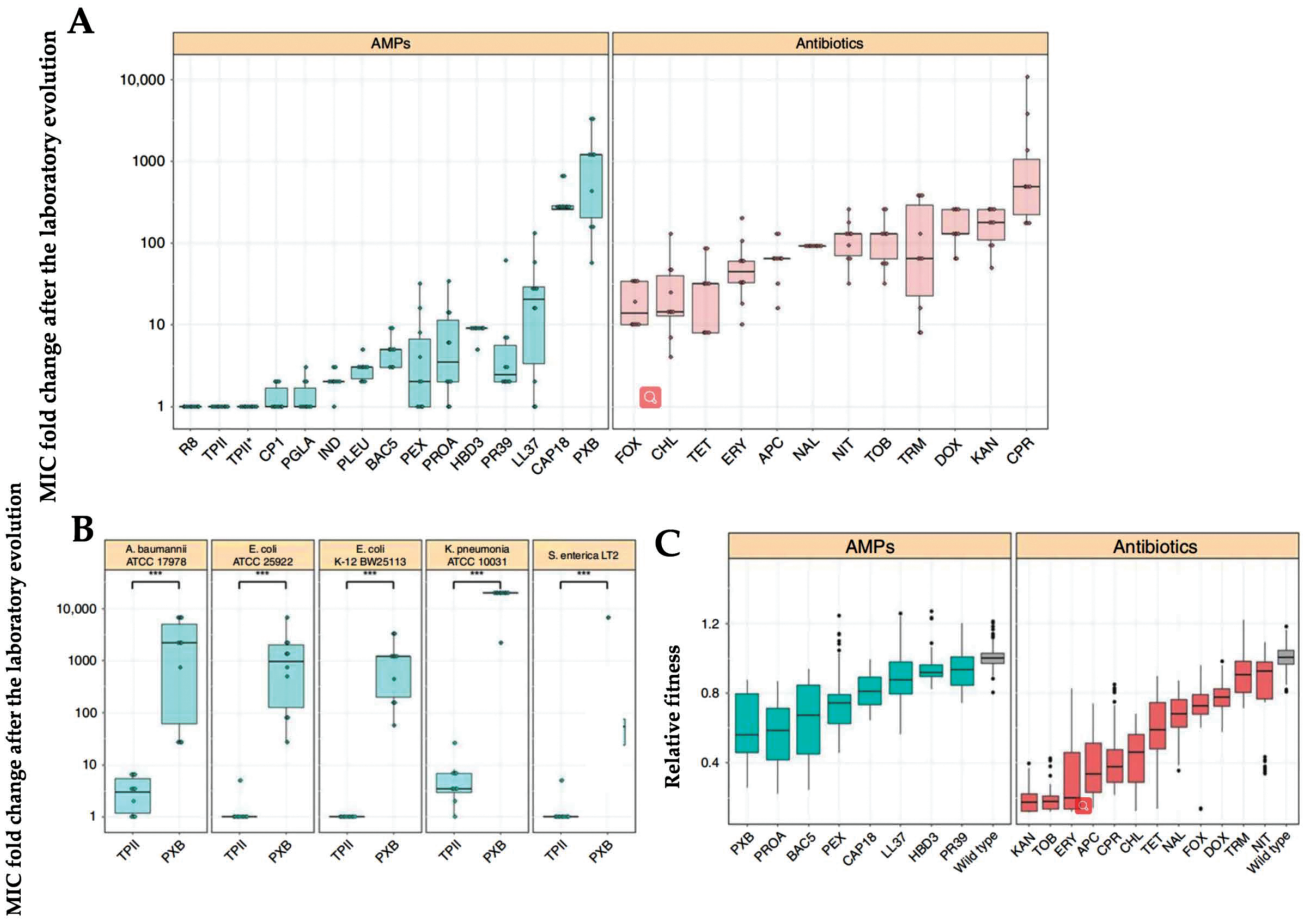

Fig. (3). Minimum inhibitory concentrations of AMPs and antibiotics after evolution of artificial bacteria in the laboratory: (**A**) Compared to antibiotics, lines exposed to AMPs resistance decreased. (**B**) Laboratory evolution of relative resistance levels of clinical isolates under TPII or PXB. TPII-treated was significantly lower than PXB. (**C**) Fitness results showed that 60 antibiotic-resistant and 38 AMP-resistant lines had more than a twofold increase in resistance level to the drug. Get permission from [6] licensed under a Creative Commons Attribution 4.0 International License. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

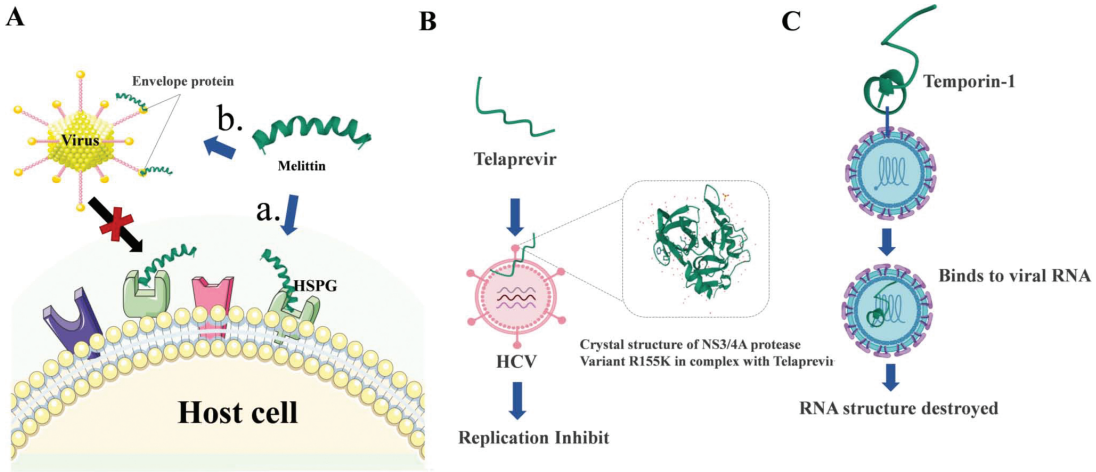

Fig. (4). Antiviral mechanisms of AMPs: (**A**) AMPs binds to HSPG on the Host cell or binds to virus, then prevent virus from infecting the host cell (**B**) AMPs binds to proteins on the virus, inhibits its replication. (**C**) AMPs' nucleic acid sequence is similar to that of virus, then enter the virus and destroys the RNA structure. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

membrane permeability, causing excess Ca^{2+} inflow and K^{+} outflow [69]. Besides, MsDef1, a defensin secreted by alfalfa, exerts its antifungal properties by binding sphingolipid glucosylceramide and interacting with fungal membranes [70]. This blocks the L-type calcium channel and activates the Mitogen-activated protein kinase (MAPK) signaling

pathway. DmAMP1 is a defensin that combines with MIP2C, a sphingolipid in the fungal membrane, inducing Ca^{2+} inflow and K^{+} outflow.

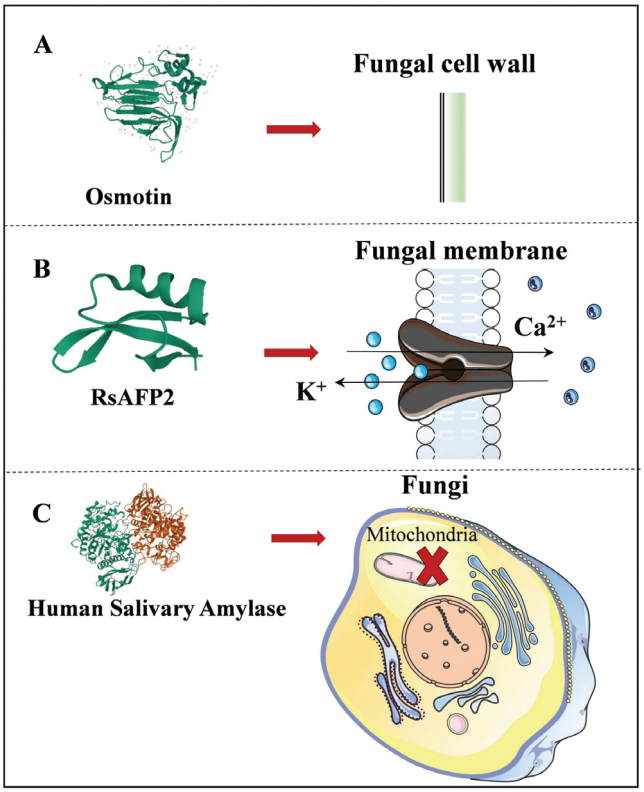

Fig. (5). Three examples antifungal mechanisms. (**A**) Destruction of fungal cell walls; (**B**) Disruption of membrane potential equilibrium in fungal cell membranes; (**C**) Interaction with mitochondria, nucleic acid and other organelles in fungal cells, leading to loss of normal functions. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Second, AMPs exert their antifungal properties by blocking (synthesis of) or destroying fungal cell walls. Antifungal activities of osmotin are mainly dependent on specific compositions of fungal cell walls and cell membranes [71]. Jiean-peptide, which contains iturin A as the active ingredient, can effectively inhibit the proliferation of Botrytis cinerea, Bolletotrichum gloeosporioides, and Phytophthora [72]. Besides, Fusarium wilt in cotton is controlled through this mode, where spore germination and hyphal growth are inhibited.

Third, AMPs exert their antifungal properties by acting on organelles such as the mitochondria and nucleic acids. For instance, the antibacterial protein in human salivary amyloid combines with receptors on Candida albicans (C. albicans) cell membranes to enter the cytoplasm [73]. In the cell, the protein differentially binds the mitochondria, impairing fungal respiration. This affects the fungal cell cycle and promotes the production of reactive oxygen free radicals, which then kills the fungi. Besides, Fusco *et al.* found that destruction of human β-defensins 2 and 3 by C. albicans did not cause cell membrane disorders or dissolution but showed energy dependence and salt sensitivity [74].

2.4. Anti-parasitic Properties

Diseases caused by parasites are often prevalent in tropical and subtropical areas as well as in areas with poor sanitation. Parasites inflict mechanical damage to host tissues *via* necrosis caused by toxins or enzymes, and eosinophilic abscesses or granulomas caused by larvae and eggs.

The use of antiparasitic treatments has resulted in resistance and toxicity. AMPs present an alternative treatment for parasitic diseases that does not cause toxicity. AMPs are effective against both protozoa (chagas disease, human, African chagas disease, malaria, and leishmania) and worms (taeniasis and onchocerciasis) [75]. Leishmaniasis is the second most fatal disease after malaria. However, the principal AMP families (melittin, cecropin, cathelicidin, defensin, magainin, temporin, dermaseptin, eumenitin, and histatin) exhibit potential anti-leishmanial activities [76-78]. AMPs can directly inhibit the parasites and sensitize the body's immunity against parasites. Dabirian *et al.* reported that human recombinant defensin (RHNP-1) suppressed leishmania infections and improved neutrophil proliferations *in vitro* [79].

Parasites are multicellular organisms, and AMPs exert their antiparasitic effects by damaging their cytoplasmic membranes, rapidly reducing the permeability of H+/OH- (Fig. **6**). This disrupts the membrane potential, thus killing the parasite. Various antiparasitic AMPs have been reported. Drosomycins, gambicins, gomesin, and dermaseptin K4-S4 are effective against plasmodium [80-83]. Antimalarial drugs such as AMPs NK-2, D-HALO-rev, and IDR-1018 in scorpion and spider venom inhibit the growth of Plasmodium falciparum [84,85]. *In vitro*, bovine-derived host defense peptide (BMAP-18) was shown to inhibit or kill kinetoplastida, and it is a potential therapeutic candidate against trypanosoma in cattle, fish, and humans [86]. The antimicrobial activity of cecropin-melittin in combination with magainin has been reported to be 10-fold higher than either drug alone. Moreover, synthetic cecropin (SB-37 and Shiva-1) and a hybrid peptide (Temporizin-1) showed superior antiparasitic properties to natural cecropin [87]. Host-defense peptides (HDPs) can also kill Trichomonas, Cryptosporidium parvum, Cryptosporidium hominis and other intracellular parasites [88]. Taenia is resistant to Temporin A and Iseganan IB-367 (IB-367), which have also been shown to have the ability to damage the capsule and the head of Taenia cysticercus [89]. Helminth defense molecules are new HDPs [90] that are highly conserved in most trematodes (liver flukes and schistosomes), modulate the immune system, and are non-cytotoxic. Thus, they can be used to control parasites and associated clinical diseases [91]. Together, AMPs can be used for disease control, treatment and to prevent transmission by parasitic insect hosts.

2.5. Tumor Suppression

Traditional treatment options for tumors involve a combination of surgical resection and chemotherapy. However, these approaches do not completely remove tumor cells. Certain AMPs can specifically recognize and kill tumor cells

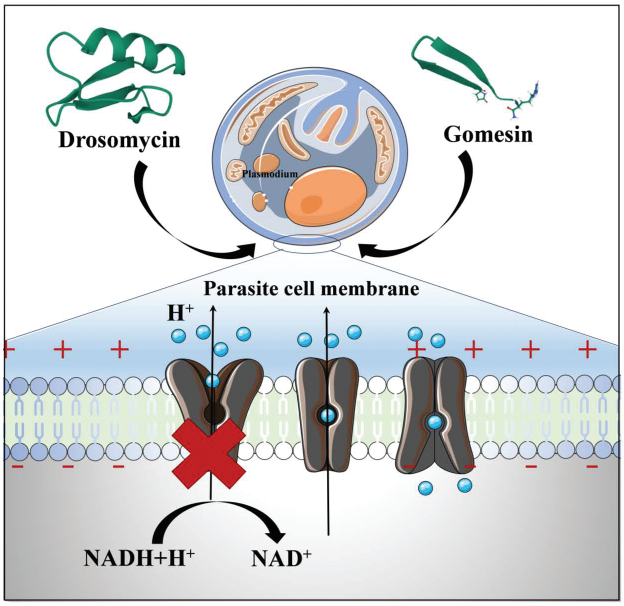

Fig. (6). Mechanism of anti-parasitic peptides: AMPs can rapidly reduce the permeability of H+/OH-, resulting in destruction of membrane potential homeostasis even morphology of plasma membrane. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

without damaging normal cells, hematopoiesis, or the immune system. Cationic peptide drugs derived from amino acids exhibit good antitumor activities. They have been shown to directly kill tumor cells without damaging normal cells [92]. Human AMPs (LL-37) exhibit effective antitumor activities against colon cancer, gastric cancer, malignant hematological diseases, and oral squamous cell carcinoma. However, their effects are dependent on tumor type [93]. AMPs inhibit and kill tumors through three main mechanisms (Fig. **7**). First, AMPs lyse tumor cell membranes, an event occasioned by electrostatic attractions between positive charges on AMPs and negative charges on phospholipids of tumor cell membranes, which disturbs tumor cell membrane integrity. Hydrophilic and hydrophobic ions in the double helix structure of AMPs polymerize to form a membrane-penetrating channel that perforates and kills tumor cells, resulting in osmotic pressure imbalances. In conclusion, AMPs target and disrupt tumor cytoskeleton structures, thereby killing cancer cells. Various cationic AMPs (cationic antimicrobial peptides, CAPs) are highly selective for tumor cell membranes [94]. Cap derivatives also have anticancer activities. Second, AMPs inhibit DNA synthesis and proliferation in cancer cells. Magainin II can penetrate the cell membrane of Hela cells, where they bind the nucleus [95]. This breaks the DNA and kills the tumor cells [37]. Besides, AMPs kill tumor cells by inducing apoptosis, shrinkage or swelling, forming cytoplasmic as well as membrane vacuoles, and *via* chromatin shrinkage [96]. In a Drosophila tumor model, tumor necrosis factor promoted interactions between phosphatidylserine in tumor cells and endogenous AMPs, leading to tumor cell killing or degeneration [97]. Lastly, AMPs enhance immune responses against tumor cells. For instance, HNP-1 inhibits the growth of breast and colon cancer tissues by inducing the aggregation and activation of dendritic cells [98].

The structures of AMPs influence their anticancer properties. Gomesin is an AMP from the Brazilian spider (Acanthoscurria gomesiana) with antibiotic and anticancer properties. These features are more pronounced when synthetic gomesin is circular rather than linear in structure. Henriques *et al.* [99] synthesized gomesin cyclic analogs and demonstrated increased antibacterial capacities by more than 10-fold. The new AMPs also killed melanoma and leukemia cells by disrupting cell membranes. However, they did not kill breast, stomach, cervical, or epithelial cancer cells. Importantly, the modified AMPs were not toxic to healthy blood cells [99]. Most of the AMPs in nature have not been isolated. Given their potential for therapeutic applications, there is a need for comprehensive studies to evaluate the efficacy and safety of these AMPs in cancer treatment. Future applications of these AMPs in antitumor therapy at a reasonable cost will be timely [100].

2.6. Promotion of Angiogenesis and Wound Healing

Wound healing and vascular regeneration are complex processes involving destruction of the wound biofilm, migration of keratinocytes, proliferation of epithelial cells and fibroblasts, and interactions between extracellular components. AMPs promote wound healing by stimulating epithelial cell movement and proliferation as well as cell division and proliferation. For instance, LL-37 is an AMP that promotes angiogenesis and wound healing (Fig. **8**). Wang *et al.* developed a composite nanofiber sheet loaded with microspheres containing vasoactive intestinal peptides, which promoted wound healing by enhancing granulation tissue growth and angiogenesis [101]. Wang *et al.* encapsulated LL-37 and vascular endothelial growth factor (VEGF) expression plasmids into nanoparticles. Ll-37 aids the expression of the VEGF plasmid in cells, improves plasmid transfection efficiency, and significantly increases VEGF expressions, thereby promoting the repair of diabetic wounds [102]. Besides, epidermal damage induces the expressions of LL-37, defensin-1, 2, 3, and other AMPs in epithelial cells, all of which promote angiogenesis and wound healing. Growth factors such as IGF-I and TGF-α also promote the secretion of LL-37 in the skin of psoriasis patients, necessary for repair of damaged skin [103,104].

Biofilms formed by P. aeruginosa and S. aureus interfere with wound healing. However, AMPs (TAT-RasCAP317-326) can effectively inhibit the formation of these biofilms [105]. Tomioka *et al.* [106] obtained a novel cationic AMP (SR-0379), which provided a further optimized compound of AG30/5C that exhibited angiogenic properties like those of LL-37 or PR39. The effects of SR-0379 were evaluated in two different wound-healing rat models, full-thickness defects under diabetic conditions and an acute S. aureus infected wound with full-thickness defects. Compared to fibroblast growth factor 2 (FGF2), treatment with SR-0379 significantly accelerated wound healing. Sr-0379 enhanced angiogenesis, granulation tissue formation, proliferation of endothelial cells and fibroblasts, and antimicrobial activities. Sinner *et al.* showed that injury or infection to epidermal tissues of adults activates the innate immune system, leading to pro-

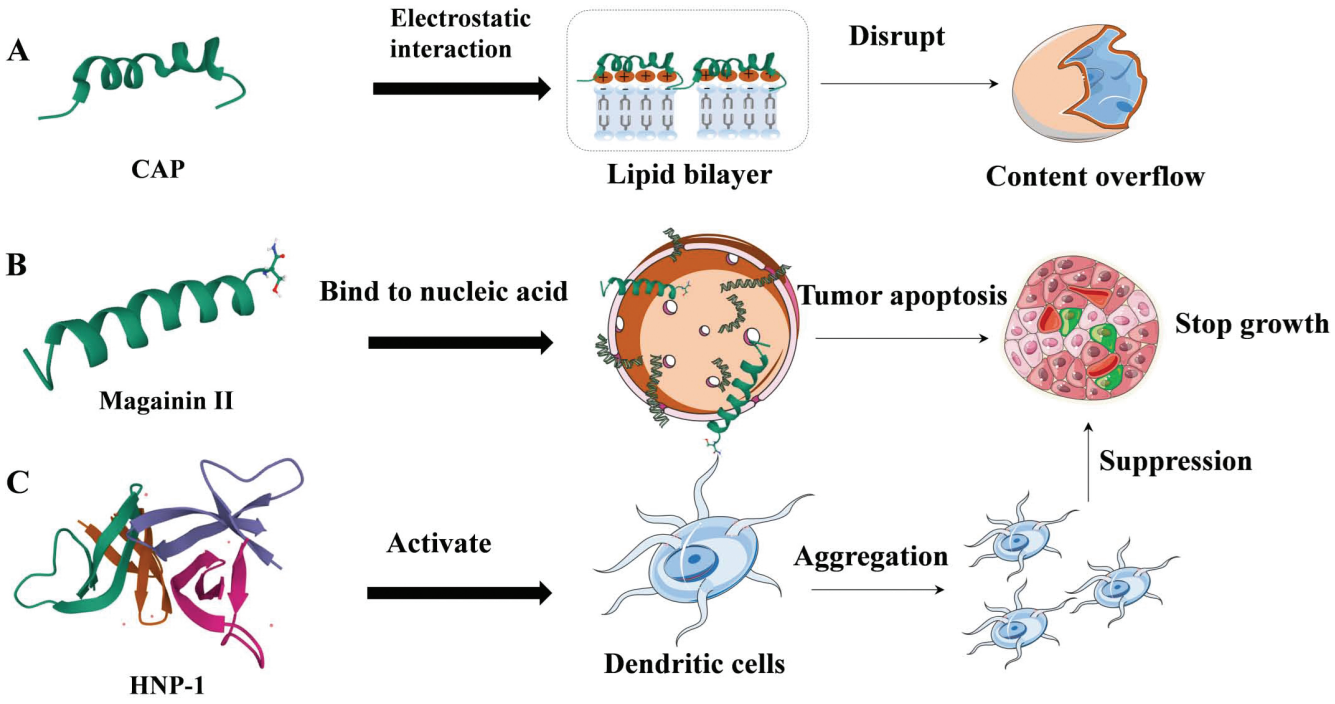

Fig. (7). Mechanisms of anti-tumors AMPs: (**A**) Due to electrostatic action, CAPs bind to the anions of the tumors, disrupting the cell membrane structure and make cell contents overflow; (**B**) AMPs combine to nucleic acid, inhibition of protein synthesis in tumors; (**C**) AMPs activates the immune system, promote the proliferation of immune cells and inhibit tumor cell proliferation. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

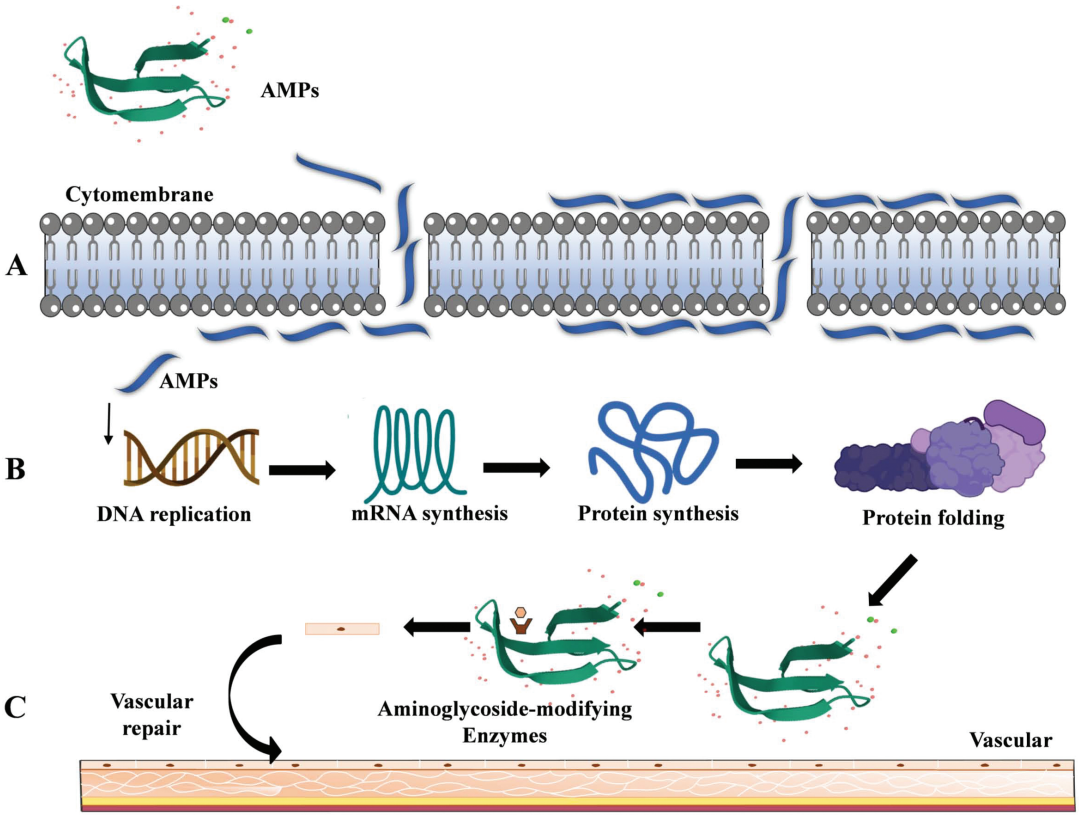

Fig. (8). AMPs promotes angiogenesis: (**A**) AMPs first penetrates the cell membrane and penetrate into the cell; (**B**) After reverse transcription and translation, proteins are synthesized and interact with aminoglycoside modifying enzymes; (**C**) Through a series of transformations, AMPs eventually act on to repair blood vessels. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

duction of sleep-related AMPs. Injuries induce the expressions of epidermal growth factor receptor (EGFR) signal, which exerts stress on cells. However, sleep increases survival chances after injury [107].

2.7. Immune Regulation

AMPs are effector molecules of innate and adaptive immunity that protect hosts from bacteria by mechanisms unrelated to their antimicrobial activities [108]. Shan *et al.* reported that lactoferrin promotes the proliferation of peripheral blood and spleen lymphocytes and effectively increases serum IgG, IgA, IgM, and IL-2 levels in weaned piglets [109]. Besides, AMPs regulate immune responses through Toll-like receptors (TLRs) and pattern recognition receptors (PRRS) on cell membrane surfaces. Bacteria or LPS can activate TLRs, which then activate the NF-KB signaling pathway to promote the expressions of various proinflammatory factors. Several AMPs (LL-37, LFP-20, pBD2, etc.) can block bacteria or LPS-activated TLRs, and inhibit downstream inflammatory responses, suggesting that AMPs can directly kill pathogens while alleviating excess inflammatory responses [110]. Due to this negative feedback, AMPs can be considered to be biologically active peptides with regulatory effects.

AMPs can selectively activate immune cells to protect against sepsis and endotoxemia. In animal models of sepsis induced by multiple standards and clinically resistant strains, cathelicidin selectively activated the natural immune responses, stimulated the expressions and release of inflammatory suppressor cytokines and immune cell chemokines *via* the P38 MAPK signaling pathway, without activating many harmful inflammatory cytokines. This shows that cathelicidin can prevent and ameliorate systemic and fatal sepsis. HCAP18 has also been shown to suppress excess immune responses induced by endotoxin [111,112]. For instance, 9-meric exhibits high antibacterial activities against gram-negative bacteria and can suppress endotoxemia induced by immune responses against lipopolysaccharides from gram-negative bacteria [113]. Some AMPs from frog skin can promote insulin secretion. This is mainly achieved by triggering extracellular Ca2+ influx, which is related to the hydrophobicity of AMPs, cation concentration, protein kinase signaling, and protein signal transduction [114,115].

Multiple AMPs can selectively increase the expressions of tight junction proteins such as claudins and occludin, improve cell transmembrane resistance values, and enhance cell barrier functions [116]. Besides, they can also stimulate the migration of intestinal epithelial cells, protect the integrity of intestinal barriers, and relieve enterocolitis [117]. AMPs improve epithelial barrier functions by enhancing the repair of damaged skin, blood vessels, and intestinal epithelium [74,118,119]. These events enhance the migration of epithelial as well as immune cells and promote epithelial cell proliferation.

3. PRACTICAL APPLICATIONS OF AMPs

Due to their physicochemical properties, biological functions, and mechanisms of action, AMPs can be applied in several industries such as agriculture, health, and medicine. The applications of AMPs in different fields are summarized in Table **2**. Applications of AMPs are limited by their low bioavailability and poor stability. This calls for the development of highly stable AMPs through collaborative research among scientists from different fields such as microbiology, chemistry, and materials science. There is also the need to design formulations combining AMPs and drugs to improve the desired effects. Such combinations can effectively control antibiotic-resistant bacteria, particularly superbugs. Nanomedicine has enabled the development of innovative vectors that can be used to create targeted delivery systems for drugs, thereby improving efficacy and reducing toxicity [120]. Finally, production costs of AMPs should be considered. Due to the high costs of solid phase synthesis, commercialization of AMPs is highly limited. With advances in controlled polymerization techniques and development of polymers that resemble AMPs, polymer design and synthesis of AMPs is likely to be enhanced in future.

3.1. Use of AMPs in Drug Research

The current antibiotics are "new versions" of old drugs that have been modified from their original formulations. These antibiotics inhibit specific enzymes but do not address the underlying causes of drug resistance. AMPs have various beneficial properties, including low antimicrobial resistance, low toxicity, high efficiency, and the absence of residue wastes. AMPs will eventually replace antibiotics in future.

Several AMPs such as polymyxin [121], daptomycin [122], and glutoxim [123], and enfuvirtide [124] have been approved for treatment of infections, lung cancer, and AIDS. In the last 40 years, less than 50 AMPs have reached the clinical trial phases. Several AMPs-based drugs, such as diapep-277 [125], pexiganan (MSI-78) [126], and omiganan MX-594AN [127] among others are in various phases of preclinical research as potential treatments for type I diabetes, diabetic ulcer, fungal infection, acne, rosacea, and other diseases. Novel AMPs with diverse functions are constantly being discovered. AMPs produced by inflammatory and epithelial cells in most mammals are involved in immune responses [154]. For example, human α-defensin 6 (HD-6) inhibits the invasion of intestinal pathogenic bacteria *in vivo* and *in vitro*. HD-6 randomly interacts with surface proteins of bacteria to form fibers and nanoparticles that encase the bacteria. This self-assembly mechanism is critical for HD-6's protection against invasion by intestinal pathogens [155]. The human defensin 5, which is expressed by epithelial cells such as small intestinal paneth and urogenital mucosal cells, exhibits strong antibacterial activities [128]. It has broad-spectrum antibacterial activities, does not induce resistance over time or disrupt the intestinal probiotic balance. It has been shown to inhibit the growth or kill gram-positive and gram-negative bacteria, fungi, spirochetes, parasites, and naked, enveloped viruses such as human papillomavirus and cervical cancer cells (HeLa) [129]. Therefore, AMPs are potential candidates for prevention and treatment of intestinal and reproductive tract bacterial infections as well as viral and sexually transmitted diseases. The OH-CATH30 component of king cobra venom can significantly alleviate keratitis caused by drug-resistant P. aeruginosa and further reduce drug resistance among bacteria [156]. An *in vivo* study

Table 2. Practical applications of AMPs.

Practical Application	Name	Function	Refs.
Drug research	Polymyxin /daptomycin / Glutoxim / Enfuvir-tide	Treatment of infections, lung cancer, and AIDS	[121-124]
	DiaPep277	Treat T1DM	[125]
	MSI-78	Treat diabetic ulcer	[126]
	Omiganan MX-594AN	Treat acne, rosacea	[127]
	HD5	Anti-fungal / anti-parasitic	[128]
	HD6	Kill HeLa cells/Treatment of reproductive bacterial infections	[129]
	MccJ25	Treat enteritis,	[130, 131]
	hArg-LL-37	Immune regulation to prevent bacterial infection	[132]
Sterilization of medical devices	Mel4	Antibacterial material for glasses	[133, 134]
	LL-37	Applied to cardiac stent materials	[135]
Livestock and poultry feeds	Mag II-CB	Maintain the integrity of the intestinal mucosal barrier	[116]
	AMP-a3, P5 (synthetic)	Promote nutrient digestibility and maintain intestinal morphology of livestock	[136]
	cecropin AD (artificial)		
Aquaculture	LcBD2	Larimichthys crocea: Anti-bacterial and anti-fungal/immuno-enhancement	[137]
	Pc-crustin 4	To prevent bacterial infections during crayfish growth	[138]
	Lactoferrin	Promote fry survival rate	[139]
	HdMolluscidin	Anti-fungal / anti-bacteria	[140]
	Chelonianin	Effectively control inflammation of tilapia infected with Vibrio harrisi	[141]
	N6NH2	Treat fish peritonitis better than norfloxacin	[142]
Food preservation and production methods	TLPs	Effective against yeast and filamentous fungi	[143,144]
	Rs AFP2	Effective against filamentous fungi	[145]
	MsDef1		
	DmAMP1		
	TPP3		
	NaD1		
	PvD1	Against Candida, Kluviomyces and Saccharomyces cerevisiae	[146,147]
	UTNGt2	Inhibit the growth of salmonella on tomato fruit surface	[148]
	6K8L/TrxAq/rHBD 3	Recombinant peptide: protects plants from fungal degradation	[149-151]
Cosmetic Additives	Lpcin	Antibacterial, non-toxic	[152]
	Carnosine + acetyl tetrapeptide-5+hexapeptide-11+ acetyl hexapeptide-3	Polypeptide mixture: protects and prevents skin aging	[153]

showed that MccJ25, a recombinant AMP, has strong antibacterial activities against *E. coli*, can alleviate intestinal inflammation, and can treat dysfunctional epithelial barriers [130]. MccJ25 can suppress excess inflammatory cytokine production, protect against intestinal injury, inhibit *E. coli* associated inflammation, balance intestinal microflora abundance, enhance the functions of epithelial barriers by increasing the expressions of occludin and claudin-1, and alleviate intestinal inflammation, thereby improving the overall host health [130]. Compared to gentamicin, MccJ25 effectively protects against *E. coli* infections. Therefore, MccJ25 is a potential therapeutic agent for the treatment of diseases caused by intestinal pathogens [131]. Human hArg-LL-37 has both strong antibacterial and immunomodulatory activities [132].

Currently, China has 140 million diabetes patients, 10% of whom suffer from 'diabetic foot,' which can be treated using AMPs. AMPs have reached the preexplosion stage due to maturity of research methods and declining costs of industrial manufacturing of peptides.

As a developing industry, applications of AMPs are associated with several challenges, including concerns about toxicity. The broad-spectrum nature of AMPs stems from the fact that they do not have a target protein but rather affect cell membranes. While bacterial and human cell membranes differ significantly, both are composed of phospholipids. Toxicity must be minimized at the source of the design of new AMP drugs while retaining their efficacy. In addition to AMPs, the development of appropriate formulations is a huge challenge. Since AMPs are polypeptides, some with un-stable structures, the most likely formulation is an injection formulation.

3.2. Sterilization of Medical Devices

Medical tools and equipment are a major source of nosocomial infections. Coating medical equipment with antimicrobial but yet safe molecules can prevent colonization or contamination by these organisms. Coatings for medical equipment have been developed using a combination of AMPs and cecropin-melittin peptide. This coat is effective against gram-positive and gram-negative bacteria (including multidrug-resistant bacteria) but is generally non-cytotoxic to human cells [157]. Molecular AMPs have been used to coat catheters, orthopedic implants, and similar implantable medical devices to prevent infections [158]. Dutta *et al.* coated lenses with silicone hydrogel supplemented Mel4 and proved that they were extremely effective against P. aeruginosa and S. aureus. A rabbit model showed that Mel4 coated contact lenses did not cause eye irritation. Therefore, Mel4 and silicone hydrogels are suitable for contact lens coating [133,134]. Implant-related infections are a serious health concern, and emergence of antibiotic-resistant bacteria exacerbates this problem. Coating spider silk suture with AMPs maintains the inherent mechanical, biomechanical, as well as biocompatibility of this device and significantly reduces related infections. Spider silk can be used to wrap medical devices to effectively prevent nosocomial infections without antibiotic supplementation [159]. Soehnlein *et al.* improved a coated cardiac artery stent with LL-37, which expedited the healing of damaged blood vessels and stent reopening. Additionally, it inhibited the hyperproliferation of vascular endothelial cells, which causes restenosis of blood vessels [135]. Various medical implants are now coated with synthetic-based AMPs to reduce infections. Particularly, melamine coating significantly reduced the adhesion and biofilm formation of P. aeruginosa and S. aureus on titanium by 62% and 84%, respectively. Even after sterilization with ethylene oxide gas, melimine retained its activity. Melimine inhibits bacterial growth without causing damage to normal cells. Thus, melimine is a promising candidate for antibacterial activities on industrial surfaces. Simultaneously, it exhibits good biocompatibility [160].

In early stages of clinical trials for prevention and treatment of infections associated with knee and hip replacement, Peter *et al.* developed a potential anti-P. aeruginosa D8, the D-enantiomer of WLBU2 [161]. In a recent study, D8 decreased lung infections and prolonged the survival time of patients with cystic fibrosis. They also evaluated the efficacy of drug use in individuals with severe pneumonia, such as severe secondary infections or potentially fatal infections that occur in COVID-19 patients.

AMPs have anti-inflammatory, anti-tumor and antibacterial properties among others. AMPs inhibit the formation of bacterial biofilms to combat serious infections caused by multidrug resistant bacteria. In recent years, peptide hydrogels have gradually increased the versatility of AMPs for modulating biological responses [162]. D, L-Peptide Nanofibrillar Hydrogel, which is a supramolecular hydrogel for the mimicry of esterase-like activity, provides new insights into self-assembling peptide design rules for biocatalysts [163]. Peptide-drug hydrogels such as anti-cancer, anti-humor, and anti-inflammatory AMPs combined with drugs can enhance AMPs' activities [164-166]. In addition, peptides can be used to control osteogenesis, and accelerate fracture healing [167-169]. For instance, Pardaxin exhibits strong anti-osteoporosis effects by regulating the osteogenic pathway [169-172].

Apart from diabetes [173] and its complications such as diabetic foot [174], AMPs have therapeutic effects against many diseases [170-172]. They can also treat psoriasis [175], autoimmune diseases and viral infections [176]. Therefore, AMPs can be applied in biomaterial and tissue engineering fields, especially in biomedical applications. However, there are various challenges, such as "low acquisition, high demand" in the market.

Although AMPs have the potential to be used for prevention of infections associated with medical materials, systematic studies should be performed to obtain the optimal surface concentration, adsorption orientation, secondary structure, stability, and excellent elasticity of carriers for AMPs. Additionally, since AMPs used in medical implants may come into direct contact with serum proteases and ions, protease and salt stability of AMPs should be evaluated to maintain a more durable antimicrobial activity. Researchers can use the previously discussed strategies to improve the stability of AMPs, thus increasing their potential as medical coatings.

3.3. AMPs in Livestock and Poultry Feed

The primary challenge facing livestock industry is stress and diseases. These problems are typically addressed using antibiotics or other drugs [177]. AMPs are effective against several infectious pathogens, and even malignant cells while having no discernible harmful effects on normal cells [178]. Microorganisms efficiently produce AMPs on a large scale, which increases farming profits, protects the safety of animal-derived foods and encourages the development of a green, pollution-free farming industry.

Accordingly, livestock and poultry feeds are widely supplemented with AMPS to improve growth and production. They aid in digestion and absorption of nutrients, maintain a healthy balance of the intestinal flora, and boost immunity. AMPs are environmentally friendly. Magainin II-cecropin B and Mag II-CB hybrid genes were transformed into Cordyceps militaris, a medical fungus, and the recombinant protein Mag II-CB exhibited broad-spectrum antibacterial activities *in vitro*. Mag II-CB upregulates the expressions of tight junction proteins (zonula occludin-1, claudin-1, and occludin) in BALB/c mice infected with *E. coli* (ATCC 25922). Additionally, it promotes the healing of *E. coli*-related damage, maintains the integrity of the intestinal mucosal barrier, and increases the abundance and diversity of intestinal microflora in mice. Mag II-CB can also modulate the secretion of immunoglobulin A in the ileum by regulating the production of pro- and anti-inflammatory cytokines. Feeding mice with pupa hyphae producing Mag II-CB reduced bacterial infections and improved immune functions in rats. Therefore, Cordyceps militaris expressing AMPs are potential substitutes for antibiotics and can improve the quality of livestock feeds [116]. In young goats, applications of AMPs increased the abundance of bacillus, anaerobic vibrio, and secretion of succinic acid, but decreased the abundance of monas, vibrio in amber, and Treponema, as well as polyplastron, entodinium, and heteromucor in a dose-dependent manner. AMPs also significantly enhanced digestion, absorption, utilization of nutrients, improved enzyme activities (pectinase, xylanase, and lipase), and increased the diversity of normal flora in the rumen [76]. In the last 50 years, antibiotics have been used to protect goats against infectious diseases. However, antibiotic abuse has led to emergence of drug-resistant bacteria and deposition of drug residues in meat products [179]. As a result, AMPs are potential alternative substitutes of antibiotics. AMPs such as AMPs-a3, P5 (synthetic), and cecropin AD (artificial) promote growth, digestibility, intestinal structure as well as function, and increase the abundance of normal intestinal flora [136]. AMPs improve nutrient absorption and promote growth in broilers [180] among several other benefits mentioned in preceding sections [181].

Future research on AMPs in this industry should focus on mechanisms of action and developing biofeed resources, including establishment of high-throughput direct isolation technology for gene resources, high-throughput screening technology methods and effective rapid functional assessment systems to obtain several new gene resources with application values and to establish biofeed products. Additionally, establishment of a biofeed fermentation technology can also advance and accelerate the pace of industrialization and practical applications. Eventually, we should establish a system for biofeed products to evaluate their safety.

3.4. Development and Applications of AMPs in Aquaculture

Due to rapid development of the aquaculture industry, farming practices have increased the accumulation of antibiotics in the water environment, and resulted in frequent occurrence of diseases in aquaculture animals, resulting in massive losses in the aquaculture industry [182].

AMPs in fish feeds significantly reduces infection rates without the risk of resistance as is the case for antibiotics. The β-defensin homolog (LcBD2) is expressed in the head, kidney, spleen, and gills of Larimichthys crocea. It is effective against various harmful bacteria, including Gram-negative Bacillus umbelliferae, Bacillus hemolyticus, Bacillus alginolyticus, Bacillus harveyi and Pseudomonas, as well as Gram-positive Bacillus subtilis. Simultaneously, it markedly improves monocyte or macrophage phagocytosis [137]. Pc-crustin 4 in red swamp improves crayfish immunity and protects against infections by S. aureus and Aspergillus flavus [138]. Lee *et al.* revealed that antibacterial activities of lactoferrin expressed in Bacillus subtilis were superior to those of ampicillin against Staphylococcus, Vibrio haemolyticus and Edwardsiella. Under a similar experimental set-up, lactoferrin increased the survival of tilapia fish by over 50%, which was attributed to a significant reduction in intestinal pathogenic bacterial infections. Thus, AMPs can effectively reduce an organism's overreliance on conventional antibiotics, reducing antibiotic resistance [139]. Seo *et al.* reported that HdMolluscidin has the ability to kill both gram-positive and gram-negative bacteria, including Bacillus subtilis, S. aureus, Aeromonas hydrophila, *E. coli*, P. aeruginosa, Salmonella enterica, Shigella flexneri, and Vibrio parahaemolyticus [140]. Chelonianin is a recombinant AMP that effectively suppresses Vibrio harveyi-associated inflammatory reactions in tilapia [141]. N6NH2 is superior to norfloxacin for treatment of fish peritonitis caused by Enterococcus [142]. In general, AMPs are suitable alternatives to antibiotics in aquaculture, with similar benefits across species.

The large-scale use of AMPs in aquaculture is complicated by various challenges, including: different types or sources of AMPs, inconsistent dosages, and the need to establish standards based on farm animal type and physiological stage.

3.5. Development and Applications of Food Preservation and Production Methods

Globally, foodborne diseases are a major public health problem. These diseases are spread through consumption of contaminated food or exposures to toxic or harmful substances (including biological pathogens). Pathogens, including bacteria and bacterial toxoids, fungi, and fungal toxoids, contaminate food at various phases of its production and preparation. Fungal contamination is the primary cause of food mildew, while fungal mycotoxins can also cause foodborne diseases, such as human liver cancer, nervous system damage, and immune system as well as fertility disorders among others. Some fungal strains can also produce toxic compounds, such as aflatoxins and patulin. Due to increasing

resistance of pathogens to traditional preservatives, applications of natural AMPs in the food production industry as new preservatives have attracted significant attention. Even though there are many types and quantities of AMPs, some AMPs derived from animal venom, particularly insect venom, have hemolytic or cytotoxic properties and are inadaptable as food preservatives. However, most AMPs (AFPs) from plants have been proven to be non-cytotoxic and are therefore, unsuitable for use as food preservatives. Most AFPs (TLPs) are used as sweeteners in some foods produced from barley [143] and chestnut [144]. TLPs inhibit the growth of yeasts and filamentous fungi, such as Fusarium and Saccharomyces.

The antifungal proteins Rs, AFP2, MsDef1, DmAMP1, TPP3, and NaD1 can inhibit the growth of various filamentous fungi [145], while PvD1 has strong antibacterial activities against Candida spp, Kluyveromyces and Saccharomyces cerevisiae [146,147]. Moreover, plant-derived defensins are capable of exerting their functions even under extreme temperature, pH, and oxidation conditions.

Although applications of antibacterial compounds in food preservation are diverse, such applications have not been extensively investigated [183]. Most of the existing reports on AMPs in food involve the use of lactobacillin, which is an antibiotic that is efficient against gram-positive bacteria [184]. Lactobacillin has a good safety profile, is avirulent, and exhibits high stability. Nisin, pediocin, and lysozyme, particularly nisin, are natural food preservatives in dairy products (fresh milk, milk powder, yogurt, and dry cool), canned food, meat products, and beverages among other applications. To improve the stability and sustained antibacterial activity of nisin, it is infused into soluble soybean polysaccharide nanoparticles. This approach extends the shelf life of fresh tomato juice [185]. When AMPs of Lactobacillus plantarum (UTNGt2) were coated on the surface of fresh tomatoes, salmonella growth was inhibited, implying antiseptic effects [148]. Synthetic peptides or recombinant peptides, such as AMPs (6k8l) of AMPs [150] in apple juice, TrxAq [151], orange and rHBD 3 [149] in bread, can protect food or ingredients from fungal degradation. Several AMPs have been approved as food preservatives. In 2012, lactoferrin was certified by the European Food Safety Authority as a food preservative. In addition to serving as preservatives, AMPs are active packaging materials [186]. Coating egg surfaces with chitosan helps to keep their interior fresh during long-term storage and transportation. Moreover, chitosan coating improves eggshell strength [187].

Active packaging is a promising technology. This technology makes use of AMPs as core carriers of microcapsules and nano-encapsulated structures to ensure their sustained release. These properties vary with type and efficacy of AMPs used [188]. Various strategies have been developed to design cost-effective and efficient encapsulation techniques. There is a critical need to investigate and capitalize on the potential of AMPs to improve food preservation.

3.6. Development and Applications of Cosmetic Additives

The HDPs, such as AMPs, bombesin, dermatan, and xenopus have a high affinity for water molecules and lipids. They are toxic to bacterial cells, but nontoxic and non-hemolytic to normal mammalian cells. Thus, they have the potential to be developed into personal care products, such as lotions, creams, ointments, or their constituents, particularly in countries or regions where the use of synthetic additives is restricted. The use of AMPs as antibacterial factors in traditional cosmetics, as opposed to the use of chemical synthetic substances and antibiotics, overcomes the irritability associated with long-term use of traditional skin care cosmetics, as well as the problem of drug resistance in pathogenic bacteria. Human skin aging can result in deterioration of the dermal extracellular matrix, decreased antibacterial function, and diminished skin barrier functions, among others, all of which contribute to development of skin inflammation. Various marine fish proteins and polypeptides have several biological activities, including antioxidant, anti-bacterial, anti-aging, and tissue regeneration functions. Because of their high biocompatibility, they can be used to design cosmeceuticals [189]. Lactophoricin (LPcin), a cationic AMP in milk, has good antibacterial effects on C. albicans, gram-positive and gram-negative bacteria, without causing toxic effects on human erythrocytes. This unusual helical shape, when paired with liposomes, has strong antibacterial and antifungal properties, and it can also alleviate the challenges associated with bacterial drug resistance. Therefore, it is a suitable natural additive in cosmetics [152]. A polypeptide mixture (carnosine + acetyl tetrapeptide-5 + hexapeptide-11 + acetyl hexapeptide-3) has been shown to significantly reduce malondialdehyde and hydroxyl radical levels in cells, improve hydroxyproline and human elastin levels, increase the activities of superoxide dismutase and glutathione peroxidase, and prevent skin aging [153].

4. DISCUSSION AND PROSPECTS

4.1. AMPs to Replace Antibiotics

Although antibiotics have saved countless lives since the discovery of penicillin in 1929 and the widespread use of antibiotics for almost half a century, antibiotic resistance is becoming increasingly common. Treatment of bacterial infections has grown increasingly difficult and challenging due to drug resistance. AMPs from different sources have shown excellent antibacterial, anti-inflammatory, antiviral, and immunomodulatory activities. AMP reagents (drugs) and antibiotics have shown good synergistic effects [190]. The combination of AMPs and antibacterial drugs has a broad development potential. On one hand, it produces a synergistic effect achieving "twice the result with half the effort" while on the other hand, it has the potential to reduce the use of antibacterial drugs while also reducing their toxic side effects. Studies on applications of AMPs are challenging, and their mechanisms of action have not been established. Furthermore, their deep mechanisms of potential toxicity, hemolytic, and aggregation effects and best optimal formula as well as administration routes have not been elucidated. There are discrepancies between prospective therapeutic effects of AMP candidates and actual results from clinical trials. Therefore, the safety, benefits and costs of AMP candidate drugs should be evaluated. Some recombinant AMPs have shown reduced cytotoxic and aggregation effects [191,192]. Truncating the smallest (KR12) sequence in innate immunity, LL-37, and coupling it with fatty acids to produce from C10-KR8d demonstrated excellent antibacterial and im-

mune-modulatory effects [193], which provides great hope for development and applications of AMPs drugs.

Therefore, the combination of AMPs with commonly used antimicrobial drugs or their modification can effectively improve antimicrobial activities of AMPs, as well as reduce the cytotoxicity and hemolytic properties of AMPs on human cells. Future studies should aim at developing new and more effective antibacterial materials.

4.2. Pathogen and AMPs Coevolution

Pathogens (including bacteria, fungi, viruses, chlamydia, mycoplasma, and spirochetes, among others) and AMPs coevolve in nature. Pathogens exist in a symbiotic relationship with native hosts. Long-term symbiosis has enabled pathogens to avoid destruction by AMPs [194]. The coevolution process improves selection pressure and antibacterial activities of AMPs. Bacteria from various sources exhibit varying degrees of tolerance to AMPs. The mechanisms and mode of bacterial tolerance to AMPs, coevolution between bacteria and AMPs, and escape mechanisms of AMPs produced by bacteria from their hosts are relatively complex or are the result of combined actions of various mechanisms. The complex intestinal microflora of mammals promotes AMPs secretion, activating inflammatory corpuscles and other mechanisms to activate innate immunity against pathogens [195]. These symbiotic and pathogen-resistant mechanisms provide new models and strategies for developing new antibacterial drugs. They may also be effective strategies for enhancing immunity, restoring drug efficacy, or minimizing drug resistance among pathogens.

Mammalian AMPs are found in neutrophils [81], paneth cells [196], epithelial cells [197], or protein degradation products. These peptides include defensins, cathelicidins, bactenecins, and indolicidins families. APMs in plant expression systems are active barriers against plant pathogen and bacterial pathogen infections. They are antibiotic peptides with important application prospects [198]. These APMs include thionin, defensins, cyclic peptides, lipid transfer proteins, and cell-penetrating peptides among others. Moreover, they exhibit similar characteristics, such as being positively charged and having a target site for disulfide bond actions all located in the extracellular membrane [198]. Extraction of AMPs from mammals and plants is labor-intensive, time-consuming, complex, expensive, and it is impossible to achieve large-scale production, which has become a great obstacle in practical applications of AMPs. The influence of AMPs on bacteria are expressed as fusion proteins, will cause significant difficulties in postprocessing result. Recently, research on yeast as a genetically engineered microorganism is becoming increasingly popular. Yeast has a more complete gene expression regulation mechanism than *E. coli*, a better ability to modify and secrete expressed products, and does not produce endotoxins, making it an excellent eukaryotic microorganism for genetic engineering [199-206]. These investigations demonstrate that the yeast expression system for AMPs could be a feasible way, which will lay a good foundation for early clinical applications of AMPs.

Studies should evaluate the significance of AMPs in COVID-19. Vitamin D has been shown to influence the expressions of AMPs [207]. The VDRE, a nuclear receptor, promotes AMP transcription. Vitamin D binds VDER to exert its antiviral activities, implying that AMPs can improve immune responses in COVID-19 patients [207]. Moreover, temporin exerts its therapeutic effects against MERS-COV, based on Homology model and protein-peptide docking [208]. A recent study showed that EK1C4, a lipopeptide derived from EK1, was highly effective against CoV such as SARS-CoV-2 [209]. Studies in mice models revealed that nasal drug delivery of EK1 may also be a potential treatment for COVID-19 [210-212]. Finally, the efficacy of AVPs against CoV has been reported, which should be clarified through clinical studies [27].

CONCLUSION

Advances in high-tech bioengineering, chemistry, and biomedicine techniques have increased research and application of AMPs. By using engineered bacteria or yeast technologies, AMPs can be produced in large quantities. Further investigations of the mechanisms of action of AMPs, as well as their purposeful designs and modification through genetic engineering and chemical synthesis will result in development of green additives based on AMPs for the benefit of mankind.

LIST OF ABBREVIATIONS

AMPs	=	Antimicrobial Peptides
CAPs	=	Cationic Antimicrobial Peptides
EGFR	=	Epidermal Growth Factor Receptor
HD-6	=	Human α-Defensin 6
HDPs	=	Host-Defense Peptide
HSPG	=	Heparan Sulfate Proteoglycan
IB-367	=	Iseganan IB-367
LPcin	=	Lactophoricin
MAPK	=	Mitogen-Activated Protein Kinase
Rs AFP2	=	Raphanussativus Antifungal Protein
TGH	=	Thanatin-GFP-HBsAg
E. giganteus	=	*Epinephelus giganteus*
P. aeruginosa	=	*Pseudomonas aeruginosa*
S. aureus	=	*Staphylococcus aureus*
A. baumannii	=	*Acinetobacter baumannii*
E. coli	=	*Escherichia coli*
C. albicans	=	*Candida albicans*
3D	=	Three-Dimensional

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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