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Review

Antimicrobial Peptides in the Fight against Drug-Resistant Superbug Infections

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Abstract: The discovery of antibiotics was one of the greatest achievements in human history, however, antibiotic resistance evolved no later than the introduction of antibiotics. The rapid evolution of antibiotic-resistant pathogens soon became a nightmare and remained a global healthcare threat. There is an urgent need to have new alternatives or new strategies to combat the multi-drug resistant superbugs such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA), extended-spectrum β-lactamases (ESBL) bearing multidrug-resistant *Acinetobacter baumannii* (MDR-AB), *Escherichia coli*, and *Klebsiella pneumonia*. Antimicrobial peptides (AMPs) have been considered promising agents equipped with unique mechanisms of action along with several other benefits to fight the battle against drug-resistant superbugs. Overall, the current review summarizes the mechanisms of drug-resistant development, the mechanism of action adopted by AMPs to combat drug-resistant pathogens, and the immunomodulatory properties of AMPs. Additionally, we have also reviewed the synergistic potential of AMPs with conventional antibiotics and the associated challenges and limitations of AMPs in the way of pharmacological development for therapeutic applications in clinical settings.

Keywords: superbugs; antibiotics; antimicrobial peptide; antibiotic-resistance; multidrug-resistance; Infections

1. Introduction

Globally world is facing nearly 5 million deaths due to microbial resistance every year, according to the World Health Organization, making it vital to identify possible alternative drug candidates or therapeutic strategies as soon as possible [1]. Drug-resistant bacteria are increasing worldwide, causing the age of antibiotics to end with the pressing need to have novel alternatives to fight drug-resistant superbugs [2]. Due to AMR's complexity, multiple approaches are required to deal with the problem. Some of them are: developing new antimicrobials, improving diagnostics, making existing drugs more effective, and developing new drug combinations. It is therefore increasingly necessary to find antibacterial therapeutics that reduce the risk of causing antimicrobial resistance [3]. AMPs (antimicrobial peptides) are emerging as viable alternatives to conventional antibiotics in the battle against rapidly evolving antibiotic resistance. It was unknown back then that MDR (multi-drug resistance) would become such a huge crisis over the years when AMPs were discovered, so translational applications for AMPs were not the priority at the time. Due to the subsequent rise in MDR strains, novel antimicrobial agents are now necessarily required and on the way to development [4].

As self-defense mechanisms, natural AMPs are potent inhibitory agents that are effective against the broadest spectrum of microorganisms, from bacteria to viruses. There are currently over 3300 AMPs in the antimicrobial peptide database (APD3). The composition of AMPs and their length vary widely. AMPs typically consist of short chains of amino acids (somewhere between 10 and 50), have

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a positive charge (between +2 and +11), are 2-9 kDa in size, and contain a majority of hydrophobic residues [5]. A key function of AMPs is to disrupt bacterial cell membranes, modulate the host's immune response, and control inflammation [6]. The diverse antimicrobial mechanisms of AMPs make them promising therapeutic candidates, in contrast to conventional small-molecule drugs, which target cellular processes such as protein and cell wall synthesis) [7]. Additionally, AMPs are advantageous because they disrupt membranes directly, and their action times are quick, therefore, it is difficult for microbes to develop resistance against them [8–10]. Throughout the past few decades, we have gained a deep understanding of antibiotics and how bacteria resist their inhibitory or killing effects, as well as the significance of context in determining the effects of many resistance mechanisms, for example, a diverse growth condition can dramatically alter the expression of resistance genes. Overall, an understanding of bacterial resistance development mechanisms also provides insights into mechanisms used by AMPs to overcome bacteria resistance (Figure 1).

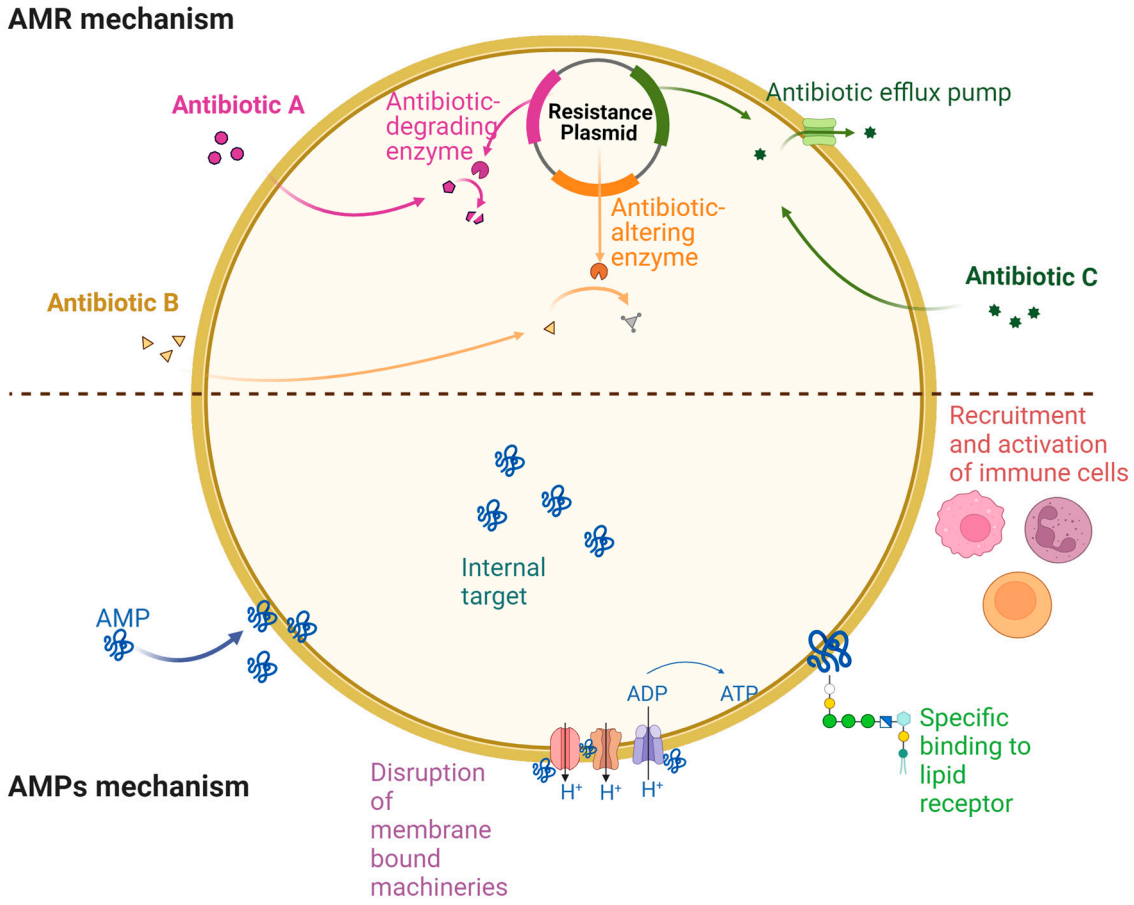

Figure 1. Antimicrobial mechanisms of action and antibiotic resistance mechanisms.

This article reviews the emergency of having new alternatives to cope drug resistance superbugs along with highlighting the various mechanisms of action used by AMPs to fight against the infections caused by drug-resistant superbugs. In addition, AMPs are discussed in conjunction with advanced new technologies for the treatment of drug-resistant bacterial infections and challenges in the way of AMPs to pharmacological development for therapeutic applications in clinical settings.

2. Antibiotic Resistance Drivers and Mechanisms

As microorganisms become resistant to antibiotics as soon as they are introduced, the new antibiotics remain ineffective for the treatment of common infections. Hospitals and other sectors in both developing and developed countries use antibiotics too frequently and irresponsibly, contributing to frequent mutations and selection pressures that lead to rapid resistance development.

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Resistance to antibiotics is a grave threat primarily due to poor hygiene and sanitation, as well as globalization in terms of trade, travel, and transmission [11]. Additionally, many factors contribute to drug resistance, including agriculture and animal husbandry. A direct route for transmitting resistant bacteria between humans and animals is the food chain, for example, cattle are often given antibiotics (even when they are healthy) to prevent illness, which leads to overuse of these antibiotics, since they are similar to those used clinically, for instance, poultry has been identified as a source of drug-resistant *E. coli* in rural villages of Barcelona [12,13]. Further, infections are often treated with broad-spectrum antibiotics in hospitals, which allows higher opportunities for resistance development. Evidence shows that the rate of resistance to antibiotics may increase with increased antibiotic usage, while resistance rates may fall with reduced antibiotic usage. Further, frequent re-administration of antibiotics over time also provides enough chances for resistance development, since antibiotics provide selective pressure on bacteria [13]. Unfortunately due to a lack of proper diagnostic tools, along with unnecessary antibiotic administration, and their low cost, antimicrobial resistance is rising uncontrollably [12,13].

The antibiotic resistance mechanism of currently used conventional antibiotics, especially target cell walls, DNA replication, and translational activity to eliminate pathogenic bacteria. Additionally, naturally resisting antibiotics or mutations in the bacterial chromosomes are also contributing factors for resistance development. The resistant mutant may continue to exist as soon as the antibiotic kills the normal bacterium while transmitting the antibiotic resistance genes by horizontal or vertical transfer.

In summary, bacteria adopted various mechanisms to develop drug-resistant that includes (i) Poor drug influx through porin channels such as, a mutation in the outer membrane of *P. aeruginosa* may lead to resistance to imipenem, (ii) Increased efflux of drugs from drug-resistant bacterial cells via efflux pumps along with the modification in regulatory proteins, (iii) Modifications to genomes affecting or protecting target areas such as Group C and G *Streptococci*, have mutations in erm genes that prevent binding to macrolides, lincosamides, and streptogramins, (iv) Covalent bonding is another common method of developing resistance to drugs for example NDM-1 (metallo β-lactamase 1, a carbapenemase-active-lactamase) that resists all antibiotics used to treat severe infections, (v) The R plasmid, a plasmid that carries several resistant genes which plays a crucial role in drug-resistance transmission such as MGE pheromone, that involved with enterococcal pheromone-responsive plasmids and assists resistance development in *E. faecalis*, (vi) Biofilm development that become resistant to available antibiotics. The biofilm matrix which is made up of exo-polysaccharides slows down the diffusion and reduces the bioavailability of antibiotics by increased viscosity [14]. (vii) Surface remodeling such as lipid A, which is a part of the Gram-negative outer membrane component LPS, that is modified with phosphoethanolamine or 4-amino-4-deoxy-l-arabinose residues in polymyxin B-resistant *P. aeruginosa*, *V. cholerae*, *A. baumannii*, and *S. enterica* [15,16]. Polymyxin B resistance is conferred by LPS modifications, which are primarily caused by regulatory complexes like PmrAB and PhoPQ, which alter gene expression [17].

3. AMP Mechanisms of Action in Treating Drug-Resistant Bacteria

In the past few years, MDR bacteria have emerged as a result of antibiotic abuse that specifically includes MRSA, MDR-AB, VRE, and CR-PA. As antibiotics have failed to treat bacterial infections, therefore, treatment and prevention have become increasingly important. The use of AMPs is one of the promising new approaches for treating multidrug-resistant bacteria due to their unique antibacterial mechanism by hitting more targets to kill bacteria. AMPs, unlike antibiotics, directly act on bacterial membranes including biofilms. Additionally, AMPs resensitize, and inhibit biofilm growth, via regulating immune responses, and thus regulate intracellular bacteriostatic functions. Overall, these factors and specific mechanisms of AMPs indicate their efficacy as an epistatic alternative to conventional antibiotics.

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3.1. AMPs Mediated Membrane Disruption

The mechanism of action of AMPs involves the disruption of membranes which typically relies on a variety of composition of pathogen and host membranes to impart selectivity. As opposed to the mammalian cell surface that has primarily neutrally charged phospholipids such as phosphatidylcholine and sphingolipids, bacteria, on the other hand, have a significant fraction of negatively charged phospholipids like cardiolipin, phosphatidylglycerol (PG), and phosphatidylserine (PS), which is a favorable factor for positively charged AMPs to act upon [18]. Furthermore, Gram-positive bacteria have large amounts of teichoic acid which is negatively charged in their peptidoglycan cell wall surrounding their membrane. In Gram-negative bacteria, the outer leaflets of their outer membranes are predominantly composed of lipopolysaccharide which is also negatively charged [19]. There are negatively charged phospholipids like PS in mammalian cell membranes, but they are broadly distributed in the cytosol leaflet of the bilayer, so AMPs usually don't target mammalian cells [20]. Overall, the outer surface of bacteria has an overall negative charge that results in electrostatic interactions with AMPs that enable the primary binding and membrane-specific killing by AMPs [21]. Studies have shown that AMP activity is decreased significantly by decreasing AMP positive charge below a certain threshold [22]. Increasing the positive charge of AMPs should generally result in the improved antimicrobial activity of those AMPs, but too high a charge could cause off-target toxic effects. A higher charge density is supposed to enhance the AMP-water interaction, stabilizing the transmembrane pores on the hydrophilic surface which is formed by AMPs after the initial binding to bacterial cell membrane. The electrostatic attraction to a membrane that is negatively charged, however, does not seem feasible when various AMPs are anionic. An example of such a type of peptide is DCD-1L [23]. Although DCD-1L has an overall negative charge of -2, it is assumed that only it's positively charged N-terminus plays a major role in the initial interaction with the target bacterial cell membrane. Additionally, it is believed that the divalent cations such as Mg^{2+}, Ca^{2+}, and Zn^{2+}, are also involved in improving the antimicrobial activity of DCD-1L by stabilization of membrane-spanning peptide oligomers, or through salt bridge formation with the anionic phospholipids. Next, interaction with the positive phospholipids or hydrophobicity is another mechanism of action for anionic AMPs against superbugs [24]. For example, microcin J25 is taken up through FhuA, an outer membrane protein that is involved in an anionic AMP transport [25].

Further, based on spectrometric data and molecular-dynamic simulations using artificial membrane bilayers and liposomes, several models have been proposed to explain the AMPs mode of action. These models are categorized as porous or nonporous. The barrel-stave model and the toroidal model are two pore-forming models that support the formation of transmembrane pores on the lipid bilayer [22,25,26]. In the barrel-stave model, AMPs interact with the fatty acyl chains surrounding the pore wall, whereas in the toroidal model, they only interact with the lipid head groups. The 26-residue peptide melittin, which is found in bee venom, is one of the most famous AMPs classified in the pore-forming model. In contrast, several non-pore-forming models have also been proposed for AMP mechanism of action, such as the carpet model and the detergent-like model [21,27]. In the carpet model, AMPs lie on the surface of the membrane and interact only with the lipid head group while the detergent-like model shows how AMPs dissolve and remove lipids from a lipid bilayer in a detergent-like fashion. Interestingly, one AMP may disrupt bacterial cell membranes through more than one mechanism depending on its concentration, conditions, and lipid composition [26]. AMPs have been studied primarily using artificial membranes, while studies of their effects on real membranes have been scarce. An AMP must accumulate to a critical concentration on the membrane surface before it can disrupt the target bacterial membrane. Depending on whether diffusion barriers exist in the outer membrane or the periplasmic space, they may be prevented from partitioning onto the membrane. There are fewer rate-limiting steps for Gram-positive bacteria because AMPs only need to diffuse through nano-sized pores in the peptidoglycan [28]. It is the peptidoglycan layer of the target bacterial membrane that facilitates the accumulation of AMPs on the target bacterial membrane via the availability of negatively charged teichoic acid that helps in providing an overall negative charge to facilitate the interaction with positively charged AMPs [26].

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Further, in the case of Gram-negative pathogens, AMPs first need to penetrate the outer envelope and then the cell membrane such as polymyxin B has strong antimicrobial activity against Gram-negative pathogens because it disrupts both the outer and cytoplasmic membranes. It has been shown that the removal of the lipid tail from the polymyxin B, allows it to permeabilize only the outer membrane of the Gram-negative bacteria and lose its antimicrobial properties [27]. This suggested the importance of lipid moiety in the antimicrobial action of polymyxin B and other lipid-containing AMPs.

3.2. AMPs Mediated Intracellular Targeting

AMPs are short polycationic peptides that have a wide range of antimicrobial properties. Membrane-lysis is recognized as the primary antibacterial mechanism, which directly impairs the integrity of the bacterial membranes and cell walls. AMPs also form transmembrane channels when they self-aggregate or polymerize, resulting in cytoplasm leakage and cell death. However, increasing evidence suggests that AMPs are capable of exerting intracellular inhibition as the primary or supporting mechanism for effective killing. Several AMPs inhibit multiple intracellular targets, such as indolicidin, buforin II, DM3, and microcin J25 [29]. In many studies, AMPs have proven to affect various physiological processes in cells, including the synthesis of DNA and proteins, the folding of proteins, enzyme activity, and the synthesis of cell walls [30]. Burofin II (Lys-C-cleaved derivative of buforin I), is a transmembrane active AMP that induces membrane permeation in *Escherichia coli* due to its proline hinge region [31]. In the gel retardation experiments, buforin II is found to exhibit a high affinity with nucleic acids and it is strongly implied that it inhibits the cellular processes by interfering with RNA and DNA metabolism [32]. Next, indolicidin, an AMP of cathelicidin family is reported to inhibit DNA biosynthesis exclusively via continuous entry into the bacterial cells without any observed cell lysis [33–36]. Further, detailed studies confirmed the strong binding of indolicidin to the duplex DNA [CG], [AG], and [AT], while weak biding to [GT] [37]. It has also been reported that indolicidin inhibits DNA replication and transcription by stabilizing the central PWWP motif on the duplex DNA [38]. Microcin J25 is reported to interfere with the transcription by binding to bacterial RNA polymerase [39]. Another example is lactoferricin B, which killed the target bacterial by interfering with the phosphorylation of the bacterial two-component system response regulators BasR and CreB along with the accumulation of pyruvate in bacterial cells [40,41].

Bac7, is a large 60 amino acid-long AMP isolated from bovine neutrophils, however, its N-terminal 35-residue (Bac7 1-35) is reported to have a role in antimicrobial activity via ribosome binding and inhibition of protein translation [42][43]. Next, a hybrid AMP, DM3, is demonstrated to exhibit broad-spectrum bactericidal activity in a rapid time interval while A genome-wide transcriptomic analysis revealed significant changes in several important intracellular pathways including those associated with DNA replication and transcription, RpoD, and RNA polymerase sigma factors down-regulation, and amino acid biosynthesis pathways [44,45].

3.3. Immune Activity Regulation by AMPs

In several studies, it has been shown that AMPs can suppress or enhance innate and adaptive immune system responses, demonstrating their immunomodulatory properties. A variety of factors influence this capacity, including environmental factors, the cells involved, receptor interactions, signaling pathways involved, and transcription factors that bind to them [46]. Several AMPs have been shown to act in a pleiotropic manner depending on the cell they are acting on, while their concentration plays a crucial role in the mechanism of action [47]. AMPs are found in NK cells and neutrophils as well as in innate immunity, including α defensins and cathelicidins. Extracellular release of AMPs can also act as a chemokine because they recruit diverse types of cells to the infection site, including neutrophils, eosinophils, mast cells, monocytes, and lymphocytes [30,48]. Human Neutrophil Peptide (HNP-1) increases pathogen elimination by stimulating macrophages for phagocytosis of apoptotic peptides and neutrophils [49]. Cathelicidin LL-37 has also been observed stimulating neutrophil phagocytosis. There is a fundamental mechanism that involves the chemokine

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CXCL8 synthesis which is regulated by p38 (MAPK) and ERK (extracellular signal-regulated kinase) signaling pathways [50]. For initiating adaptive antimicrobial immune responses, the recruitment of immune cells to infection sites includes dendritic cells, macrophages, antigen-presenting cells (APCs), B lymphocytes, and macrophages [51]. Based on their interactions particularly with CCR6, the HNP1, HNP-2, HNP-3, and hBD1-3 are the selective chemoattractants for immature dendritic cells [52–54]. Apart from recruitment, AMPs could also promote and regulate dendritic cell maturation because mouse β-defensin 2 upregulates the expression of costimulatory receptors, such as CD40, CD80, and MHC II, while the similar phenomenon reported in the case of hBD1, hBD3, and HNP-1. Through immune regulation, AMPs show promising effects in the area of sepsis because AMPs can confer bactericidal and immunomodulatory effects, which leads to the development of combination therapies with bactericidal and anti-inflammatory AMPs [55,56]. The initial focus of AMP research was on classical natural AMPs, but they could also improve immunomodulatory activities for the applications in various therapeutic applications.

3.4. AMPs as Role Players in Eradicating Biofilm-Mediated Drug Resistance

Biofilms may be as most adaptable microbial nature's feature. As a consequence, when pathogenic microbes aggregate into the biofilms, become an important virulence factor. Furthermore, microbial biofilms reduce the effectiveness of antimicrobial compounds and modulate the immune response, thereby causing antimicrobial resistance that enables persistent infection establishment. AMR is extremely complex, in which biofilms play a significant role in driving the resistance. Bacteria residing in biofilms exhibit a 100 to 1000-fold enhanced AMR than those living in a planktonic state. One of the studies examined that 100% of *S. epidermidis* strains tested were susceptible to antibiotic vancomycin in the planktonic state while nearly 75% of the biofilms were found fully resistant [57]. Similarly in the case of *K. pneumoniae*, which was found to be susceptible when tested in a planktonic state but becomes resistant in biofilms to certain antibiotics [58]. Biofilm develops a surface resistance and it is hard for antibiotics to penetrate this slimy and sticky surface. Multilayered, localized, and heterogeneous communities of bacteria make up a bacterial biofilm, which is surrounded by a matrix of extracellular polymeric substances (EPSs) [59]. Biomolecules in EPSs include polysaccharides, proteins, extracellular DNA, and lipids, which makes it difficult for the antibiotics to penetrate and reach their target bacteria. Additionally, because of the slow diffusion within the biofilms, antibiotics could be deactivated near the level of the surface rather than reaching the depth of the cell. Microenvironmental resistance inside biofilms is another aspect that makes it challenging for antibiotics at the deeper levels where waste, metabolic by-products, and nutrients, are also accumulated. Furthermore, an anaerobic environment could also be possible within the biofilms that drastically reduced oxygen levels. When these factors are combined, antibiotics vary in their effects depending on their structure and action as ciprofloxacin and tobramycin are found to have less bactericidal effect at low oxygen levels, whereas changes in pH could impact negatively aminoglycoside action [60]. Additionally, bacterial persister cell resistance is another phenomenon for the bacteria residing deeper in biofilm layers, where they become more adept at evading antibiotic therapy. Moreover, as a method of survival, a subpopulation of bacteria develops spore-like characteristics (persister cells) which make them resistant to antibiotics or chemical treatments. In the presence of antibiotics, these persister cells remain in a dormant state and don't divide. Additionally, persister cells do not genetically modify to resist and survive antibiotic treatment, and they will return to their pre-persister susceptibility profile once released from biofilms and start dividing again [61]. According to an estimation, up to 500–50,000 times the antimicrobial resistance of microorganisms can be enhanced by biofilm formation [62]. It is generally known that AMPs are highly stable at a wide range of pH and temperature, properties that are beneficial in scaling up production and incorporating them into deliverable products. Even well-established biofilms have been eliminated by low concentrations of AMPs with inhibitory and disruptive properties. As well as acting at different stages of biofilm formation, AMPs can inhibit adhesion, inhibit biofilm formation, and kill pre-formed biofilms, all of which are potential applications of AMPs [63].

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For example, natural AMP LL-37 from the cathelicidin family and synthetic AMP NA-CATH:ATRA1-ATRA1 are known to inhibit the growth of biofilms by S. *aureus* below a concentration of 3 μg/mL [64]. It has been reported that LL-37 stimulates twitching motility, down-regulates the Las and Rhl QS system, and decreases *P. aeruginosa* cell attachment to medical devices and tissues while in the case of *S. epidermidis* it inhibits both initial attachment and biofilm formation [65,66]. Several anti-biofilm agents, such as lactoferrin, conjugated lactoferricin, melimine, and citropin 1.1, are effective in medical device infections caused by *S. aureus* and *P. aeruginosa*, especially when administered in combination with conventional antibiotics, such as rifampicin and minocycline [67]. In a recent study, four chimeric AMPs are shown to inhibit multidrug-resistant biofilms of *Acinetobacter baumannii* in synergy with conventional antibiotics, while demonstrating low cytotoxicity against human skin cells [68]. Overall, AMPs displayed antibiofilm activities by direct disruption or degradation of biofilm-embedded bacterial cell membrane potential, disrupting bacterial cell signaling systems, degradation of polysaccharide and biofilm matrix, inhibition of the alarm system to avoid bacterial stringent responses, and by reduction of the expression of genes responsible for biofilm formation and protein transport [69].

4. AMPs Approved for Clinical Use or under Clinical Trials

The development of AMP-based therapies could eventually replace conventional antibiotics with broad-spectrum AMPs. To date, only a few AMPs have been approved for use in clinical settings (Table 1). Vancomycin is one of the most efficient AMP (tricyclic glycopeptide), originally produced and isolated from *Streptococcus orientalis* that has been approved for the treatment of serious Gram-positive bacterial infections [11]. It is efficiently active against Gram-positive *bacilli* as it enables to inhibit formation of the cell wall of Gram-positive bacteria. As a first-line antibiotic, vancomycin is also used to treat multiple drug-resistant infections such as endocarditis, bacteremia, pneumonia, osteomyelitis, and cellulitis [70]. Gramicidin (15 amino acids) is a natural AMP produced by *Bacillus brevis*. Gramicidin is the first peptide antibiotic discovered in 1939 and later got FDA approval for topical application against Gram-positive bacteria [71]. Bacitracin (12 amino acids) is another FDA-approved natural AMP produced by *Bacillus licheniformis* M1. It shows potent activity against Gram-positive bacteria including MRSA [72]. Next, colisitin (10 amino acids) is produced by *Paenibacillus polymyxa* and is FDA-approved. It is considered a last resort treatment for Gram-negative bacterial infections including pneumonia and also shows potent antibiofilm activities [73]. Daptomycin is a cyclic lipopeptide produced by *Streptomyces roseosporus*. It has been approved to treat serious skin infections caused by Gram-positive bacteria which include methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) [74]. Next, polymyxin B is a cyclic cationic AMP produced by *Bacillus polymyxa*. It has potent activity mainly against Gram-negative bacteria including *K. pneumoniae*, *P. aeruginosa,* and *A. baumannii* [75,76]. Also, many potential AMPs are already under clinical trials to be used against various infections (Table 2). In addition to this, there are many AMPs reported with potential activities against various drug-resistant bacteria and biofilms (Table 3). All the experimental evidences suggested that AMPs could be an efficient alternative to combat superbug infections, especially when there are great opportunity to have enormous new AMPs. Interestingly, the bacterial communities such as human gut microbiome which is constantly evolving under the pressure of other human metabolites and various interacting factors. Additionally, bacterial communities from marine ecosystem have been shown to have huge possibilities of potentially novel AMPs to fight against drug-resistant super bugs [77].

Table 1. FDA-approved selected AMPs for the treatment of different bacterial infections.

AMPs	Source/Type	Clinical Use	Mode of Action	Reference
Vancomycin	*Streptococcus orientalis*)/Tricyclic glycopeptide	Complicated infections caused by MRSA, *C. difficile*, and Gram-positive bacteria	Inhibition of cell wall biosynthesis	[88]

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Bacitracin	*B. licheniformis*)	Pneumonia and empyema in infants	Cell wall interference and peptidoglycan synthesis interference	[72]
Daptomycin	*Streptomyces roseosporus*)	Skin bacterial infections	Membrane-lytic peptide, inhibition of DNA, RNA, and protein synthesis	[89]
Polymyxin B	Bacteria (*Paenibacillus polymyxa*)	Bacterial infections caused by Gram-negative bacteria	Targets membrane phospholipids (lipopolysaccharides and lipoproteins)	[90]
Gramicidin	Bacteria (*B. brevis*)	Dermatological and ophthalmological infections	Pore-forming peptide	[71]
Colistin	Bacteria (*B. polymyxa*)	Gram-negative bacterial infections, Pneumonia	Membrane-lytic peptide	[73]

Table 2. AMPs under clinical trials to combat biofilms and drug-resistant superbug infections.

AMPs	Type	Target	Clinical Trial ID	Phase	References
Nisin	Lantibiotic	Gram-positive bacteria	NCT02928042 NCT02467972		[91]
Murepavadin (POL7080)	Derivative of protegrin	*P. aeruginosa, K. pneumoniae*	EUCTR2017-003933-27-EE	II	[92]
Iseganan (IB-367)	Derivative of protegrin	Pneumonia/oral mucositis	NCT00118781 NCT00022373	III	[93]
Surotomycin (CB-315)	Cyclic lipopeptide	*C. difficile*	NCT01597505	III	[94]
Omiganan (MBI-226)	Derivative of indolicidin	Antisepsis/ catheter infection	NCT00231153 NCT00608959	III	[95]
NVB-302	Lantibiotic	*C. difficile*	ISRCTN40071144	I	[96]
OP-145	Derivative of LL-37	Chronic middle ear infection	ISRCTN84220089	II	[97]
LTX-109	Synthetic tripeptide	MRSA, Impetigo	NCT01803035 NCT01158235	II	[98]
EA-230	Oligopeptide	Sepsis	NCT03145220	II	[99]
hLF1-11	Human lactoferrin derivative	Bacterial infections	NCT00430469	II	[100]
C16G2	Synthetic peptide	*S. mutans*	NCT03004365	II	[101]
Ramoplanin (NTI851)	Glycolipodepsipeptide	*C. difficile*, VRE	NA	III	[102]
p2TA (AB103)	Synthetic peptide	Necrotic tissue infection	NA	III	[103]
D2A21	Synthetic peptide	Burn wound infections	NA	III	[104]
LFF571	Semisynthetic thiopeptide	*C. difficile*	NCT01232595	II	[105]
GSK132232 (Lanopepde)	Synthetic hydrazide	Bacterial skin infection	NCT01209078	II	[106]
PMX-30063 (Brilacidin)	Defensin mimetic	Acute bacterial skin infection	NCT01211470 NCT02052388	II	[107]
XF-73 (Exeporfinim chloride)	Derivative of porphyrin	*Staphylococal* infection	NCT03915470	II	[108]

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Wap-8294A2 (Lotilibcin)	Naturally produced by *Lysobacter* species	Gram-positive bacteria	NA	II	[109]
PL-5	Synthetic peptide	Skin infections	NA	I	[110]
IDR-1	Bactenecin	Infection prevention	NA	I	[111]
Pexiganan	Analog of magainin isolated from the skin of the African clawed frog	Infections of diabetic foot ulcers, Gram positive and Gram negative bacteria	NCT01590758	III	

Table 3. Selected AMPs showing activity against drug-resistant superbug and biofilms.

AMPs	Peptide Sequence	Source	Spectrum of Activity	References
Mersacidin	CTFTLPGGGGVCTLTSECIC	*Bacillus* sp. HIL Y-85 54728	MRSA	[112]
Epilancin 15X	SASIVKTTIKASKKLCRGFTLT CGCHFTGKK	*S. epidermidis* 15X154	MRSA, Gram-positive	[113]
Mutacin B-Ny266	FKSWSFCTPGCAKTGSFNSYC C	*S. mutans* Ny266	MRSA	[114]
Epidermicin NI01	MAAFMKLIQFLATKGQKYVS LAWKHKGTILKWINAGQSFE WIYKQIKKLWA	*S. epidermidis* 224	MRSA, Gram-positive	[115]
Actagardine A	SSGWVCTLTIECGTVICAC	*A. garbadinensis* ATCC 31049	*C. difficile*, VRE, MRSA	[120]
Aureocin A53	MSWLNFLKYIAKYGKKAVSA AWKYKGKVLEWLNVGPTLE WVWQKLKKIAGL	*Staphylococcus aureus* A53	MRSA, Gram positive	[121]
LCI	AIKLVQSPNGNFAASFVLDG TKWIFKSKYYDSSKGYWVGIY EVWDRK	*Bacillus subtilis* strain A014	MRSA, Gram positive and Gram-negative	
Microcin E492	GETDPNTQLLNDLGNNMA WGAALGAPGGLGSAALGAA GGALQTVGQGLIDHGPVNVF IPVLIGPSWNGSGSGYNSATSS SG	*K. pneumoniae* RYC492	*K. pneumonia*, and other Gram-negative bacteria	[122]
Lassomycin	GLRRLFADQLVGRRNI	*Lentzea kentuckyensis*	*M. tuberculosis*	[123]
Enterocin AS-48	MAKEFGIPAAVAGTVINVVE AGGWVTTIVSILTAVGSGGLS LLAAAGRESIKAYLKKEIKKK GKRAVIAW	*E. faecalis* S-48	MRSA, *M. tuberculosis*	[124]
Ruminococcin C	WGCVCSGSTAVANSHNAGP AYCVGYCGNNGVVTRNANA NVAKTA	*R. gnavus* E1	*C. difficile* and other MDR strains	[126]
Actinomycesin	GFGCPWNAYECDRHCVSKG YTGGNCRGKIRQTCHCY	Actinomyces sp.	MRSA, Gram-positive	[128]
Triintsin	GFGCPLNERECHSHCQSIGRK FGYCGGTLRLTCICGKE	*Trichophyton interdigitale*	MRSA, Gram-positive, and Gram-negative	[129]
Blauticin	ITSKSLCTPGCVTGILMTCPVQ TATCGCQITGK	*Blautia producta* SCSK	MRSA, Gram-positive	[130]
Lan-Df	YKSKSVCTPGCPTGILMTCPL KTATCGCHITGK	*Dorea formicigenerans*	MRSA, Gram-positive	[130]

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Penisin	NIGLFTSTCFSSQCFSSKCFTDTCFSSNCFTGRHQCGYTHGSC	*Paenibacillus* sp. A3	MRSA, Gram-positive, and Gram-negative	[131]
Laterosporulin10	ACVNQCPDAIDRFIVKDKGCHGVEKKYYKQVYVACMNGQHLYCRTEWGGPCQL	*B. laterosporus* SKDU10	*M. tuberculosis* H37Rv, Gram-positive	[79]
CycP	CAWLWAPAWLWAC	Synthetic	Drug-resistant *S. aureus*	[132]
Plectasin	GFGCNGPWDEDDMQCHNHCKSIKGYKGGYCAKGGFVCKCY	*Pseudoplectania nigrella*	MRSA, Gram-positive	[133]
Micasin-1	GFGCPFNENECHAHCLSIGRKFGFCAGPLRATCTCGKQ	*Microsporum canis*	MRSA, Gram-positive, and Gram-negative	[134]
Lacticin 3147	CSTNTFSLSDYWGNNGAWCTLTHECMAWCK	*Lactococcus lactis* DPC3147	*S. mutans* (Biofilm)	[135]
Subtilomycin	TWATIGKTIVQSVKKCRTFTCGCSLGSCSNCN	*Bacillus subtilis* MMA7	*L. monocytogenes* (Biofilm)	[136]
Gallidermin	IASKFLCTPGCAKTGSFNSYCC	*Staphylococcus gallinarum* (F16/P57)	*S. aureus, S. epidermidis* (Biofilm)	[137]
Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ	*Apis mellifera*	*A. baumannii*, MRSA, *P. aeruginosa, K. pneumonia*, and Gram-positive bacteria	[138]
MS moricin	GKIPVKAIKQAGKVIGKGLRAINIAGTTHDVVSFFRPKKKKH	*Manduca sexta*	MRSA, Gram positive and Gram-negative	[139]
Cecropin A	RWKVFKKIEKVGRNIRDGVIKAAPAIEVLGQAKAL	*Heliothis virescens*	*A. baumannii, P. aeruginosa*, and other Gram-negative, and Gram-positive bacteria	[140]
Tachyplesin III	KWCFRVCYRGICYRKCR	*Tachypleus gigas*	*P. aeruginosa, A. baumannii*, biofilms, and Gram-positive bacteria	[141]
Arenicin-1	RWCVYAYVRVRGVLVRYRRCW	*Arenicola marina*	MRSA, Gram-positive, and Gram-negative	[142]
Magainin 2	GIGKFLHSAKKFGKAFVGEIMNS	*Xenopus laevis*	*K. pneumoniae, P. aeruginosa, A. baumannii*, Anti-biofilm	[143]
Ranalexin	FLGGLIKIVPAMICAVTKKC	*Rana catesbeiana* (Bullfrog)	MRSA, Gram-positive, and Gram-negative	[144]
CPF-ST3	GLLGPLLKIAAKVGSNLL	Frog	MRSA, Gram-positive, and Gram-negative	[145]
Brevinin-1TSa	FLGSIVGALASALPSLISKIRN	Frog	MRSA, Gram-positive, and Gram-negative	[146]

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Brevinin-1DYa	FLSLALAALPKFLCLVFKKC	Frog	MRSA, Gram-positive, and Gram-negative	[147]
Brevinin-1DYb	FLSLALAALPKLFCLIFKKC	Frog	MRSA, Gram-positive, and Gram-negative	[147]
Temporin-1Oc	FLPLLASLFSRLF	Frog	MRSA, Gram-positive,	[148]
Temporin-1Ga	SILPTIVSFLSKVF	Frog	MRSA, Gram-positive,	[148]
Temporin-1Vb	FLSIIAKVLGSLF	Frog	MRSA, Gram-positive	[149]
Temporin-SHd	FLPAALAGIGGILGKLF	Frog	MRSA, Gram-positive, and Gram-negative	[150]
CPF-SE1	GFLGPLLKLGLKGVAKVIPHL IPSRQQ	Frog	MRSA, Gram-positive, and Gram-negative	[151]
CPF-SE2	GFLGPLLKLGLKGAAKLLPQ LLPSRQQ	Frog	MRSA, Gram-positive, and Gram-negative	[151]
Japonicin-2LF	FIVPSIFLLKKAFCIALKKC	Frog	MRSA, Gram-positive, and Gram-negative	[152]
Gaduscidin-1	FIHHIIGWISHGVRAIHRAIH	*Gadus morhua* (Atlantic cod)	*P. aeruginosa* biofilms, Gram positive and Gram-negative	[153]
Piscidin 1	FFHHIFRGIVHVGKTIHRLVT G	Fish	MRSA, Gram-positive, and Gram-negative	[154]
Pleurocidin	GWGSFFKKAAHVGKHVGKA ALTHYL	*Pleuronectes americanus*	MRSA, Gram-positive, and Gram-negative	[155]
Imcroporin	FFSLLPSLIGGLVSAIK	Scorpions	MRSA, Gram-positive,	[156]
Stigmurin	FFSLIPSLVGGLISAFK	Scorpions	MRSA, Gram-positive,	[157]
MP-C	LNLKALLAVAKKIL	Insects	MRSA, Gram-positive, and Gram-negative	[158]
Chicken CATH-1	RVKRVWPLVIRTVIAGYNLYR AIKKK	*Gallus galllus*	MRSA, Gram-positive, and Gram-negative	[159]
Chicken CATH-2	RFGRFLRKIRRFRPKVTITIQGS ARFG	Chicken	MRSA, Gram-positive, and Gram-negative	[160]
Clavanin A	VFQFLGKIIHHVGNFVHGFSH VF	*Styela clava*	MRSA, Gram-positive,	[161]
SMAP-29	RGLRRLGRKIAHGVKKYGPT VLRIIRIAG	Sheep	MRSA, Gram-positive, and Gram-negative	[162]

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BMAP-27	GRFKRFRKKFKKLFKKLSPVIP LLHLG	Cattles	MRSA, Gram-positive, and Gram-negative	[163]
BMAP-28	GGLRSLGRKILRAWKKYGPII VPIIRIG	Cattles	MRSA, Gram-positive, and Gram-negative	[163]
Lactoferricin B	FKCRRWQWRMKKLGAPSITC VRRAF	*Bos taurus*	MRSA, Gram-positive, and Gram-negative	[164]
CAP18	GLRKRLRKFRNKIKEKLKKIG QKIQGFVPKLAPRTDY	*Oryctolagus cuniculus*	MRSA, Gram-positive, and Gram-negative	[165]
Rattusin	LRVRRTLQCSCRRVCRNTCSC IRLSRSTYAS	*Rattus norvegicus*	MRSA, Gram-positive, and Gram-negative	[166]
Cryptdin-4	LRGLLCYCRKGHCKRGERVR GTCGIRFLYCCPRR	*Mus musculus*	MRSA, Gram-positive, and Gram-negative	[167]
Protegrin 1	RGGRLCYCRRRFCVCVGR	*Sus scrofa*	MRSA, *A. baumannii*, *P. aeruginosa*, Anti-biofilm, Gram positive	[168]
RTD-1	GFCRCLCRRGVCRCICTR	*Rhesus Macaque* (Macaca mulatta)	MRSA, Gram-positive, and Gram-negative	[169]
LL-37	LLGDFFRKSKEKIGKEFKRIVQ RIKDFLRNLVPRTES	Human and other mammals	MRSA, *P. aeruginosa*, *A. baumannii*, Gram-positive, and Gram-negative	[170]
Indolicidin	ILPWKWPWWPWRR	Human and other mammals	MRSA, *P. aeruginosa*, Gram-positive, and Gram-negative	[171]
HNP-1	ACYCRIPACIAGERRYGTCIY QGRLWAFCC	*Homo sapiens*	MRSA, *C. difficile*, Gram-positive, and Gram-negative	[172]
hBD-3	GIINTLQKYYCRVRGGRCAVL SCLPKEEQIGKCSTRGRKCCR RKK	*Homo sapiens*	MRSA, Anti-biofilm, Gram-positive, and Gram-negative	[173]

5. Synergistic Action of AMPs with Conventional Antibiotics

It has been found that many of the conventional antibiotics become more efficient when used along with AMPs. This suggested the synergistic action potential of AMPs with antibiotics or other antimicrobials which is mainly due to their membrane-specific mechanisms of action that facilitate the entry of antibiotics in the bacterial cell for intracellular targeting (Table 4). Combining AMPs with other antibacterial agents provides a new set of drugs to achieve synergistic action, thus overcoming the limitations of using a single drug to treat a particular infection or disease. The synergistic effect of AMPs could allow the reuse of standard antibiotics and result in better expected clinical outcomes including increased efficacy, reduced toxicity, and delayed development of resistance. It has been demonstrated that a defensin-like bacteriocin, laterosporulin10 produced by *Brevibacillus laterosporus* SKDU10, and HNP-1 exhibits synergistic activity with rifampicin (a frontline anti-Mtb drug) against pathogenic stain *Mycobacterium tuberculosis* H37Rv, and significantly reduces the MIC values of rifampicin [78,79]. This is interesting, especially against drug-resistant Mtb, when there is no efficient

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antibiotic available for 100% eradication. Nisin and its variants displayed synergism with various antibiotics (Ramoplanin, Polymyxin E, Clarithromycin, Amoxicillin, Penicillin, Streptomycin, Ceftiofur, Tetracycline, Ampicillin, Chloramphenicol, Kanamycin, Lincomycin, Rifampicin, and Vancomycin) against several pathogens including, MRSA, *P. aeruginosa*, and *S. suis* [80–83]. In one of the studies, the synergistic action of colistin, pediocin, or nisin Z is confirmed with ampicillin, rifampicin, and penicillin, which results in reduced MIC values against antibiotic resistance *P. fluorescens* [84]. In another study, melamine with ciprofloxacin was confirmed to have efficient synergistic action that eliminates fluoroquinolone-resistant *P. aeruginosa* [80]. Next, variants of indolicidin are confirmed to have a synergistic mechanism of action with tobramycin, polymyxin B, amikacin, and gentamicin to combat drug-resistant *P. aeruginosa* [85]. Further, arenicin-1, a marine AMP synergistically kills *S. dermis*, *S. aureus*, *E. coli*, and *P. aeruginosa* when used in combination with conventional antibiotics including erythromycin, ampicillin, and chloramphenicol. In addition to assisting in antibiotic absorption, arenicin-1 produces hydroxyl radicals in the cells thereby blocking bacterial growth [86]. Whilst there are various reports showing AMPs act synergistically with authorized antibiotics, further studies are required to determine the specific mechanisms of action involved (Table 4). The use of AMPs in combination with antibiotics provides a huge arsenal of new antimicrobials to fight against drug-resistant superbugs.

Table 4. Selected AMPs showing synergistic antimicrobial action with conventional antibiotics.

AMPs	Antibiotics	Target pathogen	References
Nisin	Ramoplanin, Polymyxin E, Clarithromycin, Amoxicillin, Penicillin, Streptomycin, Ceftiofur, Tetracycline	MRSA, *P. aeruginosa*, *S. suis*	[81–83]
Nisin Z	Ampicillin, Chloramphenicol, Kanamycin, Lincomycin, Penicillin G, Rifampicin, Streptomycin, Tetracycline, Vancomycin	Multi-drug resistant *P. fluorescens* LRC-R73	[80]
LL-37	Polymyxin B, Azithromycin	Multi-drug resistant *E. coli*, *P. Aeruginosa*, *A. baumannii*, *K. pneumoniae*	[174][175]
Ranalexin	Endopeptidase lysostaphin	MRSA	[176]
CATH-1, CATH-3, PMAP-36	Erythromycin	Pathogenic strain of *S. aureus*, *S. enteritidis*, and *E. coli*	[177]
Lacticin 3147	Polymyxin B	*S. aureus* 5247	[178]
Actagardine	Ramoplanin, Metronidazole, Vancomycin	*C. difficile*	[179]
Thuricin CD	Ramoplanin, Vancomycin	*C. difficile*	[179]
Subtilosin A	Clindamycin phosphate, Metronidazole, Lauramide alginate, Ester poly-lysine	Vaginal pathogen *G. vaginalis*	[180]
PsVP-10	Chlorhexidine	*S. mutans*, *S. sobrinus*	[181]
Colistin	Tobramycin, Azithromycin	*P. aeruginosa*, *A. baumannii*, *K. pneumoniae*	[175,182]
Cryptdin 2	Ampicillin	*S. typhimurium*	[183]
Arenicin-1	Erythromycin, Ampicillin, chloramphenicol	*S. dermis*, *S. aureus*, *E. coli*, and *P. aeruginosa*	[86]
Laterosporulin10	Rifampicin	*M. tuberculosis* H37Rv	[79]
Gaduscidin-1	Kanamycin, Ciprofloxacin	*P. aeruginosa* biofilms	[153]
Lactoferricin	Ciprofloxacin, Ceftazidim	*P. aeruginosa*	[184]

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Human defensin 5 (HD5)	Meropenem	*C. difficile*	[185]
Human neutrophil peptide-1 (HNP1)	Rifampicin	*M. tuberculosis* H37Rv	[78]
Human β-defensin 3 (HBD3)	Meropenem, Moxifloxacin, Piperacillin-Tazobactam, Tigecycline	*C. difficile*	[185]

6. Challenges with AMPs for Therapeutic Applications against Superbugs

For future development of AMPs as therapeutics, limitations must be addressed despite their promising features. Although AMPs showed promising bioactivities against infections caused by superbugs, many limitations or disadvantages have to be overcome (Table 5). Stability is the biological system is one of the major challenges for AMPs when they are exposed to biological fluids such as serum and saliva. Unfortunately, AMPs showed significantly reduced antimicrobial potency in biological fluids when compared to the non-physiological conditions. Especially, AMPs get inactivated by host and bacterial proteases during infection due to high salt concentrations, anionic proteins, and polysaccharides in biological fluids [87]. Further, several pros and cons are mentioned in Table 5 that have a great impact on the way AMPs are developed for therapeutic applications. Additionally, the production of AMPs at the commercial level is expensive when compared to conventional antibiotics. Also, the identification, extraction, isolation, and purification of AMPs is very challenging. Especially, in the case of bacterial AMPs which are considered an enormous source of potentially novel AMPs due to huge unexplored diversity, however, several posttranslational modifications and the presence of other secondary metabolites make their purification and characterization more challenging. Further, the size of AMPs is one of the major obstacles in the way of their development in pharmacological applications. Non-specific cytotoxicity and limited routs of delivery are the major challenges due to the large size of AMPs when compared to conventional antibiotics. Overall, AMPs are providing an excellent and huge arsenal to combat drug-resistant superbugs, however, there is a long way to go before they can be used in therapeutic settings while considering the cons associated.

Table 5. AMPs in comparison with conventional antibiotics, concerning pharmacological development for therapeutic applications.

Conventional antibiotics	**AMPs**
Not amenable to bioengineering	Highly amenable to bioengineering
Non-ribosomal synthesis	Ribosomal synthesis
Toxic	A good safety and tolerability profile
No immunomodulatory properties	Excellent immunomodulatory properties
High serum/ plasma stability (depends on the drug)	Low serum/ plasma stability
Usually high (depends on the drug)	Low half-life
Not degradable/persistent	Completely metabolized
Highly stable	Rapid clearance
Less diverse	Highly diverse (endless opportunities, especially in the case of bacterial AMPs)
Resistant to biofilms	Strong biofilm activities
Easy purification/ high yield	Complex purification/ low yield
Narrow spectrum/ Specific target	Broad spectrum/ multiple mechanisms of action
Highly prone to resistant development	Less prone to resistant development
High solubility	Low solubility
Good bioavailability	Depends on size
Not affected by digestive enzymes	Prone to digestive enzymes
High absorption	Poor absorption

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Many side effects	Not identified
Narrow range for pH and temperature stability	Highly stable at a broad range of pH and temperature
Cost-effective	High cost of production
Many administration routs	Limited administration routs due to protein degradation issues

7. Conclusions and Future Directions

Since the discovery of nisin, the first bacterially produced AMP, much debate has surrounded the possibility of AMPs being considered a new anti-infective. It is been more than 35 years since nisin was FDA-approved as a safe food preservative and consumed along with food while no side effects reported so far. Also, nisin has been tested in multiple studies against many drug-resistant bacteria, however still far from therapeutic applications. There are many AMP derivatives and mimetics under clinical trial that suggest the potential of AMPs against drug-resistant superbugs. Overall, a multidisciplinary environment is essential to the development of new AMPs for therapeutic or pharmacological applications, involving several research areas, such as microbiology, medicinal chemistry, synthetic chemistry, and preclinical studies. By facilitating such collaborative and multidisciplinary work, it is possible to develop AMP-based antimicrobials that are effective against drug-resistant superbugs. Even though the current methods and technologies could be improved, we have also discussed the synergistic action of AMPs with conventional antibiotics that might provide a completely new and efficient set of antimicrobial formulations to fight against superbug infections. Overall, AMPs could be a promising, efficient, and enormous arsenal for alternatives to conventional antibiotics to combat drug-resistant superbug infections, however, further, detailed studies are needed to address the ongoing issues.

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Author Contributions: SK and PB wrote the original draft. DR, SMM, and PB revised and edited the manuscript. PB proofread and edited the final draft. PB conceived the original idea and led the manuscript.

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