Antimicrobial natural products

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To prevent and treat diseases caused by the spread of microbes, humans have invented all sorts of effective antimicrobial substances. The most widely used antimicrobial substance is antibiotics. However, misuse of antibiotics can generate various negative effects, bacterial resistance, decreased immunity, and internal flora imbalance which can lead to endogenous infection. In addition, existing non-natural antibacterial substances each have their own limitations; using these substances in food may spoil the flavor, and an overuse can cause negative impacts on human health and even lead to cancer. Thus, non-traditional natural antibacterial substances, such as antimicrobial peptides and cyclic lipopeptide substances, have become the major focus for medical and nutrition research due to their broad-spectrum and strong antibacterial nature, reliable performance, and high nutritious values. In this chapter, we will categorically describe the new natural antimicrobial peptides which possess different antibacterial mechanisms from traditional antibiotics and are less prone to drug resistance, as well as the structure, properties and antibacterial mechanics of cyclic lipopeptide.

Keywords: natural antibacterial substances; antimicrobial peptide; cyclic lipopeptide

Peptides in general hold much promise as a major ingredient in novel supra molecular assemblies. They may become essential in vaccine design, antimicrobial chemotherapy, cancer immunotherapy, food preservation, organs transplants, design of novel materials for dentistry, formulations against diabetes and other important strategic applications. The growing challenge of microbial resistance emphasizes the importance of novel antibiotics or new assemblies for old ones. With emerging infectious diseases as a major public health problem, research on antimicrobial peptides (AMPs) is timely and much work has been devoted to AMPs over the last three decades with excellent reviews available. As of December 2014, over 100 new peptides have registered into the Antimicrobial Peptide Database, increasing the total number of entries to 2493. Unique antimicrobial peptides have been identified from marine bacteria, fungi, and plants. Bacteriocins are now widely used in food science to extend food preservation duration, inhibition of pathogen infection of animal diseases, pharmaceutical industry and in the medical world for treatment of malignant cancers.

1. Antimicrobial peptides

Antimicrobial peptides (AMPs) are gene-encoded, ribosomally synthesized polypeptides, a class of polypeptide that possesses a broad spectrum of anti-bacterial, anti-fungal, antiviral, anti-protozoa, and tumor cell suppression effects, and is produced by a variety of biological cells through a specific gene encoding induced by external conditions. In 1981, scientists named the first antimicrobial peptide as cecropin, which was also the first real discovery of antimicrobial peptides in a true sense. Many types of antimicrobial peptides have been subsequently found in a variety of organisms, with approximately 2000 types of antimicrobial peptides being isolated and identified around the world today.

They usually have the common characteristics: small peptide (30–60 aa), strong cationic (pI 8.9–10.7), heat-stable (100ºC, 15 min), no drug fastness and no effect on eukaryotic cell. The natural AMPs have been isolated and characterized from practically all-living organisms, ranging from prokaryotes to humans[1,2], and the AMPs produced by bacteria are also termed bacteriocins. AMPs usually work against bacteria that are closely related to the producer strains in prokaryotes, while they play a key role in innate immunity in eukaryotes [3, 4].

The significant advantage of AMPs rests in the global mechanism of their action, which is remarkably different from that of conventional antibiotics. Usage of AMPs will experience significant growth since more and more bacteria may develop the ability to resist conventional antibiotics due to the abuse of these drugs worldwide. This book will summarize the recent AMPs and their relative mechanisms from various origins. [5]

1.1 Origins of AMPs

AMPs can be commonly classified into four groups according to their origins, from insects, other animals, synthesis and microorganism. More than 1500AMPs of different origins have been reported to date [6].

1.1.1 AMPs from microorganism

This class of antimicrobial peptides is usually called bacteriocins, which are produced by bacteria, both Gram-positive and Gram-negative, and they are active mainly against closely related bacteria [7]. The first bacteriocins was found in *E.coli*, which is dated back to 1925.So far, within the bacteriocins produced by lactic acid bacteria, *Bacillus*, *Staphylococcus*, *Streptomyces*, *Streptoverticillium*, etc. have been reported [8].Although true for the majority of compounds, it is now evident that bacteriocins produced by lactic acid bacteria display bactericidal activity beyond

species that are closely related [9]. In addition, many lactic acid bacterias are used to start cultures or co-cultures in food production processes for increasing flavor and prolonging shelf-life, which have been done by many scientists.

Peptide bacteriocins produced by lactic acid bacteria (LAB) are categorized into three different classes according to their biochemical and genetic properties[10,11].Class I peptides are the lantibiotics, which are small, post-translationally modified peptides that contain unusual amino acids such as lanthionine (nisin). Class II includes unmodified bacteriocins which are subdivided into three subclasses, namely, class IIa (pediocin-like bacteriocins), class IIb (two-peptide bacteriocins), and IIc (other [i.e., non-pediocin-like], one-peptide bacteriocins). The designation pediocin-like bacteriocins refers to pediocin PA-1/AcH, which was the first class IIa bacteriocin characterized [12,13]. The class III peptides are thermosensitive proteins [14].The inhibitory spectrum of LAB bacteriocins is relatively narrow compared to that of the antimicrobial peptides produced by eukaryotic cells, such as pleurocidin, which is active against both gram-negative and gram-positive bacteria [15]. On the other hand, LAB-produced bacteriocins kill bacteria at much lower concentrations than eukaryotic antimicrobial peptides, probably because they interact with a specific receptor present on target cells [16].

Sometimes, however, the isolation from natural sources is a labor intensive and time-consuming process, and therefore does not provide an efficient method to obtain peptides in large amounts, and large quantities of highly purified peptides are required to meet the needs of basic research and clinical trials. Currently, a less-expensive and more-effective method of active production is required in order to commercialize the bacteriocins. The expense of peptide synthesis limits this form of production to small quantity applications, such as laboratory experimentation. A solution to this problem is to utilize the recombinant methods to heterologously express the antibacterial peptides in bacteria in inactive form [16].Many host cells have been selected for expression of AMPs but *Escherichia coli* has been established as one of the most porecombinant bioreactors due to its fast growth rate and well established expression systems. However, it is difficult for small peptides to be expressed in engineered bacteria at high levels, especially the toxic peptides and be recovered from the expression system. Recently, some people have developed methylotrophic yeast. *Pichiapastor* is as an excellent host for the large-scale expression of proteins from different sources [17].

1.1.2 AMPs from animals

Antimicrobial peptides were initially discovered in invertebrate sand later also have been described in vertebrates. These peptides show diverse sequences, structures and target specificity. The genes encoding AMPs are expressed in numerous tissue and cell types from a wide variety of different species including mammals, amphibians and fish, except for insects. In higher vertebrates, many of these peptides have been found to be associated with epithelial layers or are synthesized and secreted by circulating neutrophil sand/or tissue mast cells (MCs) [18].

1.1.3 AMPs from insects

With roughly one million characterized species, insects represent the largest class within the animal kingdom. Today, more than 200 such peptides have been identified in insects. Insect antimicrobial peptides are known to play an important role in humoral defense reactions. AMPs are synthesized in the fat body (insect's functional equivalent of the mammalian liver) during systemic response against pathogens, and they are then secreted in to hemolymph [19, 20].These peptides are classified into five major groups based on their amino acid sequences and antibacterial activities: 1) cecropins, is an inducible antibacterial peptide that is found in the hemolymph of the pupae of *H.cecropia*, was the first insect antimicrobial peptide discovered [21]. Maturececrop in peptides lack cysteine residues, are 35–39 amino acids in length, and form two linear α-helices connected by a hinge, which integrate into the acidic cell membranes of bacteria leading to their disruption [22,23,24]. Cecropins constitute one of the most extensively studied antimicrobial polypeptides among them any that are synthesized by insects as components of their host defense systems against bacterial infection [25];2) insect defensins, is form a unique family of cysteine-rich cationic and structured polypeptides with three or four disulfide bridges. Solution structure of the defensin-like peptide was determined and the primary structural similarity between members of the family suggests that the global fold is robust and that the nature of the side-chains determine the functional specificity. The antimicrobial activity of defensins is salt dependent [26]. They are mainly effective against Gram-positive bacteria and also have potent activity against some Gram-negative bacteria, fungi, yeasts, and protozoa [27,28]; 3) proline-rich peptides, these AMPs are strikingly rich in glycine residues (14–22%), and this richness has a major influence on the tertiary structure of these peptides and hence on their mode of action, such as Sarco toxin IIA, Hymenoptaecin, Attacin, Diptericin and Coleoptericin; 4) glycine-rich peptides and lysozymes, which are isolated from mammals and insects, are predominantly active against Gram-negative bacteria, including a wide range of plant-associated bacteria and some human pathogens [29]. Unlike other types of AMPs, their mode of action does not involve the lysis of bacterial membranes but entails penetration into susceptible cells, where they then act intracellularly.

1.1.4 AMPs from synthesis

To induce the endogenous production of these peptides, which would avoid the possible toxicity and adverse systemic reactions, as well as the difficulty to deliver them in integral form to the desired sites of action [30]. Generation of synthetic antimicrobial peptides with high activity represents a new challenge in the development of novel antibiotics [31]. So far, many AMPs have been synthesized , such as ABP-CM4,L1,Penetratin,BP100,A3-APO,L-Bac7(1–35) etc., have all been reported.

1.2 Mechanisms of AMPs action

The mechanism of the antimicrobial activities of AMPs has been studied for some selected peptides. Functions of these peptides vary from membrane permeabilization to actions on an array of intracellular target molecules including immuno-modulatory activities. The peptides can be membrane-disruptive resulting in cell lysis, or, alternatively, membrane interaction can lead to the formation of transient pores and the transport of peptides inside the cell, bringing them into contact with intracellular targets [32, 33].

1.2.1 Ability to interact with membranes

The ability to interact with membranes is a classical countenance of AMPs, and the feature is membrane permeabilization. The peptides were facilitated by notable hydrophilic positively charged domains, interact with the negatively charged microbial surfaces, and head groups of bilayer phospholipids leading to cell membrane penetration. Therefore, the transmembrane potential and pH gradient are destroyed, the osmotic regulation is affected and respiration is inhibited. As indicated by the previous studies and the literature, peptide-membrane interactions play a crucial role in determining the activity of these membrane-active AMPs [34]. Currently, scientists have found that there are at least four different commonly used models describing possible AMP modes of action in Fig. 1[5]

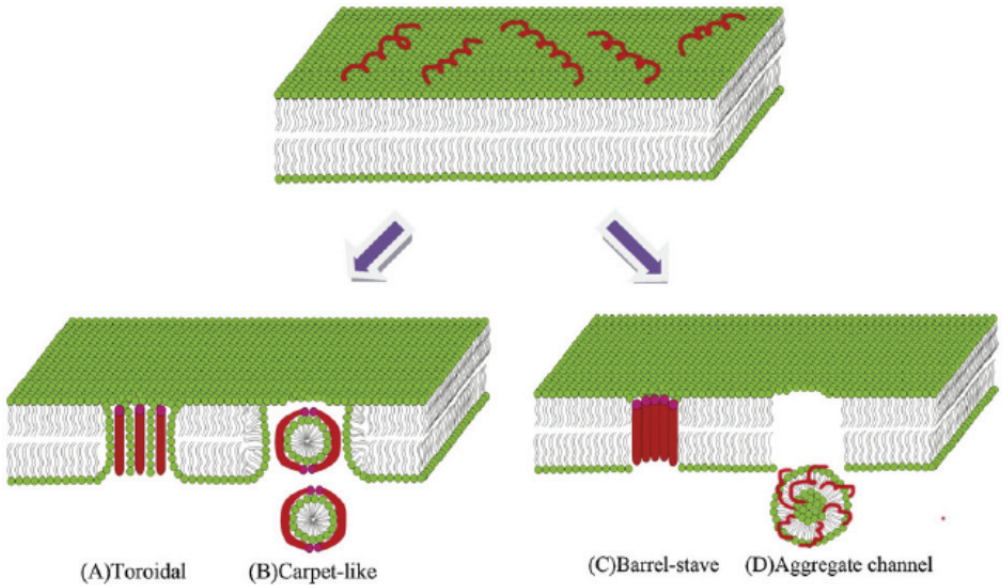

Fig. 1 Mode of action of AMPs. (A) In toroidal model, the peptides aggregate and tempt the lipid monolayers to bend continuously through the pore so that both the inserted peptides and the lipid head groups line the water core. (B) In carpet model, peptide chains covers the surface of membranes in a carpet-like manner and dissolves it like a detergent beyond a threshold concentration for which a high peptide-to-lipid ratio is required. (C) In barrel-stave model, the peptides bind to the cell membrane, then the peptides themselves insert into the hydrophobic core of the membrane forming a pore, causing leakage of cytoplasmic material and death of the cell. (D) In aggregate channel model, the peptides insert into the membrane and then cluster into unstructured aggregates that span the membrane. These aggregates are proposed to have water molecules associated with them providing channels for leakage of ions and possibly larger molecules through the membrane.

1.2.2 Ability to inhibit or disturb the intracellular targets

Besides the ability to interact with membranes, there is increasing evidence to indicate that AMPs have other intracellular targets. They can have multiple intracellular targets – they can bind DNA,RNA and proteins, inhibit cell wall synthesis, and DNA, RNA or protein synthesis. Furthermore, peptides can interfere with bacterial cytokinesis by cell filamentation provoked by several types of AMPs in vitro or in vivo. They have developed unique mechanisms to translocate to the cytoplasm, in order to alter the cytoplasmic membrane septum formation, inhibit cell-wall synthesis, inhibit nucleic acid synthesis, inhibit protein synthesis or inhibit enzymatic activity [35,36].

1.3 Application of AMPs

AMPs are gaining attention as antimicrobial alternatives to chemical food preservatives and commonly used antibiotics. They have a very good future for development particularly in pharmaceuticals industry and food additive.

1.3.1 Application in pharmaceuticals industry

Since the first antibiotic penicillin was discovered in 1928 by Alexander Fleming, many discovered antibiotics are applied to treat pathogens. Antibiotics were first approved by USFDA in1951, and used in animal feed, which significantly reduced the number of deaths due to bacterial infection cases. However, the problem with multiple drug resistance pathogens has become increasingly serious, due to concerns regarding the abuse of antibiotics. Pharmaceuticals industry is the most important market where AMPs are used, particularly given the severe resistance of antibiotics. There is an urgent need to look for antibiotic substitutes around the world. Nowadays, many scientists have made achievements in this field and went on further to the clinical application process. In addition to direct antimicrobial activity, these peptides participate in many cellular functions, including chemo taxis, wound healing and even determination of canine coat color. They can be used to kill bacteria, fungi, parasites, virus and cancer cells [37, 38]. And recombinant magaininis currently are in phase-three clinical trials.

In cancer therapy, AMPs have shown promise as anticancer therapeutics, with some research indicating that bacteriocins show activity against tumor cells. Considering that bacteriocins are naturally and legally added in foods, bacteriocins may be suitable as a potential anti-tumor drug candidate. Studies even demonstrate that the bound AMP can lyse liposomes and induce apoptosis in vitro and significantly reduce tumor size in vivo mouse studies [39].Some bacteriocins, such as pore-forming colicin A and E1 inhibit the growth of one human standard fibroblast line MRC5 and 11 human tumor-cell lines [40].On the other hand, AMPs can coat medical devices as a nonaggressive bio disinfectant to prevent adherence and biofilm formation of micro-organisms in immune compromised patients. For instance, the systemic application of radio labeled AMPs for infection detection and treatment or prophylactic application of bone and soft-tissue infections has been demonstrated. Radio labeled AMPs could be valuable treatment option for infections related to the development of invasive endocarditis, infected prosthetics, and even meningitis, all of which can be valuable in the diagnosis of infection induced amyloid aggregation in Alzheimer disease. In addition, recent studies suggest that vaccination of some AMPs can be a promising strategy for diseases. The result indicates thatβ-defensin 2 may be used for the development of immunotherapy for the intervention of melanoma [41]. AMPs are hoped to be developed into vaccine for human or other animals.

1.3.2 Application in Agricultural

AMPs are used not only for human disease, but also for plant disease control. Currently, because chemical fungicides may hurt the ecological environment and human health due to their long lasting effects and accumulation in the human body, AMPs of low toxicity became a good candidate for plant disease control. For example, application of Ace-AMP1 on tomato leaves show that the recombinant protein conferred strong resistance to the tomato pathogen *A. solani* and could be used as an effective fungicide [42].Many gene constructions with coding sequences of AMPs have been expressed in plant leading to various extents of protection against fungal and bacterial pathogens, and insect peptides are especially suitable because of their exceptionally broad antimicrobial potential [43]. The efficacy of AMPs against pathogens is prescreened by in vitro assays, and promising AMP candidates are introduced as transgenes into plants [44].

Bacteriocins also can be added to animal feed as an anti-pathogen additive to protect livestock against pathogen damage.For example, when nisin-supplemented bird diet was used to feed broiler chickens, a reduced number of *Bacteroides* and *Enterobacteriacae* in ileal digesta of nisin-supplemented chickens were found. The action of nisin was similar to that of salinomycin. After a 35-day growth, the average body weight gain of nisin-supplemented (2700 IU nisin/g) chickens was 1918 g/bird, which was higher than the 1729g of non-nisin supplemented or the 1763g of salinomycin-supplemented chickens [45]. Many results suggest that bacteriocins demonstrate potential when applied to replace antibiotics in poultry and other animal feeds.

1.3.3 Application in foodtechnology

In order to extend shelf-life, antibiotics or food preservative are incorporated (e.g., nitrite and sulfur dioxide) into foods to delay microbial growth and possible corruption. However, most commercial preservatives are developed via chemical synthesis, and long-term consumption of the synthetic preservatives may have an adverse impact on the human body. The demand for more natural antimicrobials have driven food scientists to investigate the effectiveness of inhibitory compounds such as organic acids, essential oils, bacteriocins, and extracts from plants, and insects remain to be explored [46]. Due to the sensitivity of bacteriocins to some proteases, harmless bacteriocins are possibly digested, thus, un-functional small peptides and amino acids are bacteriocin-loaded foods digested in the gastrointestinal tract. Bacteriocins are therefore considered as basically safe food additives after intake by the gastrointestinal system. AMPs have the potential to be used as food preservatives.

Bacteriocins are natural food additives due to the bacteriocin producing bacteria presence in many types of foods since ancient times, such as cheeses, yogurts, and Portuguese fermented meat. In food technology, nisin is produced by *Lactococcuslactis* and was the first antibacterial peptide found in LAB [47]. It is also the first commercial bacteriocin used as a food preservative against contamination by microorganism, which is marketed as Nisaplin. It is the only bacteriocin approved for utilization as a preservative in many foods by the U.S. Food and Drug Administration (USFDA), and licensed as a food additive in over 45 countries. In Asia, pediocin PA-1will soon become another commercially available bacteriocin, marketed as Alta2341, which inhibits the growth of *Listeria monocytogenes* in meat products [48].

Moreover, bacteriocins are now introduced as foods additives, such as nisin, which is used in kimchi, mashed potatoes, and fresh-cut products. This has been successful for in situ production of pediocin in cheese [49,50]. The in situ production of pediocin by the genetically modified starter culture reduced the numbers of *L. Monocytogenes* from a starting population of 3.65 log CFU/g to ＜1.0 log CFU/g after 92 days of ripening. Pediocin (as ALTA 2341; 3,000AU/g), combined with low-dose irradiation (2.3 kGy) had a greater inhibitory effect on the growth of *L. monocytogenes* on frankfurters [51]. Enterocin AS-48 is used in cider, fruit and vegetable juices, and canned vegetables for contamination inhibition. Enterocin CCM4231 and EJ97 are used in soy milk and zucchini purée for suppression of contamination, respectively.

In many food products, such as traditional European cheeses, the milk used in the manufacturing process is easily contaminated with animal excrement. The bacteriocinogenic *Enterococci* as starter cultures or co-cultures can be used for reducing microbiota contamination. Settanni and Corsetti [48] reviewed bacteriocinogenic LAB strains as a co-culture, protective, or starter cultures in fermented and non-fermented vegetables, such as olives, sourdough, miso, sauerkrauts, refrigerated pickles, and mungbeansprouts. AMPs can also be quality booster for food as they can activate mechanisms of cellular and adaptive immunity. Some AMPs, such as LL-37, can function as potent immune regulator acting as chemokines and/or inducing cytokine production [52]. An alternative mechanism for applying class IIa bacteriocins to foods is to deliver them as part of the packaging film. Antimicrobial packaging films have been developed for the delivery of nisin and pediocin[53,54].

2. Cyclic Lipopeptide

The continuing emergence and worldwide spread of multi-resistant human pathogenic bacteria, particularly in hospital settings, requires new antibacterial compounds, in addition to improved therapeutic regimens. Besides antimicrobial peptides mentioned above, natural cyclopeptides(CLP) are also hot spots in chemical and pharmaceutical fields because of the wide spreading bio-resources, complex molecular structures and various bioactivities.CLPs are composed of a lipid tail linked to a short oligo peptide which is cyclized to form a lactone or lactam ring either between two amino acids in the peptide chain or between an amino acid and an amino- or hydroxyl-group bearing fatty acid moiety. Bio-producers of cyclopeptides distribute over almost every kingdom from bacteria to plants and animals. Many cyclopeptides contain non-coded amino acids and non-pepditic bonds. CLP has an immense structural diversity arises from differences in the length(C6-C18) and composition of the fatty acid moiety (β-OH groups, iso-, anteiso-methyl branched forms) and from variations in the number (2-25 AA), type (basic, acidic, aromatic, aliphatic, cyclic, OH/SH-containing, α- orβ-type), and configuration (D, L) of the amino acids in the peptide portion.

Since the 1980s, Lilly Research Laboratories (Surrey, UK) reported the isolation of a series of novel antibiotics from *Streptomyces roseosporus* NRRL 11379 culture broth. Many of these natural products are either already marketed or in advanced stages of clinical development, such as polymyxin, daptomycin are being used in clinics; amphomycin, ramoplanin and fusaricidins are in the stages of clinical trial or as a candidate for drug research in Table 1.

Table 1 Cyclic lipopeptides which are applied already in the clinics or are currently in preclinical development or clinical trials.

Compound	Producer	Molecular weight	Target, mode of action	Spectrum	Phase; development	Company
polymyxin	*Bacillus polymyxa*	1188	outer membrane	Gram -	marketed	Parkedale Pharmaceuticals
daptomycin	*Streptomycesroseosporus* NRRL11379	1620	membrane	Gram+	marketed	Cubist
amphomycin	*Streptomyces canus*ATCC 12237	1290	C55-P; peptidoglycan biosynthesis	Gram+	preclinical	Migenix
ramoplanin	*Actinoplanes*sp. ATCC 33076	2254	Lipid II,peptidoglycan biosynthesis	Gram+	approved	Nanotherapeutics
fusaricidins	*Paenibacillus*sp.	883-947	still unknown	Fungi, Gram+	candidate for drug research	——

2.1 Polymyxin

Polymyxin is a group of basic decalipopeptides with a remarkable content of the non-proteinogenic amino acid 2,4-diaminobutyric acid. Generally, seven amino acids form a peptide cycle, and a fatty acid is fused to the C-terminus of the three exocyclic amino acids. 6-methyl-octanoic acid or 6-methyl-heptanoic acid can be found as lipid side chain moiety. Two representatives, polymyxin B (i.e. a mix of polymyxin B1and B2) and E (i.e. a mix of polymyxin E1and E2, syn. colistin A and B), originally obtained from *Bacillus polymyxa* and *Bacillus colistinus*, respectively, are already in clinical use. Polymyxin B is commonly administered as water soluble sulfate salt, while polymyxin E (colistin) is formulated as methanesulfonate sodium salt, an inactive drug which undergoes hydrolysis in vivo to form the active drug polymyxin E [55].

Polymyxin show little activity against Gram-positive and anaerobic bacteria, but are potently bactericidal towards many Gram-negatives including clinically relevant *pseudomonads, enterobacteria* and *Acinetobacter* species [56, 57].Since 1959, polymyxin E has been used for the treatment of Gram-negative bacterial infection. However, in the 1970s, clinical use of polymyxin E and polymyxin B was limited due to their seriousnephro toxicity and neurotoxicity after parenteral administration. Together with the emergence of less-toxic amino glycosides and other antipseudomonal agents [58], itsparenteralusewasalmostcompletelyabandonedinthe1980s.The revival of polymyxin has been coming since the mid-1990s, due to the lack of novel antibiotics against prevalent MDR Gram-negative bacteria [59]. Recent studies demonstrate that toxicity can be less severe and will be less frequently observed if a different dosing scheme is employed, and that polymyxin possess an acceptable safety profile if the doses are adjusted to the renal function. Therefore, polymyxin has been reintroduced as the last-line therapy for the treatment of serious infections caused by multidrug-resistant Gram-negative superbugs, particularly *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

The antibacterial mechanism of polymyxin involves, as a first step, a specific interaction of the pentacationic peptide ring with lipopolysaccharide (LPS) of the anionic outer membrane, a target structure which exists solely in Gram-negative bacteria. By binding to LPS, polymyxin competitively displaces calcium and magnesium bridges that stabilize the outer leaflet of the outer membrane [60]. Furthermore, the short lipid side chain also interacts with LPS molecules, which facilitates the insertion of the CLP into the outer membrane. These combined interactions perturb the integrity of the membrane, further facilitate the import of polymyxis themselves (self-promoted uptake) and result in the transient leakage of ions, molecules and small proteins, which finally leads to cell death [60,61]. In addition, polymxyins exert a neutralizing effect on on endotoxins.

2.2 Daptomycin

Daptomycin is a cyclic lipopeptide produced by *Streptomyces roseosporus* using nonribosomal peptide synthetases [62]. Daptomycin consists of 13 amino acids: 10 C-terminal residues that form a ring closed by an ester bond and a 3-amino-acid exocyclicside chain with a terminal tryptophan linked to the fatty acyl residue, decanoic acid [63]. Several of the amino acid residues that make up daptomycin are nonstandard, including three D-amino acids, ornithine, 3-methyl-glutamic acid, and kynurinine.

Daptomycin has a unique mechanism of action, not completely understood, involving a calcium-dependent dissipation of membrane potential leading to the release of intracellular ions from the cell and bacteria death. The initial binding event between daptomycin and the target Gram-positive membrane has not yet been defined but may be via interaction with the bacterial membrane lipid, phosphatidylglycerol (PG). The activity of daptomycin is strictly dependent on the presence of physiological levels of Ca^{2+}, which induce conformational changes in daptomycin [64,65]. These changes also facilitate daptomycin oligomerization and membrane insertion [66,67], possibly by increasing exposure of hydrophobic moieties in the molecule [65]. Daptomycin is an anionic molecule, and in addition to the effect on daptomycin's structure, calcium ions are believed to allow daptomycin to overcome the charge-charge repulsion between daptomycin and the anionic phospholipid heads of the bacterial membrane [66].Insertion of the daptomycin oligomers into the Gram-positive membrane are thought to generate an ion conduction structure in a process akin to that of the pore-forming toxins, which oligomerize in target membranes to form ring-like pores[68].

Daptomycin (originally designated LY146032) is one of the few antibiotics that were approved during the past decade and was successfully launched for the treatment of complicated skin and skin-structure infections, right-sided endocarditis and bacteremia caused by Gram-positive pathogens, including methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Staphylococcus aureus* (VRSA) and *enterococci* (VRE). Although initially considered to be too toxic, a once-daily administration scheme markedly reduced adverse effects [69].

2.3 Amphomycin

Amphomycin has first been described in the early 1950s and is produced as a secondary metabolite by *Streptomyces canus*ATCC12237. In the following years a series of structurally closely related peptides has been characterized, which can be basically divided into three families – the friulimicins, amphomycins and glycinocins (laspartomycins). The structural features common to these lipopeptides include the macrocyclicdeca peptide core and a lipid tail, interlinked by one exocyclic amino acid [70].

Early studies with amphomycin indicated that lipopeptide may interfere with bacterial cell wall biosynthesis pointing towards the first membrane associated step as a target reaction, i.e. the transfer of the soluble UDP-activated cell wall precursor to the membrane carrier, although further details were not reported [71]. More recent studies with amphomycin and friulimicin revealed that both peptides form a specific complex with the essential lipid carrier undecaprenol-phosphate (C55-P) in a Ca^{2+}-dependent manner, without affecting membrane integrity[72,73].

An analogue of amphomycin, MX-2401, demonstrates broad-spectrum bactericidal activity against Gram-positive organisms, including strains resistant to vancomycin, macrolides, penicillin, methicillin, gentamicin, and other marketed antimicrobials [74, 75]. In the animal models of infection, MX-2401 exhibits potent dose-dependent activity against Gram-positive organisms, including resistant strains, with an excellent ability to kill bacteria in neutropenic mice [76]. MX-2401is a semi-synthetic analog of amphomyc in that entered clinical trials with BioWest Therapeutics for the treatment of serious Gram-positive infections including hospital-acquired pneumonia [77]. MX-2401 is rapidly bactericidal and was effective in several models of infection in pre-clinical studies.

2.4 Ramoplanin

Ramoplanin, originally named A-16686, was isolated by a research group from GruppoLePetit (Biosearch Italia, Gerenzano, Italy) in 1984 as an antibiotic complex from the fermentation broth of *Actinoplanes* sp (ATCC 33076). Ramoplanin A1-A3 [78], that basically differs in the structure of the fatty acid substituent. Members of the ramoplanin family all share an identical 17-mer peptide ring structure, composed of a number of unusual and β-hydroxylated amino acids. Characteristically, the L-hydroxyphenylglycine (Hpg) residue in position 11 of the ring core is glycosylated by a dimannosyl moiety [79].

Ramoplanin contains an N-acyl chain linked to Asn-1 [80, 81] which may insert into the bacterial membrane phospho-lipidbilayers, as is the case for the lipoglycopeptide teicoplanin [82]. Recent studies have proposed that ramoplanin forms an intimate and highly amphipathic dimer in the membrane environment and binds to bacterial membranes via its hydrophobic interface [83,84].

Ramoplanin A2, the most abundant component within the mixture of analogues, is active against a wide range of Gram-positive pathogens and has been fast-tracked by the FDA as a treatment for multi resistant *Clostridium difficile* associated diseases of the gastrointestinal tract. Systemic administration of Ramoplanin A2 is currently limited due to its hydrolytic instability and its tendency to aggregate in the bloodstream [85].

2.5 Fusaricidins

Fusaricidins or LI-Fs [86,87] are a new family of cyclic lipodepsipeptide antifungal antibiotics isolated from *Paenibacillus* sp. [88,89,90]. Common structural characteristics of these natural products are the peptide ring consisting of six amino acid residues, three of which, L-Thr1, D-*a*Thr4, D-Ala6 are conserved throughout the family, and a 15-guanidino-3-hydroxypentadecanoic acid attached via amide bond to the N-terminalThr1. Fusaricidins/ LI-Fs are cyclized by a lactone bridge between *N*-terminal Thr1 hydroxyl group and C-terminal D-Ala6.

Fusaricidins/LI-Fs' mode of action is still unknown. Total synthesis of fusaricidin A/LI-F04a natural product using a combination of solid-phase and solution synthetic approaches was recently reported by Cochrane et al. Two groups, Jensen et al.[91]and Park et al.,[92]have reported identification and isolation of putative fusaricidin/LI-F synthetase gene, fusA, from *Paenibacillus polymyxa*, opening the possibility for the development of biosynthetic approaches toward this family of naturally occurring cyclic lipodepsipeptides and their analogs.

Among isolated fusaricidin/LI-F antibiotics, fusaricidin A or LI-F04a, [93] showed the most promising antimicrobial activity against a variety of fungi, including clinically important *Candida albicans* and *Cryptococcus neoformans*, and against Gram-positive bacteria such as *S. aureus* (MICs ranging from 0.78–3.12 μg/ml). Fusaricidins/LI-Fs did not, however, show activity against Gram-negative bacteria.[88,89]

3. Conclusions

We anticipate continued efforts in the development of potential applications of antimicrobial peptides, including peptide production methods. Peptide engineering, formulation, and delivery technologies may further expand the horizon of antimicrobial peptides in benefiting human beings [94]. Drug resistance is a major problem in antibacterial chemotherapy, and AMPs may solve this problem in the future. AMPs, including CLP are currently in the spotlight as potential candidates to overcome bacterial resistance to conventional antibiotics. Many AMPs have multi-functions such as antibacterial, antifungal and anti-cancer activities. Because they are able to rapidly kill broad range of infectious agents and modulate both innate and adaptive immunity, considerable efforts have been made to exploit their therapeutic potential. Such applications can vary from medical surface cleaning, water quality monitoring and disinfection, sterile surface materials, to new drugs for infectious diseases [95, 96].

Furthermore, environmental conditions prompts us to find or produce more kinds of AMPs to kill more and more pathogenic bacteria since no AMPs have been found to cope with them at present [97]. Eventually, AMPs may become useful therapeutic tools, since they have shown to fight not only bacterial, but viral, and fungal infections. Additionally,

their antimicrobial activity is exerted in several ways because of their multifunctional properties; this characteristic makes the development of resistance by microorganisms more difficult. Currently, our further research will advance knowledge within the field and highlight the potential of antimicrobial peptides as therapeutic agents.

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