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Chapter

Peptides with Therapeutic Potential against *Acinetobacter baumannii* Infections

*Karyne Rangel and Salvatore Giovanni De-Simone*

**Abstract**

Antibiotic poly-resistance (multi drug-, extreme-, and pan-drug resistance) is a major global threat to public health. Unfortunately, in 2017, the World Health Organization (WHO) introduced the carbapenem-resistant isolates in the priority pathogens list for which new effective antibiotics or new ways of treating the infections caused by them are urgently needed. *Acinetobacter baumannii* is one of the most critical ESKAPE pathogens for which the treatment of resistant isolates have caused severe problems; its clinically significant features include resistance to UV light, drying, disinfectants, and antibiotics. Among the various suggested options, one of the antimicrobial agents with high potential to produce new anti-*Acinetobacter* drugs is the antimicrobial peptides (AMPs). AMPs are naturally produced by living organisms and protect the host against pathogens as a part of innate immunity. The main mechanisms action of AMPs are the ability to cause cell membrane and cell wall damage, the inhibition of protein synthesis, nucleic acids, and the induction of apoptosis and necrosis. AMPs would be likely among the main anti-*A. baumannii* drugs in the post-antibiotic era. Also, the application of computer science to increase anti-*A. baumannii* activity and reduce toxicity is also being developed.

**Keywords:** RAMP, *Acinetobacter baumannii*, resistance, action mechanism

**1. Introduction**

Microbial infections contribute substantially to global mortality trends. Antibiotic resistance is one of the biggest challenges for the clinical sector, industry, environment, and societal development. Unfortunately, the emergence of drug-resistant pathogens is rapidly growing, and the world is heading toward the post-antibiotic era [1, 2]. Bacteria possess three defined types of antimicrobial resistance: intrinsic, acquired, and phenotypic or adaptive resistance [3–11]. Although there are multiple causes of the resistance phenomenon, it is considered that antimicrobial resistance is an old natural phenomenon when microbes are exposed to antimicrobial drugs, with an accelerated evolution triggered not only by the abusive use of antibiotics but also such as wrong choices, inadequate dosing, and poor adherence to treatment guidelines that contribute to the increasing antimicrobial resistance selection [12, 13]. In addition, antibiotic treatment for difficult-to-treat multidrug-resistant bacterial infections is limited [13]. ESKAPE pathogens
(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, A. baumannii, Pseudomonas aeruginosa, Enterobacter species) are among the most common opportunistic pathogens in nosocomial infections [14]. The abbreviation ESKAPE reflects the ability of these organisms to “escape” killing by antibiotics and defy eradication by conventional therapies, which accounts for increased morbidity and mortality for improved resource utilization in healthcare [15]. One of the ESKAPE pathogens responsible for nosocomial and community-acquired infections is A. baumannii, a Gram-negative, non-motile, non-fermentative, and non-sporulated bacterium Moraxellaceae family [16] that is part of the Acinetobacter calcoaceticus–A. baumannii complex (Acb). Currently, six species, namely A. calcoaceticus, A. baumannii, A. pittii, A. nosocomialis, A. seifertii, and A. lactucae (a later heterotypic synonym of A. dijkshoorniae) [17, 18], belonging to the Acb complex have been associated with human diseases [19]. Even though these species differ in antimicrobial resistance, pathogenicity, and epidemiology [20], the Acb complex is genetically and physiologically highly related, making it difficult to distinguish them phenotypically with standard laboratory methods [21]. Of all the species in the Acb complex, A. baumannii is the most widespread in hospitals, even associated with an increased risk of morbidity, mortality, high treatment costs, and long periods of hospitalization [22]. A. baumannii causes various infections, including wounds, skin, urinary tract infections, pneumonia, meningitis, and bacteremia [23, 24]. There are several nomenclatures in the literature based on the number of resistance classes of antibiotics. According to Magiorakos et al. (2012), a multidrug-resistant (MDR) strain is resistant to at least one antimicrobial in more than three classes of antimicrobials; and extensively drug-resistant (XDR) strain is one resistant to at least one antimicrobial in all classes of antimicrobials except two or fewer types, and a pan drug-resistant (PDR) strain is resistant to all antimicrobial agents [25]. A. baumannii has globally emerged as a highly troublesome nosocomial pathogen revealing MDR, XDR, and PDR phenotypes, and unfortunately, evidence has shown an increased A. baumannii antibiotic resistance over time [26]. A. baumannii is one of the most critical and fearful pathogens with treatment options limited due to many aspects: its extended virolome and resistome, evasion of the host’s immune effectors, ability to survive in extreme environmental conditions, to grow in biofilms, and to switch to latent growth forms with a minimal metabolic rate [27, 28]. The World Health Organization (WHO) has recently published a report, which also highlighted A. baumannii resistant to carbapenems (CRAb) [29, 30] which was classified in the group of “priority 1 for research and develop new antibiotic treatments” and was considered as a “critical” pathogen [31]. One of the antimicrobial agents with high potential for research and development of anti-Acinetobacter drugs is the antimicrobial peptides [32]. This chapter aimed to review the powerful antimicrobial peptides described with activity against A. baumannii multiresistant.

2. Antimicrobial peptides

Antimicrobial peptides (AMPs) may represent an alternative to current antibiotics in MDR A. baumannii ESKAPE pathogen [33]. AMPs (also known as host defense peptides) are small polycationic peptides naturally produced by living organisms with both microbicidal and immunomodulatory activities, acting as a primary barrier against pathogens, including protozoa, viruses, bacteria, archaea, fungi, plants, and animals as a part of innate immunity system [34–41]. However, the computational design of synthetic AMPs with improved activity is also being developed [42]. They interact with cell membrane through electrostatic
interactions, causing the inhibition of protein and nucleic acid synthesis and final cellular lysis by apoptosis and necrosis [43–44]. In addition to the antimicrobial properties, some AMPs have other activities, such as anticancer antioxidant, wound healing, immunoregulatory [38, 45, 46]. AMPs also play an essential role in regulating immune processes such as activating and recruiting immune system cells, angiogenesis, and inflammation [47]. AMPs are amphipathic molecules with a positive electric charge, varying molecular weight, and containing about 11–50 amino acid residues [47, 48]. AMPs are classified into α-helical, β-sheet, and extended peptide families [49–51] and interact with the membranes initially through electrostatic and hydrophobic interactions (Figure 1), accumulating at the surface and self-assemble on the bacterial membrane after reaching a particular concentration [52, 53].

At this stage, various models have been proposed to describe the action of AMPs. The models can be classified under two broad categories: transmembrane pore (TMP) and non-pore models (NPM), and the TMP can be further subdivided into the barrel-stave pore and toroidal pore models. In the barrel-stave model, the AMPs are initially oriented parallel to the membrane but eventually insert perpendicularly in the lipid bilayer [54] (Figure 2A), thus promoting lateral peptide-peptide interactions, like that of membrane protein ion channels. Peptide amphipathic structure (α and/or β sheet) is essential in this pore formation mechanism as the hydrophobic regions interact with the membrane lipids and hydrophilic residues from the lumen of the channels [55, 56]. A unique property associated with AMPs in this category is a minimum length of ~22 residues (α helical) or ~8 residues (β sheet) to span the lipid bilayer. Only a few AMPs, such as alamethicin [57], pardaxin [58, 59], and protegrins [55], have been shown to form barrel stave channels.

Furthermore, in the toroidal pore model, the peptides also insert perpendicularly in the lipid bilayer, but specific peptide-peptide interactions are not present [57]. Instead, the peptides induce a local curvature of the lipid bilayer with the pores partly formed by peptides and partly by the phospholipid head group (Figure 2B). Thus, the dynamic and transient lipid-peptide supramolecule is known as the “toroidal pore.” The distinguishing feature of this model compared to the barrel-stave pore is the net arrangement of the bilayer. In the barrel-stave pore, the hydrophobic and hydrophilic sequence of the lipids is maintained, whereas, in toroidal pores, the hydrophobic and hydrophilic arrangement of the bilayer is

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**Figure 1.** Interaction of cationic AMPs with eukaryotic and bacterial membranes. Images were created using BioRender.com.
disrupted, thus providing alternate surfaces for the lipid tail and the lipid head group to interact with. Furthermore, as the pores are transient upon disintegration, some peptides translocate to the inner cytoplasmic leaflet entering the cytoplasm and potentially targeting intracellular components [60]. Other features of the toroidal pore include ion selectivity and discrete size [61]. Several AMPs such as magainin 2 [62], lacticin Q [62], aurein 2.2 [63], and melittin [57, 62] have been shown to form toroidal pores. In addition, the type of pore started by aurein 2.2 has been shown to depend on the lipid composition: In a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)/1-palmitoyl-2-oleoyl-sn-glycerol-3-phospho-(1'rac-glycerol) POPG (1:1) membrane model, the peptides induce toroidal pores, whereas in a 1,2-dimyristoyl-sn-glycerol-3-phosphocholine (DMPC)/1,2-dimyristoyl-sn-glycerol-3-phospho-(1'rac-glycerol) DMPG (1,1) membrane model, the peptides work in a detergent-like model (details below) indicating the importance of the hydrophobic thickness of the lipid bilayer and the membrane composition [64, 65]. Ultimately, both pore-forming models (toroidal pore and barrel) lead to membrane depolarization and eventually cell death.

AMPs can also act without forming specific pores in the membrane. One of these models is designated as the carpet model [61, 62, 66]. In this case, the AMPs adsorb parallel to the lipid bilayer and reach a threshold concentration to cover the surface of the membrane, thereby forming a “carpet” (Figure 2C) leading to unfavorable interactions on the membrane surface. Consequently, the membrane integrity is lost, producing a detergent-like effect, which eventually disintegrates the membrane by forming micelles. The final collapse of the membrane bilayer structure into micelles is the detergent-like model (Figure 2D). The carpet model does not require specific peptide-peptide interactions of the membrane-bound peptide monomers; it also does not require the peptide to insert into the hydrophobic core to form transmembrane channels or specific peptide structures [67]. Many peptides act as antimicrobial agents despite their specific amino acid composition or the length of the sequence. Such AMPs typically act using the carpet model [66] at high

Figure 2.
Mechanisms of action of AMPs in bacteria. A) Barrel-stave model: AMPs stack into the bilayer of the cell membrane to form a channel. (B) Toroidal pore model: Accumulation of vertically and bend embedded AMPs in the cell membrane to form a pore structure, (C) carpet model: Distribution of AMPs on membrane surface that evolve to detergent-like mode, forming micelles, (D) images were created using BioRender.com.

[Image of Figure 2]
concentrations because of their amphiphilic nature. Examples of AMPs acting by the carpet model are cecropin [68], indolicidin [69], aurein 1.2 [67], and LL-37 [66].

Overall, there are many models to describe the MOA of AMPs. In addition to those given above, other related models include the interfacial activity model, the electroporation model, and the Shai-Huang-Matsuzuki model [62]. Some models do not make the specific distinctions shown in Figure 2. For example, it has been suggested that the carpet-like mechanism is a prerequisite step for the toroidal pore model [62]. Most studies to elucidate the MOA of AMPs involve the use of model membranes. The mode of action of only a few AMPs has been investigated with whole bacterial cells using imaging techniques [70, 71]. Different results may be obtained using other membrane models or assay conditions; for example, more than one MOA is possible for certain AMPs such as BP100 as the peptide-to-lipid ratio changes [72], indicating that the models described here may or may not translate directly to what is occurring in bacteria.

An online antimicrobial peptide database, APD3, list examples of AMPs, including both synthetically synthesized and compounds produced by living organisms [37]. In addition, many AMPs are currently being studied to elucidate their therapeutic efficacy against A. baumannii strains (Table 1).

2.1 Cathelicidins

Cathelicidins are a group of cationic AMPs (CAMPs) (with more than 30 members) detected in the immune system of some vertebrates that have in their structure two domains involved in antimicrobial activity [145]. Compared with carbapenems (imipenem and meropenem), which are considered the drugs of choice for infections caused by MDR A. baumannii (MIC = 16–32 mg/L) [146], these peptides exhibit excellent activity.

2.1.1 LL-37

The most studied member of the cathelicidins family is LL-37 (Human cathelicidin) with an α-helical structure. It is produced by many cell types as a part of innate immunity and exhibits broad-spectrum microbicidal activities against Gram-positive and Gram-negative bacteria by plasma-membrane disruption [147]. Other properties were also described, like immunomodulation properties such as chemotraction and activation of various immune cells, neutralizing the lipopolysaccharide (LPS), regulating the inflammatory response, wound closure, and chemotaxis [38, 148–151]. Feng et al. Investigated the anti-A. baumannii activity of LL-37 and fragments KS-30 and KR-12 against one sensitive and four MDR A. baumannii clinical isolates [73]. The minimum inhibitory concentration (MIC) for three pieces of KS-30, KR-20, and KR-12 was 8–16, 16–64, and 128–256 μg/ml, respectively. At the same time, LL-37 inhibited all sensitive and drug-resistant strains at the concentration of 16–32 μg/ml. Furthermore, LL-37 and the fragment KS-30 have been found to significantly inhibited and dispersed the A. baumannii biofilm in abiotic surfaces at 32 and 64 μg/ml, respectively [73]. A panel of synthetic peptides based on human LL-37 AMP shows potent microbicidal activity against several ESKAPE pathogens without selecting resistance and can also eliminate persistor cells and biofilms of P. aeruginosa, A. baumannii, and S. aureus in the micromolar scale [74]. SAAP-148 is an α-helical AMP, able to suppress MDR A. baumannii without causing resistance and prevents biofilm formation. Studies showed that this peptide could inhibit the growth of A. baumannii MDR at a concentration of 6 μg/m. Treatment with this peptide (animal model) appointment has been shown to eliminate acute and biofilm-related infections by A. baumannii in
<table>
<thead>
<tr>
<th>Peptide</th>
<th>Ref.</th>
<th>Sequence</th>
<th>Structure</th>
<th>MIC against <em>A. baumannii</em> (μg/mL)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>LL-37</td>
<td>[38, 52]</td>
<td>LLGDFFRKSKEKIGEKRIVQRKDFLRNLVPRTES (37aa)</td>
<td>AH</td>
<td>32</td>
<td>16–32</td>
</tr>
<tr>
<td>KR-30</td>
<td>[52]</td>
<td>KSKEKIGEKRIVQRKDFLRNLVPRTES (30aa)</td>
<td>AH</td>
<td>16</td>
<td>8–16</td>
</tr>
<tr>
<td>KR-20</td>
<td></td>
<td>KRVQRKDFLRNLVPRTES (20aa)</td>
<td>AH</td>
<td>64</td>
<td>16–32</td>
</tr>
<tr>
<td>KS-12</td>
<td></td>
<td>KRIVQRKDFLR (12aa)</td>
<td>AH</td>
<td>256</td>
<td>64–256</td>
</tr>
<tr>
<td>SAPP-148</td>
<td>[53]</td>
<td>LKRVWKRVFKLLKRYWRQKKP (24aa)</td>
<td>AH</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>CATH-BF</td>
<td>[54]</td>
<td>KFFKLLKSVKKAKRFFEKKPRVI GVSIPF (30aa)</td>
<td>AH</td>
<td>—</td>
<td>8–32</td>
</tr>
<tr>
<td>ZY4 cathercidin-BF-15 derived</td>
<td>[55]</td>
<td>VCKRWKKWKR KWKKWCV-NH₂ (17aa)</td>
<td>Cyclic SH-bridge</td>
<td>—</td>
<td>4.6–9.4</td>
</tr>
<tr>
<td>NA-CATH</td>
<td>[56]</td>
<td>KRFFKKFLLKNSVKKAKKFFK PKVIGVTPF (34aa)</td>
<td>AH</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>OH-CATH30</td>
<td>[57]</td>
<td>KFFKLLKNSVKKAKKFFKPRVI GVSIPF (30aa)</td>
<td>AH</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>DOH-CATH30</td>
<td></td>
<td>(KFFKLLSVKKAKKFFKPRVI GVSIPF, italics indicate D-amino acids)</td>
<td>AH</td>
<td>—</td>
<td>1.56–12.5</td>
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<tr>
<td>D-Myrtoxin-Mp 1a (Mp1a)</td>
<td>[58]</td>
<td>IDWKKVDFWKVSKKTCKVWXAKA CKEL-NH₂ (26aa-alpha chain)</td>
<td>Helical heterodim</td>
<td>25 nM</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LIGLVSKGTCLVXTVCVKLVQNH₂ (23aa-beta chain)</td>
<td>Helical heterodim</td>
<td>25 nM</td>
<td>—</td>
</tr>
<tr>
<td>Peptide</td>
<td>Ref.</td>
<td>Sequence</td>
<td>Structure</td>
<td>MIC against <em>A. baumannii</em> (μg/mL)</td>
<td>Source</td>
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<tr>
<td>Venon cocktail proteins</td>
<td>[59]</td>
<td>Cocktail</td>
<td></td>
<td>50.6% of inhibition at 20 mg/mL of venom</td>
<td><em>Leiurus quinquestriatus</em> (Scorpion venom)</td>
</tr>
<tr>
<td>Ranalexin</td>
<td>[60]</td>
<td>LGGLIKVIPAMICAVTKKC (19aa)</td>
<td>AH</td>
<td>4–18</td>
<td><em>Rana catesbeiana</em> (American bullfrog)</td>
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<tr>
<td>Danalexin</td>
<td></td>
<td>LGGLIKVIPAMICAVTKKC (19aa)</td>
<td>AH</td>
<td>4–16</td>
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<td>LS-sarcotoxin</td>
<td>[61]</td>
<td>GWLKKIGKIKIKERGKQHTRDAIQ</td>
<td>AH</td>
<td>4–8</td>
<td><em>Lucilla serratata</em></td>
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<tr>
<td>LS-stomoxyn</td>
<td></td>
<td>GFRKRFNKLVKKVHTIKETANV SKDVAIVAGSVAVGAAM-NH2</td>
<td>AH</td>
<td>4–16</td>
<td></td>
</tr>
<tr>
<td>Mini-ChBac7,5 N*</td>
<td>[62]</td>
<td>RRLRRPRPRLPPRPRLPRPRPRPRPRPRPRPRPRPRPR (22aa)</td>
<td>AH</td>
<td>2 μM</td>
<td>Domestic goat (<em>Capra hircus</em>)</td>
</tr>
<tr>
<td>Mini-ChBac7,5 Nβ</td>
<td></td>
<td>RRLPRRPRPRLPPRPRLPRPRPRPRPRPRPRPRPR (21aa)</td>
<td>AH</td>
<td>4 μM</td>
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<tr>
<td>AM-CATH36</td>
<td>[56]</td>
<td>GLFKKLRRKIKKGFKKLRRPPIG VGVSPLAGKR (36aa)</td>
<td>AH</td>
<td>5.2</td>
<td><em>American alligator</em></td>
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<tr>
<td>AM-CATH28</td>
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<td>KIKKGFKKLRRPPIGVGVSPLAGKR</td>
<td>AH</td>
<td>28</td>
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<tr>
<td>AM-CATH21</td>
<td></td>
<td>GLFKKLRRKIKKGFKKLRRP (21aa)</td>
<td>AH</td>
<td>42</td>
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<tr>
<td>WAM-1</td>
<td>[63, 64]</td>
<td>KRGGKFLKLRKKFHRNSIK KRLKFNVVIPIPLPG (36aa)</td>
<td>AH</td>
<td>8.12</td>
<td>Tammar wallaby (<em>Macropus eugenii</em>)</td>
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<tr>
<td>Indolicidin</td>
<td>[65, 66, 68]</td>
<td>LPWKWPWWPWR-NH (2) (13aa)</td>
<td>Other structure</td>
<td>4</td>
<td>Cytoplasmic granules of the bovine neutrophils</td>
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<tr>
<td>Bactenecin</td>
<td>[65, 67, 69]</td>
<td>LCRIVVIRVCR (12aa)</td>
<td>B-turn structure Giclyc</td>
<td>64</td>
<td>Bovine neutrophil granules, Caprine</td>
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<tr>
<td>Peptide</td>
<td>Ref.</td>
<td>Sequence</td>
<td>Structure</td>
<td>MIC against <em>A. baumannii</em> (μg/mL)</td>
<td>Source</td>
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<td>------------------------------------------------------------------------</td>
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<tr>
<td>Bac5</td>
<td>[62, 70, 71]</td>
<td>RFFPPRIRPRPPFPFPPNPPFPFRPPVRPPPFRPPFPFRPPIGFPFP-NH2 (42aa)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bac7</td>
<td>[72]</td>
<td>Bac7 N-terminal fragments Bac7(1–16; RRIRPRPRLPRPRPR), Bac7(1–35; RRIRPRPRLPRPRPRPLPRPPGPRPPIPRLPPF); Bac7(535; PRPRLRPRPLPPFPRPPRPIGRPLPPF) 59aa</td>
<td></td>
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<tr>
<td>HNP-1</td>
<td>[65]</td>
<td>ACYCRIPACIAAGERYGTCIYQGL WAFCC (30aa)</td>
<td>AH 50</td>
<td></td>
<td><em>H. sapiens</em> (Polymorphonuclear neutrophil)</td>
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<tr>
<td>HNP-2</td>
<td>[65]</td>
<td>CYCRIPACIAAGERYGTCIYQGR WAFCC (29aa)</td>
<td>AH 50</td>
<td></td>
<td></td>
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<td>HD5d5</td>
<td>[73]</td>
<td>ARARCRCRRGRAARRRRLRGVCRIR GRLRLAAR (32aa)</td>
<td>AH 40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>CL defensin</td>
<td>[74]</td>
<td>ATCDLFSPQSKWVTTPNHAACAAH CTARGNRGGRCKKAVCHCRK (43aa)</td>
<td>AH, antiparallel B-sheet; N-terminal loop</td>
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<td><em>Cimex Lectularius</em> (Bedbug)</td>
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<tr>
<td>HBD-2</td>
<td>[75]</td>
<td>GIGDPVTCLSGAICHPVFCPRY KQKGTGLPTKCCKPK (41aa)</td>
<td>Beta 3.90–9.35</td>
<td>3.25–4.5</td>
<td>Epithelial lining of respiratory/urinary tracts</td>
</tr>
<tr>
<td>HBD-3</td>
<td>[76]</td>
<td>GINTLQYVYCRVGGRCVSLCPKEEGQKCSTRGKKCCRKK (45aa)</td>
<td>AH + B-sheet</td>
<td>4</td>
<td></td>
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<td>Magainin-1</td>
<td>[65, 77]</td>
<td>GIGKFLHSAGKFGKAFVGEIKMS (23aa)</td>
<td>AH</td>
<td>256</td>
<td>Frog skin peptide</td>
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<tr>
<td>Magainin-2</td>
<td>[65, 77, 78]</td>
<td>GIGKFLHSACKFGKAFVGEIMNS (23aa)</td>
<td>AH 9.8–64</td>
<td>4.9–64</td>
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<td>Pexiganan</td>
<td>[79–81]</td>
<td>GIGKFLKKAKKFGKAFVKILKK (22aa)</td>
<td>AH 1–8</td>
<td>1–8</td>
<td>Frog skin peptide</td>
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<td>Peptide</td>
<td>Ref.</td>
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<td>Structure</td>
<td>MIC against <em>A. baumannii</em> (μg/mL)</td>
<td>Source</td>
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<tr>
<td><strong>Antibiotic-susceptible</strong></td>
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<td>Aurein 1,2</td>
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<td>GLFDIHKKIAESF (13aa)</td>
<td>AH</td>
<td>16</td>
<td>Frog skin peptide</td>
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<td>CAMEL</td>
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<td>KWKLFKKGAVLKVL-NH2 (15aa)</td>
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<td>Citropin 1.1.</td>
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<td>GLFDVVKKVASVIGL-NH2 (16aa)</td>
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<td>ILRWPPWPWRKK-NH2 (12aa)</td>
<td>AH</td>
<td>32</td>
<td></td>
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<tr>
<td>r-Omiganan</td>
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<td>KRRWPWWPWRKI-NH2 (12aa)</td>
<td>AH</td>
<td>16</td>
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<td>Temporin A</td>
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<td>FLPLGRVLSGL-NH2 (13aa)</td>
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<td>Brevinin 2 (B2RP)</td>
<td>[82]</td>
<td>GIWDTIKSMGKVFKGKILQNL-NH2 (21aa)</td>
<td>AH</td>
<td>29 7-13.9</td>
<td>Frog skin peptide</td>
</tr>
<tr>
<td>[D4K] B2RP</td>
<td>[83, 84]</td>
<td>GIWKTIKSMGKVFKGKILQNL-NH2 (21aa)</td>
<td>AH</td>
<td>4-16 4-16</td>
<td>Frog skin peptide</td>
</tr>
<tr>
<td>B2RP-Era</td>
<td>[83, 85]</td>
<td>GVIKSVLKGVKTVLGM-NH2 (19aa)</td>
<td>AH</td>
<td>8-32 8-64</td>
<td>Frog skin peptide</td>
</tr>
<tr>
<td>Alytesin-1c</td>
<td>[86]</td>
<td>GLKEIFKAGLGLVKGIAAHVSNH2 (23aa)</td>
<td>AH</td>
<td>— 11.3-22.6</td>
<td>Frog skin peptide</td>
</tr>
<tr>
<td>[E4k] Alytesin-1c</td>
<td>[83, 84]</td>
<td>GLKEIFKAGLGLVKGIAAHVSNH2 (23aa)</td>
<td>AH</td>
<td>4-16 4-16</td>
<td>Frog skin peptide</td>
</tr>
<tr>
<td>PGLa-AM1</td>
<td>[83, 88]</td>
<td>GMASKASLGKVKVAKVALNH2 (22aa)</td>
<td>AH</td>
<td>16-128 16-128</td>
<td>Frog skin peptide</td>
</tr>
<tr>
<td>CPF-AM1</td>
<td>[83, 89, 90]</td>
<td>GLGSVLGLKALKIGANLLNH2 (19aa)</td>
<td>AH</td>
<td>16-128 4-128</td>
<td>Frog skin peptide</td>
</tr>
<tr>
<td>CPF-B1</td>
<td>[91]</td>
<td>GLGSLLGGKAFKLKTGKMGAPREQ (28aa)</td>
<td>AH</td>
<td>— 11.4-22.8</td>
<td>Frog skin peptide</td>
</tr>
<tr>
<td>CPF-C1</td>
<td>[90]</td>
<td>GFGSLLGKALRGLANVL (917aa)</td>
<td>AH</td>
<td>5</td>
<td>Frog skin peptide</td>
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**MDR**

- — indicates not available.
<table>
<thead>
<tr>
<th>Peptide</th>
<th>Ref.</th>
<th>Sequence</th>
<th>Structure</th>
<th>MIC against <em>A. baumannii</em> (μg/mL)</th>
<th>Source</th>
</tr>
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<tbody>
<tr>
<td>[E6k,D9k] Hymenochirin-1B</td>
<td>[92]</td>
<td>LKLSPKTDILOKVLKGAIA IASMA-NH2 (29aa)</td>
<td>AH</td>
<td>4-9</td>
<td>Frog skin peptide</td>
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<tr>
<td>Hymenochirin-1 Pa</td>
<td>[93]</td>
<td></td>
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<tr>
<td>[G4K] XT7</td>
<td>[83, 94]</td>
<td>GLLGPLKIAAKVSNLL-NH2 (18aa)</td>
<td>AH</td>
<td>4.9-64</td>
<td>Frog skin peptide</td>
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<tr>
<td>Buforin II</td>
<td>[66, 77, 95, 96]</td>
<td>TRSSRALQFVPPYVRHLLL (21aa)</td>
<td>AH</td>
<td>8–19.5 0.25–39</td>
<td>Frog skin peptide</td>
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<tr>
<td>Melittin</td>
<td>[65, 97, 98]</td>
<td>GIGAVLVLTTGLPALISWKRQ (26aa)</td>
<td>AH</td>
<td>0.25–4 0.25–25</td>
<td>European honeybee</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(<em>Apis mellifera</em>)</td>
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<tr>
<td>Cecropin A</td>
<td>[65, 99]</td>
<td>KKWLFKIEKVGQNDGIIKAGP AVAVGQTQIAK (37aa)</td>
<td>AH</td>
<td>32 0.5–32</td>
<td>Cecropia moth</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(<em>Hyalophora cecropia</em>)</td>
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<tr>
<td>BR003-cecropin A</td>
<td>[100]</td>
<td>GGLKKLGKLKLEGKQVPNAAEK ALPVVAGAKWR (36aa)</td>
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<td>5 5</td>
<td><em>Aedes aegypti</em></td>
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<tr>
<td>Mdc</td>
<td>[101]</td>
<td>GWLKKIGKKKVENQTRDEIQ TIGVAQNAVAATLK (40aa)</td>
<td></td>
<td>4 4</td>
<td>Housefly larvae</td>
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<tr>
<td>Cecropin P1</td>
<td>[65, 102]</td>
<td>SWLSKTAKLENSAKRISEGIA IQGGPR (31aa)</td>
<td>AH</td>
<td>1.6 —</td>
<td>Pig (<em>Ascaris suum</em>)</td>
</tr>
<tr>
<td>Cecropin-4</td>
<td>[103]</td>
<td>GWLKKIGKKVGNQTRDTIQ AIGVQAANVATLK (40aa)</td>
<td>AH</td>
<td>4 4</td>
<td>Synthetic peptide</td>
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<tr>
<td>Myxinidin 2</td>
<td>[104]</td>
<td>KIKWILKYKYWS (12aa)</td>
<td>AH</td>
<td>— 12.5</td>
<td>Myxine glutinosa L</td>
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<tr>
<td>Myxinidin 3</td>
<td>[105]</td>
<td>RIRWILRYWRWS (12aa)</td>
<td>B-sheet</td>
<td>— 6.3</td>
<td></td>
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<tr>
<td>FLIP 7</td>
<td>[105]</td>
<td>???</td>
<td></td>
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<tr>
<td>Mastoparan</td>
<td>[65, 106, 107]</td>
<td>INLKALAALKIL (14aa)</td>
<td>AH</td>
<td>4 —</td>
<td>Vespula lewisi (Hornet venom)</td>
</tr>
<tr>
<td>Peptide</td>
<td>Ref.</td>
<td>Sequence</td>
<td>Structure</td>
<td>MIC against <em>A. baumannii</em> (μg/mL)</td>
<td>Source</td>
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<td>---------------------------------------------</td>
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<tr>
<td>Mastoparan-AF (EMP-AF)</td>
<td>[108]</td>
<td>INLKAIAALAKKL-F-NH2 (14aa)</td>
<td>AH</td>
<td>2–16</td>
<td>Hornet venom (<em>Vespa affinis</em>)</td>
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<tr>
<td>Histatin-8</td>
<td>[65]</td>
<td>KFHEKHHSHRGY (12aa)</td>
<td>AH</td>
<td>8</td>
<td><em>H. sapiens</em></td>
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<tr>
<td>DCD-1 L</td>
<td>[109, 110]</td>
<td>SLLLEKGLDGAKAVGGLKLGKDAVEDLSEVKGAVHDVVDVLDVSLV (48aa)</td>
<td>AH</td>
<td>16</td>
<td>Eccrine sweat glands</td>
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<tr>
<td>Tachyplesin III</td>
<td>[84]</td>
<td>KWCFRVCYRGICYRKCR-NH2 (17aa)</td>
<td>B-sheet 2 dissulfite bridges</td>
<td>—</td>
<td>Horseshoe crabs (<em>Tachypleus gigas</em>) and (<em>Carcinoscorpius rotundicauda</em>)</td>
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<tr>
<td>RR</td>
<td>[111, 112]</td>
<td>WRRRIKAWLRR (11aa)</td>
<td>AH</td>
<td>—</td>
<td>Computationally designed</td>
</tr>
<tr>
<td>RR2</td>
<td>[112]</td>
<td>WRRRIKAWRRVHK (14aa)</td>
<td>AH</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RR-4</td>
<td>[112]</td>
<td>WRRRIKAWLRIKA (14aa)</td>
<td>Ah</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DF7</td>
<td>[113-115]</td>
<td>AFLK KKKGGIFFEKA KKGK</td>
<td>AH</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Omega 76-shuft1</td>
<td>[116]</td>
<td>AFLKKGGIIFEKA KKGK</td>
<td>AH</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ω17 family peptides</td>
<td>[116]</td>
<td>RKKAIKLVKKLVKKLKKALK (20aa)</td>
<td>AH</td>
<td>2</td>
<td>1–8</td>
</tr>
<tr>
<td>Ω76 family peptides</td>
<td>[116]</td>
<td>FLKAIKFGKFKEFKIGAKLK (20aa)</td>
<td>AH</td>
<td>4</td>
<td>2–8</td>
</tr>
<tr>
<td>Stapled AMP Mag (i + 4)1,15(A9K, B21A, N22K, S23K)</td>
<td>[117]</td>
<td>Mag(i + 4)1,15(A9K,B21A,N22K,S23K) complex</td>
<td>—</td>
<td>—</td>
<td>NA, based in magainin 2 structure</td>
</tr>
<tr>
<td>Peptide</td>
<td>Ref.</td>
<td>Sequence</td>
<td>Structure</td>
<td>MIC against <em>A. baumannii</em> (μg/mL)</td>
<td>Source</td>
</tr>
<tr>
<td>-----------------------------</td>
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<tr>
<td>PNA (RXR)4 XB</td>
<td>[118]</td>
<td></td>
<td></td>
<td></td>
<td>Peptide nucleic acid conjugated to (RXR)4 Phosphorodiamidate Morpholino Oligomers</td>
</tr>
<tr>
<td>HP(2–9)-ME(1–12) (HPME)</td>
<td>[119]</td>
<td>AKKVFKRLGIGAVLKVTGG (20aa)</td>
<td>AH</td>
<td>6.25</td>
<td>3.12–12.5 Chimeric peptide</td>
</tr>
<tr>
<td>HP(2–9)-MA(1–12) (HPMA)</td>
<td></td>
<td>AKKVFKRLGIGKFLHSAKF-NH$_2$ (20aa)</td>
<td>AH</td>
<td>6.25</td>
<td>3.12–6.25 Chimeric peptide</td>
</tr>
<tr>
<td>CA(1–8)-ME(1–12) (CAME)</td>
<td></td>
<td>KWKLFKKIIGGAVKVLTTG-NH$_2$ (20aa)</td>
<td>Ah</td>
<td>3.12</td>
<td>3.12–12.5 Chimeric peptide</td>
</tr>
<tr>
<td>CA(1–8)-MA(1–12) (CAMA)</td>
<td></td>
<td>KWKLFKKIIGKFLHSAKF-NH$_2$ (20aa)</td>
<td>AH</td>
<td>12.5</td>
<td>3.12–12.5 Chimeric peptide</td>
</tr>
<tr>
<td>Octominin</td>
<td>[122]</td>
<td>GLRLGHAGKIAHGILIHRHRH (23aa)</td>
<td>AH</td>
<td>—</td>
<td>5 Synthetic derived, defensin 3 of <em>Octopus minor</em></td>
</tr>
<tr>
<td>Ceragenins; CSA-192; CSA-131; D-150-177C; HbCaAR derivative</td>
<td>[123]</td>
<td>Steroids compounds</td>
<td>??</td>
<td>—</td>
<td>— Cholic acid synthetic mimics,</td>
</tr>
<tr>
<td>Protegrin-1</td>
<td>[124]</td>
<td>RGGRGCYRRPCVCVGR-NH$_2$(18aa)</td>
<td>AH</td>
<td>—</td>
<td>— <em>Cimex lectularius</em></td>
</tr>
<tr>
<td>S4A</td>
<td>[125]</td>
<td>IOWAGOLF0FO-NH$_2$</td>
<td>AH</td>
<td>100</td>
<td>50  NA</td>
</tr>
<tr>
<td>SPO</td>
<td></td>
<td>NINONWNANGNONLFNONNF NO-NH$_2$</td>
<td>100</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
<td>Ref.</td>
<td>Sequence</td>
<td>Structure</td>
<td>MIC against A. baumannii (µg/mL)</td>
<td>Source</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>---------------------------------</td>
<td>-----------</td>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nuripep 1653</td>
<td>[126]</td>
<td>VRGLAPKSLWPFPGPFKSPFN (22aa)</td>
<td>AH</td>
<td>—</td>
<td>Derived from the P54 nutrient reservoir protein (aa 271–292) pea protein from <em>Pissum sativum</em></td>
</tr>
<tr>
<td>Agella-MPI</td>
<td>[127]</td>
<td>INWLKLGKHAIDAL (14aa)</td>
<td>AH</td>
<td>6.25</td>
<td><em>Agella pallipes</em></td>
</tr>
<tr>
<td>Polybia-MPII</td>
<td>[127]</td>
<td>INWLKLGKMVIDAL (14aa)</td>
<td>AH</td>
<td>12.5</td>
<td><em>Polybia vespi</em> testacea</td>
</tr>
<tr>
<td>Polydin-I</td>
<td>[127]</td>
<td>AVAGEKLWLLPHLLMKLLTPTP (22aa)</td>
<td>AH</td>
<td>&gt;25</td>
<td><em>Polybia dimorpha</em> (Social wasp)</td>
</tr>
<tr>
<td>Con10</td>
<td>[127]</td>
<td>FWSFLVKAASKILPSLGDDNK SSS (27aa)</td>
<td>AH</td>
<td>12.5</td>
<td>Scorpion venoms (<em>Opisthacanthus cayaporum</em>)</td>
</tr>
<tr>
<td>NDBP5.8</td>
<td>[128]</td>
<td>GILGKIWEVGKSLI (14aa)</td>
<td>—</td>
<td>&gt;25</td>
<td>Gram-negative bactéria <em>Delfia spp.</em></td>
</tr>
<tr>
<td>WLB2- arginine-rich amphiphilic peptide</td>
<td>[129]</td>
<td>RRWVRRVRRWVRRVRRVRRWV RR (24aa)</td>
<td>—</td>
<td>~7.484</td>
<td>Skin wounds</td>
</tr>
<tr>
<td>α-Helical-26 (A12L/A20L)</td>
<td>[130]</td>
<td>Ac-KWKSFLKTKSLKT7 TVLHTLLK AISS-NH2</td>
<td>AH</td>
<td>0.5–1.0</td>
<td>D- and L- diastereomeric peptides</td>
</tr>
<tr>
<td>Cy02 (cyclotide)</td>
<td>[131]</td>
<td>???</td>
<td>???</td>
<td>???</td>
<td>Viola odorata</td>
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<tr>
<td>Bicarinalin (YRTX-Tb1a)</td>
<td>[132]</td>
<td>KiKIPWGKVXDLVGMKAV (20aa)</td>
<td>AH</td>
<td>4</td>
<td>Tetramorium bicarinatum venom</td>
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</table>

Peptides with Therapeutic Potential against *Acinetobacter baumanii* Infections

DOI: http://dx.doi.org/10.5772/intechopen.100389
<table>
<thead>
<tr>
<th>Peptide</th>
<th>Ref.</th>
<th>Sequence</th>
<th>Structure</th>
<th>MIC against <em>A. baumannii</em> (µg/mL)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer acetate (synthetic COP-1)</td>
<td>[132]</td>
<td>synthetic</td>
<td>complex</td>
<td>Reduct viable cells</td>
<td><em>Homo sapiens</em></td>
</tr>
<tr>
<td>Lactoperoxidase (Lpo)</td>
<td>[133]</td>
<td>Large protein</td>
<td>complex</td>
<td>Inhibition effects, significant clearance of <em>A. baumannii</em> in lung and blood culture</td>
<td>Camel (Colostrum milk)</td>
</tr>
<tr>
<td>Lactoferrin (Lf)</td>
<td></td>
<td>Large protein</td>
<td>complex</td>
<td></td>
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<tr>
<td>Artlysin Art-175</td>
<td>[134]</td>
<td>Comprises a modified variant of endolysin KZ144 with an N-terminal fusion to SMAP-29</td>
<td>—</td>
<td>4–20</td>
<td><em>Pseudomonas aeruginosa</em> bacteriophage</td>
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<tr>
<td>Epsilon-poly L-lysine (EPL)-catechol</td>
<td>[135]</td>
<td>Complex</td>
<td>??</td>
<td>Reducing bacterial burden in vivo</td>
<td><em>Streptomyces albus</em> derived</td>
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<tr>
<td>Chexl-Arg20amide (ARV-1502)</td>
<td>[136]</td>
<td>H-Chexl-Arg-Pro-Asp-Lys-Pro-Arg-Pro-Tyr-Leu-Arg-Pro-Arg-Pro-Pro-Pro-Val-Arg-NH2</td>
<td>??</td>
<td>—</td>
<td>NA</td>
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<tr>
<td>I16K-piscidin-1 and analogs</td>
<td>[137]</td>
<td>FFHIFRGIHVGVKTHLVTG (22aa)</td>
<td>??</td>
<td>—</td>
<td>3.1</td>
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<tr>
<td>Nodule-specific cysteine-rich (NCR) peptide and its derivatives</td>
<td>[138]</td>
<td>RNGCIVDPRCPYQQCRRPLYCRRR (24aa)</td>
<td>AH</td>
<td>1.6–25 MBC</td>
<td>—</td>
</tr>
<tr>
<td>TAT-RasGAP_{327-326} anticancer peptide</td>
<td>[139]</td>
<td>G48RKRQRRQRR{W} {253} MWVTNLRTD{256} AH</td>
<td>Growth inhibitory effect</td>
<td>—</td>
<td>Chimeric (cell penetrating sequence + Src homology sequence)</td>
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<tr>
<td>Peptide</td>
<td>Ref.</td>
<td>Sequence</td>
<td>Structure</td>
<td>MIC against A. baumannii (µg/mL)</td>
<td>Source</td>
</tr>
<tr>
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<td>---------------------------------</td>
</tr>
<tr>
<td>D-150-177C, HBcARD derivative peptide</td>
<td>[140]</td>
<td>RRRGRSPRRRTSPRRRRQSRRR RRSC</td>
<td>AH</td>
<td>16</td>
<td>16-32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(28AA)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Colistin (Polymyxin E)</td>
<td>[141]</td>
<td>C52H98N16O13 (cyclic compound)</td>
<td>≠ Antibiofilm,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>side effects</td>
<td></td>
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<tr>
<td>P307NC-NC</td>
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<td>NAKDYKGAEEFPKKWNKAGGRV LAGLVRRRSQ8ESQ (39aa)</td>
<td>?</td>
<td>125</td>
<td>62.5-125</td>
</tr>
<tr>
<td>N10</td>
<td>[143]</td>
<td>ACKDVNTSCGG (13aa)</td>
<td>AH</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>NB2</td>
<td></td>
<td>ACERSIRTVGG (13aa)</td>
<td>AH</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Melitin with imipenem (IPM)</td>
<td>[144]</td>
<td>GIGAVLKLTTGLPALISWIKKR QQ (26aa) + IPM</td>
<td>AH</td>
<td>0.31-0.37</td>
<td>0.12-0.25</td>
</tr>
<tr>
<td>Melitin with colistin (COL)</td>
<td></td>
<td>GIGAVLKLTTGLPALISWIKKR QQ (26aa) + COL</td>
<td>AH</td>
<td>0.37-0.5</td>
<td>0.19-0.37</td>
</tr>
</tbody>
</table>

NA, not available; AH, alpha helical; IPM, imipenem; COL, colistin.

Table 1. List of AMP with activity anti-A. baumannii.
an ex vivo human skin infection model and an in vivo murine skin infection model at concentrations above 5% [74].

2.1.2 Snake cathelicidins

The anti-*A. baumannii* activity among the cathelicidins isolated from snakes has been reported for the peptides cathelicidin-BF (Cath-BF) [75] and *Naja atra* cathelicidin (NA-CATH). One of the best-known cathelicidins is Cath-BF having an \( \alpha \)-helical structure, isolated from the venous glands of the species *Bungattus fasciatus* [152]. It has been shown that Cath-BF causes bacterial death through two bacterial membrane disruption mechanisms and attacking intracellular targets [152].

According to available reports, this peptide is highly active against drug-resistant clinical isolates of *A. baumannii*, inhibiting its growth around 12.8 \( \mu \)g/ml concentration [75]. ZY4 cathelicidin-BF-15 derived, a cyclic peptide stabilized by a disulfide bridge with high stability in vivo (the half-life is 1.8 h), showed excellent activity against *A. baumannii*, including standard clinical MDR strains with MIC values ranging between 4.6 and 9.4 \( \mu \)g/mL. ZY4 killed bacteria by permeabilizing the bacterial membrane showed a low propensity to induce resistance, exhibited biofilm inhibition and eradication activities, and killed persister cells [76]. The peptide NA-CATH, produced by a cobra called *N. atra*, possesses an \( \alpha \)-helical structure at N-terminal and an unstructured segment at C-terminal [77, 153]. This peptide exerts antimicrobial activity through the membrane lysis by membrane thinning or transient pore formation [154] and is highly active against drug-resistant and sensitive *A. baumannii* strains, completely inhibiting bacterial growth at a concentration of 10 \( \mu \)g/ml [77, 153]. In 2018, Zhao et al. identified a novel cathelicidin (OH-CATH) from the king cobra, with its analog DOH-CATH30 found to exhibit potent microbicidal activity (MIC 1.56 to 12.5 \( \mu \)g/mL) against several Gram-negative and Gram-positive bacteria, including MDR *A. baumannii* [78].

Other cathelicidins with antimicrobial activity, identified in the venous glands, are OH-CATH30, from the venom of the cobra and mirtoxin, from *Myrmecia pilosula* [78, 79], presenting antimicrobial activity through inhibition of planktonic bacterial growth and biofilm, eradication of persistent bacterial cells, and inhibition of inflammatory process [76, 78].

Compounds with similar activity have been identified in the venom of some scorpion species and tested against antibiotic-resistant bacteria. Therefore, Al-Asmari et al. evaluate the in vitro antimicrobial activities of the toxins extracted from three medically necessary Saudi Scorpions. Among these, only *Leiurus quinquestriatus* showed significant broad-spectrum antimicrobial activity in a dose-dependent manner from 5 to 20 mg/mL, inhibiting 50.6% of growth and survival of MDR *A. baumannii* [80]. High antimicrobial activity was also observed for AMPs ranalexin and danalexin obtained from *Rana catesbeiana* [81], LS-sarcotoxin, and LS-stomoxyn (*Lucilla serricata*) [82], and minibactenecins (*Capra hircus*) [83]. However, further in vivo studies are needed to improve the pharmacokinetics of systemic administration and find solutions to avoid their degradation by proteases despite the antimicrobial activity on *A. baumannii* strains of these compounds.

2.1.3 Alligator cathelicidins

Alligator mississippiensis (American alligator), a member of order Crocodilia, lives in bacteria-laden environments but cannot often succumb to bacterial infections. Serum of alligators has antibacterial activity beyond that of human sérum [155], killing a wide range of pathogens, and it is believed that this activity is attributable at least partially to the presence of CAMPs in the alligator plasma and
extracts [156]. A study by Barksdale et al. (2017) reported the anti-
*A. baumannii*

effect of AMPs produced by American alligator: cathelicidin called AM-CATH36 and its two fragments including AM-CATH28 and AM-CATH21 [77]. Alligator cathelicidin can inhibit the growth of both drug-resistant and sensitive *A. baumannii* at the 2.5 μg/ml concentration. Furthermore, two shorter fragments of this peptide can inhibit the drug-resistant *A. baumannii* at a 10 μg/ml concentration. The anti-*A. baumannii* effect of these three peptides is through membrane permeabilization. Interestingly, MDR clinical isolates of *A. baumannii* were more susceptible to both the AM CATH21 and AM-CATH28 peptides than the sensitive strains.

### 2.1.4 Wallaby antimicrobial

The marsupial AMP Wallaby antimicrobial 1 (WAM-1) is a cathelicidin isolated from the mammary gland of the Tammar wallaby (*Macropus eugenii*) with antibacterial and antifungal activities with high potential to combat drug-resistant pathogens [84, 157]. Spencer et al. (2018) studied the AMP LL-37 and WARM-1 effects on MDR *A. baumannii*, and both peptides were able to inhibit biofilm formation in all clinical isolates at some concentrations of WAM-1 effectively dispersed 24-h biofilms in most isolates tested, including MDR strains [85]. The antibacterial effects of LL-37 are diminished in the presence of human serum. However, this is not the case with WAM-1. Although the mechanism of action has yet to be determined, WAM-1 has been shown in vitro to be 12 to 80 times more effective than LL-37 in its ability to kill several bacterial pathogens, including several clinical isolates of *A. baumannii*. Unlike LL-37, WAM-1 is not inhibited by high NaCl concentrations and does not cause hemolysis in human red blood cells (RBC), so it has the potential to be used for in vivo applications [85].

### 2.1.5 Bovine cathelicidins (Indolicidin and Bactenecin)

Indolicidin is a short tryptophan-rich cationic AMP encoded by a member of the cathelicidin gene family, isolated from cytoplasmic granules of the bovine neutrophils [158, 159]. Indolicidin acts by displacing divalent cations from their binding sites on the surface of the cell membrane and causes bacterial death through channel formation in the cytoplasmic membrane [88]. Indolicidin not only forms pores in the membrane but can also inhibit DNA processing enzymes [160, 161]. This peptide is among the potent anti-*A. baumannii* AMPs with MIC of 4–32 and 16 μg/ml against sensitive and colistin-resistant clinical isolates, respectively [86]. In a study by Giacometti et al. were investigated the in vitro activity of indolicidin and other AMPs alone and in combination with antimicrobial agents, the MIC of indolicidin against 12 MDR clinical isolates was reported as 2–64 μg/ml [87]. Isolated from bovine, ovine, and caprine neutrophil granules, Bactenecin is a short cyclic, arginine-rich cationic AMP [89] with a type I β-turn structure and forms a loop due to the disulfide bond between cysteines 3 and 11 [90]. These AMPs act by permeabilizing the cell membrane and inhibiting protein and RNA synthesis in bacteria [70]. Vila-Farres et al. (2012) reported the anti-*A. baumannii* effect of this peptide can inhibit sensitive and colistin-resistant strains of *A. baumannii* at 16 and 64 μg/ml, respectively [86].

### 2.2 Defensins

Defensins are an evolutionarily ancient class of AMPs present in animals, plants, and fungi involved in the immune system of living organisms and
contain six (invertebrates) to eight conserved cysteine residues in their structure. They are categorized into three subfamilies of α, β, and θ-defensins [162]. Most defensins bind to the cell membrane and make pores, leading to bacterial death [163].

2.2.1 α-Defensins (HNPs and HD5)

The subfamily of human neutrophil peptides (HNPs), also known as α-defensins, are secreted and released from polymorphonuclear neutrophil (PMN) granules upon activation and are conventionally involved in microbial killing [164]. Two important CAMPs HNP-1 and HNP-2, which differ in only one initial amino acid, can inhibit the growth of the standard strain of *A. baumannii* ATCC 19606 at a concentration of 50 μg/ml. Interestingly, the colistin-resistant mutant of *A. baumannii* ATCC 19606 is much more sensitive (MIC = 3.25 μg/ml) to HNP-1 than the standard strain [86]. Human defensin 5 (HD5) has a relatively low anti-*A. baumannii* effect (MIC = 320 μg/ml). However, an analog called HD5d5 obtained by sequence modification presented a stronger bactericidal effect (MIC = 40 μg/ml) against *A. baumannii*, exerting the effect through damage to the membrane, accumulation in the cytoplasm, and reduction of catalase and superoxide dismutase activities [165, 166].

2.2.2 β-Defensins

Human β-Defensin (HBD) 2, 3 of this subfamily have anti-*Acinetobacter* effects. HBD-2 is primarily produced by the epithelial lining of the respiratory and urinary tracts, and engaging is more effective on MDR clinical isolates than non-MDR isolates [167]. Longer than most of the natural AMPs, HBD-3 combined helix and β structure [147]. Even though the anti-*Acinetobacter* bactericidal effect is inhibited by exposure to human serum, it can kill all MDR and non-MDR *A. baumannii* clinical isolates at 4 μg/ml during 1.5 h in the serum-free environment. Thus, this peptide has the potential to be further studied for wounds infected by *A. baumannii* since it demonstrated wound-healing effects [97, 168].

2.2.3 α-Helical and antiparallel β-sheet defensins

CL-defensin, belonging to the family of insect defensins, is predicted to have a characteristic N-terminal loop, an α-helix, and an antiparallel β-sheet, which was supported by circular dichroism spectroscopy [95]. In addition, this peptide induces pore formation in other Gram-positive bacteria and causes a small amount of membrane permeabilization in *A. baumannii* [95].

2.3 Frog antimicrobial peptides

2.3.1 Magainin and pexiganan (its analog)

The Magainin-1 and 2 are cationic, α-helical, and amphipathic AMPs ionophores isolated from the skin of the African clawed frog (*Xenopus laevis*) [168, 169]. The primary mechanism of antimicrobial activity is probably pore formation in outer and inner membranes, although the exact mechanism of action is not yet precise [98, 170]. Despite both have anti-*Acinetobacter* training, Magainin-2 is much stronger and able to inhibit the growth of sensitive and MDR strains of *A. baumannii* at 4.9–64 μg/ml, while reported as 256 μg/ml for Magainin-1 [86, 98]. Magainin-2 has some advantages, such as anticancer effect, stability at physiological salt
concentrations, lack of hemolytic activity, and toxicity for mammalian cells [98]. Furthermore, Magainin-2 can inhibit and eliminate the biofilm of *A. baumannii* [98]. Pexiganan AMP or MSI-78 is a synthetic analog of Magainin-2 with a potent and broad spectrum of action [171, 172]; it kills bacteria by forming toroidal pores in their cell membranes [172, 173]. Several studies have been performed on anti-*Acinetobacter* activity due to its being highly active against *Acinetobacter*. Pexiganan can inhibit the growth of MDR and sensitive clinical isolates of *A. baumannii* at a concentration of 1–8 μg/ml [100, 101, 174]. Jąskiewicz et al. studied the antimicrobial activity of eight peptides on *A. baumannii* ATCC 19606 reference strains. Among these, CAMEL and pexiganan showed potent antimicrobial and anti-biofilm activity [102].

### 2.3.2 Brevinin-2 related peptide (B2RP)

B2RP is an α-helical AMP isolated from the skin secretions of the mink frog *Rana septentrionalis* [175] and carpenter frog *Rana virgatipes* [176]. This peptide forms an α-helical structure adjacent to the target cell, resulting in the perturbation of the phospholipid bilayer that may lead to growth inhibition of bacterial death, and the application of this peptide for systemic use is limited due to the moderate toxicity for human red blood cells [177]. B2RP inhibited the growth of a susceptible strain of *A. baumannii* at 29 μg/ml concentration but inhibited the MDR isolates more efficiently at 7–13.9 μg/ml [103]. The analogs of these peptides (D4K, K16A, L18K) resulted in twofolds higher anti-*A. baumannii* activity and much lower hemolytic activity [103]. A study reported that the analog of B2RP with D4K substitution inhibited sensitive and colistin-resistant [103] and XDR isolates of *A. baumannii* [105].

### 2.3.3 B2RP-ERa

B2RP-ERa is a cationic AMP from the Brevinin family isolated from the skin of the Asian frog *Hylarana erythraea* [106, 178]. Shorter and with lower molecular weight, B2RP-ERa is structurally similar to B2RP. B2RP-ERa is an anti-inflammatory peptide with no toxic effect on peripheral blood mononuclear cells [179] with low hemolytic activity [178], which could inhibit the growth of sensitive and drug-resistant *Acinetobacter* strains at 8–32 and 8–64 μg/ml, respectively [104, 106].

### 2.3.4 Alyteserin-1c

Alyte-serins are a class of cationic AMPs, which firstly reported their presence in norepinephrine-stimulated skin secretions of the midwife toad [180]. However, initial studies show that Alyte-serin-1c has more significant inhibitory activity against Gram-negative bacteria, while Alyte-serin-2a is more active against Gram-positive bacteria [180], the anti-*A. baumannii* effects of these Alyte-serins have already been proven [107, 108]. Alyte-serin-1c is a cationic α-helical AMP with low hemolytic activity on human red blood cells firstly isolated from *Alytes obstetricans* [107, 180, 181]. The MIC and MBC against clinical isolates of MDR *A. baumannii* have been reported as 11.3–22.6 μg/ml [107]. Substitution of E4K on this AMP reduced the hemolytic activity, and enhanced the antimicrobial and cationic activity [107]. The analog [E4K] inhibits the growth of colistin-sensitive, colistin-resistant, and XDR *A. baumannii* isolates at concentrations of 4–16 μg/ml, 4–16 μg/ml [104], and 8–64 μg/ml, respectively [105]. Alyte-serin-2a is also a tiny α-helical AMP that displays relatively weak antimicrobial and hemolytic activities. Despite its
anti-*A. baumannii* potential was not high mainly, some structural changes resulted in lower toxicity against human erythrocytes and higher bactericidal effect (4–8 folds) against MDR isolates with MIC of 6.8–13.6 μg/ml [108].

**2.3.5 Peptide glycine-leucine-amide**

AM1 (PGLa-AM1) PGLa-AM1 is another Anti-*Acinetobacter* AMP isolated from the frog *Xenopus amieti*. In addition to the low hemolytic activity, it is also active against other pathogens, including *E. coli* and *S. aureus* [104, 106, 109], and can kill sensitive and colistin-resistant *A. baumannii* isolates at 16–128 μg/ml concentration [104].

**2.3.6 Caerulein precursor fragment (CPF)**

CPF-AM1 is a cationic AMP firstly isolated from *X. amieti* [110]. This peptide is capable of bacterial binding LPS and has activity against Gram-negative and Gram-positive bacteria, primarily oral and respiratory pathogens, with advantages such as low hemolytic activity and lack of toxicity against fibroblast cells [109]. This anti-*A. baumannii* peptide inhibits the growth of sensitive and colistin-resistant strains at 16–128 and 4–128 μg/ml, respectively [104, 114]. CPF-B1, isolated from Marsabit clawed frog *Xenopus borealis*, is another anti-*A. baumannii* member of this family with low hemolytic activity. This peptide inhibits MDR *A. baumannii* clinical isolates at concentrations of 11.4–22.8 μg/ml [112]. Finally, CPF-C1 is a peptide member of this family with proved anti-*A. baumannii* effect with inhibitory activity against the strain at 5 μg/ml concentration [111].

**2.3.7 Hymenochirins**

Hymenochirins are a class of AMPs produced by two frogs of *Pseudhymenochirus merlini* and *Hymenochirus boettgeri* with letters P and B in the second part name of these peptides indicating the producing species of the peptide, respectively [37, 182]. Hymenochirin-1B is a cationic, α-helical amphibian host-defense peptide with antimicrobial, anticancer, and immunomodulatory properties. This peptide has anti-*A. baumannii* properties against MDR isolates with MIC of 19.1 μg/ml [113]. Among the analogs of hymenochirin-1B obtained by amino acid substitution method, [E6k and D9k] hymenochirin-1B reduced human erythrocytes’ toxicity and showed 3.9-folds higher activity against *A. baumannii*. [E6k and D9k] hymenochirin-1B is active against both MDR and XDR isolates and could inhibit the growth of these isolates at 4.9 μg/ml concentration [113]. Hymenochirin-1 Pa is another cationic member of this family with moderate hemolytic activity. This peptide inhibited the growth of XDR *A. baumannii* isolates at 7.5–15 μg/ml concentration [114, 182].

**2.3.8 XT-7**

XT-7 was first isolated from norepinephrine-stimulated skin secretions of *Xenopus tropicalis* [183]. The activity anti-*Acinetobacter* of this peptide was first reported against *A. baumannii* Euroclone I NM8 strain (MIC = 22.2 μg/ml) [111]. Later, the amino acid substitution of lysine at position 4 [G4K] increased the therapeutic index [115] principally. Subsequent studies were based on this new analog that inhibited sensitive and drug-resistant *A. baumannii* strains at concentrations of 4–32 and 4–64 μg/ml, respectively [104].
2.3.9 Buforins

Buforin II is a potent antimicrobial peptide derived from Burforin I, isolated from the stomach tissue of the Asian toad *Bufo gargarizans* [184]. It causes bacterial death by crossing the membrane, binding to intracellular targets, including DNA and RNA, and inhibiting cellular functions [116]. This peptide has a potent anti-*Acinetobacter* activity since it can hinder the growth of both sensitive and resistant isolates of *A. baumannii* at concentrations of 0.25–39 μg/ml [87, 98]. Buforin II alone or in combination with an antibiotic showed highly potent on *A. baumannii* sepsis treatment in a rat model [104].

2.4 Melittin

Melittin is a cationic amphipathic α-helical AMP isolated from the venom (approximately 50% of the dry weight) of the European honeybee (*Apis mellifera*) [185] with numerous reported properties such as antifungal [186], antiparasitic [187], antibacterial [185], antiviral, and anticancer properties [188]. The primary mechanism of melittin action is the membrane lysis through pore formation (a carpet-like mechanism) [189]. This potent anti-*Acinetobacter* peptide inhibits MDR and XDR clinical isolates at 0.125–2 μg/ml concentration [118, 119]. A study demonstrated that topical administration of melittin at concentrations of 16 and 32 μg/mL in mice killed 93.3% and 100% of an XDR *A. baumannii* on a third-degree burned area, respectively [118]. No toxicity was observed on the injured or healthy derma and circulating red blood cells in the examined mice. Recently, a study that evaluated the melittin against Brazilian clinical strains revealed that most strains were susceptible, except for one pan drug-resistant strain [190].

2.5 Cecropins

Cecropins, the lytic peptides, were initially isolated from the hemolymph of the giant silk moth, *Hyalophora cecropia*, and possess antibacterial and anticancer activity in vitro [191, 192]. The primary antimicrobial mechanism of cecropins is membrane lysis [193]. Cecropin A is a cationic amphipathic α-helical AMP that can induce apoptosis by oxidative stress in addition to attacking the membrane [194]. This peptide has potent antimicrobial activity against *A. baumannii*, inhibiting MDR clinical isolates at 0.5–32 μg/ml [99]. Vila-Farres et al. reported that this peptide inhibited the growth of sensitive and colistin-resistant strains of *A. baumannii* at 32 and 256 μg/ml, respectively [86]. A pilot study that evaluated the viability of *Caenorhabditis elegans* infected by *A. baumannii* in the presence of 68 insect-derived AMPs identified 15 cecropin or cecropin-like peptides that prolonged the survival of worms infected with *A. baumannii* [121]. Interestingly, the direct investigation of the anti-*Acinetobacter* effect also showed that these 15 AMPs could inhibit the growth of *A. baumannii* at 4.5 to over 20 μg/ml concentrations. BR003-cecropin A, isolated from *Aedes aegypti*, is the most active member of this group. This peptide inhibited sensitive and MDR *A. baumannii* strains at 4.5 μg/ml [100]. Musca domestica cecropin (Mdc) isolated from the larvae of a housefly inhibits both standard (ATCC 19606) and MDR strains of *A. baumannii* at 4 μg/ml with high speed (half an hour) [122]. Cecropin P1, an AMP isolated from *Ascaris suum* of pig intestine, showed high activity against colistin-sensitive *A. baumannii* with MIC at 1.6 μg/ml. In contrast, there was less activity against the colistin-resistant strains with MIC >25 μg/ml [86].

Other peptides that showed great activity against susceptible MDR and extensively drug-resistant (XDR) *A. baumannii* strains were Cecropin-4, an α-helical
2.6 Mastoparan

Mastoparan is a small cationic amphipathic α-helical AMP isolated from the hornet venom of *Vespula lewisi* with a robust anti- *Acinetobacter* activity. However, the anti- *Acinetobacter* solid activity, the high hemolytic activity, and toxic effects affected highly therapeutic applications. Mastoparan inhibited the growth of a sensitive wild-type *A. baumannii* ATCC 19606 and a colistin-resistant *A. baumannii* ATCC 19606 mutant at 4 and 1 μg/ml, respectively. This study also used 14 colistin-susceptible *A. baumannii* clinical isolates and 13 pan-resistant *A. baumannii* strains isolated in a hospital outbreak and reported the MIC of 1–16 and 2–8 μg/ml for sensitive and colistin-resistant isolates, respectively. Mastoparan-AF (MP-AF), isolated from the hornet venom of *Vespa affinis*, also showed effective antimicrobial activity with MICs ranging from 2 to 16 μg/ml against MDR *A. baumannii* isolates. Analogs of mastoparan were made to increase the stability of the peptide in serum. These analogs had an equal inhibitory effect with mastoparan against XDR *A. baumannii* strains (4 μg/ml); in addition, it showed stability in the presence of human serum for more than 24 h.

2.7 Histatins

Histatins belong to a distinct family of at least 12 low-molecular weight, histidine-rich cationic, salivary gland peptides with antimicrobial effect through the plasma membrane disruption. Histatin-8, known as hemagglutination-inhibiting peptide, was the only member of this group that showed antimicrobial activity against *A. baumannii*, inhibiting the growth of both sensitive standard strains colistin-resistant mutant *A. baumannii* ATCC 19606 at 32 μg/ml.

2.8 Dermcidins

Dermcidin is an anionic AMP encoded by the DCD gene in humans essentially produced in eccrine sweat glands, secreted into a sweat, and further transported to the skin’s epidermal surface. It has two parts; N-terminal peptide promotes neural cell survival under severe oxidative stress conditions called DCD-1 L. DCD-1 L, a C-terminal peptide with the net electric charge of −2, is the only anionic anti- *Acinetobacter* natural AMP found in the literature that shows partial helicity in solution. Interestingly, in exposure to this AMP, the PDR *A. baumannii* isolates are twice more susceptible as XDR isolates and the standard strain (ATCC 19606) (MIC = 8 μg/ml).

2.9 Tachyplesin III

Tachyplesin III, isolated from the hemolymph of the Southeast Asian horseshoe crabs *Tachypleus gigas* and *Carcinoscorpius rotundicauda*, consists of 17 amino acids with two disulfide bridges and is a representative antimicrobial peptide with a cyclic β-sheet structure. However, its potential toxicity hampers its use in mammalian cells. Nevertheless, Tachyplesin III could inhibit the...
XDR *A. baumannii* strains (8–16 μg/ml) and at 2 × MIC, eliminating the XDR *A. baumannii* strains [203].

### 2.10 Computationally designed antimicrobial peptide

The biosynthesis of AMPs can be a starting point for obtaining AMPS with functions similar to natural ones, being an attractive therapeutic option for preventing and controlling infections. In this sense, bioinformatics and computer science have been widely used in various aspects in many studies of *A. baumannii*, such as design evaluation of AMPs [136, 204–208], which includes two general principles that increased antimicrobial activity and reduced toxicity against eukaryotic cells [209, 210]. As an example of synthetic AMPs, we have stapled AMP [137] and PNA (RXR) 4XB, an antisense nucleic acid peptide compound [138] with intense bactericidal activity. The synthetic RR is a small α-helical AMP with fast bactericidal activity capable of retaining the antimicrobial property at physiological concentrations of NaCl and MgCl2 [132]. The anti-*A. baumannii* effect of RR against sensitive and MDR strains inhibits the growth at 25–99 μg/ml concentration. Two new analogs of this peptide were introduced with much stronger anti-*A. baumannii* properties than RR, and the AMPs RR2 and RR4 inhibit the growth of sensitive and drug-resistant strains (3–6 μg/ml) [211]. The peptide DP7 inhibits the growth of antibiotic-resistant *A. baumannii* strains at 4–16 μg/ml concentration, and the synergistic effects were showed after simultaneous treatment of some drug-resistant *A. baumannii* isolates with DP7 and antibiotics such as amoxicillin, azithromycin, and vancomycin [133]. Zhang et al. showed that DP7 invades the microbial cell through various pathways after sequencing the transcriptome of the bacteria exposed to this peptide [134]. Omega76 is a cationic AMP with an α-helical structure, causing death in *A. baumannii* through membrane disruption. This peptide was designed based on the maximum common subgraph of helices and further introduced as an appropriate alternative for colistin due to its high anti-*A. baumannii* activity against carbapenem and tigecycline-resistant isolates (MBC = 2–8 μg/ml) and lack of toxicity in the mouse model [135].

### 3. Resistance to AMPS

Although AMPs have a low likelihood to select for resistance, similar to the conventional antibiotics, another challenge is represented by the numerous reports describing the development of resistance mechanisms against some AMPs, including proteolytic degradation or sequestration by secreted proteins, impedance by exopolymers, and biofilm matrix molecules, circumvention of attraction by cell surface/membrane alteration, and export by efflux pumps [212–216]. The development of resistance to colistin by *A. baumannii* following long-term clinical application was observed [217, 218]. In *A. baumannii* stable colistin resistance was also observed following direct plating with the complete loss of LPS production due to the inactivation of one of three genes involved in lipid A biosynthesis (*lpxA, lpxD,* or *lpxC*). Resistance to colistin is an important clinical issue, considering that colistin is a last-resort drug used to treat MDR nosocomial pathogens [218–220]. Several mechanisms have been reported responsible for resistance to AMPs, including expression of efflux pumps, increased secretion of proteolytic enzymes, and surface charge modification to avoid membrane-peptide electrostatic interactions [213, 221, 222].

For delivering the AMPs, several nanocarriers were developed, which may help avoid the low bioavailability, proteolysis, or susceptibility and toxicity associated
with APMs [223, 224]. Changes in the molecular structure, modifications of biochemical characterization, and combination with common antibiotics have been reported to reduce AMP resistance [214]. The aprotinin is the first inhibitor identified to inhibit AMP resistance in multiple pathogens [225].

4. Conclusion(s)

*A. baumannii* is one of the ESKAPE pathogens responsible for nosocomial and community-acquired infections, with the incidence of MDR and virulent clones increasingly worldwide. The enormous adaptability of *A. baumannii*, as well as the remarkable ability to acquire determinants of resistance, allied to your innate ability to form biofilms, contributes to the inefficiency of most current therapeutic strategies, determining the transition to the “post-antibiotic era” and highlighting the necessity to develop new therapeutic approaches. In this context, natural and synthetic AMPs emerge as potential next-generation antibiotics to mitigate a wide array of microbial infections, including those caused by MDR *A. baumannii* strains. Moreover, the antimicrobial activity of these peptides can be effectively increased by minor modifications through the development of computer science and bioinformatics. The synthetic AMPs present a promising solution to overcome the drawbacks of using natural AMPs. They contain critical features based on natural AMPs, with slight modifications to achieve higher antimicrobial efficiency and improved chemical stability. In this research, we observed the main properties of anti-*A. baumannii* peptides with some common characteristics, such as 1. The α-helical structure was predominant. 2. Most peptides have a positive charge, and in many cases, there is a direct relationship between an increased positive charge and your activity. 3. The action mechanisms of these peptides are direct membrane attack and intracellular targeting or both simultaneously. Unfortunately, considerable experimental data describe how bacteria can develop resistance to AMPs, such as colistin and polymyxin B in *A. baumannii*. Since AMPS are considered potential novel antimicrobial drugs, understanding the mechanism of bacterial resistance to direct killing of AMPS is of great significance.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Peptides with Therapeutic Potential against Acinetobacter baumanii Infections

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