Review

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An Update of Peptides with Therapeutic Potential against *Acinetobacter baumannii* Infections

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Abstract: The rise of antibiotic-resistant strains of clinically important pathogens is a major threat to global health security. The World Health Organization (WHO) has recognized the urgent need to develop alternative treatments to address the growing list of priority pathogens. Antimicrobial peptides (AMPs) rank among the various suggested options with proven activity and a high potential to be developed into effective agents. Many AMPs are naturally produced by living organisms and protect the host against pathogens as a part of their innate immunity. Various mechanisms associated with their antimicrobial actions include cell membrane disruption, cell wall weakening, protein synthesis inhibition, and interference in nucleic acid dynamics that can induce apoptosis and necrosis. Acinetobacter baumannii is considered a critical pathogen, and severe clinical problems have appeared with isolates resistant to current antibiotic treatments and conventional control procedures such as UV light, disinfectants, and drying. Here, we review the natural AMPs representing the primary candidates for new anti-A. baumannii drugs in a post-antibiotic era and present the use of computational tools to develop the next generation of AMPs with greater microbicidal activity and reduced toxicity.

Keywords: AMP; *Acinetobacter baumannii*; resistance; action mechanism

1. Introduction

The rise in antibiotic resistance is a major contributor to global mortality statistics and represents a pressing challenge across various sectors of society, including healthcare providers, government agencies, and the pharmaceutical industry, that also impinges on environmental concerns. The inability to develop new antibiotics to hinder the rapid rise in the emergence of drug-resistant pathogens suggests that the world is heading toward a post-antibiotic era [1,2]. For bacteria, three types of antimicrobial resistance have been described as intrinsic, acquired, and or adaptive resistance through changes in phenotype [3–11]. While many mechanisms lead to resistance, the exposure of microbes to antimicrobial drugs can trigger their evolution, which can be accelerated by the incorrect use of antibiotics through wrong choices, inadequate dosing, and poor adherence to treatment guidelines that all contribute to the selection of antimicrobial resistance [12,13].

There are several terminologies in the literature used to describe microbes based on the number of classes of antibiotics to which they are resistant. According to Magiorakos et al. (2012), a multidrug-resistant (MDR) strain shows resistance to at least one antimicrobial in more than three classes of antimicrobials, and extensively drug-resistant (XDR) strains display resistance to at least one antimicrobial in all classes of antimicrobials except two or fewer types while a pan drug-resistant (PDR) strain is resistant to all antimicrobial agents [14]. In hospital settings, ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, Enterobacter species) describe the most opportunistic pathogens in nosocomial infections that "escape" the effects of antibiotics and conventional therapies that account for increased morbidity and mortality for improved resource utilization in healthcare [15,16].

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Notably, Acinetobacter baumannii has globally emerged as a concerning hospital-related pathogen, frequently presenting MDR, XDR, and PDR phenotypes. Unfortunately, evidence has shown increased antibiotic resistance over time [17]. It is a gram-negative, non-motile, non-fermentative, and non-sporulated bacterium of the Moraxellaceae family [18], part of the *Acinetobacter calcoaceticus–A. baumannii* complex (Acb) that has long been associated with human disease [19]. Consisting of the species *A. calcoaceticus*, *A. baumannii*, *A. pittii*, *A. nosocomialis*, *A. seifertii*, and A. lactucae (a later heterotypic synonym of A. dijkshoorniae) [20,21], they differ in epidemiology, pathogenicity, and antimicrobial resistance [22]. While their genetic and physiological relatedness makes them difficult to distinguish phenotypically with standard laboratory methods [23], A. baumannii is the most widespread in hospitals causing various infections, including wounds, skin and urinary tracts, and diseases such as pneumonia, meningitis, and bacteremia [24,25]. All contribute to longer hospital stays, higher treatment costs, and increased morbidity and mortality risks [26].

Treatment options have proven limited for *A. baumannii* due to its extended virolome and resistome, evasion of host immune effectors, survival in extreme environmental conditions, growth in biofilms, and latent growth forms with a minimal metabolic rate [27,28]. The World Health Organization (WHO) recently highlighted the resistance of *A. baumannii* to carbapenems (CRAb) [29,30], which included its classification as a "priority 1 for research and develop new antibiotic treatments". As a "critical" pathogen [31], AMP have a high potential for research and development of anti-Acinetobacter drugs [32,33]. In this review, we sought to update knowledge about the potential and activity of antimicrobial peptides (AMP) to act against multidrug-resistant *A. baumannii*.

2. Antimicrobial peptides

Also known as host defense peptides, AMPs are naturally produced by living organisms as a part of their innate immune system against pathogens. They are amphipathic molecules of varying molecular weights containing 11-50 amino acids with an overall positive electric charge [34,35], classified as either α-helical, β-sheet, or extended peptides [36–38]. AMPs are essential in regulating immune processes such as inflammation and activating and recruiting immune system cells [34]. In addition, they can inhibit protein and nucleic acid synthesis that can, cause apoptosis and lead to necrosis [39,40]. Their activities begin with interactions with cell membranes through electrostatic interactions.

As polycationic peptides, their multiple positive amino acids drive electrostatic interactions with lipid membranes that are also influenced by hydrophobic interactions (Figure 1). Due to the inherent differences in the surface composition between bacteria and mammalian cells, there can be differences in the preferential association of AMPs with a cell surface, leading to an accumulation at the surface and self-assembly reaching a particular concentration [41,42]. At this stage, various models have been proposed to describe the mechanism of action (MOA) of AMPs.

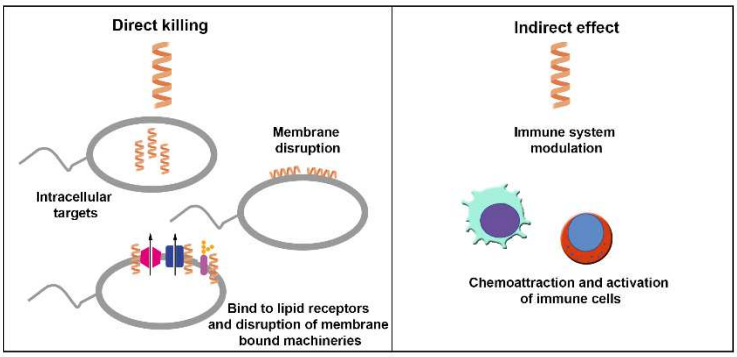

Figure 1. Interaction of cationic AMPs with eukaryotic and bacterial membranes. Images were created using BioRender.com.

Multiple MOAs have been proposed for AMPs during interactions with bacterial cell surfaces generalized as transmembrane pore and non-pore models (Figure 2). Within the pore model, the forms are differentiated as barrel-stave and toroidal, reflecting the bilayer's net arrangement. The

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barrel-stave shape preserves the bilayer organization and begins with AMPs oriented parallel to the surface before perpendicularly inserting into the lipid bilayer [43]. The amphipathic structure of α and/or β sheet peptides permits lateral peptide-peptide interactions between the hydrophilic amino acids to form the lumen, and the hydrophobic regions interact with bilayer lipids [44,45], which organize similarly to a protein ion channel (Figure 2A). A minimum length of 22 residues in an α-helical structure or eight residues in a β sheet is needed to span a lipid bilayer. Only a subset of known AMPs, such as alamethicin [46], pardaxin [47,48], and protegrins [43], have been shown to form barrel stave channels.

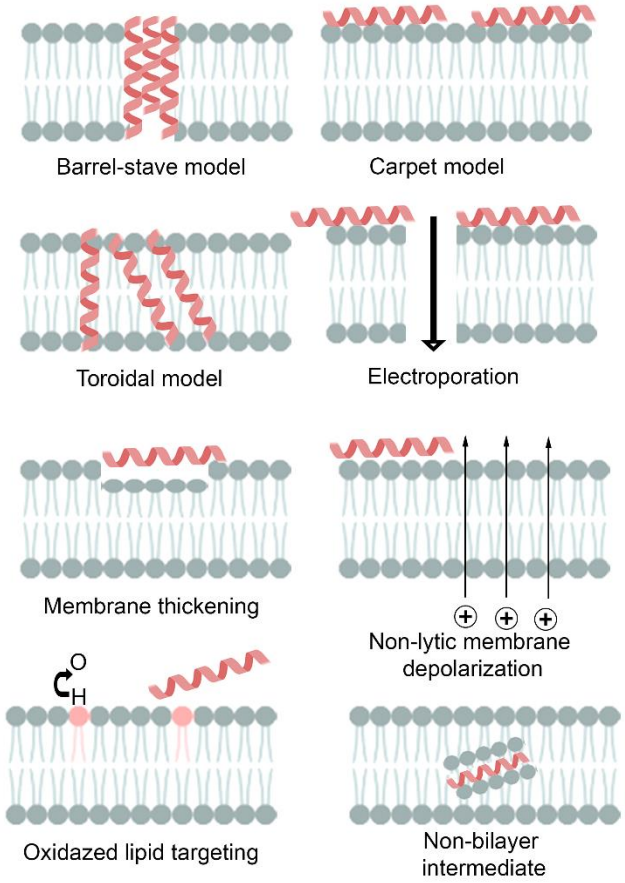

Figure 2. Mechanisms of action of AMPs on the surface of bacteria. A) Barrel-stave model: accumulated AMPs inserted into the membrane bilayer and associated into a channel. (B) Toroidal pore model: accumulated AMPs inserted in vertical and bent orientations to form a pore. (C) Carpet model: AMPs accumulate on the surface until a critical concentration displays detergent behavior to form micelles (D). Images generated at BioRender.com.

Toroidal pores also result from the perpendicular insertion of AMPs into the lipid bilayer but do not display lateral peptide-peptide interactions [46]. Rather, peptides disrupt the hydrophobic/hydrophilic arrangement of the bilayer and induce a local curvature in the lipid bilayer (Figure 2B). Pores are formed from a dynamic interaction between the inserted peptides and phospholipid head groups that create transient lipid-peptide supramolecules. In toroidal pores, the disruption in the hydrophobic and hydrophilic arrangement of the bills is temporary. Upon disintegration, some peptides are translocated to the inner cytoplasmic leaflet allowing cell entry to target intracellular components [49]. Several AMPs, such as magainin 2 [50], lacticin Q [50], aurein 2.2 [51], and melittin [46,50], have been shown to form toroidal pores. For aurein 2.2, lipid composition and thickness have been shown to influence pore formation [52,53]. In a 1:1 mixture of 1-palmitoyl-2-oleoyl-sn-glycerol-3-phospho-(1-rac-glycerol) with 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine toroidal pores are formed. In a membrane model of 1:1 1,2-dimyristoyl-sn-glycero-3-phospho-(1-rac-glycerol) with 1,2-dimyristoyl-sn-glyce rol-3-phosphocholine, aurein 2.2 does not

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form discrete pores. Other features of the toroidal pore include ion and size selectivity [54]. Both toroidal and barrel-stave pores ultimately lead to membrane depolarization and cell death.

The carpet model describes AMPs that do not insert into the lipid bilayer to form pores [50,54–56]; peptides adsorb to the cell surface (Figure 2C). Upon reaching a threshold concentration, membrane integrity is compromised by a detergent-like effect that leads to the formation of micelles (Figure 2D). As the results in the carpet model are not dependent on specific amino acid compositions, lengths, or interactions, it can describe the MOA of several AMPs at high concentrations due to their amphiphilic nature, such as cecropin [57], indolicidin [58], aurein 1.2 [56], and LL-37 [55]. It has been suggested that the carpet-like mechanism is a prerequisite step for the toroidal pore model [51]. Other models have been proposed, including interfacial activity, electroporation, and Shai-Huang-Matsazuki models [51]. However, in most cases, the results from model membrane systems. Only a few AMPs have been studied in whole bacterial cells to define their MOAs [59,60], suggesting that the results from model membranes describe potential MOAs and may need to explain their actions against pathogens fully.

Many AMPs are currently being studied to describe their therapeutic efficacy against A. baumannii strains. We have curated the online antimicrobial peptide database, APD3, to list many examples of AMPs under study (Table 1 and Table 2). These include both peptides produced by living organisms and novel peptides inspired by their activities.

Table 1. AMP produced by living organisms with activity anti-*A. baumannii*.

Peptide	Source	Sequence (nº amino acid)	Structure	MIC against A. baumannii (μg/mL)		Ref.
				Antibiotic-susceptible	MDR	
LL-37	H. sapiens	LLGDFFRKSKEKIGKEFKRIVQRI K DFLRNLVPRTES (37aa)	AH	32	16–32	[61,62]
KR-30	H. sapiens	KSKEKIGKEFKRIVQRIKDFLRN LV PRTES (30aa)	AH	16	8–16	[62]
KR-20	H. sapiens	KRIVQRIKDFLRNLVPRTES (20aa)	AH	64	16–32	[62]
KS-12	H. sapiens	KRIVQRIKDFLR (12aa)	AH	256	64–256	[62]
SAAP-148	H. sapiens	LKRVWKRVFKLLKRYWRQLKK PVR (24aa)	AH	—	6	[63]
CATH-BF derivative (Cath-A and OH-	Bungarus fasciatus (Snak e venom)	KFFRKLKKSVKKRAKEFFKKPR VI GVSIPF(30aa)	AH	—	8–32	[64]
ZY4 cathelicidin-BF-15 derived	Bungarus fasciatus (Snak e venom)	VCKRWKKWKR KWKKWCV-NH2 (17aa)	Cyclic SH-bridge	—	4.6–9.4	[65]
NA-CATH	Naja atra (Snake venom)	KRFKKFFKKLKNSVKKRAKKFF KK PKVIGVTFPF (34aa)	AH	10	10	[66]
OH-CATH30	King cobra (Snake venon)	KFFKKLKNSVKKRAKKFFKKPR VI GVSIPF(30aa)	AH	10	10	[67]
DOH-CATH30	King cobra (Snake venon)	KFFKKLKNSVKKRAKKFFKKPR VIGVSIPF (30aa)	AH	—	1.56–12.5	[67]
BMAP-27	Bovine myeloid	GRFKRFRKKFKKLFKKLSPVIPL LHLG (27aa)	AH	8-16	4-16	[68]
SMAP29	Sheep myeloid	RGLRRLGRKIAHGVKKYGPTVL RIIRIAG (29aa)	AH	8	4-32	[68]

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Latarcin 2a	Winter flounder (Pleuronectes americanos)	H-GLFGKLIKKFGRKAISYAVKKARGKH-OH (26aa)	**AH**	16	8-64	[68]
Maximin H2	**Nile Tilapia (Oreochromis niloticus)**	ILGPVLSMVGSALGGLIKKI-NH2 (20aa)	**AH**	64	16-128	[68]
NRC12	**Flatfish Genes**	GWKKWFNRAKKVGKTVGGLAVDHYL-NH2 (25aa)	**AH**	16	8-32	[68]
Pilosulin	**Ant venom (toxin pilosulin)**	GLGSVFGRLARILGRVIPKV-NH2 (20aa)	**AH**	16	8-16	[68]
Pleurocidin		GWGSFFKKAAHVGKHVGKAALTHYL-NH2 (25aa)	**AH**	16	8-32	[68]
TP4		FIHHIIGGLFSAGKAIHRLIRRRRR (25aa)	**AH**	16	8-32	[68]
D-Myrtoxin-Mp 1a (Mp1a)	Venom of Myrmecia pilosula	IDWKKVDWKKVSKKTCKVMXKACKEL-NH2 (26aa)	AH	0.025*	—	[69]
Venon cocktail proteins	Leiurus quinquestriatus (Scorpion venom)	Cocktail	—	—	50.6% of inhibition at 20 mg/mL of venom	[70]
Ranalexin	Rana catesbeiana (American bulfrog)	LGGLIKIVPAMICAVTKKC (19aa)	AH	—	4–18	[71]
Danalexin	Rana catesbeiana (American bulfrog)	LGGLIKIVPAMICAVTKKC (19aa)	AH	—	4–16	[71]
LS-sarcotoxin	Lucilla serricata	GWLKKIGKKIERVGQHTRDATIQTIGVAQQAANVAATLK-NH2 (39aa)	AH	4	4–8	[72]
LS-stomoxyn	Lucilla serricata	GFRKRFNKLVKKVKHTIKETANVSKDVAIVAGSGVAVGAAM-NH2 (41aa)	AH	8	4–16	[72]
Mini-ChBac7.5 Nα	Domestic goat (Capra hircus)	RRLRPRRPRLPRPRPRPRPRPR (22aa)	AH	—	2*	[73]
Mini-ChBac7.5 Nβ	Domestic goat (Capra hircus)	RRLRPRRPRLPRPRPRPRPRP (21aa)	AH	—	4*	[73]
AM-CATH36	American alligator	GLFKKLRRKIKKGFKKIFKRLPPIG VGVSIPLAGKR (36aa)	AH	5.2	5.2	[66]
AM-CATH28	American alligator	KIKKGFKKIFKRLPPIGVGVSIPLAGKR (28aa)	AH	28	10	[66]
AM-CATH21	American alligator	GLFKKLRRKIKKGFKKIFKRL (21aa)	AH	42	10	[66]
WAM-1	Tammar wallaby (Macropus eugenii)	KRGFGKKLRKRLKKFRNSIKKRLKNFNVVIPIPLPG (36aa)	AH	8.12	4–64	[74,75]

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Indolicidin	Cytoplasmic granules of the bovine neutrophils	LPWKWPWWPWRR-NH2 (13aa)	Other structure	4	2–64	[75–77]
Bactenecin	Bovine neutrophil granules, Caprine	LCRIVVIRVCR (12aa)	B-turn structure Ciclyc	64	—	[75,78,79]
Histatin-8	H. sapiens	KFHEKHHSHRGY (12aa)	AH	8	—	[77]
HNP-1	H. sapiens (Polymorphonuclear neutrophil)	ACYCRIPACIAGERRYGTCIYQGRLWAFCC (30aa)	AH	50	—	[76]
HNP-2	H.sapiens (Polymorphonuclear neutrophil)	CYCRIPACIAGERRYGTCIYQGRLWAFCC (29aa)	AH	50	—	[76]
HD5d5	H.sapiens (Polymorphonuclear neutrophil)	ARARCRRGRAARRRRLRGVCRIRGRLRRLAAR (32aa)	AH	40	40	[80]
CL defensin	Cimex Lectularius (Bedbug)	ATCDLFSFQSKWVTPNHAACAAHCTARGNRGGRCKKAVCHCRK (43aa)	AH, antiparallel BS; N-terminal loop	—	—	[81]
HBD-2	Epithelial lining of respiratory /urinary tracts	GIGDPVTCLKSGAICHPVFCPRRY KQIGTCGLPGTKCCKKP (41aa)	Beta	3.90–9.35	3.25–4.5	[82]
HBD-3	Epithelial lining of respiratory /urinary tracts	GIINTLQKYYCRVRGGRCAVLSCL PKEEQIGKCSTRGRKCCRRKK (45aa)	AH + BS	4	4	[83]
Magainin-1	Frog skin peptide	GIGKFLHSAGKFGKAFVGEIMKS (23aa)	AH	—	256	[84,85]
Magainin-2	Frog skin peptide	GIGKFLHSAKKFGKAFVGEIMNS (23aa)	AH	9.8–64	4.9–64	[84–86]
Pexiganan	Frog skin peptide	GIGKFLKKAKKFGKAFVKILKK (22aa)	AH	1–8	1–8	[87–89]
Aurein 1,2	Frog skin peptide	GLFDIIKKIAESF (13aa)	AH	16	—	[89]
Citropin 1.1.	Australian tree frog of the Litora genus	GLFDVIKKVASVIGGL-NH2 (16aa)	AH	16	—	[89]
Temporin A	European red frog Rana temporaria	FLPLIGRVLSGIL-NH2 (13aa)	AH	128	—	[89]
Brevinina 2 (B2RP)	Frog skin peptide	GIWDTIKSMGKVFAGKILQNL-NH2 (21aa)	AH	29	7–13.9	[90]
[D4K] B2RP	Frog skin peptide	GIWKTIKSMGKVFAGKILQNL-NH2 (21aa)	AH	4–16	4–16	[91,92]
B2RP-Era	Frog skin peptide	GVIKSVLKGVAKTVALGML-NH2 (19aa)	AH	8–32	8–64	[91,93]

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Alytesirin-1c	Frog skin peptide	GLKEIFKAGLGSLVKGIAAHVA S-NH2 (23aa)	AH	—	11.3–22.6	[94]
[E4k] Alytesirin-1c	Frog skin peptide	GLKEIFKAGLGSLVKGIAAHVA S-NH2 (23aa)	AH	4–16	4–16	[91,92]
Tachyplesin III	Horseshoe crabs (Tachypleus gigas) and (Carcinoscorpius rotundicauda)	KWCFRVCYRGICYRKCR-NH2 (17aa)	BS 2 dissulfite bridges	—	8-16	[92]
[S7K, G11K] Alytesirrin-2a	Frog skin peptide	ILGKLLKTAAKLLSNL-NH2 (16aa)	AH	—	8	[95]
PGLa-AM1	Frog skin peptide	GMASKAGSVLGKVAKVALKA AL-NH2 (22aa)	AH	16–128	16–128	[91,96]
CPF-AM1	Frog skin peptide	GLGSVLGKALKIGANLL (19aa)	AH	16–128	4–128	[91,97,98]
CPF-B1	Frog skin peptide	GLGSLLGKAFKIGLKTVGKMM GGAPREQ (28aa)		—	11.4–22.8	[99]
CPF-C1	Frog skin peptide	GFGSLLGKALRLGANVL (17aa)		5	—	[98]
[E6k,D9k] Hymenochirin-1B	Frog skin peptide	LKLSPKTKDTLKKVLKGAIKGAI A IASMA-NH2 (29aa)	AH	—	4.9	[100]
Hymenochirin-1 Pa	Frog skin peptide	LKLSPKTKDTLKKVLKGAIKGAI AIASMA-NH2 (29aa)	AH	—	—	[101]
[G4K] XT7	Frog skin peptide	GLLGPLLKIAAKVGSNLL-NH2 (18aa)	AH	4–32	4–64	[91,102]
Buforin II	Frog skin peptide	TRSSRAGLQFPVGRVHRLLRK (21aa)	AH	8–19.5	0.25–39	[84,85,103,104]
Melittin	European honeybee (Apis mellifera)	GIGAVLKVLTTGLPALISWIKRK RQQ (26aa)	AH	0.25–4	0.25–25	[76,105,106]
Cecropin A	Cecropia moth (Hyalophora cecropia)	KWKLFKKIEKVGQNIRDGIIKA GP AVAVVGQATQIAK (37aa)	AH	32	0.5–32	[76,107]
BR003-cecropin A	Aedes aegypti	GGLKKLGKKLEGAGKRVFNAA EK ALPVVAGAKALRK (36aa)		5	5	[108]
Mdc	Housefly larva e	GWLKKIGKKIERVGQHTRDATI Q TIGVAQQANAVAATLKG (40aa)		4	4	[109]
Cecropin P1	Pig (Ascaris suum)	SWLSKTAKKLENSAKKRISEGIA IA IQGGPR (31aa)		1.6	—	[76,110]
Myxinidin 2	Myxine glutinosa L	KIKWILKYWKWS (12aa)	AH	—	12.5	[111]
Myxinidin 3	Myxine glutinosa L	RIRWILRYWRWS (12aa)	BS	—	6.3	[111]
FLIP 7	Calliphora vicina (Medicinal Maggots)		AH	—	125-416 biofilm bactéria sensitivity	[112]

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Mastoparan	Vespula lewisii (Hornet venom)	INLKALAALAKKIL (14aa)	AH	4	—	[76,113,114]
Mastoparan-AF (EMP-AF)	Hornet venom (Vespa affinis)	INLKAIAALAKKLF-NH2 (14aa)	AH	2–16	2–16	[115]
Mastoparan-Chitosan Nanoconstruct	Wasp venom(Vespula lewissi)	INLKALAALAKKIL-NH2 (14aa)	AH	-	2-4	[116]
DCD-1 L	Eccrine sweat glands	SSLLEKGLDGAKKAVGGLGKL GKDAVEDLESVGKGAVHDVK DVLD SVL (48aa)	AH	16	—	[117,118]
Hp l404 analogs (A, K, V, L, I, W)	Venom gland scorpion (Heterometnus pertersii)	GILGKLWEGVKSIF-NH2 (14aa)	AH	3.13–12.5	3.13–16.25	[119,120]
Protegrin-1	Cimex lectularius	RGGRLCYCRRRFCVCVGR-NH2 (18aa)	AH	—	2-8	[121]
Nuripep 1653	Derived from the P54 nutrient reservoir protein (aa 271–292) pea protein from Pisum sativum	VRGLAPKKSLWPFGGPFKSPFN (22aa)	AH	—	12	[122]
Agelaia-MPI	Agelaia pallipes pallipes	INWLKLGKAIIDAL (14aa)	AH	6.25	12.5–25	[123]
Polybia-MPII	Pseudopolybia vespiceps testacea	INWLKLGKMVIDAL (14aa)	AH	12.5	25	[123]
Polydin-I	Polybia dimorpha (Soci al wasp)	AVAGEKLWLLPHLLKMLLTPT P (22aa)	AH	>25	>25	[123]
Con10	Scorpion venoms (Opist hacanthus cayaporum)	FWSFLVKAASKILPSLIGGGDD NKSSS (27aa)	AH	12.5	12.5	[123]
NDBP5.8	Scorpion venoms (Opist hacanthus cayaporum)	GILGKIWEGVKSLI (14aa)	AH	>25	>25	[123]
Delfibactin A	Gram-negative bactéria Delfia spp.	C40H68N14O18	—	—	16	[124]
WLBU2- arginine-rich amphiphilic peptide	Skin wounds	RRWVRRVRRWVRRVVRVVRR WVRR (24aa)	—	~7.484	~7.484	[125]
α-Helical-26 (A12L/A20L)	D- and L-diastereomeric peptides	Ac-KWKSFLKTFKSLKKTVLHTLLK AISS-NH2 (26aa)	AH	—	0.5–1.0	[126]

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Cy02 (cyclotide)	Viola odorata	GIPCGESCVWIPCISSAIGCSCKS KVCYRN (30aa)	BSs	—	15*	[127]
Bicarinalin (YRTX-Tb1a)	Tetramorium bicarinatum venom	KIKIPWGKVKDFLVGGMKAV (20aa)	AH	—	4	[128]
Glatiramer acetate	Homo sapiens	EAYKAAEKAYAAKEAAKEAA KAKAEKKAAYAKAKAAKYEK KAKKAAAEYKKK (52aa)	—	Reduct viable cells	Reduct viable cells	[129]
Lactoperoxidase (Lpo)	Camel (Colostrum milk)	Large protein	complex	—	Inhibition effects, significant clearance of Ab in lung and BC	[130]
Lactoferrin (Lf)	Camel (Colostrum milk)	Large protein	complex	—	Inhibition effects, significant clearance of Ab in lung and BC	[130]
Artlysin Art-175	Pseudomonas aeruginosa bact eriophage	Comprises a modified variant of endolysin KZ144 with an N-terminal fusion to SMAP-29	—	—	4–20	[131]
Epsilon-poly L-lysine (EPL)-catechol	Streptomyces albulus derived	Complex	—	—	Reducing bacterial burden in vivo	[132]
Nodule-specific cysteine-rich (NCR) peptide and its derivatives	Medicago trunculata	RNGCIVDPRCPYQQCRRPLYCR RR (24aa)	AH	1.6–25 MBC	—	[133,134]
D-150-177C, HBcARD derivative peptide	Hepatitis B virus	RRRGRSPRRRTPSPRRRRSQSPR R RRSC (28aa)	AH	16	16–32	[135]
Colistin (Polymyxin E)	Bacillus colistinus	C52H98N16O13 (cyclic compound)	—	Antibiofilm, side effects	—	[136]
PlyF307 (P307)	Phage Lysin	146 aa (Access number KJ740396)	—	750	750–2000	[137]
P307SQ–8C	Hepatitis B virus	NAKDYKGAAAEFPKWNKAGG RV LAGLVKRRKSQSRESQC (39aa)	—	125	62.5–125	[137]
N10	Blood biopanning	ACKDVNTSMCGGK (13aa)	AH	500	500	[138]
NB2	Biofilm biopanning	ACERSIRTVCGGK (13aa)	AH	500	500	[138]
Melittin with imipenem (IPM)	European honeybee and antimicrobial	GIGAVLKVLTTGLPALISWIKRK R QQ (26aa) + IPM	AH	0.31–0.37	0.12–0.25	[139]

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Melittin with colistin (COL)	European honeybee and antimicrobial	GIGAVLKVLTTGLPALISWIKRK R QQ (26aa) + COL	AH	0.37–0.5	0.19–0.37	[139]
LS-AMP-E1	**Chinese wolf spider (Lycosa sinensis)**	AGMKNIIDAIKKKLGGKL (18aa)	**AH**	-	25-100*	[140]
LS-AMP-F1	**Chinese wolf spider (Lycosa sinensis)**	TGLGKIGYLMKKLLSKAKV(19a a)	**AH**	-	3.1-12.5*	[140]
Caerin 1.1	Australian tree frog	GLLSVLGSVAKHVLPHVVPVIA EHL-NH2	**AH**	7.5	-	[141]
Caerin 1.9	Australian tree frog	GLFGVLGSIAKHVLPHVVPVIA EKL-NH2	**AH**	3.75	-	[141]
Caerin 1.1 + Caerin 1.9	Australian tree frog	-	**AH**	0.9375- 1.875	-	[141]
Am23SK	**Alligator mississippiens is**	SCRFSGGYCIWNWERCRSGHFL VALCPFRKRCCK (34aa)	**AH**	-	2	[142]
Nisin	**Probiotic bacterium (Lactococcus lactis)**	(34aa)	**-**	128	64-128	[143]
P10 + Nisin in combination	**-**	-	**-**	32	16-32	[143]
Hp1404	**Scorpion venom gland (Heterometrus petersii)**	GILGKLWEGVKSIF (14aa)	**AH**	5	5-10	[144,145]
VsCT1	Scorpion venom gland (Heterometrus petersii)	FLKGIIDTVSNWL (13aa)	AH	>40	-	[144]
BmKn1	Scorpion venom gland (Heterometrus petersii)	FIGAVAGLLSKIF (13aa)	AH	>40	-	[144]
Spiniferin	Scorpion venom gland (Heterometrus petersii)	ILGEIWKGIKDIL (13aa)	AH	>40	-	[144]
Im4	Scorpion venom gland (Heterometrus petersii)	FIGMIPGLIGGLISAIK (17aa)	AH	>40	-	[144]
Ctriporin	Scorpion venom gland (Heterometrus petersii)	FLWGLIPGAISAVTSLIKK (19aa)	AH	20	20-40	[144]
Im5	Scorpion venom gland (Heterometrus petersii)	FLGSLFSIGSKLLPGVIKLFQRKK Q (25aa	AH	2.5	2.5-10	[144]

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Hp1404 analogs	Scorpion venom gland (Heterometrus petersii)	-	AH	3.13-25*	-	[145]
Lynronne-1	**Bovine rumen microbiome**	LPRRNRWSKIWKKVVTVFS (19aa)	AH	4	-	[146]
BmKn2	**Scorpion (Mesobuthus martensii Karsch)**	FIGAIARLLSKIF-NH2 (13aa)	AH	10	5-10	[147]
Hylin a1	**American frog (Hypsiboas albopunctatus)**	IFGAILPLALGALKNLIK-NH2 (18aa)	AH	2*	2-8*	[148]
Hylin a1-11K	**American frog (Hypsiboas albopunctatus)**	IAKAILPLALKALKNLIK-NH2 (19aa)	AH	1-2*	1-2*	[148]
aHylin a1-15K	**American frog (Hypsiboas albopunctatus)**	IAKAILPLALKALKKLIK-NH2 (19aa)	AH	1-2*	1-2*	[148]
Esc(1-21)	**Frog-skin**	GIFSKLAGKKIKNLLISGLKG-NH2 (21aa)	AH	-	17.5-35	[149]
Esc(1-21) + Colistina	**Frog-skin**	GIFSKLAGKKIKNLLISGLKG-NH2 (21aa) + Colistina	**AH**	-	1.1-4.4	[149]
HBD-3	**Epithelial cells**	GIINTLQKYYCRVRGGRCAVLS CLPKEEQIGKCSTRGRKCCRRK K (45aa)	**-**	-	4-16	[150]
Epi-122–42	**Orange-spotted grouper (Epinephelus coioides)**	GFIFHIIKGLFHAGKMIHGLV (21aa)	**-**	-	4–32	[150]

Table 2. Synthetic AMPs with activity anti-*A. baumannii*. c.

Peptide	**Source**	**Structure**		**MIC against *A. baumannii* (μg/mL)**		**Ref.**
				Antibiotic-susceptible	**MDR**	
GW-A2	Synthetic peptide	GAKYAKIIYNYLKKIANALW (20aa)	**AH**	32	8-32	[68]
GW-H1a	Synthetic peptide	GYNYAKKLANLAKKFANALW-NH2 (20aa)	**AH**	32	8-32	[68]
GW-Q6	Synthetic peptide	GIKIAKKAITIAKKIAKIYW (20aa)	**AH**	16	8-16	[68]
Omiganan	Synthetic peptide	ILRWPWWPWRRK-NH2 (12aa)	AH	32	—	[89]
r-Omiganan	Synthetic peptide	KRRWPWWPWRLI-NH2 (12aa)	AH	16	—	[89]
SAAP-148 NPs	*Synthetic peptide*	LKRVWKRVFKLLKRYWRQLKKP VR (24aa) + NPs	AH	—	—	[151]
Cecropin-4	Synthetic peptide	GWLKKIGKKIERVGQNTRDATIQ AIGVAQQAANVAATLKG (40aa)	AH	4	*4*	[152,153]

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Octopromycin	**Synthetic peptide**	N-RRLIRTDTGPIIYDYFKDQLLKKG MVILRESMKNLKGM-C *(38aa)*	***AH***	-	50	[154]
LyeTx I-bPEG	Synthetic peptide		**AH**			[155]
zp3	**Synthetic peptide**	GIIAGIIIKIKK-NH2 (12aa)	**AH**	4	-	[156]
P10	**Synthetic derivated**	LAREYKKIVEKLKRWLRQVLRTLR (24aa)		4	8-32	[143]
P10 + Nisin in combination	**-**	-		1	4-16	[143]
NCR169C and its substitution derivatives	*Synthetic peptide*	KSKKPLFKIWKCVENVCVLWYK	AH	1.6-12.5 MBC	—	[157]
OMN6	**Synthetic peptide**	H-M-C-KWKLFKKIEKVGQNIRDGIIKA-GP-AVAVVGQATQIAK-C-NH2(40aa)	**AH**	8	4-8	[158,159]
BmKn2-7	**Synthetic peptide**	FIKRIARLLRKIF-NH2 (13aa)	**AH**	5	5-10	[147]
BmKn2-7R	**Synthetic peptide**	FIRRIARLLRRIF-NH2 (13aa)	**AH**	2.5	2.5-5	[147]
BmKn2-7K	**Synthetic peptide**	FIKKIAKLLKKIF-NH2 (13aa)	**AH**	2.5	2.5-5	[147]
AS-CATH8	**Synthetic peptide**	KRVNWAKVGRTALKLLPYIFG (21aa)	**AH**	0.6	-	[142]
LJ-hep2$_{(66–86)}$	**Synthetic peptide**	IKCKFCCGCCTPGVCGVCCRF *(21aa)*		-	1.5-3	[160]
DGL 13K	**Synthetic derived D-enantiomers of GL13K derived from the salivary protein BPIFA2**	GKIIKLKASLKLL-NH2 (13aa)	**-**	-	8-32	[161]
PLP-3	**Synthetic peptide derived from the innate immune system of vertebrates**		**Antiparallel BS**	1-2	1-2	[162]
ECPep-D	**Synthetic peptide**	*RPFTRAQWFAIQHISPRTIAMRAIN NYRWR (30aa)*	**-**	37.57	-	[163]
ECPep-2D-Orn	**Synthetic peptide**	*OPFTOAQWFAIQHISPOTIAMOAI NNYOWO (30aa)*	**-**	17.53	-	[163]
Mt6	**Synthetic peptide**	KKFKKTAKWLIKSAWLLLKSLAL KMK (26aa)	**AH**	8	-	[164]
D-Mt6	**Synthetic peptide**	KFKKTAKWLIKSAWLLLKSLALK MK (25aa)	**AH**	8	-	[164]

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Octominin, Octominin-CNPs	Synthetic derived, defensin 3 of *Octopus minor*	GWLIRGAIHAGKAIHGLIHRRRH (23aa)	AH	—	5	[165,166]
Ceragenins; CSA-192; CSA-131; D-150-177C; HBcARDderivative	Cholic acid synthetic mimics,	Steroids compounds	-	—	—	[167]
OG1410	**ApoE-based synthetic peptide**	acetyl-ASAib-LRKL-Aib-KRLL-amide	**AH**	16	16	[168]
MSI-78	**Synthetic peptide, magainin analogue**	GIGLPLLLALLPGLAPVLILLL-NH2 *(22aa)*	**AH**	-	5	[169]
mCM11, cecropin–melittin 11	**Synthetic peptide**	NH2-WRLFRRILRVL-NH2 (11aa)	**AH**	32	< 4 - > 512	[170]
Scolopendin A2	**Synthetic peptide**	AGLQFKVGRIGRLLRK (16aa)		-	16	[171]
Trichogin analogs	**Synthetic peptide**	1-Oct-Aib-Gly-Leu-Aib-Gly-Gly-Leu-Aib-Gly-Ile-Lol		2- >128	-	[172]
RR	Computationally designed	WLRRIKAWLRR (11aa)	AH	—	25–99	[173,174]
RR2	Computationally designed	WIRRIKKWIRRVHK (14aa)	AH	—	3–6	[174]
RR-4	Computationally designed	WLRRIKAWLRRIKA (14aa)	AH	—	3–6	[174]
DP7	Computationally designed	VQWRIRVAVIRK (12aa)	AH	—	4–16	[175–177]
Omega 76-shuft1	Computationally designed	AFLLKKKKGIIFFEKAKKGK (20aa)	AH	—	4–16	[178]
'Ω17 family peptides	Computationally designed	RKKAIKLVKKLVKKLKKALK (20aa)	AH	2	1–8	[178]
'Ω76 family peptides	Computationally designed	FLKAIKKFGKEFKKIGAKLK (20aa)	AH	4	2–8	[178]
pepD2	**Computationally designed**	WKKLKKLLKKLKKL-NH2 (14aa)	**AH**	8	-	[179]
Pro9-3	**Computationally designed**	RLWLAIWRR-NH2 (9aa)	**AH**	16	8-64	[180]
Pro9-3D	Computationally designed	RLWLAIWRR-NH2 (9aa)	**AH**	8	4-16	[180]
R-Pro9-3	Computationally designed	RRWIALWLR-NH2 (9aa)	**AH**	16	8-32	[180]
R-Pro9-3D	Computationally designed	RRWIALWLR-NH2 (9aa)	**AH**	8	4-16	[180]
TP2-5	Computationally designed	KKCIAKAILKKAKKLLKKLVNP (22aa)	**AH**	3.125	1.56-3.125	[181]
TP2-6	Computationally designed	KKCIAKAILKKAKKLLKDLVNP (22[a])	**AH**	3.125	3.125-12.5	[181]

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IKR18	**Computationally designed**	IKRQYKRFFKLFKWFLKK (18aa)	**AH**	1	-	[182]
HP(2–9)-ME(1–12) (HPME)	Chimeric peptide	AKKVFKRLGIGAVLKVLTTG (20aa)	AH	6.25	3.12–12.5	[183]
HP(2–9)-MA(1–12) (HPMA)	Chimeric peptide	AKKVFKRLGIGKFLHSAKKF-NH_2 (20aa)	AH	6.25	3.12–6.25	[183]
CA(1–8)-ME(1–12) (CAME)	Chimeric peptide	KWKLFKKIGIGAVLKVLTTG-NH_2 (20aa)	AH	3.12	3.12–12.5	[183]
CA(1–8)-MA(1–12) (CAMA)	Chimeric peptide	KWKLFKKIGIGKFLHSAKKF-NH_2 (20aa)	AH	12.5	3.12–12.5	[183]
TAT-RasGAP$_{317–326}$ anticancer peptide	Chimeric (cell penetrating sequence + Src homology sequence)	G48RKKRRQRRR^{57} + W^{317}MWVTN LRTD^{326}	AH	Growth inhibitory effect	—	[184,185]
TAT-RasGAP$_{317–326}$	**Chimeric peptide**	G48RKKRRQRRR57 (10aa)		-	-	[186]
Cecropin A (1–8) melittin (1–10) (CAME)	Hybrid peptide	KWKLFKKIGIGAVLKVLTTG-NH2 (20aa)	AH	32	8-32	[68]
BP100	Hybrid peptide	KKLFKKILKYL (11aa)	AH	—	4	[128]
I16K-piscidin-1 and analogs	Hybrid striped bass *Morone saxatilis x M. chrysops*	FFHHIFRGIVHVGKTIHRLVTG (22aa)	—	—	3.1	[187]
PapMA	**Hybrid peptide**	RWKIFKKIPKFLHSAKKF-NH2 *(18aa)*	**AH**	32	16-32	[188]
D-AP19	**Hybrid peptide**	RLFRRVKKVAGKIAKRIWK-NH2 (19aa)		7.81	3.91-15.63	[189]
BP214	**Hybrid peptide**	KKLFKKILRYL (11aa)	AH	2	-	[190]
BP214 analogs	**Hybrid peptide**	-	**AH**	2- >64	-	[190]
PNA (RXR)4 XB	**Peptide nucleic acid conjugated to (RXR)4 Phosphorodiamidate Morpholino Oligomers**	RXRRXRRXRRXRXB (14aa)	—	—	1.25*	[191]
Stapled AMP Mag (i + 4)1, 15(A9 K, B21A, N22 K, S23 K)	**NA, based in magainin 2 structure**	Mag(i + 4)1,15(A9K,B21A,N22K,S23 K)	**complex**	—	—	[192]
S4A	NA	IOWAGOLFOLFO-NH2 (12aa)	AH	100	50	[193]
SPO	NA	NINONWNANGNONLNFNONLN FNO-NH2 (22aa)	AH	100	50	[193]

Chex1-Arg20 amide (ARV-1502)	NA	H-Chex-Arg-Pro-Asp-Lys-Pro-Arg-Pro-Tyr-Leu-Pro-Arg-Pro-Arg-Pro-Pro-ArgPro-Val-Arg-NH2	—	—	Reduction of bacterial load	[194]

AH, alpha helical; BS, beta sheet; NA, unavailble; *, μM; aa, amino acid; NPs, nanoparticles.

2.1. Cathelicidins

Cathelicidins are a group of more than 30 cationic AMPs (CAMPs) identified in the immune system of several vertebrates. Their structure comprises two domains involved in their antimicrobial activity [195,196]. In comparison to the broad-spectrum antibiotics imipenem and meropenem of the carbapenem class that is often chosen to treat MDR A. baumannii (MIC = 16–32 mg/L) [197], these peptides have shown good activity.

2.1.1. Humans

The human cathelicidin LL-37 has an α-helical structure and is produced as a component of the innate immune response. It exhibits a broad-spectrum microbicidal activity against Gram-positive and Gram-negative bacteria observed as plasma-membrane disruption [198]. It also neutralizes lipopolysaccharide (LPS) and modulates the immune response through cellular activation, inflammation regulation, chemotaxis, and wound healing [61,199–202]. Against *A. baumannii*, LL-37 and its fragments KS-30 and KR-12 showed activity against a sensitive and four MDR clinical isolates [62]. LL-37 inhibited all sensitive and drug-resistant strains at concentrations between 16–32 μg/ml, while the minimum inhibitory concentration (MIC) for KS-30 and KR-12 was 8–16 and 128–256 μg/ml, respectively. In biofilms, LL-37 and the fragment KS-30 were observed to significantly inhibit and disperse the *A. baumannii* on abiotic surfaces at 32 and 64 μg/ml, respectively [62].

Against the ESKAPE pathogens *P. aeruginosa*, *A. baumannii*, and *S. aureus*, a group of synthetic peptides based on LL-37 AM showed potent microbicidal activity without selecting resistance and could eliminate persistent cells and biofilms at micromolar concentrations [63]. One peptide, SAAP-148, is an α-helical AMP that could inhibit the growth of *A. baumannii* MDR and prevent biofilm formation at a concentration of 6 μg/ml. An ex vivo human skin infection model and an in vivo murine skin infection model eliminated acute and biofilm-related infections at concentrations of ~5% [63]. Its anti-biofilm activity improved when incorporated into nanoparticles of Poly(lactic-co-glycolic) (PLGA) that gradually increased over time, suggesting a sustained local release of the peptide based on the dose-effect in vitro profile [64].

Another synthetic derivative of LL-37, P10, is cationic, which showed stronger activity than LL-37 [143,203]. Also, based on LL-37, the de novo pepD2 was designed with a trigonal distribution of positive charges in its helical structure and displayed a MIC value of 8 μg/mL against the ATCC strain of *A. baumannii*. WLBU2 (also called PLG0206) is an engineered cationic amphipathic α-helix derived from the LL-37 peptide that can insert into bacterial membranes leading to cell death as well as potent antibacterial effects against biofilms of MDR *A. baumannii* and *K. pneumoniae* [125]. MIC values for WLBU2 were reported to be 1.5-3.2 μM for an XDR *A. baumannii* [204], 7.484 μM for clinical isolates [128], and 7.943 μM for *K. pneumoniae*.

2.1.2. Snake

Various cathelicidins have been identified from snakes. Cathelicidin-BF (Cath-BF) was isolated from the venous glands of banded krait (*Bungatus fasciatus*) [205]. It is one of the best-known cathelicidins and presents an α-helical structure. Two mechanisms attributed to its antimicrobial activity: disrupting bacteria membranes and directly targeting intracellular targets [205]. It has proven highly active against drug-resistant clinical isolates of *A. baumannii* and can inhibit growth at a concentration of 12.8 μg/ml [64]. A disulfide bridge stabilized cyclic peptide derivative of Cath-BF, ZY4, also displayed activity against clinical MDR isolates of *A. baumannii* with MIC values ranging between 4.6 and 9.4 μg/mL. It killed bacteria by membrane permeabilization and could inhibit biofilm formation [65]. With a half-life of 1.8h in vivo, ZY4 displayed good stability and a low tendency to induce resistance. NA-CATH has an N-terminal α-helical structure with an unstructured C-terminal [66]. Identified in Chinese cobra (Naja atra) [206], it can inhibit the growth of drug-resistant strains of *A. baumannii* at 10 μg/ml [206]. Its antimicrobial MOA appears to be through membrane deformation and the formation of transient pores [207]. From the king cobra (*Ophiophagus hannah*), OH-CATH was

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identified [67]. Its analog, DOH-CATH30, exhibits microbicidal activity against MDR *A. baumannii* with a MIC of 1.56 to 12.5 μg/mL.

2.1.3. Alligator

The antibacterial activity of serum from American alligators (*Alligator mississippiensis*) can be attributed to the presence of CAMPs, and several have been identified [208]. AM-CATH36 inhibited the growth of both drug-resistant and sensitive *A. baumannii* at 2.5 μg/ml, while its two fragments, AM-CATH28 and AM-CATH21, inhibited at 10 μg/ml [66]. All three appear to permeabilize bacterial membranes. MDR clinical isolates appeared more sensitive to the fragments than full length. The recently identified As-CATH8 displayed in vitro activity profiles similar to the last-resort vancomycin and polymyxin B antibiotics. In a murine abscess model of high-density bacterial infections, As-CATH8 demonstrated good activity against *A. baumannii* (MIC = 0.6 μg/mL) and another ESKAPE pathogen, S. aureus [142].

2.1.4. Wallaby

WAM-1 is a cathelicidin present in the milk of marsupials and isolated from the mammary gland of Tammar wallaby (*Macropus eugenii*) with antimicrobial activity [74,209]. In studies on biofilms, WAM-1 inhibited biofilm formation in clinical isolates and could disperse 24h-old biofilms of most isolates tested that included MDR strains [75]. In comparison to LL-37, WAM-1 shows several desirable properties. It's in vitro activity was 12 to 80 times more effective than LL-37 at eliminating clinical isolates of *A. baumannii*, and its activity as a peptide is not reduced in the presence of total serum or high NaCl concentrations. While its MOA is unknown, it does not lead to hemolysis and has the potential for in vivo applications [75].

2.1.5. Hoofed animals

Domesticated animals have yielded several cathelicidins. The cytoplasmic granules of the bovine neutrophils contain indolicidin, a short tryptophan-rich cationic peptide that displaces divalent cations on the surface of cell membranes, forms pores and can inhibit DNA processing enzymes [78,210–213]. It displays potent anti-*A. baumannii* activity with a MIC of 4–32 for sensitive clinical isolates and 16 μg/ml against colistin-resistant strains [76]. In combination in vitro with antimicrobial agents, the MIC of indolicidin against 12 MDR clinical isolates was reported to be between 2–64 μg/ml [78]. Bactenecin is a cyclic, arginine-rich cationic AMP isolated from cows, sheep, and goats with a type I β-turn structure and a disulfide bond between cysteines at positions 3 and 11 [77,78]. It can permeabilize cell membranes and inhibit RNA and protein synthesis with a MIC of 16 and 64 μg/ml against sensitive and colistin-resistant *A. baumannii*, respectively [59,76]. Other studies of cathelicidins include bovine BMAP-27, sheep SMAP29, and goat minibactenecins [73], which have been shown to inhibit the growth of clinical MDR *A. baumannii* strains [68].

2.2. Defensins

Animals, plants, and fungi produce an ancient class of AMPs called defensins that contain six to eight conserved cysteine residues. Their MOA includes binding cell membranes and forming pores that kill pathogens [214]. Defensins have been categorized into α, β, and θ-defensins subfamilies [215].

2.2.1. Human α-Defensins

The CAMPs HNP-1 and HNP-2 are α-defensins produced in human neutrophils that differ by their N-terminal amino acid. They are components of the human neutrophil peptides contained in polymorphonuclear neutrophil granules that are released for secretion upon activation to microbes [216]. The standard strain of *A. baumannii* (ATCC 19606) was affected by concentrations of 50 μg/ml, while a colistin-resistant strain appeared more sensitive (MIC = 3.25 μg/ml) [76]. HD5, another human defensin, has little effect on *A. baumannii* effect (MIC = 320 μg/ml), buts its derivative HD5d5 showed a lower MIC (40 μg/ml) through cell membrane damage and cell entry that reduced the activities of superoxide dismutase and catalase [217,218].

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2.2.2. β-. Defensins

HBD-2 and HBD-3 are human β-defensins found in the epithelial lining of the respiratory system and urinary tracts. Interestingly, they appear more effective against MDR clinical isolates [219]. Another β-defensins, HBD-3, combines an α-helical segment with the β strand and can kill both non-MDR and MDR strains of *A. baumannii* in serum-free conditions [220]. It also displayed wound healing properties and has a potential application in wound dressings [83,221]. In *A. mississippiensis*, the AM23sk isoform of its β-Defensin showed in vitro antibacterial activity against *A. baumannii* (MIC = 2 μg / ml) [142].

2.2.3. Insect defensins

The insect defensin CL-defensin can partially permeabilize A. baumannii and, different from others, is predicted to have an N-terminal loop, an α-helix segment, and an antiparallel β-sheet according to circular dichroism spectroscopy [81].

2.3. Frog AMP

2.3.1. Magainin and pexiganan

The skin of the African clawed frog (*Xenopus laevis*) has two α-helical cationic amphipathic AMPs, Magainin-1 and 2 [222]. Their primary MOA against microbes is pore formation [85,223]. Magainin-2 shows higher activity against MDR strains *of A. baumannii* at 4.9–64 μg/ml and can both inhibit and eliminate biofilms [76,85]. It also offers greater stability in physiological conditions and low hemolytic activity. Interestingly, it shows anticancer potential with low toxicity against non-cancerous mammalian cells [85]. A synthetic analog of Magainin-2, Pexiganan, or MSI-78 also displays a broad potent action against the formation of toroidal pores [224–226]. Against *A. baumannii*, pexiganan can inhibit the growth of MDR clinical isolates at a concentration of 1–8 μg/ml [87,88,227]. Studies with the ATCC 196060 reference strain of *A. baumannii* confirmed pexiganan's antimicrobial and anti-biofilm activity [89].

2.3.2. Brevinin-2 related peptide

Skin secretions from both the mink frog (Rana septentrionalis) and carpenter frog (R. virgatipes) contain B2RP, a brevinin-related AMP with an α-helical structure that affects the organization of bacterial membranes [228,229]. It can inhibit sensitive strains of A. baumannii at a concentration of 29 μg/ml and MDR strains at 7–13.9 μg/ml [90]. However, its hemolytic properties limit its potential use [230]. Three analogs of B2RP (D4K, K16A, and L18K) showed reduced red blood cell toxicity and a two-fold increase in activity against *A. baumannii* growth. [90,91]. The D4K substitution also showed activity against colistin-resistant and XDR clinical isolates [92]. B2RP-ERa is a smaller cationic peptide structurally similar to B2RP found in the skin of the Asian frog (*Hylarana erythraea*) [93, 231]. It can inhibit sensitive Acinetobacter strain growth at concentrations of 8–32 and drug-resistant strains 8–64 μg/ml, respectively [91]. It shows anti-inflammatory characteristics without toxicity on peripheral blood mononuclear cells or red blood cells [231,232].

2.3.3. Alyteserins

Alyteserin-1c and Alyteserin-2a are two of the alyteserin class of cationic AMPs with anti-*A. baumannii* activity released in skin secretions following norepinephrine stimulation of the midwife toad (Alytes obstetricans) [94,95,233]. Against clinical isolates of MDR A. baumannii, Alyteserin-1c inhibited growth and caused death at concentrations between 11.3–22.6 μg/ml with low hemolytic activity [94]. The substitution E4K reduced effects on red blood cells further while improving growth inhibition of colistin-resistant and XDR isolates of *A. baumannii* isolates [92]. Structural changes of Alyteserin-2a also resulted in an analog with a 4-8 fold greater antimicrobial activity and lower hemolytic effects [95].

2.3.4. Peptide glycine-leucine-amide

The volcano-clawed frog (*Xenopus amieti*) produces PGLa-AM1, peptide glycine-leucine-amide, an AMP with anti-Acinetobacter AMP activity. It can kill sensitive and colistin-resistant *A. baumannii*

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isolates at 16–128 μg/ ml [91]. With low hemolytic activity, it is also active against other ESKAPE pathogens, including *E. coli* and *S. aureus* [91,93,100].

2.3.5. Caerulein precursor fragment

Also isolated from the volcano-clawed frog, caerulein precursor fragment (CPF-AM1) is a cationic AMP that binds LPS [92,93]. It inhibits the growth of sensitive and colistin-resistant strains with minimal fibroblast toxicity and hemolytic activity [101]. CPF-B1 was isolated from the Marsabit clawed frog (*Xenopus borealis*) that displays anti-A. baumannii activity at concentrations between 11.4–22.8 μg/ml with low hemolysis [99]. From the Peracca clawed frog (*Xenopus clivii*), CPF-C1 is another member of the caerulein family of peptides with proven activity against *A. baumannii* with inhibitory activity at concentrations as low as 5 μg/ml concentration [98].

2.3.6. Hymenochirins

Hymenochirin-1B was isolated from the Zaire Dwarf Clawed Frog (*Hymenochirus boettgeri*) and is the first member of hymenochirins class of AMPs of their host defense system [234,235]. It is an α-helical cationic peptide that can inhibit the growth of MDR isolates of *A. baumannii* properties with a MIC of 19.1 μg/ml [100]. In addition to its antimicrobial activity, it displays anticancer and immunomodulatory properties. Hymenochirin-1B, which was generated by E6K and D9K substitutions, showed a nearly 4-fold increase in activity against *A. baumannii*, including MDR and XDR isolates with reduced toxicity to human erythrocytes [100]. Hymenochirin-1Pa was isolated from Merlin's dwarf gray frog (*Pseudhymenochirus merlini*) that inhibited the growth of XDR clinical isolates of *A. baumannii* at a concentration between 7.5–15 μg/ml. However, it also showed moderate hemolytic activity [101, 235].

2.3.7. XT-7

Norepinephrine stimulation of the western clawed frog (*Xenopus tropicalis*) permitted isolation from skin secretions XT-7 [236], an AMP with anti-Acinetobacter activity against the Euroclone I NM8 strain with a MIC of 22.2 μg/ml [98]. A substitution, G4K, increased its therapeutic index [102], inhibiting sensitive and drug-resistant *A. baumannii* strains at concentrations as low as 4 μg/ml [91].

2.3.8. Buforins

The stomach of the Asian toad (*Bufo gargarizans*) yielded Burfoin I [237]. Its derivative, Buforin II, is a potent antimicrobial peptide that kills bacteria by crossing the membrane to bind intracellular targets, including DNA and RNA that inhibit cellular activities [103]. Against Acinetobacter, Buforin II can hinder the growth of sensitive and resistant isolates at concentrations between 0.25–39 μg/ml [84,85]. In combination with antibiotic treatments or alone, it showed good potential in a rat model of sepsis with *A. baumannii* [91].

2.3.9. Caerin 1.1 and 1.9

The host defense peptides caerin 1.1 and caerin 1.9 of the Australian tree frog(Litoria caerulea) were isolated from skin secretions. They are α-helical cationic amphipathic AMP with antiviral, antitumor, antimicrobial, and neuropeptide-type activities [238]. Each displayed anti-*A. baumannii* growth activity that was additive in combination [141].

2.3.10. Hyalin a1

Hylin a1 is an α-helical cationic amphipathic AMP isolated from the skin secretions of the white spotted tree frog (*Hypsiboas albopunctatus*) [239]. Its antimicrobial activity has been attributed to its action on bacterial membranes, but it also displays a strong hemolytic activity. Two analogs, Hylin a1-11K and Hylin a1-15K, showed good antimicrobial activity against carbapenem-resistant A. baumannii clinical isolates at 1–2 μM with no report on changes to the hemolytic activity [148].

2.4. Fish piscins

Fish possess a strong innate immune system that is the first line of defense against a broad spectrum of pathogens [240]. Various antimicrobial components can be found within the epidermal

mucus, including AMPs, lysozyme, proteases, and lectins [241]. Piscidins are cationic AMPs expressed by fish mast cells [242], which comprise a family of structurally related mature peptides between 21 and 44 residues. They possess an amphipathic α-helical structure, which suggests that piscins have bactericidal activities against various microorganisms [243]. The piscidin family includes pleurocidin, moronecidin, chrysophsin, dicentracin, epinecidin-1, and myxinidin [244].

Pleurocidin is an amphipathic α-helical cationic peptide found in the gills, gut, and on the skin of winter flounder (*Pseudopleuronectes americanus*) [245], which is genetically similar to piscidin [246]. It displays a broad-spectrum activity against pathogenic bacteria and fungi such as *K. pneumoniae*, *S. aureus*, *P. aeruginosa*, and the opportunistic oral pathogen *C. albicans* [245,247]. Against MDR isolate strains of *A. baumannii*, this peptide can inhibit growth at concentrations between 16 and 8–32 [68]. Its MOA appears to be through membrane disruption through its binding [248], although it shows lower hemolysis compared with other natural peptides by in vitro toxicity studies [249].

Tilapia piscidin 2 (TP2) is an inactive antibacterial peptide found in Nile tilapia (Oreochromis niloticus) [250], which was modified to develop the peptides TP2-5 and TP2-6 that improved cationic and amphipathic balance [251]. The changes resulted in a significant improvement in their antimicrobial potential in normal media against the A. baumannii wild-type strains (MIC = 3.1 μg/ml) and MDR isolates (MIC = 1.6-12.5 μg/ml) [181]. Another AMP in Nile tilapia (TP4) displayed antimicrobial activity against sensitive and MDR *A. baumannii* strains between 16-32 μg/ml [68].

2.5. Hepcidin

First identified in human blood ultrafiltrate and urine samples and called a liver-expressed antimicrobial peptide (LEAP-1) [252,253], hepcidin is a cationic amphipathic peptide that functions in multiple vertebrates. It has been reported to be involved in iron metabolism, inflammation, and clearance of invading pathogens [254]. Since the first fish hepcidin was reported in hybrid striped bass in 2002 [255], many isoforms have been found across numerous fish species. Unlike a single gene in humans, many teleost fish have more than two hepcidin genes, most notably in Perciformes and Pleuronectiformes [256]. Fish hepcidin isoforms are currently phylogenetically classified into two groups, HAMP1-type and HAMP2-type [257–259]. From Japanese seabass (*Lateolabrax japonicus*), the peptide LJ-hep2 has been investigated using its recombinant precursor protein (rLJ-hep2) expressed in *Pichia pastoris* and a chemically synthesized mature peptide LJ-hep2(66–86) with LJ-hep2(66–86) displaying a stronger antimicrobial activity against several clinically isolated MDR *A. baumannii* (MIC = 1.5-3 μg/ml) [160].

2.6. Melittin

The cationic amphipathic α-helical AMP melittin was isolated from the European honeybee (*Apis mellifera*) 's venom, comprising nearly half its dry weight [260]. Numerous properties have been reported, including antibacterial [260], antiparasitic [261], and antifungal [262], along with anticancer and antiviral properties [263]. Its primary MOA is a carpet-like interaction with membranes, leading to pore formation and lysis [264]. Melittin displays potent antimicrobial activity against MDR and XDR clinical isolates of Acinetobacter at concentrations as low as 0.125 μg/ml [105,106]. In a mouse model of third-degree burns, topical application of melittin at 16 μg/ml concentrations eliminated 93.3% of an XDR isolate of *A. baumannii,* and doubling the dosage stopped the bacteria [105]. Importantly, the injured derma and surrounding tissue, including red blood cells, showed no toxicity. Brazilian clinical studies confirmed the activity of melittin against most strains except for one pan-drug-resistant strain [265].

Trypsin Modulating Oostatic Factor (AeaTMOF) is a proline-rich amphipathic decapeptide analogous to the PrAMP first reported in honeybees [266]. AeaTMOF (5 mM) was very effective against *A. baumannii,* inhibiting cell growth during 15 h incubations [267].

2.7. Cecropins

Cecropin describes a class of AMPs with a primary MOA attributed to membrane lysis [268]. The founding member, cecropin A, was isolated from the hemolymph of the giant silk moth (*Hyalophora cecropia*) [269]. Initial results showed in vitro antibacterial and anticancer activity [270]. Viability studies in a *Caenorhabditis elegans* model for A. baumannii infections demonstrated that 15 cecropin or cecropin-like peptides displayed antimicrobial activity and improved survival [108].

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Several studies have further defined the growth inhibition of individual peptides, including cecropin A against colistin-resistant strains and MDR clinical isolates [76,107], BR003-cecropin A from *Aedes aegypti* against MDR A. baumannii isolates [108], Musca domestica cecropin (Mdc) from housefly (*Musca domestica*) larvae against standard and MDR isolates [109], cecropin-4 from houseflies against MDR and XDR clinical isolates [151–153], cecropin P1 from pig roundworms (*Ascaris suum*) against colistin-sensitive *A. baumannii* [76]. Many cecropins also display anti-biofilm activity, such as myxinidin isolated from hagfish (Myxine glutinosa) [111] and the AMP complex FLIRP7 (Fly Larvae Immune Peptides 7) in blowfly (Calliphora vicina) larvae [112].

The fusion of cecropin A to endolysin ST01 has been shown to have increased bactericidal activity against ESKAPE pathogens, with *A. baumannii* (ATCC 17978) eliminated at a concentration of 0.25 [271]. Another hybrid of cecropin with melittin, CAMEL, rapidly kills *A. baumannii* [89]. OMN6 is a 40-amino acid synthetic cyclic peptide based on cecropin A that displays an increase in stability and a significant decrease in proteolytic degradation and low cytotoxicity against eukaryote cells. This peptide exerts a rapid bactericidal effect by causing the selective disruption of the bacterial membrane integrity [272], which is effective on *A. baumannii* laboratory strains (MIC = 8 μg/ml) and clinical isolates (MIC = 4-8 μg/ml) suggesting a low likelihood for the development of resistance [158].

2.8. Mastoparan

Mastoparan was isolated from the venom of hornets (*Vespula lewisii*) [218]. While it displays good activity against wild-type *A. baumannii* and colistin-resistant and pan-resistant clinical isolates [76,273], it also shows high hemolytic activity that would prevent its therapeutic applications [274]. Activity against MDR clinical isolates of *A. baumannii* was observed with mastoparan-AF isolated from the venom of another hornet (*Vespa affinis*) with a MIC between 2-16 μg/ml [109]. Improvements in serum stability (24h) have been achieved in analogs of mastoparan that maintain the growth inhibition of XDR clinical isolates [76]. Greater therapeutic efficacy against MDR clinical isolates has been acquired by conjugating mastoparan with chitin to form nanoconstructs [*Afreenish hassan*]. Improvements in hemolytic toxicity have not been reported.

2.9. Histatins

Histatins are a family of low-molecular-weight, histidine-rich cationic peptides isolated from salivary glands, which display antimicrobial activity through membrane disruption [222]. The only member that affects *A. baumannii* is histatin-8, a hemagglutination-inhibiting peptide [230]. It could inhibit the growth of colistin-sensitive and -resistant strains at a concentration of 32 μg/ml [76].

2.10. Dermcidin

The DCD gene in humans encodes dermcidin, an anionic AMP with two regions produced and secreted by eccrine sweat glands for transport to the skin surface [117,275]. While the N-terminal peptide is involved with neuronal cell survival in response to oxidative stress [117], the C-terminal fragment shows anti-Acinetobacter activity [276]. With a net charge of -2, DCD-1L can interact with negatively charged bacterial phospholipids. PDR clinical isolates of A. baumannii isolates show a two-fold increase in susceptibility than XDR isolates and the standard ATCC 19606 strain [118]. DCD-1L can also inhibit bacterial attachment and biofilm formation, which could affect infection initiation [118].

2.11. Tachyplesin III

The hemolymph of the Southeast Asian horseshoe crabs (*Tachypleu gigas* and *Carcinoscorpius rotundicauda*) contains tachyplesin III, an AMP of 17 amino acids. As opposed to an α-helical structure, this peptide presents a cyclic β-sheet with two disulfide bridges. Against an XDR clinical isolate of *A. baumannii*, tachyplesin III had a measured MIC of 8–16 μg/ml and could fully eliminate the bacteria at twice the MIC concentration [277]. However, it also displays high toxicity against mammalian cells, preventing therapeutic applications [277].

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2.12. Spider peptides

Various AMPs have been isolated from the venom of spiders. Lycosin-I is a 23-amino acid peptide from the venom of the Chinese wolf spider (*Lycosa singoriensis*) that had MIC against MDR isolates of *A. baumannii* between 8-32 μg/ml [140,278]. In the venom of ant spiders (Lachesana tarabaevi), latarcins 2a also displayed potent antimicrobial activity against MDR clinical isolates *A. baumannii* at concentrations between 8–64 μg/ml [68]. Similar to Lycosin-I, LS-AMP-E1 and LS-AMP-F1 from the burrowing wolf spider (*Lycosa sinensis*) had different inhibitory activity against other clinical drug-resistant bacteria and could effectively inhibit the formation of biofilms with no obvious hemolytic effects. Among the ESKAPE pathogens, LS-AMP-F1 was the most effective against *A. baumannii*, with the lowest MIC of 3.1 μM [140]. LyeTx I was isolated from a wolf spider from Brazil (Lycosa erythrognatha) and showed inhibitory activity against several multidrug-resistant bacteria but also showed hemolytic and cytotoxic effects. Conjugating a derivative, LyeTx I-b, to PEG could eliminate these contradictory effects while maintaining the MIC values against *A. baumannii*, anti-biofilm formation, and did not induce resistance [155].

2.13. Scorpion

Many AMPs have been identified in the venom of scorpions that display antimicrobial activity against *A. baumannii*, such as Hp1404, ctriporin, and Im5 [144]. In many instances, these peptides also show harmful effects, such as hemolysis, that alterations in their sequences could remedy. Hp1404 was isolated from the venomous gland of the giant forest scorpion (*Heterometrus petersii*) and is an amphipathic α-helical peptide that exhibited antimicrobial activity against methicillin-resistant S. aureus along with cytotoxicity. Many analogs showed lower cytotoxic activity against MDR isolates of *A. baumannii* [145]. BmKn2 is another naturally occurring cationic α-helical AMP from the Chinese scorpion (Mesobuthus martensii Karsch) with antimicrobial and strong hemolytic activity. It merely shows against gram-positive bacteria, such as *S. aureus*. Its mutant BmKn2-7 has lower hemolytic activity and maintains a broadened antimicrobial spectrum [279]. Another analog, BmKn2-7K, is non-toxic at antimicrobial dosages and exhibits potent antimicrobial activity via a membrane-lytic mechanism against a series of clinically isolated antibiotic-resistant ESKAPE pathogens. For MDR A. baumannii, BmKn2-7K and BmKn2-7R (MIC = 2.5–5 μg/ml) showed potent and improved antimicrobial activity than that of BmKn2-7 (MIC = 5–10 μg/ml) [147].

2.14. Lynronne-1

Lynronne-1 is an α-helical cationic amphipathic peptide identified using a metagenomics investigation of the bovine rumen microbiome for the presence of novel AMPs. Although it is in vivo activity was lower than conventional antibiotics, it showed selectivity for bacterial cells with low hemolytic activity and minimal cytotoxicity against mammalian cells [280]. Against some common gram-positive and gram-negative pathogenic bacteria, Lynronne-1 displayed broad-spectrum activity, including methicillin-resistant *S. aureus* (MRSA) (MIC of 8–32 μg/mL) and *A. baumannii* (MIC of 4 μg/mL) [280].

2.15. Hybrid peptides

The combination of different AMPs offers a rational approach to developing non-natural AMP. The peptide PapMA consists of 18 amino acids that combine the first eight amino acids from papiliocin, a 37-residue AMP purified from larvae of the swallowtail butterfly (*Papilio xuthus*) with resides 4-12 of magainin 2, a 23-residue AMP purified from the skin of the African clawed frog (Xenopus laevis). A proline hinge joined the two fragments. While PapMA showed high antimicrobial activity, it was cytotoxic to mammalian cells [281]. The hybrid peptides P7A3 and A3P7 combined cathelicidin (P7) and aurein (A3) were obtained by a flipping technique [282]. The serial truncation of the C-terminal led to an optimal candidate, AP19, that was stabilized against proteolytic enzymes by a D-amino acid substitution (D-AP19). The final peptide rapidly killed A. baumannii ATCC 19.606 (MIC = 7.81 μg/mL) via membrane disruption and showed a low tendency to induce bacterial resistance. It also exhibited potent antibacterial activity against multidrug-resistant (MDR) and extensively drug-resistant (XDR) clinical isolates of *A. baumannii* (MIC = 3.91-15.63) [189]. BP214 is a cationic amphipathic all-D decapeptide developed from a short cecropin A-melittin hybrid

peptide BP100 [283], which showed excellent activity against colistin-resistant *A. baumannii* and modest hemolytic properties [284].

3. Resistance to AMPS

Resistance to AMPs can be acquired by their degradation, sequestration, impedance by exopolymers or biofilm matrix molecules, alteration of the membrane lipid composition, and export mechanisms [285–291]. Resistance to colistin has been documented for A. baumannii following its long-term clinical application [292,293]. Resistance was also observed after the inactivation of one of the genes involved in LPS biosynthesis, resulting in loss. As colistin is a last-resort drug to treat MDR nosocomial pathogens, resistance is an important clinical issue [293–295]. Several nanocarriers have been developed to overcome low bioavailability, proteolysis, and toxicity associated with AMPs [296,297]. Changes in the molecular structure, modifications of biochemical characteristics, and their combination with common antibiotics have been reported to minimize AMP resistance [287].

4. Conclusions

Of the ESKCAPE pathogens, A. baumannii is a growing concern for nosocomial and community-acquired infections. With a high capacity to acquire resistance and form biofilms, there has been an alarming increase in the loss of antibiotic efficacy and a rise of MDR strains worldwide. Projections combined with the scarcity of new antibiotic treatments [13] show the need to transition to a "post-antibiotic era" by developing new therapeutics based on alternative approaches. AMPs have emerged as excellent candidates due to the breadth of natural peptides found as part of innate immune systems that demonstrate activity against many A. baumannii strains, including MDR and XDR clinical isolates. While many of these AMPs also display undesirable effects such as hemolysis and host toxicity, studies have demonstrated the ability to modify their sequences to improve performance. Future advances in bioinformatics combined with more studies on the sequence/structure/function relationship can generate synthetic AMPs to address a major health concern. Our review of AMPs highlights common characteristics such as cationic, α-helical structure, interactions with bacterial membranes, bilipid pore formation, and intracellular component targeting. Many instances of improved performance combined with traditional treatments and their use as bioconjugates show promise for future applications. In addition to their antimicrobial properties, many AMPs have demonstrated other beneficial activities such as anticancer, antioxidant, wound healing, and angiogenesis that further support additional research [34,61,298,299].

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