

Review Article

Marine Antimicrobial Peptides: A New Wave in the Fight Against Resistance

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Marine environments host a vast and underexplored reservoir of antimicrobial peptides (AMPs), many of which exhibit potent activity against multidrug-resistant pathogens and biofilms. These peptides, shaped by evolutionary pressures in extreme ecological niches, display diverse structures, broad-spectrum efficacy, and immunomodulatory functions that make them compelling candidates for next-generation anti-infectives. Recent advances in sequencing, synthetic biology, and peptide engineering have accelerated the discovery, optimization, and functional characterization of marine AMPs. Beyond infection control, these molecules have been applied in clinical, industrial, and environmental contexts, including medical device coatings, aquaculture biosecurity, biofouling prevention, and environmental biosensing. However, translational barriers remain, including challenges in large-scale production, pharmacokinetics, and resistance prediction. Standardized protocols, integrated databases, and artificial intelligence (AI)-driven design platforms are now transforming marine AMP research from descriptive cataloging to hypothesis-driven innovation. This Review synthesizes the current landscape of marine AMP discovery, mechanistic insight, application, and infrastructure, and outlines priorities for future research to harness their full therapeutic and ecological potential.

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1. Introduction

The global rise of antimicrobial resistance (AMR) has created an urgent need for new antimicrobial agents beyond traditional antibiotics^[1]. Recent estimates attribute over 4.7 million annual deaths to drug-resistant infections^[2], with projections that resistant bacterial infections could surpass cancer in mortality by 2050^[3]. This crisis stems from decades of antibiotic overuse, stagnation in antibiotic discovery, and the intrinsic evolution of bacterial defense mechanisms^{[4][5][6]}. Antimicrobial peptides (AMPs) have emerged as promising alternatives, owing to their broad-spectrum activity and distinct mechanisms of action that differ fundamentally from classical antibiotics^{[7][8][9][10]}. AMPs are short innate immune molecules, usually 10 to 50 amino acids in length, that are produced by virtually all forms of life, including bacteria, plants, invertebrates, and vertebrates^{[7][11][12][13][14][15]}. Unlike conventional antibiotics, many AMPs can directly disrupt microbial membranes, inhibit biofilm formation, modulate host immune responses, and target persister cells, making them effective against even multidrug-resistant pathogens^{[8][9][16][17][18]}. These multifaceted activities, which include membrane lysis, immunomodulation, and disruption of quorum sensing, provide a broad therapeutic spectrum that is inherently difficult for bacteria to evade^{[8][14][19][20][21][22]}.

Within the vast repertoire of AMPs, marine-derived AMPs have garnered special interest as underexplored assets in the fight against AMR. The marine environment covers over 70% of Earth's surface and harbors greater genetic and organismal diversity than any other ecosystem^{[23][24]}. It encompasses extremophilic habitats characterized by high salinity, pressure, and temperature, as well as intense and unique microbial competition, which together have driven the evolution of novel bioactive molecules^{[24][25][26]}. Indeed, despite the ocean's rich biodiversity, marine AMPs remain relatively underrepresented in known databases, accounting for only approximately 4% of all documented AMPs, which suggests that a vast reservoir of antimicrobial chemistry in the marine environment remains largely unexplored^{[27][28][29][30]}. The first marine AMP, tachyplesin from the horseshoe crab, was identified in 1988^[31], and numerous others have since been discovered in fish, mollusks, crustaceans, marine bacteria, and even seaweeds^{[13][32][33][34][35][36][37][38][39]}. Marine organisms frequently face intense microbial challenges in their environment, from waterborne pathogens to biofouling communities, and have evolved potent AMPs as part of their defense^{[40][41]}. These peptides often retain activity in high-salinity conditions where terrestrial AMPs lose efficacy^{[33][42][43][44]}, an adaptation critical for function in seawater and physiological fluids.

The ecological uniqueness of marine environments, including extreme hydrostatic pressure in the deep sea, fluctuating salinity and pH in tidal zones, and intense microbial competition in coral reef ecosystems, has shaped the distinctive structural and functional features of marine AMPs^{[45][46][47]}. As detailed in the sections below, marine AMPs exhibit unusual chemical modifications, including halogenation and sulfation, as well as diverse structural motifs that endow them with high stability and potent biological activity. Such features position marine AMPs as promising drug leads that might overcome some limitations of existing antibiotics, such as narrow target scope or susceptibility to resistance^{[8][9][21]}. However, translating these natural peptides into therapeutics comes with challenges: large-scale sustainable production, potential cytotoxicity at high doses, and limited clinical validation to date^{[48][49][50]}. Ongoing advances in peptide engineering and delivery, including peptide stapling and nanocarrier-based systems, are actively addressing these issues^{[51][52]}. In parallel, breakthroughs in genomics and artificial intelligence are accelerating the discovery of new AMPs from marine genomes and metagenomes^{[10][24][53]}.

This Review provides a comprehensive overview of marine antimicrobial peptides in the context of the antimicrobial resistance crisis. It first examines how marine ecological pressures shape AMP chemistry, followed by an analysis of their structural diversity and biophysical properties. The mechanisms of action are then discussed, ranging from membrane disruption to the targeting of specific intracellular components, together with the coevolutionary dynamics between microbial resistance strategies and evolutionary innovation in AMPs. State-of-the-art pipelines for AMP discovery and design are described, alongside recent engineering efforts that enhance peptide stability and delivery. The translational potential of marine AMPs is highlighted through applications in medicine, industry, and aquaculture, including infection control, anti-biofilm and antifouling technologies, and disease prevention in aquatic systems. Considerations related to environmental safety and governance are also addressed, emphasizing the need for responsible integration of AMPs into antimicrobial resistance stewardship. Finally, the Review calls for greater standardization in AMP research, including harmonized reporting protocols and centralized databases, and outlines a roadmap for the next decade of marine AMP development by identifying key knowledge gaps and future opportunities.

2. Chemical Ecology and Evolutionary Pressures in Marine Environments

Marine AMPs are deeply shaped by the ocean's distinctive chemical ecology. Life under high salinity, hydrostatic pressure, temperature gradients, and intense microbial competition has driven the evolution of structurally diverse and chemically modified AMPs^{[24][25][26]}. These peptides often feature non-canonical amino acids and post-translational modifications (PTMs) rarely found in terrestrial analogs^{[54][55]}.

Halogenation is a hallmark of marine AMPs, enabled by the abundance of halogens like bromine and chlorine in seawater^{[54][56]}. Brominated tryptophan and tyrosine residues enhance hydrophobicity and facilitate membrane disruption, boosting antimicrobial potency without elevating toxicity^{[54][57][58]}. Flavin-dependent halogenases and haloperoxidases, widespread in marine microbes, catalyze these modifications^{[59][60]}, exemplified by potent anti-biofouling peptides from sponges and tunicates^[61].

Sulfation is another adaptive modification, with sulfated tyrosine or serine residues found in some invertebrate and venom peptides^[62]. These negatively charged groups may mimic host glycosaminoglycans, improve solubility in saline environments, or enhance targeting to bacterial surfaces. Though less common than halogenation, sulfation likely contributes to salt-tolerant activity through membrane-specific interactions. Peptides like arenicins illustrate how structural modifications underlie AMP function in high-ionic-strength conditions^[63].

Marine AMPs frequently derive from non-ribosomal peptides (NRPs) or ribosomally synthesized and post-translationally modified peptides (RiPPs), enabling incorporation of D-amino acids, N-methylation, and complex ring structures. For example, polytheonamide, a sponge-derived cytotoxic peptide, contains 28 non-proteinogenic residues and 49 PTMs, showcasing extreme marine biosynthetic capability^{[64][65][66]}. Similarly, ocean-derived lantibiotics feature lanthionine bridges and dehydroamino acids that confer protease resistance and structural rigidity^{[67][68]}.

Adaptations to high salinity are also evident: marine AMPs typically exhibit strong net positive charges (+4 to +9) to interact with negatively charged microbial membranes, yet remain functional in seawater-level ionic strengths^{[43][69]}. Peptides from marine fish, such as piscidins and clavanins, retain their activity in 300 to 500 millimolar sodium chloride, owing to enhanced hydrophobicity, oligomer formation, or enrichment in aromatic residues^{[33][43][69]}. Deep-sea peptides, such as those from

echinoderms, often stabilize via multiple disulfide bridges to resist pressure- and temperature-induced unfolding^[70].

Finally, biofilm-rich niches exert selective pressure on sessile organisms like sponges and corals, many of which depend on symbiotic microbes to produce AMPs^{[71][72][73]}. These often target both planktonic and biofilm forms of pathogens. For instance, diketopiperazines (DKPs) from marine bacteria act as quorum sensing inhibitors that synergize with AMPs to disrupt biofilms^{[74][75]}. The co-evolution of host and symbionts has yielded AMP cocktails with complementary or multifunctional roles, including antimicrobial, anti-fouling, and immunomodulatory effects.

Altogether, the chemical boldness and structural robustness of marine AMPs, as evidenced by features such as halogenation, sulfation, cyclic backbone architectures, and the incorporation of non-standard amino acid residues, reflect the intense evolutionary pressures of the marine environment and provide valuable templates for the design of next-generation antimicrobial agents.

3. Structural Diversity and Biophysical Properties of Marine AMPs

Marine AMPs exhibit exceptional structural diversity, spanning all major conformational classes: α -helical, β -sheet, extended/unstructured, and cyclic peptides^{[27][50]}. This diversity reflects the evolutionary adaptation of marine organisms to complex, microbe-rich environments and is closely linked to key biophysical traits, including amphipathicity, positive charge, and the ability to form oligomers, all of which contribute to membrane disruption, intracellular targeting, and evasion of microbial resistance mechanisms.

3.1. α -Helical Peptides: Versatile and Responsive Membrane Disruptors

Linear α -helical AMPs are among the most common marine antimicrobial scaffolds. Typically unstructured in solution, these peptides adopt amphipathic helices upon membrane contact. Fish-derived piscidins exemplify this class: 22-residue peptides with polar/cationic and hydrophobic faces that insert into bacterial membranes, forming pores^{[76][77]}. Related peptides, such as pleurocidin and clavamin A, retain potent activity in physiological salt due to helix-stabilizing features like C-terminal amidation and salt-tolerant hydrophobicity.

Marine α -helices often possess net charges of +2 to +7 and contain proline/glycine-induced "hinge" regions that facilitate membrane curvature or pore formation. Some, such as halocidin from the ascidian

Halocynthia, form coiled-coil heterodimers that enhance local concentration and membrane disruption^[78]. The relative simplicity, rapid bactericidal action, and amenability to synthetic engineering (e.g., helix stapling, truncation) make marine α -helical AMPs attractive drug candidates.

3.2. β -Sheet and β -Hairpin Peptides: Compact, Rigid, and Stable

β -structured AMPs, defined by disulfide-stabilized β -strands or hairpins, are abundant in marine invertebrates. Horseshoe crab-derived tachyplesins and polyphemusins form cyclic β -hairpins via two disulfide bonds, creating amphipathic, protease-resistant scaffolds that target membranes or microbial surface components like LPS^[31]. Arenicin-1 from the lugworm *Arenicola marina* adopts an antiparallel β -hairpin stabilized by a single disulfide (Cys3–Cys20) and forms pores/ion channels in Gram-negative membranes^[79]; by contrast, arenicin-3 contains two disulfide bonds^[80].

Marine shellfish also express defensin-like β -peptides, such as mytilins from mussels, whose rigidity confers heat and enzyme resistance^[81]. Functionally, β -sheet AMPs act by wedging into lipid bilayers or forming β -barrel pores. Their structured surfaces can also mediate enzyme inhibition or immunomodulation. Despite biosynthetic challenges, their high stability in harsh conditions enhances their therapeutic potential.

3.3. Extended and Proline-Rich Peptides: Flexible Intracellular Inhibitors

Extended AMPs, often rich in proline, tryptophan, or arginine, lack stable secondary structure but exert potent intracellular effects. They thread into bacteria, targeting nucleic acids or ribosomes. Marine fish histone-derived peptides, including parasin from catfish skin mucus, are unstructured histone H2A fragments that penetrate membranes and bind DNA^[82]. Proline-rich AMPs (PrAMPs), exemplified by shrimp penaeidins, display a bifunctional architecture comprising an unstructured N-terminal proline-rich domain (PRD) and a disulfide-stabilized cysteine-rich C-terminal domain (CRD) with a compact α/β fold^{[83][84]}.

These hybrid peptides often bypass membrane lysis and instead inhibit bacterial translation or protein folding^{[85][86][87]}. Their flexible, low-lytic profile may reduce immunogenicity and bacterial resistance detection^{[19][48][85][88]}. Rich in arginine and tryptophan, many acquire ordered conformation upon binding targets, and some also modulate host immunity by interacting with Toll-like receptors or chemokines^{[89][90][91]}.

3.4. Cyclic and Loop-Structured Peptides: Maximizing Stability

Cyclization, via head-to-tail linkage or internal loops formed by disulfide/lactam bridges, is a common strategy in marine AMPs to enhance proteolytic stability^{[92][93]}. While most cyclotides are plant-derived, marine sponge symbionts have also yielded cyclic peptides with antimicrobial potential^{[94][95][96]}. Gramicidin S, a cyclic decapeptide produced by *Bacillus* (*Brevibacillus/Aneurinibacillus*) *brevis*, exemplifies a potent membrane-disrupting AMP with strong activity against Gram-positive bacteria^{[97][98][99]}, and related *Brevibacillus* spp. have also been isolated from marine habitats^{[100][101]}.

Marine organisms frequently combine cyclic scaffolds with other chemical strategies. Tunicate peptides incorporate D-amino acids alongside cyclization to evade degradation^{[102][103][104]}. Marine bacteria produce cyclic lipopeptides and depsipeptides, including surfactin-like molecules, that disrupt membranes or bind lipid II^{[105][106]}. These motifs exemplify evolution's combinatorial use of structural elements for potent and persistent antimicrobial function.

Across all classes, marine AMPs share convergent biophysical principles: short length (<50 residues), high cationicity (+2 to +9), amphipathicity, and structural strategies for stability under extreme conditions, including salinity, proteases, and pressure^{[14][27][69]}. Disulfide bridges, amidation, and cyclization are common adaptive features. Hybrid structures are frequent: penaeidins blend β -sheets and proline-rich motifs, while epinecidin-1 combines helical and flexible domains^{[83][107]}. These modular architectures suggest evolutionary optimization for multitarget engagement, environmental resilience, and persistent innate immunity in organisms lacking adaptive defense systems.

This structural heterogeneity equips marine AMPs for diverse antimicrobial roles, from membrane lysis to intracellular targeting, and offers a rich scaffold space for therapeutic engineering (Table 1). Their architecture not only determines the mechanism of action but also influences pharmacokinetics, stability, and synthetic tractability, thereby laying the foundation for the next section on the molecular mechanisms of antimicrobial action.

Structural class	AMP	Marine source	Length (aa)	Fold / scaffold	Key features	Functional highlights
α -helical	Clavanin A	Tunicate (<i>Styela clava</i>)	23	Amphipathic α -helix	C-terminal amidation; His-rich; salt tolerant	Active under high salinity; rapid membrane disruption
α -helical	Piscidin 1	Marine fish (hybrid striped bass)	22	α -helix	His-rich; membrane-inserted helix	Potent broad-spectrum membrane activity
α -helical (heterodimer)	Halocidin	Tunicate (<i>Halocynthia aurantium</i>)	18 + 15	Helical heterodimer	Inter-chain disulfide; heterodimeric	Enhanced local concentration on membranes
α -helical	Epinecidin-1	Marine fish (<i>Epinephelus coioides</i>)	25	α -helix	Net charge +5; amphipathic	Broad-spectrum antibacterial
β -hairpin	Tachyplesin I	Horseshoe crab (<i>Tachyplesus tridentatus</i>)	17	β -hairpin	2 disulfide bonds; rigid	LPS binding; membrane permeabilization
β -hairpin	Polyphemusin I	Horseshoe crab (<i>Limulus polyphemus</i>)	18	β -hairpin	Disulfide-stabilized	Potent Gram-negative activity
β -hairpin	Arenicin-1	Polychaete (<i>Arenicola marina</i>)	21	β -hairpin	Single disulfide; +6 charge	Ion-channel-like membrane pores
β -defensin-like	MGD-1	Mussel (<i>Mytilus galloprovincialis</i>)	~43	β -sheet defensin	4 disulfide bonds	Salt- and protease-stable
β -defensin-like	Mytilin A	Mussel (<i>Mytilus galloprovincialis</i>)	~34	Cys-rich β -structure	8 cysteines	Antibacterial and antiviral
Pro-rich / extended	Parasin I	Fish (histone H2A fragment)	~19-21	Extended coil	Histone-derived; DNA	Intracellular targeting

Structural class	AMP	Marine source	Length (aa)	Fold / scaffold	Key features	Functional highlights
					binding	
Pro-rich + Cys-rich	Penaeidin-4	Shrimp (<i>Litopenaeus vannamei</i>)	domain-structured	Hybrid PRD + CRD	Modular architecture	Translation inhibition; non-lytic
Pro-rich	Nereis peptide	Ragworm (<i>Nereis diversicolor</i>)	~30	Pro-rich extended	Ribosome targeting	Protein synthesis inhibition
Cyclic	Gramicidin S	<i>Bacillus</i> (incl. marine isolates)	10	Cyclic β -sheet	Head-to-tail cyclization	Potent membrane disruption
Cyclic (cyanobactin)	Patellamide A	Tunicate-cyanobacteria symbiosis	variable	Macrocyclic peptide	Enzymatic cyclization; heterocycles	Chemical defense scaffold
Bicyclic	Theonellamide A	Marine sponge (<i>Theonella</i>)	bicyclic	Bicyclic peptide	Sterol-binding	Membrane disruption via sterols

Table 1. Representative marine antimicrobial peptides (AMPs) across major structural classes.

4. Mechanisms of Action: From Membranes to Intracellular Targets

Marine AMPs exhibit multifaceted modes of action that contrast sharply with the narrow-target strategies of conventional antibiotics. While many antibiotics act on a single molecular target, AMPs often simultaneously disrupt membranes, impair intracellular processes, and modulate host immunity^[8]^[12]^[19]. This multipronged strategy not only broadens their antimicrobial spectrum, particularly against dormant or resistant cells, but also makes resistance development more difficult.

4.1. Membrane Disruption

Membrane disruption is a canonical mechanism of many marine AMPs, driven by electrostatic attraction between cationic peptides and negatively charged bacterial membranes. These peptides integrate into the lipid bilayer and perturb its integrity through several well-characterized models.

In the barrel-stave model, peptides oligomerize within the membrane to form transmembrane pores lined by their hydrophilic surfaces, leading to ion leakage and depolarization^{[108][109]}. Toroidal pores involve peptides bending the membrane leaflets into a continuous pore lined by both lipids and peptides^[110]. Carpet-like mechanisms instead involve peptides coating the membrane surface and inducing lysis in a detergent-like manner once a threshold density is reached^[111]. Notably, AMPs like tachyplesin and pleurocidin exhibit combined mechanisms, forming transient pores at low concentrations and membrane dissolution at higher levels^{[112][113]}.

Membrane disruption affects more than structural integrity. It collapses the proton motive force, halts ATP synthesis, and alters membrane protein functions. Peptides such as polyphemusin bind to lipopolysaccharides (LPS), destabilizing the Gram-negative outer membrane and neutralizing endotoxins^[114]. These physicochemical interactions are difficult for bacteria to evade without incurring a significant fitness cost, preserving AMP efficacy in natural systems.

4.2. Intracellular Targets

Many marine AMPs can traverse bacterial membranes and engage intracellular targets, expanding their impact beyond membrane lysis^[115]. Nucleic acids are common targets: peptides like pleurocidin bind DNA, inhibiting replication and transcription^[116]. Analogous to insect-derived PrAMPs, some marine peptides may impede ribosomal activity, halting protein synthesis^[117]. In particular, pleurocidin and fish-derived PrAMPs show inhibition of translation and gene expression at sub-lethal doses^[118].

Marine AMPs may also inhibit essential enzymes, including polymerases, topoisomerases, and proteins that interact with lipid II, resembling the mode of action observed in lantibiotics^{[119][120][121]}. Though not all such peptides are of marine origin, their mechanisms inform the potential of marine analogues. Peptides mimicking microcin J25, for instance, could disrupt RNA polymerase and ATP synthase, targeting bacterial energy metabolism^[119].

The bacterial division protein FtsZ, homologous to tubulin, represents another emerging target^[122]. Peptides interfering with FtsZ polymerization can halt cytokinesis^{[123][124]}. Although direct evidence from marine sources remains limited, this represents a promising direction, as engineered FtsZ-targeting peptides have shown potent antibacterial activity^[125].

4.3. Anti-Biofilm and Immunomodulatory Functions

Marine AMPs also impair bacterial persistence through anti-biofilm activity. They prevent surface attachment, degrade extracellular polymeric substances, and inhibit quorum sensing^{[126][127][128][129]}. Peptides such as tachyplesin III and pleurocidin markedly reduce biofilm biomass, enhancing antibiotic penetration^{[130][131][132]}. Others interfere with bacterial communication, disrupting biofilm maturation without direct killing^{[133][134]}.

In parallel, many marine AMPs exhibit immunomodulatory properties, such as neutralizing inflammatory molecules like LPS, recruiting immune cells, and modulating cytokine production^[135]. Piscidins stimulate chemotaxis^[136], while cathelicidins from turtles and sea snakes suppress excessive inflammation and support host defense^{[137][138]}. Peptides like tilapia hepcidin simultaneously boost phagocytosis and reduce tissue damage, demonstrating dual antimicrobial and host-protective functions^[139].

4.4. Multimodal Synergy

Crucially, marine AMPs rarely act via a single mechanism^{[12][48]}. Many simultaneously disrupt membranes, interfere with intracellular processes, and reshape immune responses. For instance, gaduscidin-1 from Atlantic cod damages membranes while sensitizing bacteria to antibiotics by altering gene expression^[140]. This synergistic action, targeting both microbial structure and function, is a hallmark of marine AMP effectiveness.

5. Bacterial Resistance and Coevolutionary Dynamics

Marine AMPs, though once considered “resistance-proof,” are now known to encounter diverse bacterial countermeasures. These mechanisms, which are often less potent than classical antibiotic resistance and typically involve substantial fitness trade-offs, have evolved under sustained selective pressure from AMPs over long evolutionary timescales. Hosts, in turn, have coevolved by diversifying AMP repertoires and delivery strategies, generating a dynamic arms race between host defense and microbial evasion. This section synthesizes the molecular mechanisms of bacterial resistance to marine AMPs, the potential for cross-resistance, and the evolutionary trade-offs shaping their coadaptation.

5.1. Mechanisms of Bacterial Resistance to AMPs

The most common strategy employed by bacteria is surface charge modification, which reduces the electrostatic attraction between cationic AMPs and negatively charged bacterial envelopes^[141]. Gram-negative bacteria achieve this by adding 4-amino-4-deoxy-L-arabinose or phosphoethanolamine (PEtN) to the lipid A moiety of lipopolysaccharide (LPS), as observed in colistin-resistant strains harboring the *mcr-1* gene^{[142][143]}. Analogous modifications exist in marine vibrios, often regulated by environmental sensing systems such as PhoP/PhoQ and PmrA/PmrB^[144]. Gram-positives like *Staphylococcus aureus* (*S. aureus*) counter AMPs via D-alanylation of teichoic acids, similarly decreasing net surface negativity^[145]. These adaptive responses elevate resistance thresholds but typically do not provide full protection^[9].

Capsular polysaccharides and biofilm matrices act as physical barriers that impede AMP penetration^[9]^[146]. Biofilm-forming pathogens such as *Pseudomonas aeruginosa* secrete alginate, which can sequester AMPs and necessitate higher effective concentrations^[147]. The upregulation of outer membrane proteins like OprH under stress conditions further stabilizes the cell envelope and contributes to reduced susceptibility^{[148][149]}. Some marine pathogens similarly produce mucilaginous extracellular polymers, especially under osmotic or oxidative stress, limiting AMP efficacy^[150].

Another defense mechanism is proteolytic degradation, where secreted or surface-associated proteases cleave AMPs^[151]. Proteases such as *Pseudomonas* elastase, omptins (for example, OmpT), and aureolysin in *S. aureus* can inactivate host peptides including LL-37 and cathelicidins^{[152][153][154]}. Some marine bacteria likely secrete analogous enzymes, particularly in host-associated environments like fish mucus^{[155][156]}. Notably, D-residue substitution and backbone cyclization endow AMPs with protease resistance, a host-evolved countermeasure that preserves antimicrobial function in protease-rich niches^[157].

Bacteria may also rely on efflux systems, including broad-spectrum pumps like AcrAB-TolC or specialized exporters like MtrCDE in *Neisseria*, to reduce intracellular peptide accumulation^{[158][159]}. Although efflux contributes to resistance, it is often insufficient against membrane-active AMPs that cause immediate disruption.

Additionally, cytoplasmic adaptations allow bacteria to mitigate intracellular damage. These include the induction of chaperones, DNA repair enzymes, and changes in lipid biosynthesis^{[160][161]}. For instance, increasing lysyl-phosphatidylglycerol or altering fatty acid saturation stiffens membranes, rendering

them less penetrable^[162]. However, such adaptations frequently impair growth and virulence, reducing bacterial fitness in the absence of AMPs.

Many of these mechanisms, though first characterized in response to human or insect AMPs, are conserved and likely active against marine AMPs. Laboratory evolution experiments confirm that bacteria can incrementally increase AMP tolerance through these routes, yet full resistance remains rare outside of highly selective conditions.

5.2. Cross-Resistance and Evolutionary Trade-Offs

Cross-resistance arises when a single adaptation reduces susceptibility to multiple antimicrobials. Modifications that confer resistance to one AMP, such as LPS remodeling, can reduce susceptibility to other AMPs or even to antibiotics^[151]. For example, colistin-resistant *Salmonella* strains often exhibit reduced sensitivity to host defensins^[163]. In *P. aeruginosa*, selection for resistance to LL-37 has been associated with increased resistance to ciprofloxacin and carbapenems, driven by efflux pump upregulation and enhanced biofilm production^{[164][165]}.

Bacteria that inhabit AMP-rich niches, such as marine animal epithelia, may evolve broad tolerance to peptide mixtures after prolonged exposure; however, these adaptations often impose measurable costs. Remodeling of membrane lipids and porin flux can reduce nutrient uptake, and secretion of extracellular proteases creates a substantial metabolic burden^[166]. In plasmid-mediated colistin resistance, *mcr* genes frequently carry fitness costs and decline when colistin use ceases^{[167][168]}, although some studies indicate that *mcr-1* can enhance gut colonization in specific host-strain contexts in the absence of drug pressure^[169]. Experimental evolution further shows that tolerance to AMPs can increase incrementally, yet removal of selective pressure commonly leads to reduced growth rates, attenuated virulence, or partial reversion to susceptibility^{[88][170]}.

Coevolution plays a critical role in this dynamic. Hosts typically deploy multiple AMPs simultaneously, limiting the probability of resistance via any single mechanism. Fish mucus, for example, may contain over ten distinct AMPs with synergistic or complementary modes of action^{[33][171]}. A surface modification that impairs binding of one peptide may not confer protection against another targeting intracellular functions^{[9][172]}. Moreover, AMP genes often exhibit signatures of positive selection, particularly in invertebrates, underscoring adaptive diversification in response to pathogen pressure^{[173][174]}.

Symbiotic marine bacteria represent a special case of coevolved tolerance rather than antagonism. These microbes may resist host AMPs in a finely tuned, species-specific manner that enables mutualism without provoking immune rejection^{[175][176][177]}. Such specificity highlights the evolutionary precision achievable in long-term host-microbe associations.

From a therapeutic standpoint, these dynamics underscore the need for strategic deployment of AMP-based interventions. Monotherapy risks selecting for cross-resistant strains^{[178][179]}, whereas peptide combinations or cycling with conventional antibiotics may attenuate resistance emergence^{[179][180]}. Encouragingly, resistance to AMPs in vitro typically results in only modest MIC shifts (2-10 fold), and bacteria rarely achieve the high-level resistance seen with small-molecule antibiotics^[181]. In some cases, mutations conferring antibiotic resistance may even sensitize bacteria to AMPs, owing to altered membrane properties or efflux trade-offs^[181].

Overall, although bacteria have developed various mechanisms to resist marine AMPs, including surface shielding, enzymatic degradation, active efflux, and physiological adaptation, these defense strategies are rarely fully effective and often impose a significant fitness cost on the organism. This partial resistance, shaped by evolutionary constraints and offset by host coadaptation, suggests that marine AMPs, if thoughtfully applied, may offer a more sustainable antimicrobial strategy than conventional agents.

6. Discovery and Computational Design Pipelines

The discovery and optimization of marine AMPs have evolved into a multidisciplinary process, integrating omics technologies, machine learning, and synthetic biology. From gene mining in metagenomes to in silico design and scalable production, current pipelines are dramatically accelerating AMP development.

6.1. High-Throughput Discovery through Omics and Metagenomics

Given that most marine microbes cannot be cultured, researchers rely heavily on metagenomic sequencing of environmental samples, including seawater, sediments, and host-associated microbiomes, to access novel AMP genes^{[182][183][184]}. Functional metagenomics, where environmental DNA is expressed in surrogate hosts and screened for activity, has uncovered new gramicidin-like peptides and lantibiotics^{[185][186][187][188]}. Peptidogenomic approaches, focusing on RiPP biosynthetic gene clusters,

predict mature AMP structures based on conserved precursor motifs and tailoring enzymes, revealing chemically diverse peptides that often escape traditional assays^{[189][190][191]}.

Machine learning further enhances discovery. For instance, models trained on the global ocean microbiome predicted over 5,000 candidate AMPs, with 79 synthesized and 63 confirmed active against *E. coli* or *Staphylococcus*^[192]. In parallel, transcriptomic and proteomic profiling of marine organisms under infection has identified upregulated AMP genes or peptide masses directly in host secretions^{[193][194][195]}. Databases like APD, DRAMP, CAMP, and BACTIBASE serve as critical repositories for motif mining and homology-based identification, facilitating rapid annotation of novel sequences^{[196][197][198][199]}.

6.2. Computational Design and Optimization

Once candidate sequences are identified, computational tools enable rapid optimization. Machine learning and deep learning models trained on datasets containing both AMP and non-AMP sequences are used to predict antimicrobial activity, cytotoxicity, and physicochemical properties^{[192][200][201][202]}. Deep generative models have produced entirely synthetic, active peptides, some effective against multidrug-resistant bacteria^{[200][203][204]}. Tools such as AMPScanner, DeepAMP, and CAMPR3 help assess key features including charge distribution, amphipathicity, and folding propensities^{[205][206][207][208]}.

Structure-based approaches using AlphaFold2 and molecular dynamics simulations support in silico screening by modeling how peptides interact with bacterial membranes or protein targets^{[209][210][211]}. These insights help prioritize candidates with high predicted efficacy. Rational design strategies, including the truncation of long peptides and the fusion of active motifs into hybrid chimeras, are guided by physicochemical modeling and have produced shorter, potent analogs with reduced toxicity^{[212][213][214]}. Incorporation of D-amino acids and noncanonical residues enhances protease resistance, with computational docking confirming preserved structural integrity and target binding^{[215][216]}.

6.3. Synthetic Biology for Scalable AMP Production

To translate optimized sequences into usable therapeutics, synthetic biology enables efficient production. Heterologous expression in *E. coli*, *Pichia pastoris*, or *Lactococcus lactis* allows high-yield

synthesis, often employing secretion tags or fusion proteins to mitigate host toxicity^{[217][218][219]}. Cell-free peptide synthesis systems further enable rapid generation of toxic or non-natural peptides^{[220][221]}.

For non-ribosomal peptides and heavily modified RiPPs, entire biosynthetic gene clusters can be cloned into model microbes, such as *Streptomyces* or *Bacillus*, facilitating full maturation and even analog engineering^{[222][223][224]}. Engineered probiotics offer targeted delivery, with strains like *Lactobacillus* or *E. coli* Nissle secreting AMPs in situ, as demonstrated in *L. lactis* strains engineered to combat *H. pylori* through guided AMPs^{[225][226]}.

Nanotechnology complements these efforts, enabling surface display of AMPs on phage particles or their incorporation into self-assembling biomaterials such as antimicrobial hydrogels^{[227][228][229][230]}. Together, these strategies bridge the gap between sequence identification and practical application, transforming AMP discovery from a labor-intensive natural product screening process into an integrated design-build-test pipeline grounded in computational and synthetic biology.

7. Engineering and Delivery Platforms for Marine AMPs

Realizing the therapeutic and environmental potential of marine AMPs requires overcoming major challenges in stability, bioavailability, and tissue-specific targeting. Contemporary strategies integrate peptide engineering, chemical modification, and advanced delivery systems to enhance AMP performance and applicability.

7.1. Stabilization and Engineering for Therapeutic Use

Marine AMPs, while naturally evolved for marine environments, often suffer from proteolytic degradation, immunogenicity, and off-target effects in human systems. Chemical modifications have proven essential to improving their pharmacokinetic and pharmacodynamic profiles. Substitution with D-amino acids or complete D-enantiomerization protects peptides from enzymatic cleavage, as stereoselective proteases poorly recognize such configurations^{[231][232]}. These D-forms frequently retain antimicrobial potency, as membrane-disruptive mechanisms are often chirality-independent^{[233][234]}. Similarly, incorporation of unnatural residues, such as β -amino acids or peptoids, confers protease resistance while preserving amphipathic secondary structures^{[235][236][237]}. For example, halogenated tripeptides with non-canonical side chains have demonstrated enhanced activity and low cytotoxicity^[54]
^{[238][239]}.

Cyclization further improves peptide robustness by constraining conformation, eliminating termini susceptible to exopeptidases, and reducing renal clearance^{[240][241][242]}. Engineered cyclic analogs of θ -defensins illustrate enhanced serum stability and attenuated immunogenicity^{[243][244][245]}. However, cyclization must preserve amphipathic topology, and computational modeling aids in predicting structural and functional retention^{[240][245][246]}. Rational sequence tailoring, including the truncation of hemolytic regions and the substitution of hydrophobic residues, can reduce host toxicity while preserving bactericidal efficacy^{[247][248][249]}. In one case, a single leucine-to-lysine substitution dramatically reduced hemolysis with marginal loss of antimicrobial activity^{[247][248]}.

PEGylation, through covalent attachment of polyethylene glycol chains, enhances circulation time and shields peptides from proteases, albeit at a potential cost to membrane affinity^{[250][251]}. Careful tuning of PEG size allows retention of antimicrobial function with improved pharmacological profiles^{[252][253]}. Conversely, lipidation with fatty acid tails increases membrane targeting but can elevate toxicity, requiring delicate optimization^{[254][255][256]}. Self-assembling peptide prodrugs present another innovative modality, forming micelles or nanostructures that protect peptides in transit and release active monomers upon encountering bacterial membranes^{[257][258][259][260]}. Dendritic AMP nanoparticles, for instance, have shown potent biofilm disruption with low host cell toxicity^{[261][262][263]}.

7.2. Advanced Delivery Systems

To ensure effective therapeutic deployment, AMPs must be shielded during systemic circulation and released in a controlled manner at the site of infection. Nanocarriers such as liposomes and polymeric nanoparticles offer protective encapsulation^[264]. Liposomal formulations reduce proteolysis, limit host cytotoxicity, and enhance bacterial targeting through membrane fusion^{[265][266]}. Functionalization with targeting ligands allows tissue-specific delivery, such as to pulmonary or biofilm-associated infections^{[267][268][269]}. Polymeric particles (for example, PLGA-based) enable sustained release, particularly valuable in chronic infections where continuous antimicrobial presence is needed^{[270][271]}.

Localized delivery via hydrogels and surface coatings provides additional advantages. Hydrogels embedded with AMPs create a moist wound environment and release peptides in a stimuli-responsive manner, triggered by factors such as pH changes or bacterial enzymes^{[272][273][274]}. Self-healing hydrogels incorporating marine AMPs combine physical protection with prolonged antimicrobial action^{[275][276]}. Surface-tethered AMPs on medical devices function as contact-kill coatings, reducing

biofilm formation without systemic diffusion^{[277][278]}. Immobilized peptides retain long-term surface activity and minimize host exposure^[279]. Optimal spacer design and orientation are crucial to preserve membrane-disruptive activity^{[280][281]}.

Stimuli-responsive release systems introduce smart control over AMP activation. Pro-AMPs with pathogen-specific cleavage sites remain inert until cleaved by bacterial enzymes^{[282][283]}, ensuring on-demand activity at infection sites. Thermo- or photo-responsive carriers further refine release dynamics, particularly useful in febrile or superficial infections^{[284][285][286]}.

Engineered probiotic bacteria represent a frontier in programmable delivery. Strains such as *E. coli* Nissle have been modified to secrete AMPs in situ in response to quorum sensing signals, providing context-dependent protection^{[287][288][289]}. Topical probiotics engineered to produce human or marine AMPs offer potential for skin barrier defense^{[290][291][292]}. These living delivery platforms integrate environmental sensing with AMP production, enabling precise spatial and temporal control^{[289][293][294]}.

Finally, combination devices such as AMP-releasing sutures and orthopedic bone cements extend these technologies into surgical and implantable applications^{[295][296][297][298]}. Early-stage studies show efficacy against multidrug-resistant pathogens such as MRSA^{[295][299][300][301]}, underscoring the feasibility of AMP-functionalized materials in clinical settings.

Across these platforms, the central objective remains maximizing local antimicrobial efficacy while minimizing systemic exposure and production costs. Biodegradability, low environmental impact, and tunable activity profiles make AMPs ideal candidates for integration into advanced material systems^{[274][302][303]}. Regulatory frameworks currently favor familiar modifications such as D-substitution and cyclization^{[304][305][306]}, but the pressing urgency of AMR is accelerating innovation. Notably, Lytxar (LTX-109), a synthetic peptide inspired by marine AMPs^{[307][308][309]}, has progressed to clinical trials as a topical treatment for MRSA nasal decolonization^[310], exemplifying the clinical promise of engineered marine peptides^[151].

8. Applications in Health, Industry, and Environment

Marine AMPs, with their potent and broad-ranging activities, are finding diverse applications across clinical medicine, industrial settings, and environmental management. In this section, we explore how marine AMPs or their derivatives are being translated into real-world use cases: from novel therapeutics

tackling drug-resistant infections, to anti-biofilm coatings in medical and marine industries, to tools for improving aquaculture biosecurity and environmental conservation.

8.1. Clinical and Healthcare Applications

Marine AMPs represent a promising class of therapeutics for combating infections refractory to conventional antibiotics. Their unique structures, potent broad-spectrum activity, and reduced potential for resistance make them suitable for multiple clinical applications, ranging from topical treatments to systemic and device-associated infection control.

Topical formulations are among the most advanced applications. For instance, omiganan, a synthetic analog inspired by fish AMPs and indolicidin, has reached Phase III clinical trials for preventing catheter-associated infections and treating acne, demonstrating efficacy in reducing *S. aureus* and *Candida* colonization^{[311][312][313]}. Marine snail-derived peptides are also under investigation for chronic wound healing, particularly in diabetic ulcers, by combining antimicrobial action with inflammation modulation^{[314][315][316]}.

Systemic delivery of AMPs remains challenging due to enzymatic degradation and rapid renal clearance. However, specific marine peptides or AMP-mimetic derivatives have shown translational potential. Plitidepsin (Aplidin®), originally developed as an anticancer agent, is undergoing repurposing for viral infections including COVID-19^{[317][318]}. Meanwhile, tachyplesin analogs have demonstrated efficacy in murine sepsis models by neutralizing endotoxin and exerting bactericidal activity^[319]. Such studies support further development of stabilized and targeted formulations for systemic use.

The antibiofilm properties of marine AMPs are especially valuable for managing chronic infections. Pleurocidin-incorporated hydrogels have shown strong inhibition of *Candida* and *Streptococcus* biofilms in oral care settings^{[320][321][322]}. In respiratory diseases such as cystic fibrosis, shellfish-derived peptides remain active in high-salt sputum, showing potential for nebulized delivery^{[323][324]}. Synergistic combinations further enhance their utility; tachyplesin III has been shown to potentiate the efficacy of piperacillin-tazobactam in peritonitis models^{[325][326]}, while gaduscidin-1 enhances ciprofloxacin activity against *P. aeruginosa* in sputum by increasing biofilm permeability^{[140][327]}.

In hospital environments, marine AMPs are being explored as antimicrobial coatings on medical devices. For example, a catheter coated with a LL-37 analog and chlorhexidine achieved ~90% reduction in colonization^{[44][328]}, and experimental coatings with marine peptides have shown superior biofilm

resistance compared to silver^{[281][329][330]}. These coatings may become standard in indwelling devices to prevent nosocomial infections^{[331][332]}.

Expanding beyond bacteria, marine AMPs are gaining attention for their antiviral and antiparasitic properties. Mytilin from mussels inhibits herpesvirus entry^{[333][334]}, fish hepcidins have been shown to retain biological activity in murine hosts and can be systemically administered^{[335][336]}, while mammalian studies have established that hepcidin-driven iron sequestration limits *Plasmodium* liver-stage infection^{[337][338][339][340]}. These findings suggest utility in niche clinical contexts, including tropical diseases and viral co-infections.

8.2. Industrial and Environmental Applications

The potential of marine AMPs extends beyond medicine, offering sustainable, biodegradable solutions in industrial biofilm control, food safety, aquaculture, agriculture, and environmental monitoring.

Antifouling and anti-biofilm coatings are key targets in marine industries. Traditional antifouling agents such as copper pose ecological risks^[341], while AMP-based coatings offer non-toxic alternatives^{[342][343][344]}. Peptides derived from sea anemones and brominated cyclic peptides have demonstrated efficacy in deterring bacterial colonization, indirectly preventing macrofouling by barnacles^{[345][346]}. AMP-functionalized polymer coatings on aquaculture nets are under development to improve water exchange and disease control without chemical pollution^{[347][348]}.

In the food industry, AMPs can be incorporated into surface sanitizers and packaging materials^[349]. While nisin is widely used in food preservation^{[350][351]}, marine AMPs active under variable pH or against Gram-negative pathogens could fill existing gaps^[56]. Films composed of shrimp-derived chitosan and AMPs have successfully prolonged the shelf-life of seafood by inhibiting spoilage bacteria, underscoring their value in active packaging solutions^{[352][353][354]}.

Water treatment systems benefit from AMP-functionalized filtration membranes, which resist biofilm formation without relying on chlorine^{[355][356]}. Membranes grafted with synthetic AMP hybrids such as cecropin-melittin analogs have shown sustained biofilm resistance in desalination setups^{[357][358][359]}. AMPs may also prevent *Legionella* contamination in cooling towers, offering chemical-free alternatives for industrial hygiene^{[360][361][362]}.

In aquaculture, marine AMPs offer antibiotic-free disease control strategies. Dietary supplementation with algae-derived AMPs has reduced *Vibrio* load and mortality in shrimp^{[363][364]}. Transgenic fish expressing AMPs like cecropin exhibit enhanced resistance to bacterial pathogens^{[365][366]}. Recent work therefore prioritizes boosting salmonid endogenous cathelicidins^[367], rather than introducing heterologous AMPs^[368], to stay within aquaculture regulatory frameworks and to strengthen mucosal defence against *Vibrio* spp. and *Lepeophtheirus salmonis*^{[144][369]}. AMP-treated larval tanks and feed additives may become standard practices in sustainable aquaculture biosecurity^{[370][371]}.

Crop protection applications, though less explored, are emerging. Marine *Bacillus* strains producing AMP-like lipopeptides (e.g., iturins) exhibit antifungal activity^{[372][373]}, and marine *Pseudomonas*-derived peptides are being considered for managing plant pathogens^{[374][375]}. Their rapid degradation and low environmental persistence make them attractive replacements for copper-based pesticides^{[376][377][378]}.

Environmental bioremediation and biosensing also benefit from AMP-based innovations. AMP-coated biosensors have been developed to detect *Listeria* in food wash water and *E. coli* in environmental samples, offering stable, robust alternatives to antibodies^{[379][380][381][382]}. In oil reservoir management, selective AMPs may suppress sulfate-reducing bacteria without disrupting beneficial microbial communities, aiding in souring control^{[383][384]}. Furthermore, AMP-based surface coatings are being explored in public health settings, including applications on hospital bed rails and doorknobs, to provide persistent antimicrobial protection without the use of chemical disinfectants^{[385][386]}.

Collectively, these translational applications underscore the versatility of marine AMPs as next-generation bioactive agents. Their integration into diverse technological platforms, including therapeutics, materials, sensors, and ecological interventions, marks a new phase in which marine-derived peptides provide sustainable solutions to challenges in both human and environmental health (Table 2).

Application	Use case	AMP / product	Source	Model	Target	Key outcome
Clinical	Nasal decolonization	LTX-109	AMP-inspired	Human (Phase 2)	<i>Staphylococcus aureus</i> (MRSA)	Significant reduction in nasal carriage after 2 days of topical treatment
Clinical	Burn wound infection	Epinecidin-1	Marine fish	Pig	<i>Staphylococcus aureus</i> (MRSA)	Complete wound healing within 25 days
Clinical	Systemic infection	Epinecidin-1	Marine fish	Pig	<i>Staphylococcus aureus</i> (MRSA)	Protection against pyemia at 2.5 mg kg ⁻¹
Preclinical	Wound infection	Piscidin-3	Marine fish	Mouse	<i>Staphylococcus aureus</i> (MRSA)	Survival increased to 100% with early dosing
Aquaculture	Disease resistance	Piscidin-3 (transgenic)	Marine fish	<i>Danio rerio</i>	<i>Streptococcus agalactiae</i>	Markedly improved survival after challenge
Aquaculture	Acute infection	Piscidin-3 / Piscidin-4	Marine fish	Tilapia	<i>Vibrio vulnificus</i>	Survival increased to >88%
Medical device	CAUTI prevention	AMP-coated catheter	AMP-based	Mouse	Mixed uropathogens	Biofilm reduced by >4 log units
Medical device	Implant infection	AMP film	AMP-based	Mouse	<i>Staphylococcus aureus</i>	Sustained biofilm inhibition for >24 days
Food safety	Preservation	Epinecidin-1	Marine fish	Food matrix	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	Up to 6 log reduction during storage
Antiviral	Microbicide	Q-Griffithsin	Marine algae	Clinical trial	HIV-1	Advanced to human testing

Application	Use case	AMP / product	Source	Model	Target	Key outcome
Combination therapy	Sepsis	Epinecidin-1 plus antibiotic	Marine fish	Mouse	<i>Klebsiella pneumoniae</i>	Survival increased to >90%

Table 2. Translational and applied uses of marine antimicrobial peptides.

9. Environmental Fate and Risk Assessment

As marine AMPs transition into medical, agricultural, and industrial applications, understanding their environmental behavior and potential ecological risks becomes crucial. Unlike conventional small-molecule antibiotics, AMPs are generally expected to degrade into non-toxic amino acids^{[387][388]}. However, comprehensive assessments are necessary to evaluate their degradation pathways, potential bioaccumulation, and influence on microbial communities and resistance gene dynamics.

9.1. Environmental Degradation and Persistence

AMPs are inherently biodegradable, undergoing breakdown via enzymatic and abiotic mechanisms. In aquatic and soil environments, proteases secreted by microbes rapidly cleave peptide bonds, especially for linear peptides^{[389][390][391]}. Cyclic peptides such as colistin or bacitracin demonstrate slower degradation but still exhibit significant attenuation in wastewater treatment systems, primarily through adsorption and microbial action^{[392][393]}. For example, when spiked into biologically active sludge/biofilm matrices, colistin undergoes rapid attenuation within days, driven primarily by strong sorption to solids and microbial transformation^{[388][392][394]}. Photodegradation also contributes, particularly for peptides with aromatic residues like tryptophan or tyrosine under UV-B exposure^[395].

AMPs tend to adsorb strongly to sediments and organic matter, which reduces their bioavailability but may extend environmental residence time^{[388][396]}. Adsorbed peptides can still be degraded by sediment-associated microbes^{[388][389][397]}. Despite these interactions, most AMPs have environmental half-lives that range from several days to a few weeks, which are substantially shorter than the persistence typically observed for sulfonamides or fluoroquinolones^{[388][398]}. Nevertheless, chronic input from

continuous use in aquaculture or antifouling materials could result in pseudo-persistence, underscoring the importance of monitoring actual concentrations in situ rather than assuming rapid dissipation^[399].

9.2. Ecotoxicological Profiles and Non-target Effects

Available data suggest that AMPs pose low acute toxicity risks to non-target aquatic and terrestrial organisms at environmentally relevant concentrations^{[388][400][401]}. For instance, the LC50 of bacitracin for *Daphnia magna* exceeds 100 mg/L, which is several orders of magnitude higher than projected environmental concentrations^{[401][402][403]}. Similar findings apply to vancomycin and daptomycin, with negligible effects on algae and fish^{[404][405][406]}. Soil assays with earthworms exposed to colistin up to 100 mg/kg showed no lethality, though some sublethal stress responses (e.g., heat shock protein expression) were noted^[407].

The main ecological concern lies in potential disruption of microbial communities and selection for resistance. High concentrations of AMPs may alter soil or aquatic microbiomes, as observed with colistin in long-term soil exposure studies. However, such concentrations far exceed typical environmental levels. Even so, chronic low-level exposure, such as that resulting from effluents, could impose subtle selection pressure. While most AMP resistance mechanisms are chromosomally encoded and non-mobile, exceptions like plasmid-borne *mcr* genes (e.g., *mcr-1* conferring resistance to polymyxins) highlight the need for vigilance. Broader use of AMPs may co-select for membrane modifications that impact both resistance and host-pathogen interactions^{[408][409]}.

9.3. Regulatory and Stewardship Implications

Most AMPs are likely to pass environmental risk assessments due to their rapid degradation and low toxicity. Regulatory agencies such as the European Medicines Agency may exempt certain peptide-based agents from residue limits if environmental persistence is minimal. Nonetheless, combination effects warrant attention; co-occurrence with other antimicrobials could lead to synergistic ecotoxicity, as demonstrated by increased algal toxicity when vancomycin was combined with gentamicin^[404]. Environmental risk assessments must therefore account for realistic exposure scenarios involving mixtures.

From a One Health perspective, AMP stewardship should align with antimicrobial governance strategies. In medical settings, targeted use of AMPs, especially against biofilms or multidrug-resistant pathogens, may help minimize the development of resistance. Narrow-spectrum AMPs may also spare beneficial

microbiota, reducing collateral selection pressure. In agriculture, replacing growth-promoting antibiotics with marine AMPs could mitigate classical AMR propagation, provided AMP choices avoid overlap with those critical to human health.

Environmental monitoring frameworks should integrate AMP surveillance early in their deployment cycle. Effluent guidelines and predicted no-effect concentrations (PNECs) can guide safe use thresholds. While acute toxicity appears minimal, long-term studies in realistic environmental contexts are necessary to evaluate chronic effects and resistance dynamics.

In conclusion, marine AMPs offer an environmentally preferable alternative to traditional antibiotics, with favorable degradation profiles and limited ecotoxicity. Their deployment could alleviate environmental antimicrobial resistance pressures, but this benefit depends on the implementation of robust stewardship, continuous monitoring, and effective regulatory oversight.

10. Standardization, Databases, and Knowledge Integration

With the rapid expansion of marine AMP research, the field increasingly requires standardized methodologies and integrated knowledge resources. Historically, heterogeneous experimental designs have led to inconsistent results, complicating comparisons and slowing translation^{[48][410][411]}. The adoption of harmonized protocols and interoperable databases is now essential to accelerate discovery, facilitate regulatory approval, and enable rational development of marine AMPs.

Standardization efforts focus on unifying experimental parameters that critically influence reported outcomes. Minimal inhibitory concentrations are now recommended to be measured under physiologically relevant conditions, such as salt-adjusted media with serum supplementation, accompanied by time-kill analyses that distinguish bacteriostatic from bactericidal activity. Parallel protocols for resistance evolution, such as serial passage under increasing AMP exposure, provide comparable metrics of resistance propensity across studies. Equally important is the uniform assessment of host toxicity, with hemolysis assays on standardized human erythrocytes and cytotoxicity profiling in common cell lines, yielding reliable selectivity indices. Stability testing in serum or across physiological pH ranges, together with consistent reporting of solubility and formulation conditions, provides essential data for therapeutic optimization. To ensure comparability, authors are encouraged to report sequences in standardized formats, use μM concentrations, and adopt frameworks such as “Minimum Information about an Antimicrobial Peptide Experiment” (MIAPE), which specify required details on sequence, source, assay protocols, and purity. As translation advances, these principles must extend into

manufacturing, where specifications for sequence identity, purity, and endotoxin-free preparations will be required, potentially codified in pharmacopeial monographs similar to those for polymyxins.

The growing corpus of AMP data is increasingly supported by curated databases. APD3 now catalogs over 5000 entries with sequence and structural annotations^{[27][412]}; CAMPR3 integrates predictive modeling tools alongside natural and synthetic peptides^{[208][413]}; DRAMP 2.0/3.0 provides more than 24,000 manually curated entries with extensive metadata^[197]; and DBAASP emphasizes quantitative activity values and three-dimensional visualization^[414]. Cross-referencing among these repositories, and integration into larger frameworks such as UniProt, allows comparative analyses and supports computational design pipelines. The convergence of these platforms underscores a shift toward data-driven discovery.

The next stage of integration lies in knowledge graphs that interconnect AMP sequences with their source organisms, structures, mechanisms, activity spectra, toxicity data, and literature. Such graph-based infrastructures enable advanced queries, such as identifying peptides that share structural motifs and mechanisms, or predicting gaps in experimental validation. Emerging initiatives, including SATPdb and biofilm-related knowledge bases, illustrate this trajectory, while semantic web technologies facilitate federated searches across multiple resources^{[415][416][417][418]}. In regulatory contexts, standardized datasets and community-defined benchmarks, such as MIC <10 μ M against *E. coli*, <20% hemolysis at 100 μ M, or therapeutic index >20, provide valuable reference points for evaluating new candidates^{[192][200][201][419][420][421]}.

For marine AMPs in particular, an integrated Marine AMP Atlas consolidating sequence, structural, activity, toxicity, and resistance data would represent a transformative resource. Such an atlas would not only guide therapeutic prioritization but also advance ecological understanding of peptide functions across marine taxa. By anchoring AMP science in standardized protocols and interoperable data systems, the field is well positioned to transition from fragmented discoveries toward systematic innovation and translational impact.

11. Conclusions and Outlook

Marine AMPs exemplify nature's evolutionary ingenuity and represent a promising frontier in the battle against AMR. Originating from organisms adapted to extreme marine environments, these peptides possess unique structural features, including noncanonical amino acids and cyclic backbones, which

confer potent antimicrobial activity and resilience under physiological stress. Unlike traditional antibiotics, many marine AMPs exhibit multitarget modes of action, disrupt biofilms and persister cells, and show enhanced biodegradability, suggesting reduced ecological impact.

Over the next decade, marine AMPs are poised to transition from experimental therapeutics to clinical reality. Several candidates are already progressing through the pipeline, with 23 marine-derived compounds in preclinical or clinical trials spanning infectious diseases and oncology. Regulatory approval of topical formulations or implant coatings to combat multidrug-resistant infections appears feasible. In infectious disease management, AMP-antibiotic combination therapies, inhalable formulations for cystic fibrosis, or endotoxin-neutralizing peptides for sepsis may soon complement or replace conventional agents. However, scalable production, potentially through the use of engineered marine microbes or algae, and comprehensive safety evaluation remain critical bottlenecks. Advances in peptide stabilization strategies, such as D-amino acid substitution and peptide stapling, are accelerating translation by enhancing pharmacokinetics and reducing toxicity.

Beyond therapeutic applications, marine AMPs are reshaping fundamental microbiology and drug development. These peptides have illuminated immune defense mechanisms in extreme habitats and inspired synthetic mimetics and polymeric SMAMPs that replicate their action with improved manufacturability. Their integration into One Health frameworks, especially in aquaculture and agriculture, offers avenues to reduce antibiotic dependence and interrupt zoonotic transmission, highlighting their broader ecological and public health relevance.

Several knowledge gaps must be addressed to fully realize the clinical and ecological promise of marine AMPs. Mechanistically, atomic-resolution insights into peptide–lipid interactions, membrane insertion dynamics, and intracellular targets are needed. Tools such as NMR in membrane mimetics and super-resolution microscopy will be pivotal. The immunological roles of marine AMPs remain poorly characterized; their potential signaling functions, akin to human defensins, warrant investigation through genetic manipulation in marine models or transgenic systems.

Proactive resistance surveillance is essential if marine AMPs enter widespread use. Environmental baseline studies, including AMP susceptibility profiles in marine *Vibrio* species and sponge-associated bacteria, can help anticipate the emergence of resistance. Early data suggest limited resistance, but vigilant monitoring remains imperative. In parallel, harmonized manufacturing guidelines, impurity standards, and dedicated regulatory pathways for peptide therapeutics will streamline development.

The field's progress hinges on interdisciplinary integration. Computational modeling can decode sequence-activity relationships, while materials science will drive next-generation delivery systems. Ecology provides essential context on environmental deployment and unintended microbiome perturbations. AI-driven knowledge graphs may soon enable predictive design of AMP libraries optimized for specific infections or ecological niches.

In sum, marine AMPs illustrate the translational potential of natural molecules evolved under extreme conditions. With rigorous science, responsible development, and global collaboration, these peptides could reinvigorate our antimicrobial arsenal and provide sustainable tools to mitigate the escalating AMR crisis.

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