Review

Not peer-reviewed version

Marine Particles as Reservoirs of Novel Antimicrobial Peptides: An Emerging Frontier in Marine Drug Discovery

Xin Liu , Yilin Gu , Qingxia Kong * , Hongyue Dang *

Posted Date: 17 July 2026

doi: 10.20944/preprints202607.1303.v1

Keywords: marine particles; antimicrobial peptides; biosynthetic gene clusters; RiPPs; NRPs; smORFs; marine microbiome; machine learning; deep learning; bioprospecting

 doi:10.20944/preprints202607.1303.v1

Review

Marine Particles as Reservoirs of Novel Antimicrobial Peptides: An Emerging Frontier in Marine Drug Discovery

Xin Liu [1], Yilin Gu [2], Qingxia Kong [3,*] and Hongyue Dang [4,*]

[1] Institute of Biotechnology, Beijing Academy of Agriculture and Forestry Sciences, Beijing, China
[2] College of Horticulture and Plant Protection, Inner Mongolia Agricultural University, Hohhot, China
[3] College of Aquaculture, Tianjin Agricultural University, Tianjin, China
[4] State Key Laboratory of Marine Environmental Science, College of Ocean and Earth Sciences, Xiamen University, Xiamen, China
* Correspondence: xiaokong3155@163.com (Q.K.); DangHY@xmu.edu.cn (H.D.)

Abstract

The increasing global antibiotic resistance has created a pressing need for new antimicrobial drugs. Antimicrobial peptides (AMPs) come into the spotlight for their antibacterial properties, particularly against multidrug-resistant pathogens. Since AMPs act locally, they achieve optimal antimicrobial effectiveness and face maximum evolutionary pressure within spatially confined, highly competitive microbiomes. This ecological principle justifies marine particles as promising reservoirs of untapped marine AMPs. Marine particles are ubiquitous throughout the ocean, ranging from the sunlit surface waters to the deepest hadal environments. They are densely colonized microhabitats where nutrient gradients, spatial proximity, chemical signaling, and interspecies competition among microorganisms converge—unique characteristics that position marine particles as natural laboratories for the evolution of novel AMPs. However, most marine microorganisms are challenging to cultivate. Fortunately, metagenomics is revolutionizing marine AMP discovery by enabling researchers to screen for elusive peptide-encoding genes and complex biosynthetic gene clusters in uncultivated microbial communities. Additionally, advancements in artificial intelligence are further transforming marine AMP bioprospecting by moving from passive exploration to active molecular understanding and navigation. This review synthesizes our current understanding of the microbial ecology and emerging technologies that drive marine AMP discovery, and explores the application potentials of marine AMPs in human medicine, agriculture, and mariculture.

Keywords: marine particles; antimicrobial peptides; biosynthetic gene clusters; RiPPs; NRPs; smORFs; marine microbiome; machine learning; deep learning; bioprospecting

1. Introduction

Antibiotics have transformed modern medicine, making formerly lethal infections treatable and enabling procedures that depend on effective infection control, including surgery, transplantation, intensive care, cancer chemotherapy, and neonatal care [1–3]. Each year, hundreds of millions of people receive antibiotic treatment for infections. Ever since their discovery and widespread use, antibiotics have saved countless lives and significantly extended the average human lifespan [4,5]. However, the effectiveness and future achievements of antibiotics are threatened by antimicrobial resistance (AMR), a global ecological and evolutionary issue accelerated by antibiotic misuse and overuse in human medicine, animal production, agriculture, aquaculture, and the broader engineered and natural environments [6–12]. Worldwide estimates indicate that, in 2019, bacterial AMR was linked to approximately 5 million deaths [13], with over half a million of those occurring in China alone [14]. Systematic analyses predict that, without effective intervention, AMR could cause

 doi:10.20944/preprints202607.1303.v1

between 8 and 10 million deaths annually by 2050 [15,16]. These figures underscore AMR as one of the most pressing public-health and development challenges of the twenty-first century.

The slow pace of conventional antibiotic discovery exacerbates the AMR crisis [17–19]. Many antibiotics currently used in clinical settings target a limited set of conserved bacterial processes, such as cell wall biosynthesis, protein synthesis, DNA replication, RNA transcription, or folate metabolism [20,21]. The repeated targeting of these processes, combined with widespread antibiotic exposure, has selected for various resistance mechanisms, including reduced permeability, efflux, target modification, enzymatic inactivation, and biofilm-associated tolerance (Figure 1a) [11,20–25]. To make matters worse, most molecular mechanisms of AMR are associated with mobile genetic elements (MGEs), facilitating the global transmission of AMR through horizontal gene transfer (HGT) [26–30]. Multidrug-resistant pathogens, including those from the ESKAPE group [31–36], are now undermining the effectiveness of last-line therapies and highlighting the limitations of current discovery pipelines, which tend to rediscover variations of known drug scaffolds. This situation has sparked a renewed interest in developing antimicrobial agents with alternative structures, mechanisms, ecological origins, and evolutionary histories.

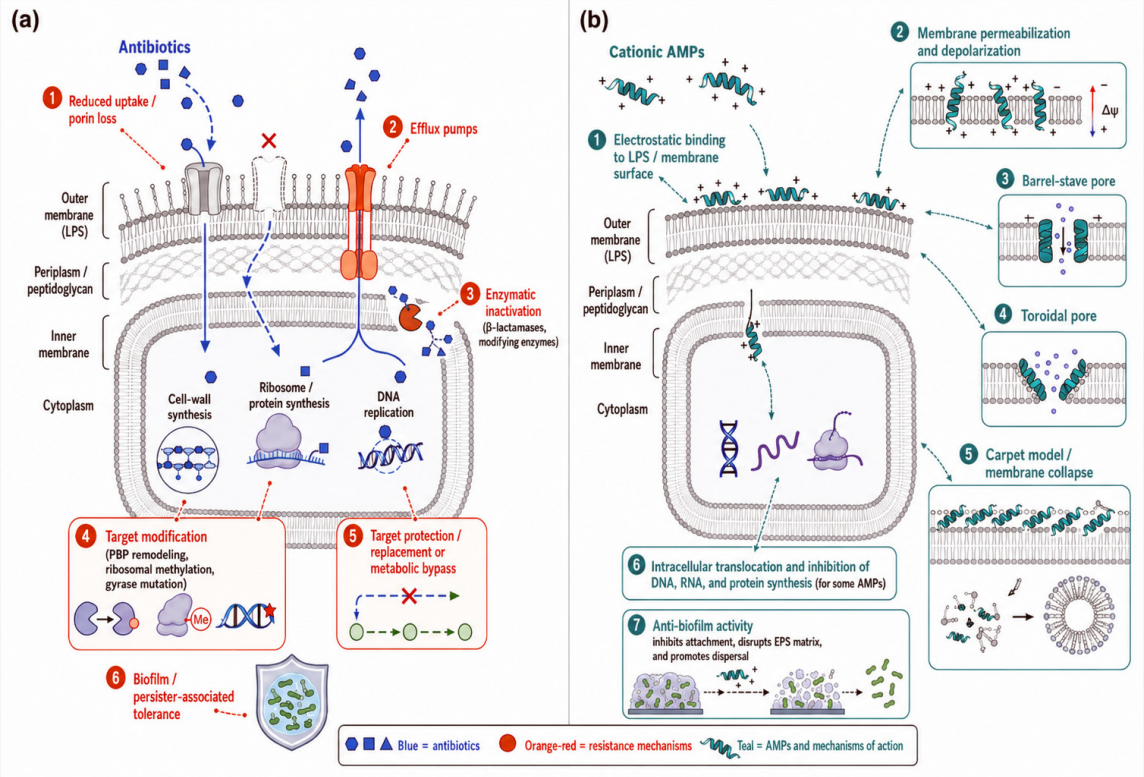

Figure 1. Cartoon presentation of the major bacterial resistance mechanisms against conventional antibiotics and the antibacterial mechanisms of antimicrobial peptides in Gram-negative bacteria. (a) Schematic overview of major strategies by which bacteria resist conventional antibiotics. These include reduced membrane permeability through porin loss or closure, active efflux of antibiotics, enzymatic inactivation of antibiotics, modification of envelope-associated or intracellular drug targets, target protection/replacement or metabolic bypass, and biofilm-associated protection and persister-cell formation with reduced drug penetration. These mechanisms collectively limit intracellular antibiotic accumulation, reduce target accessibility, or preserve essential cellular functions. (b) Schematic overview of principal antibacterial mechanisms of cationic antimicrobial peptides (AMPs). Cationic AMPs act primarily through electrostatic interactions with negatively charged lipopolysaccharides (LPS) and bacterial membranes, disrupt membrane integrity, form transmembrane pores, destabilize membranes through carpet-like surface interactions, and induce membrane depolarization and leakage of ions or intracellular contents. Some AMPs can further translocate into the cytoplasm and interfere with DNA, RNA, or protein synthesis, while others exhibit anti-biofilm activity by inhibiting attachment,

 doi:10.20944/preprints202607.1303.v1

disrupting the extracellular polymeric substance (EPS) matrix, and promoting biofilm dispersal. Together, these mechanisms illustrate the contrast between bacterial strategies that reduce antibiotic efficacy and the multi-target actions of AMPs.

Antimicrobial peptides (AMPs), also referred to as host-defense peptides when produced by multicellular organisms [37–42], represent a promising new class of anti-infective agents [43–51]. Given the global threat of AMR, AMPs have come into the spotlight for their effectiveness against diverse microbial pathogens, including bacteria, fungi, protozoan parasites, and viruses [52–57]. For example, colistin, a cationic cyclic lipodecapeptide produced by Gram-positive bacteria of the genus Paenibacillus, is a last-line-of-defense antibiotic reserved for serious infections caused by multidrug-resistant Gram-negative bacterial pathogens [58]. Many AMPs act rapidly by directly interacting electrostatically with negatively charged microbial envelopes, leading to membrane permeabilization, pore formation, or destabilization. Some AMPs cross the microbial membrane and disrupt intracellular processes, impacting nucleic acid synthesis, protein translation, enzyme activity, and cell wall precursor cycling (Figure 1b) [57,59–65]. Beyond direct killing, many AMPs exhibit immunomodulatory, anti-inflammatory, antibiofilm, wound-healing, or synergistic activities, making them attractive not only as antibiotics but also as anti-infective adjuvants [39,64–70]. For instance, certain AMPs act as chemoattractants, recruiting host immune cells to sites of infection, while others help neutralize the cytotoxic effects of endotoxins, such as lipopolysaccharides (LPS) from Gram-negative bacteria, thereby preventing septic shock caused by excessive inflammation [71–74].

AMPs are typically short, cationic, and amphipathic peptides produced in all life forms, including bacteria, archaea, protists, fungi, plants, invertebrates, and vertebrates [42,75–78]. They constitute a critical component of the innate immune systems of fungi, plants, and animals, serving as the first line of defense against various pathogens [79–86]. AMPs exhibit a vast diversity in biological origins, sequences, lengths, structures, and bioactivities (Figure 2) [57,62–65,87,88]. Their defining advantages over traditional small-molecule antibiotics include remarkably broad-spectrum activity and rapid bactericidal kinetics [51,66,89–93]. Colistin (polymyxin E), for example, has been reserved as the last-line antimicrobial therapy for treating recalcitrant bacterial infections caused by multidrug-resistant pathogens [94]. Most critically, AMPs have a lower propensity than conventional antibiotics to promote bacterial resistance [92,95–98]. This resistance-avoidance property is largely attributable to the fundamental, non-specific, multi-target, and multifunctional nature of the AMP membrane-active mechanism, which creates a narrow time window and steep evolutionary barrier to microbial counter-adaptation [60,66,90,99,100]. There is also a low propensity for cross-resistance among different AMPs and between AMPs and antibiotics; instead, they typically demonstrate functional synergy, resulting in enhanced antimicrobial efficacy [67,97,101,102]. In addition, bacteria with multidrug resistance generally exhibit a high tendency toward collateral sensitivity to AMPs, a physiological phenomenon likely caused by antibiotic-induced changes in the lipopolysaccharide composition of the bacterial outer membrane [103]. Furthermore, limited functional compatibility poses a significant barrier to HGT of AMP resistance among phylogenetically distant bacteria [104]. As a result, their efficacy and low tendency to develop and spread resistance make AMPs “the most promising alternative to antibiotics” for the treatment of microbial diseases, particularly those caused by multidrug-resistant ESKAPE bacteria and WHO-priority fungi [105–111]. AMPs are highly regarded as the “pillars of next-generation antimicrobial agents” and “the game-changer in the epic battle against multidrug-resistant bacteria” [112,113].

 doi:10.20944/preprints202607.1303.v1

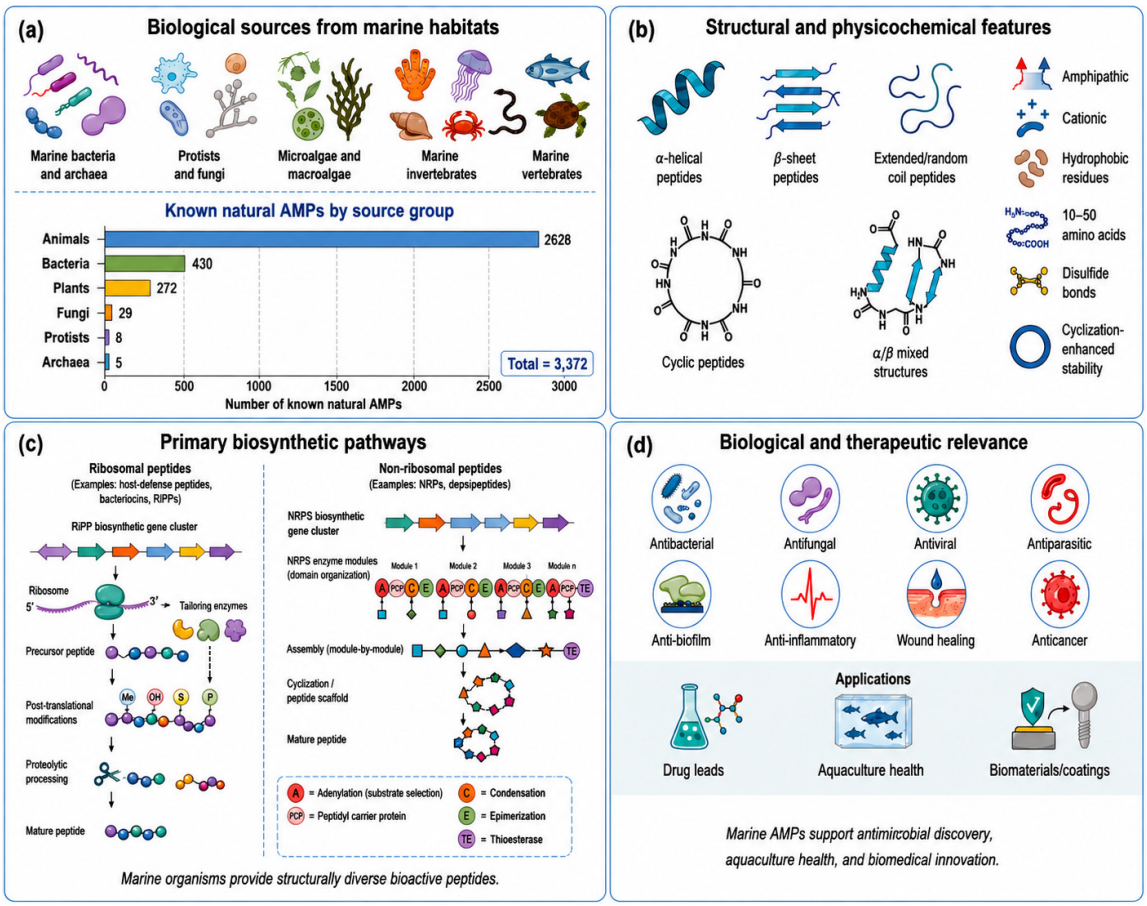

Figure 2. Overview of marine antimicrobial peptides (AMPs): biological sources, structural characteristics, biosynthetic pathways, and application potential. (a) Marine AMPs are derived from diverse biological sources across marine habitats, including marine bacteria, archaea, protists, fungi, algae, invertebrates, and vertebrates. The bar chart summarizes the number of natural AMPs with known sequences and activities reported from major source groups of both marine and non-marine living organisms retrieved from the APD6 antimicrobial peptide database (accessed on 10 June 2026) [42]. (b) Representative structural and physicochemical features of AMPs. Marine AMPs can adopt α-helical, β-sheet, extended/random-coil, cyclic, and mixed α/β conformations. Their biological activities are commonly associated with amphipathicity, cationic charge, hydrophobic residues, relatively short peptide length, disulfide bond formation, and cyclization-enhanced stability. (c) Primary biosynthetic pathways contributing to marine AMP diversity. Ribosomal peptides, such as ribosomally synthesized and post-translationally modified peptides (RiPPs), are encoded by biosynthetic gene clusters, translated as precursor peptides, and subsequently processed through enzymatic tailoring, post-translational modification, and proteolytic cleavage to generate mature peptides. Non-ribosomal peptides (NRPs) are assembled by non-ribosomal peptide synthetases (NRPSs) through modular domain-mediated biosynthesis. Adenylation (A), peptidyl carrier protein (PCP), condensation (C), epimerization (E), and thioesterase (TE) domains mediate substrate selection, carrier loading, peptide bond formation, stereochemical conversion, and product release or cyclization, respectively. (d) Biological activities and translational relevance of marine AMPs. Marine AMPs exhibit broad antibacterial, antifungal, antiviral, antiparasitic, anti-biofilm, anti-inflammatory, wound-healing, and anticancer activities. These functional properties support their potential development as antimicrobial drug leads, aquaculture health-promoting agents, and bioactive biomaterials or surface coatings.

AMPs are produced by virtually all cellular organisms, from prokaryotes to humans, as a means of signaling, competition, or defense [114,115]. They have evolved over billions of years in response to the diverse and ever-changing biological and physicochemical environments on planet Earth [116,117]. This extensive evolutionary history suggests that natural-based AMPs may possess nearly unlimited sequence diversity and remarkable functional versatility [118–122]. Microbial AMPs, in particular, play a substantial role in contributing to and expanding this vast chemical space [123–

 doi:10.20944/preprints202607.1303.v1

131]. Bacteriocins, lanthipeptides, lasso peptides, thiopeptides, microcins, and other ribosomally synthesized and post-translationally modified peptides (RiPPs) are produced by microorganisms as weapons, signals, and niche-structuring molecules [132]. These peptides can exhibit high potency, narrow or broad antimicrobial spectra, unusual post-translational modifications, and mechanisms distinct from those of many conventional antibiotics [133–140]. In addition to RiPPs, microbial AMPs can also be produced as non-ribosomally synthesized peptides (NRPs), a chemically rich and pharmacologically important class of peptidic natural products [141–148]. NRPs are biosynthesized by large modular non-ribosomal peptide synthetases (NRPSs), encoded by specific biosynthetic gene clusters (BGCs) [149–152]. The diversity and complexity of the BGCs and enzyme systems responsible for the cellular synthesis of RiPPs and NRPs yield an immense array of bioactive peptides [121,153–159], the vast majority of which remain undiscovered and unexplored [160–162]. Currently, both RiPPs and NRPs are experiencing a surge of research interest in genome mining and peptide engineering to generate non-natural peptides with enhanced or novel bioactivities, thereby further expanding the chemical space of AMPs [136,163–169].

Despite their vast diversity and inherent advantages over conventional antibiotics, only a handful of AMPs have successfully transitioned to clinical use to date [47,100,170–174], with challenges such as in vivo instability, systemic toxicity, and high manufacturing costs tempering early enthusiasm [37,75,175–179]. Nevertheless, the sustained acceleration of peptide engineering technologies, chemical modification strategies, and recombinant production platforms continues to drive a renaissance in AMP-based drug development [56,57,180–186]. In addition, recent innovations in genome mining and synthetic biology have demonstrated that previously undetected BGCs for RiPP and NRPs can now be rapidly identified, refactored, and expressed, yielding new AMP molecules with potentially novel bioactivities [96,187–194]. A central bottleneck, however, persists at the earliest stage of the AMP drug development pipeline: the identification of new lead sequences and novel scaffolds from underexplored biological and ecological origins [195–197]. This limitation reinforces the need to search for AMPs in unexplored and underexplored habitats where they have naturally evolved under chemically demanding, competitive, and fluctuating conditions [198].

The ocean, occupying approximately 71% of the Earth's surface and 95% of the planet's biosphere [199,200], harbors an extraordinary breadth of phylogenetic, metabolic, and ecological diversity that has been recognized since the mid-twentieth century as a prolific source of structurally unprecedented bioactive specialized metabolites [201–205]. As of June 1, 2026, the MarinLit database [206] documents 44,710 marine-derived metabolic compounds, showcasing a wide variety of structures and biological activities. These complex molecules reveal a vast chemical landscape with significant potential for pharmacological development and applications [195]. Landmark therapeutic translations include the anticancer drugs cytarabine (approved in 1969), eribulin mesylate (2010), brentuximab vedotin (2011), trabectedin (2015), plitidepsin (2018), and lurbinectedin (2020), as well as the analgesic drug ziconotide (2004), establishing the ocean as a vital forefront in natural product pharmacology [207–215]. Crucially, the past two decades have witnessed a decisive paradigm shift in marine natural products research: from a near-exclusive focus on sessile invertebrates (e.g., sponges, ascidians, and cnidarians) to the exploration of microorganisms and their communities, which often serve as the true biosynthetic producers of the valuable natural compounds identified from marine animals [216–224]. Microorganisms make up more than 95% of the total biomass in the ocean [225]. In particular, marine microorganisms represent a promising yet underexplored resource for bioactive peptides [226–228]. This refocusing has been further driven by advancements in cultivation-independent metagenomic technologies, which have revealed that the uncultured majority of marine microorganisms may represent a vast reservoir of novel BGCs for the biosynthesis of RiPPs and NRPs, as well as small open reading frames (smORFs) encoding AMPs that remain to be characterized and explored [192,229–236]. Another key factor fueling the search for new marine natural products is drug resistance. Beyond the issue of widespread antibiotic resistance in bacteria [9,34,237], cancer treatment drugs face the same challenge [238–240]. For instance, certain cancer cell lines have developed resistance to cytarabine and trabectedin, and cancer stem cells can enter a

 doi:10.20944/preprints202607.1303.v1

reversible dormant state to escape the therapeutic effects of eribulin mesylate and brentuximab vedotin [241]. The arms race between cellular (including microbial) evolutionary processes and human efforts to combat disease will probably never end, keeping the marine environment a central arena for drug discovery and development.

Within the marine ecosystem, particulate organic matter — collectively termed marine particles — constitutes a ubiquitous, unique, and microbiologically active microhabitat in the vast water body of the ocean [242–244]. These particles, which range in size from sub-micron colloidal aggregates to centimeter-scale macroscopic flocs, are continuously generated in the euphotic zone through the coagulation of phytoplankton exudates, cellular debris, zooplankton fecal pellets, and other organic matrices [245–250]. Marine particles play critical roles in the ocean's biogeochemical cycling and climate regulation [251–255]. As they descend through the water column, they serve as concentrated oases of labile carbon and nutrients amidst the vast oligotrophic pelagic background, supporting microbial population densities that can exceed those in the surrounding seawater by three to five orders of magnitude [256–259]. Critically, this extraordinary enrichment transforms marine particles into intense arenas of microbial competition and antagonism, where densely packed, phylogenetically diverse assemblages of bacteria, archaea, protists, fungi, metazoa, and viruses engage in fierce, sustained ecological interactions for space and resources [243,260–270]. Moreover, the composition of particle-associated microbial communities differs from that of free-living microbial communities [243,271], thus enhancing the potential for functional innovation in marine microbiomes. It is precisely this elevated level of biotic conflict and functional novelty that positions marine particles as putative "hotspots" for the evolution, expression, and diversification of marine AMPs.

Marine-sourced peptides are at the forefront of novel natural product discovery and therapeutic drug development [272,273]. In this perspective article, we propose that marine particles represent a promising yet underexplored frontier for the discovery of marine AMPs. We synthesize current knowledge spanning marine microbial ecology and potential applications to evaluate the proposition that marine particles constitute a vast, untapped reservoir of novel marine AMPs. By connecting the global need for new anti-infective strategies with the ecological function of AMPs and the unique microscale ecology of marine particles, we highlight a conceptual shift: marine particles should not be viewed only as micro-reactors for important ecological and biogeochemical activities, but also as chemically active, interaction-rich niches where AMPs may evolve, accumulate, and function. Exploring these marine particle-associated peptide repertoires could expand the known diversity of AMPs and provide new leads for combating antibiotic-resistant infections and beyond.

2. Marine Particles: Ecology-Driven Hotspots for AMP Discovery

Life likely originated in the ocean [274,275], which currently hosts more living species than land does [276]. Populated by an estimated 10 billion microbial species [277], the ocean presents a fundamentally distinct biological and chemical landscape, where varying hydrostatic pressures, temperatures, salinities, and biological interactions create a variety of habitats that have driven the evolution of unique metabolic pathways and bioactive compounds not found in terrestrial ecosystems [278–282]. Anthropogenic perturbations, such as eutrophication, pollution, excessive CO2 emissions, and the resulting ocean warming, acidification, hypoxia, and harmful algal blooms, impose additional stresses on marine organisms, forcing them to adapt to changing environments and unseen biological interactions [283–293]. Biochemical and metabolic innovation, the key to ecological adaptation and physiological tolerance in such challenging and competitive environments, may yield novel molecules with unprecedented chemical scaffolds or enhanced specificity and potency—qualities that are increasingly critical as resistance to conventional therapeutics becomes more prevalent [294–300]. Moreover, marine biodiversity remains vastly unexplored, with less than 1% of marine microorganisms successfully cultured, less than 0.01% characterized, and far fewer screened for their bioprospecting potential [301]. To put this into perspective, it is estimated that fewer than one in a trillion microbes in soil have ever been screened globally for antibiotic activity

 doi:10.20944/preprints202607.1303.v1

[302], even though the terrestrial environment has been explored significantly more extensively than the marine realm. The ocean's vast biological and environmental diversity highlights an enormous, untapped resource for pharmacologically relevant discoveries [234].

However, exploring this immense ocean comes with considerable challenges. To date, for example, only a tiny fraction (<0.01%) of the deep-sea floor has been thoroughly investigated [303]. In fact, it is simply not feasible to sample every milliliter of seawater or every gram of marine sediment. Moreover, not all seawater or sediment is the same. Some marine habitats are more abundant in natural product diversity than others due to specific environmental conditions and prevalent biological interactions [219]. Strategic habitat selection is essential in the quest to discover novel AMPs because habitats not only serve as sampling locations but also act as evolutionary filters [299,302,304–307]. Each habitat has its unique evolutionary history in natural product chemistry and imposes distinct physical, chemical, and biological selection pressures that influence the repertoire of AMPs and the likelihood of discovering novel ones. Recent global microbiome studies have confirmed that AMPs are indeed habitat-specific [235,308,309]. Effective abiotic and biotic factors—including temperature, salinity, pH, oxygen levels, pressure, microbial density, symbiosis, competition, amensalism, and antagonism (such as predation, parasitism, and pathogenesis)—can affect which AMPs are created, retained, diversified, transferred, and expressed within a given habitat [122,310]. Recent reviews indicate that marine environments produce AMPs with distinct structures, chemical modifications, amino acid preferences, salt tolerance, specialized membrane-targeting behaviors, and bioactive functions compared to AMPs from other habitats, suggesting an ecological adaptation of marine peptide chemistry [311,312]. A notable example is digitiferin, a novel AMP identified from *Acropora digitifera*. Its bactericidal activity against the coral pathogen *Vibrio coralliilyticus* is evident only under the low-salt conditions found in coral mucus, rather than at bulk seawater salinity [313]. Such a finding is strategically significant. Without an understanding of the habitat's microenvironment and ecological complexity, a potential AMP could easily be overlooked during screening. Therefore, ecology-driven habitat selection is crucial for the discovery of natural products, and targeted investigations guided by habitat prioritization can greatly increase the likelihood of finding novel AMPs rather than repeatedly rediscovering known compounds and their close analogs.

Nowadays, bioprospecting for marine natural products primarily focuses on two types of marine habitats. The first type includes environments with significantly high densities of microorganisms and complex interactions, such as the holobionts of marine sponges, corals, and ascidians, the mucus layers found on marine invertebrates and vertebrates, and the biofilm communities [311,314–325]. Such habitats are the biological "front lines" where AMPs are under continuous, direct selection pressure for defense and competition, driving their structural and functional diversification. The second type consists of challenging and extreme marine environments, such as mangrove sediments, polar oceans, and deep-sea and hadal trench sediments [282,308,326–331]. Extreme environmental conditions, such as rapid salinity shifts, low temperatures, and high hydrostatic pressures, in such habitats impose unusual stability and functional constraints on AMPs, driving their structural innovation. Some habitats, such as deep-sea hydrothermal vents and cold seeps, fall into both categories [234,308,332–339]. In such habitats, where high microbial abundance and environmental extremity coexist, both biological and environmental selection pressures are at play. In addition to these traditionally targeted habitats for natural product discovery, the vast oceans likely harbor other promising habitats that warrant exploration. Modern AMP discovery is increasingly focused on marine microorganisms and is becoming progressively more genomics- and metagenomics-driven [233,320,323,340–347]. Recently, a marine particle-targeted investigation identified hundreds of microbial BGCs encoding diverse RiPPs, NRPs, and non-ribosomal peptide-polyketide hybrids [348]. This study highlights marine particles as hotspot (micro)habitats for natural product bioprospecting, supporting the long-held hypothesis that marine particle-associated bacteria could be a rich source of unexplored antimicrobial agents [260,304,349,350].

 doi:10.20944/preprints202607.1303.v1

Most microorganisms lead social lifestyles characterized by diverse interactions [351–353]. In marine particle-associated microbiomes, various forms of cooperation, as well as competitive and antagonistic interactions, are common among microorganisms [243,261,348,354,355]. Intuitively, microorganisms employ competitive and antagonistic mechanisms to exclude competitors and monopolize shared resources such as nutrients, electron donors/acceptors, and space. Competition is a key factor in both the evolution of species within a population and the coevolution of multiple species in a community by driving microbial innovation to improve fitness and strengthen defense mechanisms [353,356]. However, counterintuitively, competition can also promote the stability and resilience of microbial communities [357]. In complex or spatially structured environments, such as biofilms and marine particles, competition can lead microorganisms to occupy distinct niches, either temporally or spatially [358]. This process enhances biodiversity and supports community succession through niche construction and partitioning, providing a strategy for adaptation to complex or changing environments [243,264,348,357,359]. Additionally, interspecies competition can stimulate both intraspecies and interspecies cooperation among collaborating partners, helping stabilize the interaction network of keystone species and, consequently, the core functions of a microbial community [356]. Therefore, the balance between competition and cooperation is crucial in shaping the community structure, dynamics, and ecological functions of the marine particle-associated microbiomes [360]. An in-depth understanding of microbial interactions and the ecological and evolutionary constraints that determine their distribution and dynamics in the ocean may aid in bioprospecting for marine AMPs.

Marine particles create unique ecological conditions that differ from the surrounding seawater. These particles concentrate organic carbon, nitrogen, phosphorus, trace metals, extracellular enzymes, metabolites, extracellular genetic materials, and microbial cells. They also create microscale gradients in oxygen, pH, redox state, and nutrients [243,258]. Such gradients promote spatial structuring and metabolic specialization among microorganisms. In densely colonized marine particle microhabitats, microorganisms compete for attachment sites, nutrients, and other resources, while antimicrobial compounds can provide selective advantages. As a result, marine particles may function as evolutionary microincubators for structurally diverse AMPs in the ocean. Numerous studies indicate that marine particles are characterized by steep physicochemical gradients, variable availability of nutrients and electron donors/acceptors, extremely high microbial densities and activities, rapid colonization–succession dynamics, biofilm-like structural organization, frequent chemical signaling, spatial confinement of competing taxa, and high incidences of antibiotic resistance genes and HGT [243,249,257,258,264,279,361–369]. These conditions intensify direct microbial competition and quorum-regulated chemical warfare [243,370–376], in which antimicrobial compounds may function as arsenals for competitive exclusion and chemical defense [324,354,377,378]. Multiple studies highlight that particle-associated microbial assemblages undergo rapid succession from primary degraders to secondary consumers [379,380], creating repeated interaction windows in which antagonistic traits—including AMP production—are likely to be selectively favored. As a result, marine particles transform the ocean from a dilute system, dominated by random microbial encounters, into a structured arena of deterministic microbial competition and antagonism. Metagenomic reconstruction of particle-associated microbial communities provides direct evidence that these habitats are enriched in biosynthetic potential. The particle-associated fractions contain diverse BGCs encoding RiPPs and NRPs. More importantly, expression-level analyses demonstrate that particle-associated lifestyles are associated with elevated transcription of secondary metabolite genes compared with free-living fractions [348]. These findings indicate that marine particles are not only reservoirs of latent biosynthetic potential but also active sites of secondary metabolite expression, reinforcing their relevance as functional AMP discovery hotspots.

Microbial community analyses reveal that marine particles are inherently multi-domain ecosystems [269,381]. Within these ecosystems, bacteria are the dominant colonizers of marine particles [243,266,382,383]. In particular, bacteria phylogenetically affiliated with competitive, copiotrophic groups that are adapted to rapid substrate exploitation and surface colonization likely

 doi:10.20944/preprints202607.1303.v1

dominate the AMP-relevant biosynthetic pathways [250,380,384]. In addition, several archaeal taxa have been recognized as an inherent component of the marine particle-associated microbiomes [385–387]. As the third domain of life on Earth, archaea possess unique cell membrane structures, distinct cell wall compositions, and extraordinary metabolic potentials alongside specialized stress-adaptation mechanisms not found in bacteria and eukaryotes [388]. These wide ranges of uniqueness suggest that archaea may also innovate to produce novel AMPs with distinct structural, mechanistic, and functional properties [389], equipping them with specialized molecular weaponry for ecological competition, defense, and survival in their environments. Indeed, recent proteome and (meta)genome mining efforts have revealed thousands of archaeal peptide candidates [337,347,348,390–395]. Some archaeal peptides have been experimentally validated to have antimicrobial activity against bacterial pathogens [347,395–397]. A recent investigation found that archaea have a higher density of smORFs than bacteria at the phylum level [398]. These previously overlooked potentials suggest that archaeal participation in marine particle-associated communities may expand the diversity of marine AMPs. Moreover, marine fungi have recently been found to colonize marine particles, a previously overlooked component of particulate microbiomes [381,399,400]. The biomass of fungi in the global ocean exceeds that of archaea by nearly one order of magnitude [401], and they actively participate in oceanic biogeochemical cycles by mediating enzymatic activities that degrade polysaccharides and proteins [270,402]. Their ability to produce cyclic peptides, depsipeptides, and other peptide-derived metabolites positions marine fungi as complementary sources of antimicrobial scaffolds [125,403–408], particularly in competitive detrital and biofilm-like particle environments. The competition among archaea, bacteria, and fungi intensified within confined particulate microenvironments likely represents an underexplored dimension of AMP evolution. Collectively, these prokaryotic and eukaryotic microorganisms form a convergent ecological unit in which inter-domain interactions may amplify the selective pressures that drive the development of new AMPs with unique structures and functions.

A defining but often underappreciated property of marine particles is their environmental heterogeneity in the ocean [248,409]. These particulate structures are ubiquitous throughout the entire water column, ranging from the sunlit surface waters to the deepest hadal environments. As a result, marine particle-associated microbial communities are exposed to a wide range of physicochemical conditions, including variations in temperature, pressure, oxygen levels, redox states, and substrate composition [410], thereby expanding the chemical landscape of antimicrobial evolution. Once formed, marine particles are rapidly colonized by various microorganisms, which often engage in dynamic, complex interactions and community succession as they sink to deeper waters [243,264,266,411–413]. The productive epipelagic zone is rich in phytoplankton-derived fresh aggregates, while the mesopelagic twilight zone is a hotspot environment for POM remineralization [414–420]. Although aged particulate materials populate the bathypelagic and abyssopelagic zones, particle association remains important, as over 95% of DOC is refractory to microbial utilization here [421,422]; thus, marine particles provide the primary source of organic carbon and energy for the survival and activity of both particle-associated and free-living microbes [271,418,419,423–427]. Interestingly, the hadopelagic zone hosts particle-associated microbial communities that likely exhibit enhanced metabolic activities, including both chemolithoautotrophy and heterotrophy, despite the extreme pressure conditions [428]. Such stratification indicates that marine particles do not represent a single ecological niche; rather, they comprise a globally distributed system of microhabitats that support distinct microbial communities and functions, expanding the chemical search space for marine AMP discovery.

The discovery of novel AMPs from marine microorganisms remains constrained by inadequate ecological targeting of biosynthetically rich and active habitats. Marine particles, such as phytodetritus, fecal pellets, transparent exopolymer particles, and detrital aggregates, function as discrete, nutrient-confined microhabitats embedded within the oligotrophic ocean matrix. They are active ecological “microreactors” where microbial interactions are intensified and metabolically costly traits, including antimicrobial production, become selectively advantageous. Throughout the

 doi:10.20944/preprints202607.1303.v1

immense oceanic gradients—from the euphotic surface waters to the mesopelagic twilight zone and further into the deep dark ocean and hadal zone—marine particles promote the expression of secondary metabolite BGCs, representing globally distributed yet underexploited resources that should be prioritized for uncovering structurally and functionally novel AMPs across marine bacteria, archaea, and fungi. Marine particles are not simply reservoirs of microbial life—they are engineered by nature as competitive arenas where antimicrobial chemistry is continuously selected, tested, and diversified. Prioritizing these systems, therefore, represents not only a methodological improvement but also a conceptual advance in our understanding of and search for AMPs in the global ocean.

3. Metagenomics: The Horsepower Driving Marine AMP Discovery

The ocean harbors the largest biome of microorganisms, with a tremendous diversity of taxa and functions. The extensive microbiomes in the world's oceans have evolved over billions of years under a variety of challenging abiotic and biotic conditions, resulting in remarkable genetic and biosynthetic potential that is largely untapped [225,429–432]. According to the International Census of Marine Microbes (ICoMM), the ocean contains approximately 3.6×1030 microbial cells [433]. In just one liter of seawater, there can be over 100 million microbes, representing up to 20 thousand different bacterial species [429,433]. Marine particles, in particular, often have much higher microbial densities [256–259], making them an immense resource for AMPs. However, most marine microorganisms remain difficult, or even impossible, to cultivate [434,435], limiting the targeting of their biosynthetic capabilities in traditional natural product discovery.

Historically, marine natural product discovery has led to the identification of numerous bioactive compounds [201,203,205,436–438], yet the vast majority of marine microbial diversity remains poorly characterized and uncultivated. The traditional process of discovering natural products faces significant challenges, including high costs, time demands, and the need for early dereplication to eliminate metabolite candidates that have already been identified [439,440]. Consequently, only a small fraction of marine biosynthetic potential has been captured to date. To tackle these issues, it is strategically important to focus on underexplored biological resources or environments, such as marine particles, to increase the yield of previously uncharacterized chemical structures [430,441,442]. Additionally, metagenomics is revolutionizing this field by providing a central means of accessing hidden, unculturable diversity. Metagenomics, particularly genome-resolved metagenomics, overcomes the limitations of microbial cultivation, enabling the direct mining of genes and BGCs from complex environmental microbial communities for AMP discovery [192,233,345,431,443,444]. Metagenomics is the enabling engine that converts environmental microbial dark matter into a searchable chemical possibility (Figure 3). When coupled to genome-resolved reconstruction, metagenomics can link antimicrobial candidates to taxa, ecological niches, and evolutionary contexts [445–447]. When coupled to machine learning and deep learning, it can prioritize peptide candidates from billions of sequences [448–450]. When coupled to synthetic biology and robust activity validation, it can generate experimentally testable molecules at an unprecedented scale [451–453]

 doi:10.20944/preprints202607.1303.v1

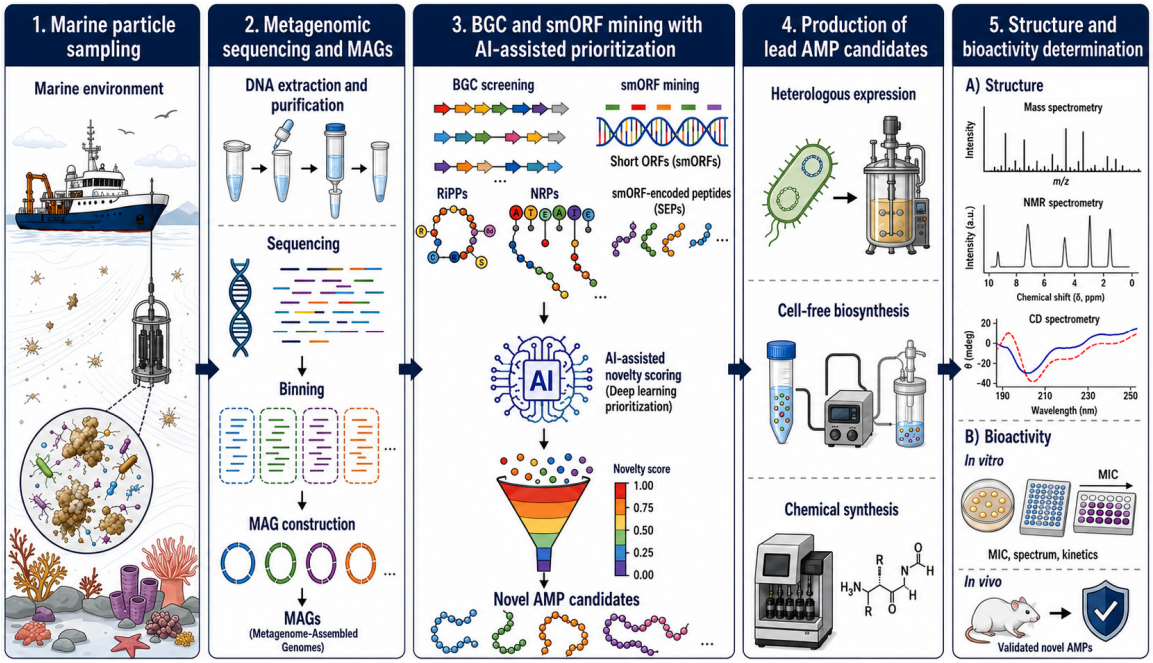

Figure 3. Metagenomics-centered workflow for discovering novel antimicrobial peptides (AMPs) from marine particle-associated microbiomes. The figure summarizes a discovery-to-validation pipeline for mining marine microbial communities as reservoirs of novel AMP candidates. (1) Marine particle sampling: marine particles and particle-associated microbial assemblages are collected from the marine environment, capturing complex microhabitats enriched in taxonomically and metabolically diverse microorganisms. (2) Metagenomic sequencing and MAG reconstruction: environmental DNA is extracted and purified, followed by high-throughput metagenomic sequencing. Sequencing reads are assembled, binned, and reconstructed into metagenome-assembled genomes (MAGs), providing genome-resolved access to uncultured or poorly characterized marine microorganisms. (3) BGC and smORF mining with AI-assisted prioritization: MAGs are screened for biosynthetic gene clusters (BGCs), including ribosomally synthesized and post-translationally modified peptides (RiPPs) and nonribosomal peptides (NRPs), as well as short open reading frames (smORFs) encoding putative smORF-encoded peptides (SEPs). Candidate peptides are then ranked using AI-assisted novelty scoring and deep-learning-based prioritization to identify sequences with high predicted novelty and AMP potential. (4) Production of lead AMP candidates: prioritized candidates are generated using complementary production platforms, including heterologous expression, cell-free biosynthesis, and chemical synthesis. (5) Structure and bioactivity determination: purified lead compounds are subjected to structural characterization by mass spectrometry, nuclear magnetic resonance (NMR), and circular dichroism (CD) spectroscopy, followed by bioactivity evaluation. In vitro assays determine antimicrobial potency, minimum inhibitory concentration (MIC), activity spectrum, and killing kinetics, whereas in vivo assays provide further validation of efficacy and biological relevance. This integrated pipeline links marine particle microbiome exploration, genome-resolved mining, AI-guided candidate selection, scalable peptide production, and experimental validation to accelerate the discovery of novel marine-derived AMPs.

The rare biosphere is increasingly recognized as a reservoir of functional novelty [454–459]. Low-abundance microorganisms may experience unique evolutionary pressures, thrive in specific environmental conditions, and produce specialized metabolites absent from dominant taxa [323,460,461]. Rare species may be prevalent and particularly important in the marine particle-associated microbiomes. Marine particles are transient, heterogeneous, and rich in unique microenvironments, allowing rare taxa to flourish under certain emerging conditions and persist if they can provide core functions or occupy stable micro-niches [462]. In densely populated marine particle-associated communities, rare taxa may use AMPs to compete, survive, and respond to environmental and interspecific challenges. Although rare microorganisms are often low in

 doi:10.20944/preprints202607.1303.v1

abundance, they can be rich in biosynthetic variety [463,464]. As a result, marine particle-focused metagenomics, particularly through deep sequencing [465], may uncover a surprising diversity of bioactive peptides.

An important frontier in marine natural product discovery is the identification of AMPs encoded by smORFs [235,320,346,466]. Conventional genome annotation pipelines often overlook these short ORFs, treating them as noncoding noise or unlikely candidates for protein-coding regions [467–469]. However, small peptides can possess potent biological functions, including antimicrobial activity, signaling, stress response, and membrane interaction [470]. As a result, smORF-encoded peptides (SEPs) are now seen as hidden treasures in the search for AMPs [470]. This is especially relevant for metagenomic datasets, where short peptide-coding regions can be abundant but difficult to distinguish from random ORFs. Consequently, conventional bioinformatics methods tend to yield a high rate of false-positive predictions [471]. Recent advances driven by artificial intelligence (AI), including machine learning and deep learning, have effectively addressed this issue by enabling the screening of large sequence spaces for AMP-like characteristics with much improved accuracy [236,395,472–475]. Deep learning, in particular, has shifted AMP discovery from small-scale screening toward large-scale prediction and design. Traditional AMP identification depended on known sequence motifs or physicochemical filters. Modern deep learning models can learn higher-order sequence patterns and predict activity from large peptide datasets [476–478]. The discovery of bioactive SEPs from environmental microbiomes has been further accelerated by integrating genome-resolved metagenomics with other state-of-the-art meta-omics analytical platforms, such as metatranscriptomics, ribosome profiling, and metaproteomics [236,320,470,472]. For marine particle samples, these techniques can reveal which SEP genes are actively expressed under specific ecological conditions. For instance, expression levels may increase during particle colonization, nutrient depletion, competitor invasion, or environmental stress. By integrating DNA-based metagenomics with RNA- and ribosome-level data, AMP discovery can become more biologically relevant.

Other important classes of peptides include RiPPs and NRPs, the synthesis of which is linked to specific BGCs [136,137,140,149,152]. Genome- and metagenome-based BGC screening is transforming the discovery of microbial RiPPs and NRPs. Traditionally, the discovery of natural products has relied on a series of steps: isolation, cultivation, extraction, bioactivity screening, and chemical characterization. While this strategy remains valuable, it is insufficient to capture the full biosynthetic diversity present in marine microbiomes. Most marine microorganisms are difficult to cultivate [434,435], and many BGCs are silent under laboratory conditions [479–484], making them difficult to discover. Additionally, repeated screening efforts often result in the rediscovery of known compounds. Genome and metagenome mining overcomes these limitations by uncovering the biosynthetic potential prior to cultivation and metabolite isolation [485,486]. This innovative approach operates at high speed and throughput. When combined with AI-driven models for big data analysis and prediction [161,432,441,487–491], it significantly improves the detection rate of novel natural product-encoding BGCs in microbial genomes and metagenome-assembled genomes (MAGs).

Genome sequencing and analysis have revealed that microorganisms possess many more BGCs than traditional laboratory screening methods could detect [192,480]. Large-scale metagenomic studies of oceanic environments have shown that marine microbial communities encode vast numbers of previously uncharacterized genes, many of which lack close homologs in existing reference databases [492]. Recent metagenomic analyses of marine microbial communities, including those at a global ocean scale, have uncovered extensive biosynthetic potential, including abundant BGCs for RiPPs and NRPs [233,234,337,338,341,493,494]. These studies indicate that marine microorganisms produce not only simple ribosomal AMPs, such as SEPs, but also more complex peptide molecules, such as RiPPs and NRPs. The RiPP class encompasses various types of peptides, including ribosomally synthesized lanthipeptides, lasso peptides, thiopeptides, microcins, and other modified peptide families. In contrast, the highly diverse NRPs are synthesized nonribosomally by

 doi:10.20944/preprints202607.1303.v1

multimodular NRPSs. Many SEPs, RiPPs, and NRPs exhibit antimicrobial activity, making them promising targets for marine metagenomic discovery.

Marine particles represent spatially concentrated reservoirs of antimicrobial genetic potential, and metagenomics provides the core methodological engine for recovering all three major peptide-discovery targets: genes encoding SEPs and distinctive classes of BGCs for RiPPs and NRPs, respectively. For marine AMP discovery, BGC mining complements smORF and peptide prediction. Some AMPs are encoded by simple, small genes, while others require modifying enzymes, transporters, immune proteins, and regulatory elements. A comprehensive AMP discovery pipeline should therefore include both direct peptide prediction and BGC-aware mining. Although these three classes are often discussed together under the broad label of peptide natural products or AMPs, and they all can be mined from metagenomic data, they require different analytical strategies. RiPPs are ribosomally encoded but post-translationally modified, and their discovery depends on recognizing both precursor peptides and tailoring enzymes. NRPS products (i.e., NRPs) are assembled by large modular enzymes rather than being directly translated from a peptide gene, and thus NRPS discovery depends on predicting both the architectures of modular enzymatic domains and their substrates. A typical NRPS module contains adenylation, thiolation, and condensation domains. Adenylation domains select substrates; thiolation domains carry activated monomers; and condensation domains form peptide bonds. In addition, thioesterase domains (i.e., the termination domains located exclusively on the final module of a complete NRPS assembly line) release or cyclize products, and auxiliary modifying domains catalyze epimerization, methylation, hydroxylation, halogenation, or ring formation. So the lengths of BGCs encoding functional NRPSs can typically reach tens and even hundreds of kb [151,152,495]. SEPs are short ribosomal peptides encoded by smORFs that may lack an obvious biosynthetic context and are easily missed by conventional annotation, and their discovery depends on sensitive short-gene detection, coding-potential assessment, and downstream AMP prediction.

Different analytical strategies require specific technical details. Short-read sequencing is commonly used in metagenomic studies due to its high accuracy and depth. This method is suitable for community profiling, gene catalog construction, and the detection of abundant genes [496]. However, while metagenomes derived from short-read sequencing may not significantly influence the discovery of smORFs, short reads can fragment BGCs and complicate strain-resolved assembly [497]. These problems pose challenges for mining BGCs for RiPPs and NRPs. RiPP BGCs can be disrupted if precursor genes and genes for tailoring enzymes are located on separate contigs, making BGC mining difficult or even impossible. BGCs that encode NRPSs are often large, repetitive, and modular. Thus, gene cluster fragmentation may disrupt module boundaries and repeated domains, leading to truncated BGCs that do not produce mature, functional peptides. Long-read sequencing can improve assembly contiguity and aid in the recovery of complete BGCs [345,498,499]. Hybrid approaches that combine the accuracy of short-read sequencing with the scaffolding capabilities of long-read sequencing are particularly valuable for the metagenomic analysis of RiPPs and NRPSs [500–502]. The discovery of smORFs also benefits from accurate metagenome assemblies and error correction, though it is less dependent on the long-range continuity of BGCs.

Studies of microbial communities show that marine particles harbor dense bacterial populations whose activities transform and degrade particulate organic materials [261,503]. The high density of microbial cells and high microbial metabolic activities on marine particles increase the probability of competition and antagonism [250,379]. Microorganisms attached to the same marine particle may compete for carbon sources, nutrients, electron donors/acceptors, metabolic by-products, and microniches on and inside marine particles [243]. Under such spatially confined conditions, antimicrobial molecules may serve ecological functions by inhibiting competitors, shaping community structure, protecting producer lineages, or mediating colonization and community succession. Thus, marine particles create localized, resource-rich microenvironments within surrounding oligotrophic seawater. Additionally, there is significant microscale variability both within and between these marine particles [243,504]. Therefore, ecology-focused AMP discovery

 doi:10.20944/preprints202607.1303.v1

should be conducted with single-particle precision [380,505,506]. Employing single-particle sequencing and metagenomic studies will enhance our understanding of the intricate ecological interactions, their variations, and dynamics within the microbiomes colonizing individual marine particles, as well as their ecological roles in the evolution and expression of AMPs in these hotspot microenvironments.

4. Potential Applications of Marine AMPs in Human Medicine

The global crisis of antimicrobial resistance has created an urgent need for new anti-infective agents with a low likelihood of inducing pathogen resistance [9–12]. Marine AMPs represent a highly promising class of bioactive molecules with broad potential applications. Many marine AMPs exhibit unique structural features that are superior to those of conventional small-molecule antibiotics, including rare heterocyclic scaffolds, modified non-proteinogenic residues, and salt-tolerant, lipophilic backbones, evolved to help host microbes thrive in specialized, competitive marine environments [201,507]. Their generally rapid, multi-target antimicrobial actions, along with their effectiveness against diverse bacteria, fungi, parasites, and viruses, make marine AMPs attractive candidates for addressing the growing challenge of antimicrobial resistance and for developing next-generation anti-infective products [312,508,509]. Potential applications for marine AMP candidates include novel topical anti-infectives, wound-healing formulations, antibiofilm coatings for medical devices, and immunomodulatory therapeutics [510–513].

Unlike many antibiotics that target a single conserved enzyme or biosynthetic pathway, AMPs often employ multiple mechanisms to exert their effects. These mechanisms include destabilizing membranes, causing rapid depolarization, forming pores, remodeling cell envelopes, binding to intracellular targets, regulating the immune response, or employing multimodal approaches [47,49,56,87,201,437,514–516]. This ability to target multiple pathways or cellular structures can reduce, though not eliminate, the likelihood of resistance development [66,103,228,517–521]. Many marine AMPs act through electrostatic attraction to microbial membranes, followed by processes such as insertion, thinning, curvature induction, membrane permeabilization, or pore formation [201,507]. The membrane-targeting nature of AMPs offers several therapeutic advantages. Their killing action can be rapid, and modifying the target may be more challenging than simply mutating a single cellular component or enzyme. However, membrane activity also raises safety concerns. Excessive hydrophobicity or poor selectivity can lead to issues such as hemolysis, toxicity to mammalian membranes, or local tissue irritation [109,521–525]. Therefore, modern developments in AMPs focus on maximizing pathogen selectivity rather than solely disrupting membranes. Some marine AMPs have been found to interfere with intracellular processes or components [308]. These mechanisms are therapeutically significant, as they may enhance selectivity, reduce host-cell damage, and confer drug-like effects similar to those of traditional antibiotics while retaining the advantageous ability of AMPs to penetrate cells. Moreover, due to their long-term adaptation to the marine environment, certain marine AMPs can maintain their antimicrobial efficacy under physiological ionic conditions, showcasing promising therapeutic potential [526].

Many bacterial and fungal pathogens form biofilms that lead to persistent infections, increased antibiotic resistance, and the ability to evade host immune responses [22,527–531]. Biofilms play a significant role in various disease conditions, including chronic wounds, catheter infections, prosthetic joint infections, dental and airway infections, and recurrent urinary tract infections [532–534]. Some marine AMPs have shown strong antibiofilm activity. They prevent microbial adhesion, reduce extracellular polymeric substance production, inhibit biofilm maturation, disrupt microbial membranes within biofilms, block quorum-sensing signals, downregulate virulence toxin gene expression, promote degradation of the biofilm matrix, or enhance immune clearance [508,511,512,535–542]. These properties make marine AMPs highly attractive for developing coatings for catheters, implants, wound dressings, contact lenses, and dental materials, as well as marine-inspired anti-infective therapeutics and biomaterials.

 doi:10.20944/preprints202607.1303.v1

Marine AMPs represent a promising but still underdeveloped class of therapeutic agents and drug leads. Beyond direct antimicrobial activities such as direct killing, antivirulence, and antibiofilm effects, some marine AMPs also exhibit antifungal, antiparasitic, antiviral, anti-cancer, anti-proliferative, anti-inflammatory, antioxidant, anti-diabetic, antihypertensive, antithrombotic, anticoagulant, anti-obesity, anti-allergic, anti-aging, antifatigue, and wound-healing activities [54,55,70,157,201,204,210,227,321,405,436,437,543–557]. Marine AMPs are structurally diverse molecules, including α-helical peptides, β-sheet disulfide-rich peptides, cyclic peptides, lipopeptides, and non-ribosomal peptide derivatives, offering great potential for a broad range of therapeutic applications [510,511]. For systemic therapy, substantial progress is needed in stability, selectivity, delivery, pharmacokinetics, and safety of marine AMPs [201,437].

Beyond their applications in human medicine, marine AMPs also hold promise in various other fields. In agriculture, AMPs offer potential as environmentally compatible alternatives or complements to conventional antibiotics and chemical pesticides, effectively suppressing bacterial and fungal phytopathogens, controlling pest insects, enhancing crop disease resistance, and reducing the selection pressure for antibiotic resistance within integrated plant protection systems [437,438]. In aquaculture, where infectious outbreaks and antibiotic dependence remain persistent challenges, marine AMPs may be developed as disease control agents, functional feed additives, immunostimulatory compounds, or antimicrobial surface coatings to improve the health and resilience of farmed fish and shellfish [558–560]. Other applications of marine AMPs include veterinary medicine [561], food preservation and safety [321,437,562,563], nutraceuticals [321], cosmeceuticals [321,437,562,563], and the prevention of biofouling and biocorrosion [511,536,537,564–568]. Given this translational potential, the ocean—particularly the marine particles within it—represents an underexplored source of AMP-producing microorganisms and peptide diversity, underscoring the need for in-depth investigation.

5. Perspectives

The next frontier in marine AMP discovery will require a transition from sequence-centered prospecting to ecology-informed functional bioprospecting. Rather than viewing marine particles merely as passive carriers of microbial diversity, they should be regarded as dynamic evolutionary microhabitats in which microbial competition, antagonism, chemical communication, and environmental heterogeneity collectively shape the emergence and expression of antimicrobial traits. Future investigations should therefore integrate single-particle ecology, genome-resolved metagenomics, metatranscriptomics, metaproteomics, metabolomics, and spatial imaging to identify not only which AMP genes are present but also when, where, why, and how they are expressed during particle colonization, microbial community succession, and interspecies interactions. Such an ecological framework will enable researchers to distinguish constitutively encoded peptides from environmentally induced antimicrobial molecules and to prioritize AMP candidates with demonstrated ecological functions. Equally important, coupling these multi-omics datasets with artificial intelligence, structural prediction, synthetic biology, and high-throughput functional validation will establish an end-to-end discovery pipeline that links environmental selection pressures to peptide structure, biological activity, and translational potential, thereby substantially improving the efficiency of identifying truly novel antimicrobial scaffolds from the vast uncultivated marine microbiome [192,229,231,235,395].

More broadly, this review advocates a conceptual shift in marine natural product discovery. The greatest opportunities may no longer lie simply in sampling unexplored marine organisms or environments, but in identifying ecological systems where natural selection continuously drives chemical innovation. Marine particles represent precisely such systems, functioning as globally distributed microscale arenas in which antimicrobial chemistry is repeatedly generated, tested, and refined through intense microbial interactions. As antimicrobial resistance continues to outpace conventional antibiotic discovery, integrating marine microbial ecology with natural products chemistry, computational biology, and peptide engineering offers a promising strategy for expanding

 doi:10.20944/preprints202607.1303.v1

the chemical space of next-generation anti-infective agents. Although substantial challenges remain—including experimental validation, scalable production, pharmacokinetic optimization, and clinical translation—the convergence of ecology-guided habitat prioritization, cultivation-independent (meta)genomics, and AI-enabled prediction and molecular design is poised to transform marine particle-associated microbiomes into one of the most productive frontiers for future AMP discovery. Ultimately, understanding why AMPs evolve in nature may become as important as identifying the peptides themselves, providing a new ecological paradigm for marine drug discovery.

Author Contributions: Conceptualization, X.L. and H.D.; writing—original draft preparation, X.L.; writing—review and editing, Y.G., Q.K. and H.D.; visualization, X.L. and H.D.; supervision, Q.K. and H.D.; project administration, H.D.; funding acquisition, X.L., Y.G. and H.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Science and Technology Major Project of Inner Mongolia Autonomous Region of China, Natural Science Foundation of Beijing Municipality (8222047), National Key Research and Development Program of China (2020YFA0608302), and National Natural Science Foundation of China (42076111). The APC was funded by the Natural Science Foundation of Beijing Municipality (8222047).

Conflicts of Interest: The authors declare no conflicts of interest.:

Abbreviations

The following abbreviations are used in this manuscript:

AI	Artificial intelligence
AMP	Antimicrobial peptide
AMR	Antimicrobial resistance
BGC	Biosynthetic gene cluster
CD	Circular dichroism
EPS	Extracellular polymeric substance
ESKAPE	*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.
HGT	Horizontal gene transfer
LPS	Lipopolysaccharides
MAG	Metagenome-assembled genome
MGE	Mobile genetic element
MIC	Minimum inhibitory concentration
NMR	Nuclear magnetic resonance
NRP	Non-ribosomally synthesized peptide
NRPS	Non-ribosomal peptide synthetase
PCP	Peptidyl carrier protein
RiPP	Ribosomally synthesized and post-translationally modified peptide
SEP	smORF-encoded peptide
smORF	Small open reading frame

References

1. Hutchings, M.I.; Truman, A.W.; Wilkinson, B. Antibiotics: Past, Present and Future. *Curr. Opin. Microbiol.* **2019**, *51*, 72–80. https://doi.org/10.1016/j.mib.2019.10.008
2. Cook, M.A.; Wright, G.D. The Past, Present, and Future of Antibiotics. *Sci. Transl. Med.* **2022**, *14*, eabo7793. https://doi.org/10.1126/scitranslmed.abo7793
3. Tahmasebi, H.; Arjmand, N.; Monemi, M.; Babaeizad, A.; Alibabaei, F.; Alibabaei, N.; Bahar, A.; Oksenych, V.; Eslami, M. From Cure to Crisis: Understanding the Evolution of Antibiotic-Resistant Bacteria in Human Microbiota. *Biomolecules* **2025**, *15*, 93. https://doi.org/10.3390/biom15010093
4. Demain, A.L. Antibiotics: Natural Products Essential to Human Health. *Med. Res. Rev.* **2009**, *29*, 821–842. https://doi.org/10.1002/med.20154

 doi:10.20944/preprints202607.1303.v1

5. Multisanti, C.R.; Celi, V.; Dibra, A.; Pintus, A.; Calogero, R.; Rizzo, C.; Faggio, C. Microbial Blue Bioprospecting: Exploring the Advances of Compounds Post-Discovery. *Mar. Drugs* **2025**, *23*, 406. https://doi.org/10.3390/md23100406
6. Liu, X.; Steele, J.C.; Meng, X.-Z. Usage, Residue, and Human Health Risk of Antibiotics in Chinese Aquaculture: A Review. *Environ. Pollut.* **2017**, *223*, 161–169. https://doi.org/10.1016/j.envpol.2017.01.003
7. Watts, J.E.M.; Schreier, H.J.; Lanska, L.; Hale, M.S. The Rising Tide of Antimicrobial Resistance in Aquaculture: Sources, Sinks and Solutions. *Mar. Drugs* **2017**, *15*, 158. https://doi.org/10.3390/md15060158
8. Larsson, D.G.J.; Flach, C.-F. Antibiotic Resistance in the Environment. *Nat. Rev. Microbiol.* **2022**, *20*, 257–269. https://doi.org/10.1038/s41579-021-00649-x
9. Okeke, I.N.; de Kraker, M.E.A.; Van Boeckel, T.P.; Kumar, C.K.; Schmitt, H.; Gales, A.C.; Bertagnolio, S.; Sharland, M.; Laxminarayan, R. The Scope of the Antimicrobial Resistance Challenge. *Lancet* **2024**, *403*, 2426–2438. https://doi.org/10.1016/S0140-6736(24)00876-6
10. Elbehiry, A.; Marzouk, E. From Farm to Fork: Antimicrobial-Resistant Bacterial Pathogens in Livestock Production and the Food Chain. *Vet. Sci.* **2025**, *12*, 862. https://doi.org/10.3390/vetsci12090862
11. Ho, C.S.; Wong, C.T.H.; Aung, T.T.; Lakshminarayanan, R.; Mehta, J.S.; Rauz, S.; McNally, A.; Kintses, B.; Peacock, S.J.; de la Fuente-Nunez, C.; Hancock, R.E.W.; Ting, D.S.J. Antimicrobial Resistance: A Concise Update. *Lancet Microbe* **2025**, *6*, 100947. https://doi.org/10.1016/j.lanmic.2024.07.010
12. La Rosa, M.C.; Maugeri, A.; Favara, G.; La Mastra, C.; Magnano San Lio, R.; Barchitta, M.; Agodi, A. The Impact of Wastewater on Antimicrobial Resistance: A Scoping Review of Transmission Pathways and Contributing Factors. *Antibiotics* **2025**, *14*, 131. https://doi.org/10.3390/antibiotics14020131
13. Antimicrobial Resistance Collaborators. Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis. *Lancet* **2022**, *399*, 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0
14. Zhang, C.; Fu, X.; Liu, Y.; Zhao, H.; Wang, G. Burden of Infectious Diseases and Bacterial Antimicrobial Resistance in China: A Systematic Analysis for the Global Burden of Disease Study 2019. *Lancet Reg. Health West. Pac.* **2024**, *43*, 100972. https://doi.org/10.1016/j.lanwpc.2023.100972
15. O'Neill, J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The Review on Antimicrobial Resistance. 2016. Available online: http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf (accessed on 2 May 2026)
16. GBD 2021 Antimicrobial Resistance Collaborators. Global Burden of Bacterial Antimicrobial Resistance 1990–2021: A Systematic Analysis with Forecasts to 2050. *Lancet* **2024**, *404*, 1199–1226. https://doi.org/10.1016/S0140-6736(24)01867-1
17. Brown, E.D.; Wright, G.D. Antibacterial Drug Discovery in the Resistance Era. *Nature* **2016**, *529*, 336–343. https://doi.org/10.1038/nature17042
18. Lewis, K. The Science of Antibiotic Discovery. *Cell* **2020**, *181*, 29–42. https://doi.org/10.1016/j.cell.2020.02.056
19. Miethke, M.; Pieroni, M.; Weber, T.; Brönstrup, M.; Hammann, P.; Halby, L.; Arimondo, P.B.; Glaser, P.; Aigle, B.; Bode, H.B.; Moreira, R.; Li, Y.; Luzhetskyy, A.; Medema, M.H.; Pernodet, J.-L.; Stadler, M.; Tormo, J.R.; Genilloud, O.; Truman, A.W.; Weissman, K.J.; Takano, E.; Sabatini, S.; Stegmann, E.; Brötz-Oesterhelt, H.; Wohlleben, W.; Seemann, M.; Empting, M.; Hirsch, A.K.H.; Loretz, B.; Lehr, C.-M.; Titz, A.; Herrmann, J.; Jaeger, T.; Alt, S.; Hesterkamp, T.; Winterhalter, M.; Schiefer, A.; Pfarr, K.; Hoerauf, A.; Graz, H.; Graz, M.; Lindvall, M.; Ramurthy, S.; Karlén, A.; van Dongen, M.; Petkovic, H.; Keller, A.; Peyrane, F.; Donadio, S.; Fraisse, L.; Piddock, L.J.V.; Gilbert, I.H.; Moser, H.E.; Müller, R. Towards the Sustainable Discovery and Development of New Antibiotics. *Nat. Rev. Chem.* **2021**, *5*, 726–749. https://doi.org/10.1038/s41570-021-00313-1
20. Baran, A.; Kwiatkowska, A.; Potocki, L. Antibiotics and Bacterial Resistance—A Short Story of an Endless Arms Race. *Int. J. Mol. Sci.* **2023**, *24*, 5777. https://doi.org/10.3390/ijms24065777
21. Halawa, E.M.; Fadel, M.; Al-Rabia, M.W.; Behairy, A.; Nouh, N.A.; Abdo, M.; Olga, R.; Fericean, L.; Atwa, A.M.; El-Nablaway, M.; Abdeen, A. Antibiotic Action and Resistance: Updated Review of Mechanisms, Spread, Influencing Factors, and Alternative Approaches for Combating Resistance. *Front. Pharmacol.* **2024**, *14*, 1305294. https://doi.org/10.3389/fphar.2023.1305294
22. Ciofu, O.; Moser, C.; Jensen, P.Ø.; Høiby, N. Tolerance and Resistance of Microbial Biofilms. *Nat. Rev. Microbiol.* **2022**, *20*, 621–635. https://doi.org/10.1038/s41579-022-00682-4

 doi:10.20944/preprints202607.1303.v1

23. Darby, E.M.; Trampari, E.; Siasat, P.; Solsona Gaya, M.; Alav, I.; Webber, M.A.; Blair, J.M.A. Molecular Mechanisms of Antibiotic Resistance Revisited. *Nat. Rev. Microbiol.* **2023**, *21*, 280–295. https://doi.org/10.1038/s41579-022-00820-y
24. Salam, M.A.; Al-Amin, M.Y.; Salam, M.T.; Pawar, J.S.; Akhter, N.; Rabaan, A.A.; Alqumber, M.A.A. Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. *Healthcare* **2023**, *11*, 1946. https://doi.org/10.3390/healthcare11131946
25. Almatroudi, A. Biofilm Resilience: Molecular Mechanisms Driving Antibiotic Resistance in Clinical Contexts. *Biology* **2025**, *14*, 165. https://doi.org/10.3390/biology14020165
26. von Wintersdorff, C.J.H.; Penders, J.; van Niekerk, J.M.; Mills, N.D.; Majumder, S.; van Alphen, L.B.; Savelkoul, P.H.M.; Wolffs, P.F.G. Dissemination of Antimicrobial Resistance in Microbial Ecosystems through Horizontal Gene Transfer. *Front. Microbiol.* **2016**, *7*, 173. https://doi.org/10.3389/fmicb.2016.00173
27. Partridge, S.R.; Kwong, S.M.; Firth, N.; Jensen, S.O. Mobile Genetic Elements Associated with Antimicrobial Resistance. *Clin. Microbiol. Rev.* **2018**, *31*, e00088-17. https://doi.org/10.1128/CMR.00088-17
28. Imran, M.; Das, K.R.; Naik, M.M. Co-Selection of Multi-Antibiotic Resistance in Bacterial Pathogens in Metal and Microplastic Contaminated Environments: An Emerging Health Threat. *Chemosphere* **2019**, *215*, 846–857. https://doi.org/10.1016/j.chemosphere.2018.10.114
29. Michaelis, C.; Grohmann, E. Horizontal Gene Transfer of Antibiotic Resistance Genes in Biofilms. *Antibiotics* **2023**, *12*, 328. https://doi.org/10.3390/antibiotics12020328
30. Zhu, C.; Wu, L.; Ning, D.; Tian, R.; Gao, S.; Zhang, B.; Zhao, J.; Zhang, Y.; Xiao, N.; Wang, Y.; Brown, M.R.; Tu, Q.; Global Water Microbiome Consortium; Ju, F.; Wells, G.F.; Guo, J.; He, Z.; Nielsen, P.H.; Wang, A.; Zhang, Y.; Chen, T.; He, Q.; Criddle, C.S.; Wagner, M.; Tiedje, J.M.; Curtis, T.P.; Wen, X.; Yang, Y.; Alvarez-Cohen, L.; Stahl, D.A.; Alvarez, P.J.J.; Rittmann, B.E.; Zhou, J. Global Diversity and Distribution of Antibiotic Resistance Genes in Human Wastewater Treatment Systems. *Nat. Commun.* **2025**, *16*, 4006. https://doi.org/10.1038/s41467-025-59019-3
31. Santajit, S.; Indrawattana, N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. *BioMed Res. Int.* **2016**, *2016*, 2475067. https://doi.org/10.1155/2016/2475067
32. Mancuso, G.; Midiri, A.; Gerace, E.; Biondo, C. Bacterial Antibiotic Resistance: The Most Critical Pathogens. *Pathogens* **2021**, *10*, 1310. https://doi.org/10.3390/pathogens10101310
33. De Oliveira, D.M.P.; Forde, B.M.; Kidd, T.J.; Harris, P.N.A.; Schembri, M.A.; Beatson, S.A.; Paterson, D.L.; Walker, M.J. Antimicrobial Resistance in ESKAPE Pathogens. *Clin. Microbiol. Rev.* **2020**, *33*, e00181-19. https://doi.org/10.1128/CMR.00181-19
34. Miller, W.R.; Arias, C.A. ESKAPE Pathogens: Antimicrobial Resistance, Epidemiology, Clinical Impact and Therapeutics. *Nat. Rev. Microbiol.* **2024**, *22*, 598–616. https://doi.org/10.1038/s41579-024-01054-w
35. Macesic, N.; Uhlemann, A.-C.; Peleg, A.Y. Multidrug-Resistant Gram-Negative Bacterial Infections. *Lancet* **2025**, *405*, 257–272. https://doi.org/10.1016/S0140-6736(24)02081-6
36. Sati, H.; Carrara, E.; Savoldi, A.; Hansen, P.; Garlasco, J.; Campagnaro, E.; Boccia, S.; Castillo-Polo, J.A.; Magrini, E.; Garcia-Vello, P.; Wool, E.; Gigante, V.; Duffy, E.; Cassini, A.; Huttner, B.; Pardo, P.R.; Naghavi, M.; Mirzayev, F.; Zignol, M.; Cameron, A.; Tacconelli, E.; the WHO Bacterial Priority Pathogens List Advisory Group. The WHO Bacterial Priority Pathogens List 2024: A Prioritisation Study to Guide Research, Development, and Public Health Strategies against Antimicrobial Resistance. *Lancet Infect. Dis.* **2025**, *25*, 1033–1043. https://doi.org/10.1016/S1473-3099(25)00118-5
37. Hancock, R.E.W.; Sahl, H.-G. Antimicrobial and Host-Defense Peptides as New Anti-Infective Therapeutic Strategies. *Nat. Biotechnol.* **2006**, *24*, 1551–1557. https://doi.org/10.1038/nbt1267
38. Takahashi, D.; Shukla, S.K.; Prakash, O.; Zhang, G. Structural Determinants of Host Defense Peptides for Antimicrobial Activity and Target Cell Selectivity. *Biochimie* **2010**, *92*, 1236–1241. https://doi.org/10.1016/j.biochi.2010.02.023
39. Mookherjee, N.; Anderson, M.A.; Haagsman, H.P.; Davidson, D.J. Antimicrobial Host Defence Peptides: Functions and Clinical Potential. *Nat. Rev. Drug Discov.* **2020**, *19*, 311–332. https://doi.org/10.1038/s41573-019-0058-8
40. Guryanova, S.V.; Ovchinnikova, T.V. Innate Immunity Mechanisms in Marine Multicellular Organisms. *Mar. Drugs* **2022**, *20*, 549. https://doi.org/10.3390/md20090549

 doi:10.20944/preprints202607.1303.v1

41. Gao, N.; Wang, J.; Fang, C.; Bai, P.; Sun, Y.; Wu, W.; Shan, A. Combating Bacterial Infections with Host Defense Peptides: Shifting Focus from Bacteria to Host Immunity. *Drug Resist. Updat.* **2024**, *72*, 101030. https://doi.org/10.1016/j.drup.2023.101030
42. Wang, G.; Schmidt, C.; Li, X.; Wang, Z. APD6: The Antimicrobial Peptide Database Is Expanded to Promote Research and Development by Deploying an Unprecedented Information Pipeline. *Nucleic Acids Res.* **2026**, *54*, D363–D374. https://doi.org/10.1093/nar/gkaf860
43. Zasloff, M. Antimicrobial Peptides of Multicellular Organisms. *Nature* **2002**, *415*, 389–395. https://doi.org/10.1038/415389a
44. Findlay, B.; Zhanel, G.G.; Schweizer, F. Cationic Amphiphiles, a New Generation of Antimicrobials Inspired by the Natural Antimicrobial Peptide Scaffold. *Antimicrob. Agents Chemother.* **2010**, *54*, 4049–4058. https://doi.org/10.1128/AAC.00530-10
45. Mahlapuu, M.; Håkansson, J.; Ringstad, L.; Björn, C. Antimicrobial Peptides: An Emerging Category of Therapeutic Agents. *Front. Cell. Infect. Microbiol.* **2016**, *6*, 194. https://doi.org/10.3389/fcimb.2016.00194
46. Bertrand, B.; Munoz-Garay, C. Marine Antimicrobial Peptides: A Promising Source of New Generation Antibiotics and Other Bio-active Molecules. *Int. J. Pept. Res. Ther.* **2019**, *25*, 1441–1450. https://doi.org/10.1007/s10989-018-9789-3
47. Magana, M.; Pushpanathan, M.; Santos, A.L.; Leanse, L.; Fernandez, M.; Ioannidis, A.; Giulianotti, M.A.; Apidianakis, Y.; Bradfute, S.; Ferguson, A.L.; Cherkasov, A.; Seleem, M.N.; Pinilla, C.; de la Fuente-Nunez, C.; Lazaridis, T.; Dai, T.; Houghten, R.A.; Hancock, R.E.W.; Tegos, G.P. The Value of Antimicrobial Peptides in the Age of Resistance. *Lancet Infect. Dis.* **2020**, *20*, e216–e230. https://doi.org/10.1016/S1473-3099(20)30327-3
48. Wang, L.; Wang, N.; Zhang, W.; Cheng, X.; Yan, Z.; Shao, G.; Wang, X.; Wang, R.; Fu, C. Therapeutic Peptides: Current Applications and Future Directions. *Sig. Transduct. Target. Ther.* **2022**, *7*, 48, https://doi.org/10.1038/s41392-022-00904-4
49. Li, G.; Lai, Z.; Shan, A. Advances of Antimicrobial Peptide-Based Biomaterials for the Treatment of Bacterial Infections. *Adv. Sci.* **2023**, *10*, 2206602. https://doi.org/10.1002/advs.202206602
50. Xuan, J.; Feng, W.; Wang, J.; Wang, R.; Zhang, B.; Bo, L.; Chen, Z.-S.; Yang, H.; Sun, L. Antimicrobial Peptides for Combating Drug-Resistant Bacterial Infections. *Drug Resist. Updat.* **2023**, *68*, 100954. https://doi.org/10.1016/j.drup.2023.100954
51. Datta, M.; Rajeev, A.; Chattopadhyay, I. Application of Antimicrobial Peptides as Next-Generation Therapeutics in the Biomedical World. *Biotechnol. Genet. Eng. Rev.* **2024**, *40*, 2458–2496. https://doi.org/10.1080/02648725.2023.2199572
52. Ashaolu, T.J.; Nawaz, A.; Walayat, N.; Khalifa, I. Potential "Biopeptidal" Therapeutics for Severe Respiratory Syndrome Coronaviruses: A Review of Antiviral Peptides, Viral Mechanisms, and Prospective Needs. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 3457–3470. https://doi.org/10.1007/s00253-021-11267-1
53. Rojas-Pirela, M.; Kemmerling, U.; Quiñones, W.; Michels, P.A.M.; Rojas, V. Antimicrobial Peptides (AMPs): Potential Therapeutic Strategy against Trypanosomiases? *Biomolecules* **2023**, *13*, 599. https://doi.org/10.3390/biom13040599
54. Bharathi, D.; Lee, J. Recent Advances in Marine-Derived Compounds as Potent Antibacterial and Antifungal Agents: A Comprehensive Review. *Mar. Drugs* **2024**, *22*, 348. https://doi.org/10.3390/md22080348
55. Finamore, C.; Festa, C.; Cammarota, M.; De Marino, S.; D'Auria, M.V. A Journey into the Blue: Current Knowledge and Emerging Insights into Marine-Derived Peptaibols. *Mar. Drugs* **2025**, *23*, 458. https://doi.org/10.3390/md23120458
56. Oliveira Júnior, N.G.; Souza, C.M.; Buccini, D.F.; Cardoso, M.H.; Franco, O.L. Antimicrobial Peptides: Structure, Functions and Translational Applications. *Nat. Rev. Microbiol.* **2025**, *23*, 687–700. https://doi.org/10.1038/s41579-025-01200-y
57. Yang, R.; Ma, X.; Peng, F.; Wen, J.; Allahou, L.W.; Williams, G.R.; Knowles, J.C.; Poma, A. Advances in Antimicrobial Peptides: From Mechanistic Insights to Chemical Modifications. *Biotechnol. Adv.* **2025**, *81*, 108570. https://doi.org/10.1016/j.biotechadv.2025.108570

 doi:10.20944/preprints202607.1303.v1

58. Biswas, S.; Brunel, J.-M.; Dubus, J.-C.; Reynaud-Gaubert, M.; Rolain, J.-M. Colistin: An Update on the Antibiotic of the 21st Century. *Expert Rev. Anti-Infect. Ther.* **2012**, *10*, 917–934. https://doi.org/10.1586/eri.12.78
59. Brogden, K.A. Antimicrobial Peptides: Pore Formers or Metabolic Inhibitors in Bacteria? *Nat. Rev. Microbiol.* **2005**, *3*, 238–250. https://doi.org/10.1038/nrmicro1098
60. Bechinger, B.; Gorr, S.-U. Antimicrobial Peptides: Mechanisms of Action and Resistance. *J. Dent. Res.* **2017**, *96*, 254–260. https://doi.org/10.1177/0022034516679973
61. Luo, Y.; Song, Y. Mechanism of Antimicrobial Peptides: Antimicrobial, Anti-Inflammatory and Antibiofilm Activities. *Int. J. Mol. Sci.* **2021**, *22*, 11401. https://doi.org/10.3390/ijms222111401
62. Chen, N.; Jiang, C. Antimicrobial Peptides: Structure, Mechanism, and Modification. *Eur. J. Med. Chem.* **2023**, *255*, 115377. https://doi.org/10.1016/j.ejmech.2023.115377
63. Ma, X.; Wang, Q.; Ren, K.; Xu, T.; Zhang, Z.; Xu, M.; Rao, Z.; Zhang, X. A Review of Antimicrobial Peptides: Structure, Mechanism of Action, and Molecular Optimization Strategies. *Fermentation* **2024**, *10*, 540. https://doi.org/10.3390/fermentation10110540
64. Gani, Z.; Kumar, A.; Raje, M.; Raje, C.I. Antimicrobial Peptides: An Alternative Strategy to Combat Antimicrobial Resistance. *Drug Discov. Today* **2025**, *30*, 104305. https://doi.org/10.1016/j.drudis.2025.104305
65. Zhang, H.; Lv, J.; Ma, Z.; Ma, J.; Chen, J. Advances in Antimicrobial Peptides: Mechanisms, Design Innovations, and Biomedical Potential. *Molecules* **2025**, *30*, 1529. https://doi.org/10.3390/molecules30071529
66. Lazzaro, B.P.; Zasloff, M.; Rolff, J. Antimicrobial Peptides: Application Informed by Evolution. *Science* **2020**, *368*, eaau5480. https://doi.org/10.1126/science.aau5480
67. Mhlongo, J.T.; Waddad, A.Y.; Albericio, F.; de la Torre, B.G. Antimicrobial Peptide Synergies for Fighting Infectious Diseases. *Adv. Sci.* **2023**, *10*, 2300472. https://doi.org/10.1002/advs.202300472
68. Chen, C.; Shi, J.; Wang, D.; Kong, P.; Wang, Z.; Liu, Y. Antimicrobial Peptides as Promising Antibiotic Adjuvants to Combat Drug-Resistant Pathogens. *Crit. Rev. Microbiol.* **2024**, *50*, 267–284. https://doi.org/10.1080/1040841X.2023.2186215
69. Roque-Borda, C.A.; Primo, L.M.D.G.; Medina-Alarcón, K.P.; Campos, I.C.; Nascimento, C.F.; Saraiva, M.M.S.; Berchieri Junior, A.; Fusco-Almeida, A.M.; Mendes-Giannini, M.J.S.; Perdigão, J.; Pavan, F.R.; Albericio, F. Antimicrobial Peptides: A Promising Alternative to Conventional Antimicrobials for Combating Polymicrobial Biofilms. *Adv. Sci.* **2025**, *12*, 2410893. https://doi.org/10.1002/advs.202410893
70. Guryanova, S.V.; Belogurova-Ovchinnikova, O.Y.; Ovchinnikova, T.V. Human and Marine Host Defense Peptides for Healthy Skin. *Mar. Drugs* **2026**, *24*, 134. https://doi.org/10.3390/md24040134
71. Mookherjee, N.; Hancock, R.E.W. Cationic Host Defence Peptides: Innate Immune Regulatory Peptides as a Novel Approach for Treating Infections. *Cell. Mol. Life Sci.* **2007**, *64*, 922–933. https://doi.org/10.1007/s00018-007-6475-6
72. Guilhelmelli, F.; Vilela, N.; Albuquerque, P.; Derengowski, L.d.S.; Silva-Pereira, I.; Kyaw, C.M. Antibiotic Development Challenges: The Various Mechanisms of Action of Antimicrobial Peptides and of Bacterial Resistance. *Front. Microbiol.* **2013**, *4*, 353. https://doi.org/10.3389/fmicb.2013.00353
73. Boto, A.; Pérez de la Lastra, J.M.; González, C.C. The Road from Host-Defense Peptides to a New Generation of Antimicrobial Drugs. *Molecules* **2018**, *23*, 311. https://doi.org/10.3390/molecules23020311
74. Wedamulla, P.G.; Straus, S.K. Tackling Sepsis Using Host Defense Peptides That Reduce Proinflammatory Cytokine Production. *ACS Infect. Dis.* **2026**, *12*, 967–977. https://doi.org/10.1021/acsinfecdis.5c01040
75. Kumar, P.; Kizhakkedathu, J.N.; Straus, S.K. Antimicrobial Peptides: Diversity, Mechanism of Action and Strategies to Improve the Activity and Biocompatibility In Vivo. *Biomolecules* **2018**, *8*, 4. https://doi.org/10.3390/biom8010004
76. Dini, I.; De Biasi, M.-G.; Mancusi, A. An Overview of the Potentialities of Antimicrobial Peptides Derived from Natural Sources. *Antibiotics* **2022**, *11*, 1483. https://doi.org/10.3390/antibiotics11111483
77. Ji, S.; An, F.; Zhang, T.; Lou, M.; Guo, J.; Liu, K.; Zhu, Y.; Wu, J.; Wu, R. Antimicrobial Peptides: An Alternative to Traditional Antibiotics. *Eur. J. Med. Chem.* **2024**, *265*, 116072. https://doi.org/10.1016/j.ejmech.2023.116072

 doi:10.20944/preprints202607.1303.v1

78. Zhong, H.; Chen, X.; Han, S.; Zhang, L. The Functional Mechanism and Structure-Activity Relationship of Antibacterial Peptides. *Curr. Top. Med. Chem.* **2025**, *25*, 2385–2398. https://doi.org/10.2174/0115680266350153250121072651
79. Zhang, Q.-Y.; Yan, Z.-B.; Meng, Y.-M.; Hong, X.-Y.; Shao, G.; Ma, J.-J.; Cheng, X.-R.; Liu, J.; Kang, J.; Fu, C.-Y. Antimicrobial Peptides: Mechanism of Action, Activity and Clinical Potential. *Military Med. Res.* **2021**, *8*, 48. https://doi.org/10.1186/s40779-021-00343-2
80. Hancock, R.E.W.; Brown, K.L.; Mookherjee, N. Host Defence Peptides from Invertebrates – Emerging Antimicrobial Strategies. *Immunobiology* **2006**, *211*, 315–322. https://doi.org/10.1016/j.imbio.2005.10.017
81. Wilmes, M.; Cammue, B.P.A.; Sahl, H.-G.; Thevissen, K. Antibiotic Activities of Host Defense Peptides: More to It Than Lipid Bilayer Perturbation. *Nat. Prod. Rep.* **2011**, *28*, 1350–1358. https://doi.org/10.1039/c1np00022e
82. Pasupuleti, M.; Schmidtchen, A.; Malmsten, M. Antimicrobial Peptides: Key Components of the Innate Immune System. *Crit. Rev. Biotechnol.* **2012**, *32*, 143–171. https://doi.org/10.3109/07388551.2011.594423
83. Campos, M.L.; de Souza, C.M.; de Oliveira, K.B.S.; Dias, S.C.; Franco, O.L. The Role of Antimicrobial Peptides in Plant Immunity. *J. Exp. Bot.* **2018**, *69*, 4997–5011. https://doi.org/10.1093/jxb/ery294
84. Finkina, E.I.; Melnikova, D.N.; Bogdanov, I.V.; Ovchinnikova, T.V. Peptides of the Innate Immune System of Plants. Part I. Structure, Biological Activity, and Mechanisms of Action. *Russ. J. Bioorg. Chem.* **2018**, *44*, 573–585. https://doi.org/10.1134/S1068162019010060
85. Haney, E.F.; Straus, S.K.; Hancock, R.E.W. Reassessing the Host Defense Peptide Landscape. *Front. Chem.* **2019**, *7*, 43. https://doi.org/10.3389/fchem.2019.00043
86. Cresti, L.; Cappello, G.; Pini, A. Antimicrobial Peptides towards Clinical Application—A Long History to Be Concluded. *Int. J. Mol. Sci.* **2024**, *25*, 4870. https://doi.org/10.3390/ijms25094870
87. Shirsat, H.; Datt, M.; Kale, A.; Mishra, M. Plant Defense Peptides: Exploring the Structure–Function Correlation for Potential Applications in Drug Design and Therapeutics. *ACS Omega* **2025**, *10*, 7583–7596. https://doi.org/10.1021/acsomega.4c11339
88. Islam, M.M.; Shuvo, F.R.; Yadab, S.K.; Chowdhury, S.M.M.H.; Botul, U.; Hisham, A.A.; Hasan, M. Unlocking the Therapeutic Potential of AMPs: From Mechanism to Future Research Approaches. *Microbe* **2026**, *11*, 100715. https://doi.org/10.1016/j.microb.2026.100715
89. Li, J.; Koh, J.-J.; Liu, S.; Lakshminarayanan, R.; Verma, C.S.; Beuerman, R.W. Membrane Active Antimicrobial Peptides: Translating Mechanistic Insights to Design. *Front. Neurosci.* **2017**, *11*, 73. https://doi.org/10.3389/fnins.2017.00073
90. Ciumac, D.; Gong, H.; Hu, X.; Lu, J.R. Membrane Targeting Cationic Antimicrobial Peptides. *J. Colloid Interface Sci.* **2019**, *537*, 163–185. https://doi.org/10.1016/j.jcis.2018.10.103
91. Mwangi, J.; Hao, X.; Lai, R.; Zhang, Z.-Y. Antimicrobial Peptides: New Hope in the War Against Multidrug Resistance. *Zool. Res.* **2019**, *40*, 488–505. https://doi.org/10.24272/j.issn.2095-8137.2019.062
92. Yang, R.; Hou, E.; Cheng, W.; Yan, X.; Zhang, T.; Li, S.; Yao, H.; Liu, J.; Guo, Y. Membrane-Targeting Neolignan-Antimicrobial Peptide Mimic Conjugates to Combat Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infections. *J. Med. Chem.* **2022**, *65*, 16879–16892. https://doi.org/10.1021/acs.jmedchem.2c01674
93. Bakare, O.O.; Gokul, A.; Niekerk, L.-A.; Aina, O.; Abiona, A.; Barker, A.M.; Basson, G.; Nkomo, M.; Otomo, L.; Keyster, M.; Klein, A. Recent Progress in the Characterization, Synthesis, Delivery Procedures, Treatment Strategies, and Precision of Antimicrobial Peptides. *Int. J. Mol. Sci.* **2023**, *24*, 11864. https://doi.org/10.3390/ijms241411864
94. Sierra, J.M.; Fusté, E.; Rabanal, F.; Vinuesa, T.; Viñas, M. An Overview of Antimicrobial Peptides and the Latest Advances in Their Development. *Expert Opin. Biol. Ther.* **2017**, *17*, 663–676. https://doi.org/10.1080/14712598.2017.1315402
95. Lam, S.J.; O'Brien-Simpson, N.M.; Pantarat, N.; Sulistio, A.; Wong, E.H.H.; Chen, Y.Y.; Lenzo, J.C.; Holden, J.A.; Blencowe, A.; Reynolds, E.C.; Qiao, G.G. Combating Multidrug-Resistant Gram-Negative Bacteria with Structurally Nanoengineered Antimicrobial Peptide Polymers. *Nat. Microbiol.* **2016**, *1*, 16162. https://doi.org/10.1038/nmicrobiol.2016.162

 doi:10.20944/preprints202607.1303.v1

96. Li, Y.-X.; Zhong, Z.; Zhang, W.-P.; Qian, P.-Y. Discovery of Cationic Nonribosomal Peptides as Gram-Negative Antibiotics Through Global Genome Mining. *Nat. Commun.* **2018**, *9*, 3273. https://doi.org/10.1038/s41467-018-05781-6
97. Spohn, R.; Daruka, L.; Lázár, V.; Martins, A.; Vidovics, F.; Grézal, G.; Méhi, O.; Kintses, B.; Számel, M.; Jangir, P.K.; Csörgő, B.; Györkei, Á.; Bódi, Z.; Faragó, A.; Bodai, L.; Földesi, I.; Kata, D.; Maróti, G.; Pap, B.; Wirth, R.; Papp, B.; Pál, C. Integrated Evolutionary Analysis Reveals Antimicrobial Peptides with Limited Resistance. *Nat. Commun.* **2019**, *10*, 4538. https://doi.org/10.1038/s41467-019-12364-6
98. Mulkern, A.J.; Oyama, L.B.; Cookson, A.R.; Creevey, C.J.; Wilkinson, T.J.; Olleik, H.; Maresca, M.; da Silva, G.C.; Fontes, P.P.; Bazzolli, D.M.S.; Mantovani, H.C.; Damaris, B.F.; Mur, L.A.J.; Huws, S.A. Microbiome-Derived Antimicrobial Peptides Offer Therapeutic Solutions for the Treatment of *Pseudomonas aeruginosa* Infections. *npj Biofilms Microbiomes* **2022**, *8*, 70. https://doi.org/10.1038/s41522-022-00332-w
99. Peschel, A.; Sahl, H.-G. The Co-Evolution of Host Cationic Antimicrobial Peptides and Microbial Resistance. *Nat. Rev. Microbiol.* **2006**, *4*, 529–536. https://doi.org/10.1038/nrmicro1441
100. Zheng, S.; Tu, Y.; Li, B.; Qu, G.; Li, A.; Peng, X.; Li, S.; Shao, C. Antimicrobial Peptide Biological Activity, Delivery Systems and Clinical Translation Status and Challenges. *J. Transl. Med.* **2025**, *23*, 292. https://doi.org/10.1186/s12967-025-06321-9
101. Luong, H.X.; Ngan, H.D.; Thi Phuong, H.B.; Quoc, T.N.; Tung, T.T. Multiple Roles of Ribosomal Antimicrobial Peptides in Tackling Global Antimicrobial Resistance. *R. Soc. Open Sci.* **2022**, *9*, 211583. https://doi.org/10.1098/rsos.211583
102. Zhu, Y.; Hao, W.; Wang, X.; Ouyang, J.; Deng, X.; Yu, H.; Wang, Y. Antimicrobial Peptides, Conventional Antibiotics, and Their Synergistic Utility for the Treatment of Drug-Resistant Infections. *Med. Res. Rev.* **2022**, *42*, 1377–1422. https://doi.org/10.1002/med.21879
103. Lázár, V.; Martins, A.; Spohn, R.; Daruka, L.; Grézal, G.; Fekete, G.; Számel, M.; Jangir, P.K.; Kintses, B.; Csörgő, B.; Nyerges, Á.; Györkei, Á.; Kincses, A.; Dér, A.; Walter, F.R.; Deli, M.A.; Urbán, E.; Hegedűs, Z.; Olajos, G.; Méhi, O.; Bálint, B.; Nagy, I.; Martinek, T.A.; Papp, B.; Pál, C. Antibiotic-Resistant Bacteria Show Widespread Collateral Sensitivity to Antimicrobial Peptides. *Nat. Microbiol.* **2018**, *3*, 718–731. https://doi.org/10.1038/s41564-018-0164-0
104. Kintses, B.; Méhi, O.; Ari, E.; Számel, M.; Györkei, A.; Jangir, P.K.; Nagy, I.; Pál, F.; Fekete, G.; Tengölics, R.; Nyerges, Á.; Likó, I.; Bálint, A.; Molnár, T.; Bálint, B.; Vásárhelyi, B.M.; Bustamante, M.; Papp, B.; Pál, C. Phylogenetic Barriers to Horizontal Transfer of Antimicrobial Peptide Resistance Genes in the Human Gut Microbiota. *Nat. Microbiol.* **2019**, *4*, 447–458. https://doi.org/10.1038/s41564-018-0313-5
105. Rima, M.; Rima, M.; Fajloun, Z.; Sabatier, J.-M.; Bechinger, B.; Naas, T. Antimicrobial Peptides: A Potent Alternative to Antibiotics. *Antibiotics* **2021**, *10*, 1095. https://doi.org/10.3390/antibiotics10091095
106. Chen, X.; Zhou, J.; Qian, Y.; Zhao, L. Antibacterial Coatings on Orthopedic Implants. *Mater. Today Bio* **2023**, *19*, 100586. https://doi.org/10.1016/j.mtbio.2023.100586
107. Gonçalves, R.M.; Dutra Monges, B.E.; Oshiro, K.G.N.; Cândido, E.d.S.; Pimentel, J.P.F.; Franco, O.L.; Cardoso, M.H. Advantages and Challenges of Using Antimicrobial Peptides in Synergism with Antibiotics for Treating Multidrug-Resistant Bacteria. *ACS Infect. Dis.* **2025**, *11*, 323–334. https://doi.org/10.1021/acsinfecdis.4c00702
108. Roque-Borda, C.A.; Medina-Alarcón, K.P.; Gonçalves Pereira, J.P.S.; dos Anjos Sevilhano, T.C.; Aguilar-Morón, B.; Díaz-Cárdenas, F.; da Cruz, L.S.; Xavier-Júnior, F.H.; Vicente, E.F.; Perdigão, J.; de la Torre, B.G.; Albericio, F.; Pavan, F.R. Repositioning Antimicrobial Peptides Against WHO-Priority Fungi. *Adv. Sci.* **2025**, *12*, e09567. https://doi.org/10.1002/advs.202509567
109. Rashid, Z.; Ahmed, H.; Saleem, K.; Siddiqui, M.R.U. Towards Safer Antimicrobial Peptide Therapeutics: A Predictive–Generative Framework Targeting ESKAPE Pathogens. *Probiotics Antimicro. Prot.* **2026**, Online ahead of print. https://doi.org/10.1007/s12602-026-11022-w
110. Surabhi, V.; Prabhu, V.; Nayak, U.Y.; Kumar, N.; Prasad AS, B. Harnessing AMPs to Tackle ESKAPE Pathogens. *ACS Infect. Dis.* **2026**, *12*, 32–47. https://doi.org/10.1021/acsinfecdis.5c00667

 doi:10.20944/preprints202607.1303.v1

111. Wu-Mo, C.; Flores-González, A.; Meléndez-Delgado, J.; Ortiz-Gómez, V.; Meléndez-González, H.; Maldonado-Hernández, R. Artificial Intelligence-Driven Discovery and Optimization of Antimicrobial Peptides Targeting ESKAPE Pathogens and Multidrug-Resistant Fungi. *Microorganisms* **2026**, *14*, 591. https://doi.org/10.3390/microorganisms14030591
112. Hetta, H.F.; Sirag, N.; Alsharif, S.M.; Alharbi, A.A.; Alkindy, T.T.; Alkhamali, A.; Albalawi, A.S.; Ramadan, Y.N.; Rashed, Z.I.; Alanazi, F.E. Antimicrobial Peptides: The Game-Changer in the Epic Battle Against Multidrug-Resistant Bacteria. *Pharmaceuticals* **2024**, *17*, 1555. https://doi.org/10.3390/ph17111555
113. Behera, B.; Singh, R.; Sharma, K.; Rai, A.; Singh, S.; Balan, B. A Comprehensive Review of Advanced Strategies to Combat Antimicrobial Resistance. *Arch. Microbiol.* **2025**, *207*, 281. https://doi.org/10.1007/s00203-025-04464-3
114. Mahlapuu, M.; Björn, C.; Ekblom, J. Antimicrobial Peptides as Therapeutic Agents: Opportunities and Challenges. *Crit. Rev. Biotechnol.* **2020**, *40*, 978–992. https://doi.org/10.1080/07388551.2020.1796576
115. Saubenova, M.; Rapoport, A.; Yermekbay, Z.; Oleinikova, Y. Antimicrobial Peptides, Their Production, and Potential in the Fight Against Antibiotic-Resistant Pathogens. *Fermentation* **2025**, *11*, 36. https://doi.org/10.3390/fermentation11010036
116. Linde, A.; Wachter, B.; Höner, O.P.; Dib, L.; Ross, C.; Tamayo, A.R.; Blecha, F.; Melgarejo, T. Natural History of Innate Host Defense Peptides. *Probiotics Antimicro. Prot.* **2009**, *1*, 97–112. https://doi.org/10.1007/s12602-009-9031-x
117. Smith, W.P.J.; Wucher, B.R.; Nadell, C.D.; Foster, K.R. Bacterial Defences: Mechanisms, Evolution and Antimicrobial Resistance. *Nat. Rev. Microbiol.* **2023**, *21*, 519–534. https://doi.org/10.1038/s41579-023-00877-3
118. Yu, G.; Baeder, D.Y.; Regoes, R.R.; Rolff, J. Combination Effects of Antimicrobial Peptides. *Antimicrob. Agents Chemother.* **2016**, *60*, 1717–1724. https://doi.org/10.1128/AAC.02434-15
119. Torres, M.D.T.; Sothiselvam, S.; Lu, T.K.; de la Fuente-Nunez, C. Peptide Design Principles for Antimicrobial Applications. *J. Mol. Biol.* **2019**, *431*, 3547–3567. https://doi.org/10.1016/j.jmb.2018.12.015
120. Annunziato, G.; Costantino, G. Antimicrobial Peptides (AMPs): A Patent Review (2015–2020). *Expert Opin. Ther. Pat.* **2020**, *30*, 931–947. https://doi.org/10.1080/13543776.2020.1851679
121. Lozo, J.; Topisirovic, L.; Kojic, M. Natural Bacterial Isolates as an Inexhaustible Source of New Bacteriocins. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 477–492. https://doi.org/10.1007/s00253-020-11063-3
122. Angeles Flores, G.; Cusumano, G.; Venanzoni, R.; Angelini, P. Biodiversity-Driven Natural Products and Bioactive Metabolites. *Plants* **2026**, *15*, 104. https://doi.org/10.3390/plants15010104
123. Rojas, V.; Rivas, L.; Cárdenas, C.; Guzmán, F. Cyanobacteria and Eukaryotic Microalgae as Emerging Sources of Antibacterial Peptides. *Molecules* **2020**, *25*, 5804. https://doi.org/10.3390/molecules25245804
124. Ayswaria, R.; Vijayan, J.; Nathan, V.K. Antimicrobial Peptides Derived from Microalgae for Combating Antibiotic Resistance: Current Status and Prospects. *Cell Biochem. Funct.* **2023**, *41*, 142–151. https://doi.org/10.1002/cbf.3779
125. Hafez Ghoran, S.; Taktaz, F.; Sousa, E.; Fernandes, C.; Kijjoa, A. Peptides from Marine-Derived Fungi: Chemistry and Biological Activities. *Mar. Drugs* **2023**, *21*, 510. https://doi.org/10.3390/md21100510
126. Perera, R.M.T.D.; Herath, K.H.I.N.M.; Sanjeewa, K.K.A.; Jayawardena, T.U. Recent Reports on Bioactive Compounds from Marine Cyanobacteria in Relation to Human Health Applications. *Life* **2023**, *13*, 1411. https://doi.org/10.3390/life13061411
127. Mihaylova-Garnizova, R.; Davidova, S.; Hodzhev, Y.; Satchanska, G. Antimicrobial Peptides Derived from Bacteria: Classification, Sources, and Mechanism of Action against Multidrug-Resistant Bacteria. *Int. J. Mol. Sci.* **2024**, *25*, 10788. https://doi.org/10.3390/ijms251910788
128. Chitthan, S.V.; Rasheed, A.S.; Muniyandi, M.; Dhanasekaran, D.; Thajuddin, N. Bioactive Peptides from Microalgae and Cyanobacteria and Their Possible Mechanisms of Action. *Int. J. Pept. Res. Ther.* **2025**, *31*, 86. https://doi.org/10.1007/s10989-025-10746-7
129. Erriah, P.; Puan, S.L.; Yahaya, N.M.; Kamil, W.N.I.W.A.; Nordin, S.A.; Muhamad, A.; Sabri, S. Harnessing Bacterial Antimicrobial Peptides: a Comprehensive Review on Properties, Mechanisms, Applications, and Challenges in Combating Antimicrobial Resistance. *J. Appl. Microbiol.* **2025**, *136*, lxae290. https://doi.org/10.1093/jambio/lxae290

 doi:10.20944/preprints202607.1303.v1

130. Qoms, M.S.; Wong, S.K.; Mohd Fauzi, N.; Husain, K.; Makpol, S.; Tan, J.K. Microalgae-Derived Peptides Targeting Lifestyle-Related Diseases: Discovery, Mechanisms, Structure–Activity Relationships, and Structural Modifications. *Antioxidants* **2025**, *14*, 1170. https://doi.org/10.3390/antiox14101170
131. Pei, H.; Bao, K.; Han, T.; Cao, X. Comprehensive Insights into Microbial-Derived Antimicrobial Peptides (AMPs): Classification, Mechanisms, Applications, and Purification Strategies. *Crit. Rev. Biotechnol.* **2025**, *45*, 1652–1679. https://doi.org/10.1080/07388551.2025.2518308
132. Hudson, G.A.; Mitchell, D.A. RiPP Antibiotics: Biosynthesis and Engineering Potential. *Curr. Opin. Microbiol.* **2018**, *45*, 61–69, https://doi.org/10.1016/j.mib.2018.02.010
133. Riley, M.A.; Gordon, D.M. The Ecological Role of Bacteriocins in Bacterial Competition. *Trends Microbiol.* **1999**, *7*, 129–132. https://doi.org/10.1016/S0966-842X(99)01459-6
134. Heilbronner, S.; Krismer, B.; Brötz-Oesterhelt, H.; Peschel, A. The Microbiome-Shaping Roles of Bacteriocins. *Nat. Rev. Microbiol.* **2021**, *19*, 726–739. https://doi.org/10.1038/s41579-021-00569-w
135. Ramírez-Rendón, D.; Guzmán-Chávez, F.; García-Ausencio, C.; Rodríguez-Sanoja, R.; Sánchez, S. The Untapped Potential of Actinobacterial Lanthipeptides as Therapeutic Agents. *Mol. Biol. Rep.* **2023**, *50*, 10605–10616. https://doi.org/10.1007/s11033-023-08880-w
136. Han, S.-W.; Won, H.-S. Advancements in the Application of Ribosomally Synthesized and Post-Translationally Modified Peptides (RiPPs). *Biomolecules* **2024**, *14*, 479. https://doi.org/10.3390/biom14040479
137. Pfeiffer, I.P.-M.; Schröder, M.-P.; Mordhorst, S. Opportunities and Challenges of RiPP-Based Therapeutics. *Nat. Prod. Rep.* **2024**, *41*, 990–1019. https://doi.org/10.1039/d3np00057e
138. Jangra, M.; Travin, D.Y.; Aleksandrova, E.V.; Kaur, M.; Darwish, L.; Koteva, K.; Klepacki, D.; Wang, W.; Tiffany, M.; Sokaribo, A.; Chen, X.; Deng, Z.; Tao, M.; Coombes, B.K.; Vázquez-Laslop, N.; Polikanov, Y.S.; Mankin, A.S.; Wright, G.D. A Broad-Spectrum Lasso Peptide Antibiotic Targeting the Bacterial Ribosome. *Nature* **2025**, *640*, 1022–1030. https://doi.org/10.1038/s41586-025-08723-7
139. Qiao, X.; Sun, X.; Wang, S.; Zhai, C.; Tang, W.; Tang, T.; Zhang, J.; He, Z. Characterization of Flexusin A, a Novel Circular Bacteriocin Produced by Marine Bacterium *Bacillus flexus* R29-2. *Mar. Drugs* **2025**, *23*, 95. https://doi.org/10.3390/md23030095
140. Liang, J.; Shi, R.; Cheng, L.; Huang, C.; Tu, Z.; Wang, X.; Hu, L.; Wang, J.; Fang, X.; Wang, L. Food-Grade Microbial-Origin Antimicrobial Peptides: Structure–Activity Relationships, Mechanisms of Action, and Applications in Food Preservation. *Compr. Rev. Food Sci. Food Saf.* **2026**, *25*, e70438. https://doi.org/10.1111/1541-4337.70438
141. Lohans, C.T.; van Belkum, M.J.; Li, J.; Vederas, J.C. Characterization of Bacterial Antimicrobial Peptides Active Against *Campylobacter jejuni*. *Can. J. Chem.* **2015**, *93*, 381–388. https://doi.org/10.1139/cjc-2014-0411
142. Tajbakhsh, M.; Karimi, A.; Fallah, F.; Akhavan, M.M. Overview of Ribosomal and Non-Ribosomal Antimicrobial Peptides Produced by Gram Positive Bacteria. *Cell. Mol. Biol.* **2017**, *63*, 20–32. http://dx.doi.org/10.14715/cmb/2017.63.10.4
143. Abdel Monaim, S.A.H.; Somboro, A.M.; El-Faham, A.; de la Torre, B.G.; Albericio, F. Bacteria Hunt Bacteria through an Intriguing Cyclic Peptide. *ChemMedChem* **2019**, *14*, 24–51. https://doi.org/10.1002/cmdc.201800597
144. Rončević, T.; Puizina, J.; Tossi, A. Antimicrobial Peptides as Anti-Infective Agents in Pre-Post-Antibiotic Era? *Int. J. Mol. Sci.* **2019**, *20*, 5713. https://doi.org/10.3390/ijms20225713
145. Buda De Cesare, G.; Cristy, S.A.; Garsin, D.A.; Lorenz, M.C. Antimicrobial Peptides: A New Frontier in Antifungal Therapy. *mBio* **2020**, *11*, e02123-20. https://doi.org/10.1128/mBio.02123-20
146. Bin Hafeez, A.; Jiang, X.; Bergen, P.J.; Zhu, Y. Antimicrobial Peptides: An Update on Classifications and Databases. *Int. J. Mol. Sci.* **2021**, *22*, 11691. https://doi.org/10.3390/ijms222111691
147. Lopes, B.S.; Hanafiah, A.; Nachimuthu, R.; Muthupandian, S.; Md Nesran, Z.N.; Patil, S. The Role of Antimicrobial Peptides as Antimicrobial and Antibiofilm Agents in Tackling the Silent Pandemic of Antimicrobial Resistance. *Molecules* **2022**, *27*, 2995. https://doi.org/10.3390/molecules27092995
148. Prazdnova, E.V.; Kulikov, M.P.; Khmelevtsova, L.E. The Potential of Non-Ribosomal Peptide Engineering for Creating New Antimicrobial Complexes. *Molecules* **2026**, *31*, 683. https://doi.org/10.3390/molecules31040683

 doi:10.20944/preprints202607.1303.v1

149. Schwarzer, D.; Finking, R.; Marahiel, M.A. Nonribosomal Peptides: from Genes to Products. *Nat. Prod. Rep.* **2003**, *20*, 275–287. https://doi.org/10.1039/b111145k
150. Desriac, F.; Jégou, C.; Balnois, E.; Brillet, B.; Chevalier, P.L.; Fleury, Y. Antimicrobial Peptides from Marine Proteobacteria. *Mar. Drugs* **2013**, *11*, 3632-3660. https://doi.org/10.3390/md11103632
151. Walsh, C.T. Insights into the Chemical Logic and Enzymatic Machinery of NRPS Assembly Lines. *Nat. Prod. Rep.* **2016**, *33*, 127–135. https://doi.org/10.1039/c5np00035a
152. Süssmuth, R.D.; Mainz, A. Nonribosomal Peptide Synthesis—Principles and Prospects. *Angew. Chem. Int. Ed.* **2017**, *56*, 3770–3821. https://doi.org/10.1002/anie.201609079
153. Arnison, P.G.; Bibb, M.J.; Bierbaum, G.; Bowers, A.A.; Bugni, T.S.; Bulaj, G.; Camarero, J.A.; Campopiano, D.J.; Challis, G.L.; Clardy, J.; Cotter, P.D.; Craik, D.J.; Dawson, M.; Dittmann, E.; Donadio, S.; Dorrestein, P.C.; Entian, K.-D.; Fischbach, M.A.; Garavelli, J.S.; Göransson, U.; Gruber, C.W.; Haft, D.H.; Hemscheidt, T.K.; Hertweck, C.; Hill, C.; Horswill, A.R.; Jaspars, M.; Kelly, W.L.; Klinman, J.P.; Kuipers, O.P.; Link, A.J.; Liu, W.; Marahiel, M.A.; Mitchell, D.A.; Moll, G.N.; Moore, B.S.; Müller, R.; Nair, S.K.; Nes, I.F.; Norris, G.E.; Olivera, B.M.; Onaka, H.; Patchett, M.L.; Piel, J.; Reaney, M.J.T.; Rebuffat, S.; Ross, R.P.; Sahl, H.-G.; Schmidt, E.W.; Selsted, M.E.; Severinov, K.; Shen, B.; Sivonen, K.; Smith, L.; Stein, T.; Süssmuth, R.D.; Tagg, J.R.; Tang, G.-L.; Truman, A.W.; Vederas, J.C.; Walsh, C.T.; Walton, J.D.; Wenzel, S.C.; Willey, J.M.; van der Donk, W.A. Ribosomally Synthesized and Post-Translationally Modified Peptide Natural Products: Overview and Recommendations for a Universal Nomenclature. *Nat. Prod. Rep.* **2013**, *30*, 108–160. https://doi.org/10.1039/c2np20085f
154. Payne, J.A.E.; Schoppet, M.; Hansen, M.H.; Cryle, M.J. Diversity of Nature's Assembly Lines – Recent Discoveries in Non-Ribosomal Peptide Synthesis. *Mol. BioSyst.* **2017**, *13*, 9–22. https://doi.org/10.1039/c6mb00675b
155. Koehbach, J.; Craik, D.J. The Vast Structural Diversity of Antimicrobial Peptides. *Trends Pharmacol. Sci.* **2019**, *40*, 517–528. https://doi.org/10.1016/j.tips.2019.04.012
156. Wenski, S.L.; Thiengmag, S.; Helfrich, E.J.N. Complex Peptide Natural Products: Biosynthetic Principles, Challenges and Opportunities for Pathway Engineering. *Synth. Syst. Biotechnol.* **2022**, *7*, 631–647. https://doi.org/10.1016/j.synbio.2022.01.007
157. Cutolo, E.A.; Campitiello, R.; Caferri, R.; Pagliuca, V.F.; Li, J.; Agathos, S.N.; Cutolo, M. Immunomodulatory Compounds from the Sea: From the Origins to a Modern Marine Pharmacopoeia. *Mar. Drugs* **2024**, *22*, 304. https://doi.org/10.3390/md22070304
158. Sugrue, I.; Ross, R.P.; Hill, C. Bacteriocin Diversity, Function, Discovery and Application as Antimicrobials. *Nat. Rev. Microbiol.* **2024**, *22*, 556–571. https://doi.org/10.1038/s41579-024-01045-x
159. Nivina, A.; Pizarro, P.T. Evolutionary Strategies of Late-Stage Diversification in Bacterial Biosynthetic Gene Clusters. *Essays Biochem.* **2026**, EBC20250026. Online ahead of print. https://doi.org/10.1042/EBC20250026
160. Adamska, A.; Janecka, A. Endless Peptides—Circular Forms in Nature. *Curr. Med. Chem.* **2015**, *22*, 352–359. https://doi.org/10.2174/0929867322666141128162308
161. Kloosterman, A.M.; Cimermancic, P.; Elsayed, S.S.; Du, C.; Hadjithomas, M.; Donia, M.S.; Fischbach, M.A.; van Wezel, G.P.; Medema, M.H. Expansion of RiPP Biosynthetic Space through Integration of Pan-Genomics and Machine Learning Uncovers a Novel Class of Lanthipeptides. *PLoS Biol.* **2020**, *18*, e3001026. https://doi.org/10.1371/journal.pbio.3001026
162. Kumar, V.; Singh, B.; van Belkum, M.J.; Diep, D.B.; Chikindas, M.L.; Ermakov, A.M.; Tiwari, S.K. Halocins, Natural Antimicrobials of Archaea: Exotic or Special or Both? *Biotechnol. Adv.* **2021**, *53*, 107834. https://doi.org/10.1016/j.biotechadv.2021.107834
163. Ruijne, F.; Kuipers, O.P. Combinatorial Biosynthesis for the Generation of New-to-Nature Peptide Antimicrobials. *Biochem. Soc. Trans.* **2021**, *49*, 203–215. https://doi.org/10.1042/BST20200425
164. Fu, Y.; Xu, Y.; Ruijne, F.; Kuipers, O.P. Engineering Lanthipeptides by Introducing a Large Variety of RiPP Modifications to Obtain New-to-Nature Bioactive Peptides. *FEMS Microbiol. Rev.* **2023**, *47*, fuad017. https://doi.org/10.1093/femsre/fuad017
165. Vinogradov, A.A.; Yin, Y.; Suga, H. Macrocyclic Peptides as Drug Candidates: Recent Progress and Remaining Challenges. *J. Am. Chem. Soc.* **2019**, *141*, 4167–4181. https://doi.org/10.1021/jacs.8b13178

 doi:10.20944/preprints202607.1303.v1

166. Zimmer, L.; Crüsemann, M. Amino Acid Tailoring Strategies in Peptide Natural Product Biosynthesis. *Trends Chem.* **2025**, *7*, 705–718. https://doi.org/10.1016/j.trechm.2025.09.014
167. Butler, L.; Awan, A.R.; Ellis, T.; Akram, M.S. Engineering Non-Ribosomal Peptide Synthesis: Tuning the Antibiotics Engine of the Microbial World. *Crit. Rev. Biotechnol.* **2026**, *46*, 501–521. https://doi.org/10.1080/07388551.2026.2615819
168. Chen, B.; Bülbül, E.F.; Bang, S.G.; Minas, H.A.; Bozhüyük, K.A.J. Toward a Unified Pipeline for Natural Product Discovery: Tools and Strategies for NRPS and PKS Pathway Exploration and Engineering. *Nat. Prod. Rep.* **2026**, *43*, 352–370. https://doi.org/10.1039/d5np00041f
169. Chen, S.Q.; Xiang, H.; Chen, Y.; Bode, H.B.; Shi, Y.M. From Known Knowns to Unknown Unknowns: Synthetic Biology Paths to Antimicrobial Discovery. *Curr. Opin. Microbiol.* **2026**, *91*, 102759. https://doi.org/10.1016/j.mib.2026.102759
170. Dijksteel, G.S.; Ulrich, M.M.W.; Middelkoop, E.; Boekema, B.K.H.L. Review: Lessons Learned From Clinical Trials Using Antimicrobial Peptides (AMPs). *Front. Microbiol. 2021*, *12*, 616979. https://doi.org/10.3389/fmicb.2021.616979
171. Costa, L.; Sousa, E.; Fernandes, C. Cyclic Peptides in Pipeline: What Future for These Great Molecules? *Pharmaceuticals* **2023**, *16*, 996. https://doi.org/10.3390/ph16070996
172. Bucataru, C.; Ciobanasu, C. Antimicrobial Peptides: Opportunities and Challenges in Overcoming Resistance. *Microbiol. Res.* **2024**, *286*, 127822. https://doi.org/10.1016/j.micres.2024.127822
173. Al Musaimi, O. FDA-Approved Antibacterials and Echinocandins. *Antibiotics 2025*, *14*, 166. https://doi.org/10.3390/antibiotics14020166
174. Wang, Y.; Cong, H.; Shen, Y.; Yu, B. Advances in the Discovery, Mechanism of Action, Optimization of Activity and Potential for Clinical Application of Antimicrobial Peptides. *Chem. Eng. J.* **2025**, *504*, 158962. https://doi.org/10.1016/j.cej.2024.158962
175. Yeung, A.T.Y.; Gellatly, S.L.; Hancock, R.E.W. Multifunctional Cationic Host Defence Peptides and Their Clinical Applications. *Cell. Mol. Life Sci.* **2011**, *68*, 2161–2176. https://doi.org/10.1007/s00018-011-0710-x
176. Afacan, N.J.; Yeung, A.T.Y.; Pena, O.M.; Hancock, R.E.W. Therapeutic Potential of Host Defense Peptides in Antibiotic-resistant Infections. *Curr. Pharm. Des.* **2012**, *18*, 807–819. https://doi.org/10.2174/138161212799277617
177. Mansour, S.C.; Pena, O.M.; Hancock, R.E.W. Host Defense Peptides: Front-Line Immunomodulators. *Trends Immunol.* **2014**, *35*, 443–450. https://doi.org/10.1016/j.it.2014.07.004
178. Nagarajan, K.; Marimuthu, S.K.; Palanisamy, S.; Subbiah, L. Peptide Therapeutics Versus Superbugs: Highlight on Current Research and Advancements. *Int. J. Pept. Res. Ther.* **2018**, *24*, 19–33. https://doi.org/10.1007/s10989-017-9650-0
179. Ting, D.S.J.; Beuerman, R.W.; Dua, H.S.; Lakshminarayanan, R.; Mohammed, I. Strategies in Translating the Therapeutic Potentials of Host Defense Peptides. *Front. Immunol.* **2020**, *11*, 983. https://doi.org/10.3389/fimmu.2020.00983
180. Fjell, C.D.; Hiss, J.A.; Hancock, R.E.W.; Schneider, G. Designing Antimicrobial Peptides: Form Follows Function. *Nat. Rev. Drug Discov.* **2012**, *11*, 37–51. https://doi.org/10.1038/nrd3591
181. Chen, C.H.; Lu, T.K. Development and Challenges of Antimicrobial Peptides for Therapeutic Applications. *Antibiotics* **2020**, *9*, 24. https://doi.org/10.3390/antibiotics9010024
182. Gan, B.H.; Gaynord, J.; Rowe, S.M.; Deingruber, T.; Spring, D.R. The Multifaceted Nature of Antimicrobial Peptides: Current Synthetic Chemistry Approaches and Future Directions. *Chem. Soc. Rev.* **2021**, *50*, 7820–7880. https://doi.org/10.1039/D0CS00729C
183. Gare, C.L.; White, A.M.; Malins, L.R. From Lead to Market: Chemical Approaches to Transform Peptides into Therapeutics. *Trends Biochem. Sci.* **2025**, *50*, 467–480. https://doi.org/10.1016/j.tibs.2025.01.009
184. Martínez, H.; Santos, M.; Pedraza, L.; Testera, A.M. Advanced Technologies for Large Scale Supply of Marine Drugs. *Mar. Drugs* **2025**, *23*, 69. https://doi.org/10.3390/md23020069
185. Sadeeq, M.; Li, Y.; Wang, C.; Hou, F.; Zuo, J.; Xiong, P. Unlocking the Power of Antimicrobial Peptides: Advances in Production, Optimization, and Therapeutics. *Front. Cell. Infect. Microbiol.* **2025**, *15*, 1528583. https://doi.org/10.3389/fcimb.2025.1528583

 doi:10.20944/preprints202607.1303.v1

186. Zhang, Q. Antimicrobial Peptides: From Discovery to Developmental Applications. *Appl. Environ. Microbiol.* **2025**, *91*, e02115-24. https://doi.org/10.1128/aem.02115-24
187. Ayikpoe, R.S.; Shi, C.; Battiste, A.J.; Eslami, S.M.; Ramesh, S.; Simon, M.A.; Bothwell, I.R.; Lee, H.; Rice, A.J.; Ren, H.; Tian, Q.; Harris, L.A.; Sarksian, R.; Zhu, L.; Frerk, A.M.; Precord, T.W.; van der Donk, W.A.; Mitchell, D.A.; Zhao, H. A Scalable Platform to Discover Antimicrobials of Ribosomal Origin. *Nat. Commun.* **2022**, *13*, 6135. https://doi.org/10.1038/s41467-022-33890-w
188. Xu, Y.; Du, X.; Yu, X.; Jiang, Q.; Zheng, K.; Xu, J.; Wang, P. Recent Advances in the Heterologous Expression of Biosynthetic Gene Clusters for Marine Natural Products. *Mar. Drugs* **2022**, *20*, 341. https://doi.org/10.3390/md20060341
189. Han, P.; Ma, A.; Ning, Y.; Chen, Z.; Liu, Y.; Liu, Z.; Li, S.; Jia, Y. Global Gene-Mining Strategy for Searching Nonribosomal Peptides as Antimicrobial Agents from Microbial Sources. *LWT* **2023**, *180*, 114708. https://doi.org/10.1016/j.lwt.2023.114708
190. Park, H.; Jin, H.; Kim, D.; Lee, J. Cell-Free Systems: Ideal Platforms for Accelerating the Discovery and Production of Peptide-Based Antibiotics. *Int. J. Mol. Sci.* **2024**, *25*, 9109. https://doi.org/10.3390/ijms25169109
191. Blin, K.; Shaw, S.; Vader, L.; Szenei, J.; Reitz, Z.L.; Augustijn, H.E.; Cediel-Becerra, J.D.D.; de Crécy-Lagard, V.; Koetsier, R.A.; Williams, S.E.; Cruz-Morales, P.; Wongwas, S.; Segurado Luchsinger, A.E.; Biermann, F.; Korenskaia, A.; Zdouc, M.M.; Meijer, D.; Terlouw, B.R.; van der Hooft, J.J.J.; Ziemert, N.; Helfrich, E.J.N.; Masschelein, J.; Corre, C.; Chevrette, M.G.; van Wezel, G.P.; Medema, M.H.; Weber, T. AntiSMASH 8.0: Extended Gene Cluster Detection Capabilities and Analyses of Chemistry, Enzymology, and Regulation. *Nucleic Acids Res.* **2025**, *53*, W32–W38. https://doi.org/10.1093/nar/gkaf334
192. Dinglasan, J.L.N.; Otani, H.; Doering, D.T.; Udwary, D.; Mouncey, N.J. Microbial Secondary Metabolites: Advancements to Accelerate Discovery Towards Application. *Nat. Rev. Microbiol.* **2025**, *23*, 338–354. https://doi.org/10.1038/s41579-024-01141-y
193. Rice, A.J.; Sword, T.T.; Chengan, K.; Mitchell, D.A.; Mouncey, N.J.; Moore, S.J.; Bailey, C.B. Cell-Free Synthetic Biology for Natural Product Biosynthesis and Discovery. *Chem. Soc. Rev.* **2025**, *54*, 4314–4352. https://doi.org/10.1039/d4cs01198h
194. Zhou, H.; Gao, Y.; Wu, B.; Xu, G.; Tian, L.; Sun, Y.; Yang, F.; Ni, K. Phyllosphere Microbiomes in Grassland Plants Harbor a Vast Reservoir of Novel Antimicrobial Peptides and Biosynthetic Diversity. *J. Adv. Res.* **2025**, in press. https://doi.org/10.1016/j.jare.2025.12.017
195. Ragozzino, C.; Casella, V.; Coppola, A.; Scarpato, S.; Buonocore, C.; Consiglio, A.; Palma Esposito, F.; Galasso, C.; Tedesco, P.; Della Sala, G.; de Pascale, D.; Vitale, L.; Coppola, D. Last Decade Insights in Exploiting Marine Microorganisms as Sources of New Bioactive Natural Products. *Mar. Drugs* **2025**, *23*, 116. https://doi.org/10.3390/md23030116
196. Toulis, V.; Marfany, G.; Mirra, S. Marine Derived Strategies Against Neurodegeneration. *Mar. Drugs* **2025**, *23*, 315. https://doi.org/10.3390/md23080315
197. Correia, S.; Ribeiro, I.; Braga-Henriques, A.; Leão, P.N.; Urbatzka, R.; Carvalho, M.F. Exploring Deep-Sea Actinomycetota Chemical Diversity by Using the OSMAC Approach. *Front. Mar. Sci.* **2026**, *13*, 1754764. https://doi.org/10.3389/fmars.2026.1754764
198. Tan, L.T.; Widyantoro, C.; Hanif, N. Tides of Promise: Sponge-Derived Marine Natural Products in Southeast Asia. *Molecules* **2026**, *31*, 914. https://doi.org/10.3390/molecules31050914
199. Davidson, B.S. New Dimensions in Natural Products Research: Cultured Marine Microorganisms. *Curr. Opin. Biotechnol.* **1995**, *6*, 284–291. https://doi.org/10.1016/0958-1669(95)80049-2
200. Jimeno, J.; Faircloth, G.; Sousa-Faro, J.F.; Scheuer, P.; Rinehart, K. New Marine Derived Anticancer Therapeutics — A Journey from the Sea to Clinical Trials. *Mar. Drugs* **2004**, *2*, 14-29. https://doi.org/10.3390/md201014
201. Gao, B.; Yang, N.; Teng, D.; Hao, Y.; Wang, J.; Mao, R. Marine Antimicrobial Peptides: Advances in Discovery, Multifunctional Mechanisms, and Therapeutic Translation Challenges. *Mar. Drugs* **2025**, *23*, 463. https://doi.org/10.3390/md23120463
202. Xue, J.; Lu, Y. Marine Natural Products as Drug Leads: A Recent Overview of Bioactivity and Mechanistic Insights. *Chem. Biodivers.* **2025**, *22*, e00970. https://doi.org/10.1002/cbdv.202500970

 doi:10.20944/preprints202607.1303.v1

203. Carroll, A.R.; Copp, B.R.; Grkovic, T.; Keyzers, R.A.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2026**, *43*, 89–131. https://doi.org/10.1039/D5NP00080G
204. Huang, Z.; Du, Y.; Hu, J.; Ying, L.; Zhou, B.; Hua, Y.; Wang, H.; Yang, Z. Marine Natural Products as Potent Anticancer Agents (2020–2024): Structural Diversity, SARs and Target Prediction. *Mar. Drugs* **2026**, *24*, 173. https://doi.org/10.3390/md24050173
205. Mayer, A.M.S.; Mayer, V.A.; Swanson-Mungerson, M.; Pierce, M.L.; Roberts, C.M.; Rodríguez, A.D.; Nakamura, F.; Taglialatela-Scafati, O. Marine Pharmacology in 2022–2023: Marine Compounds with Antibacterial, Antidiabetic, Antifungal, Anti-Inflammatory, Antiprotozoal, Antituberculosis and Antiviral Activities, Affecting the Immune and Nervous Systems, and Other Miscellaneous Mechanisms of Action. *Mar. Drugs* **2026**, *24*, 133. https://doi.org/10.3390/md24040133
206. Dabb, S.; Blunt, J.; Munro, M. MarinLit: Database and Essential Tools for the Marine Natural Products Community. *Abstr. Pap. Am. Chem. Soc.* **2014**, *248*, 1–34.
207. Olivera, B.M.; Gray, W.R.; Zeikus, R.; McIntosh, J.M.; Varga, J.; Rivier, J.; de Santos, V.; Cruz, L.J. Peptide Neurotoxins from Fish-Hunting Cone Snails. *Science* **1985**, *230*, 1338–1343. https://doi.org/10.1126/science.4071055
208. Schwartsmann, G.; da Rocha, A.B.; Berlinck, R.G.S.; Jimeno, J. Marine Organisms as a Source of New Anticancer Agents. *Lancet Oncol.* **2001**, *2*, 221–225. https://doi.org/10.1016/S1470-2045(00)00292-8
209. Molinski, T.F.; Dalisay, D.S.; Lievens, S.L.; Saludes, J.P. Drug Development from Marine Natural Products. *Nat. Rev. Drug Discov.* **2009**, *8*, 69–85. https://doi.org/10.1038/nrd2487
210. Cheung, R.C.F.; Ng, T.B.; Wong, J.H. Marine Peptides: Bioactivities and Applications. *Mar. Drugs* **2015**, *13*, 4006-4043. https://doi.org/10.3390/md13074006
211. Dyshlovoy, S.A.; Honecker, F. Marine Compounds and Cancer: Updates 2022. *Mar. Drugs* **2022**, *20*, 759. https://doi.org/10.3390/md20120759
212. Haque, N.; Parveen, S.; Tang, T.; Wei, J.; Huang, Z. Marine Natural Products in Clinical Use. *Mar. Drugs* **2022**, *20*, 528. https://doi.org/10.3390/md20080528
213. Papon, N.; Copp, B.R.; Courdavault, V. Marine Drugs: Biology, Pipelines, Current and Future Prospects for Production. *Biotechnol. Adv.* **2022**, *54*, 107871. https://doi.org/10.1016/j.biotechadv.2021.107871
214. Nguyen, L.T.T.; Craik, D.J.; Kaas, Q. Bibliometric Review of the Literature on Cone Snail Peptide Toxins from 2000 to 2022. *Mar. Drugs* **2023**, *21*, 154. https://doi.org/10.3390/md21030154
215. Kantarjian, H.M.; DiNardo, C.D.; Kadia, T.M.; Daver, N.G.; Altman, J.K.; Stein, E.M.; Jabbour, E.; Schiffer, C.A.; Lang, A.; Ravandi, F. Acute Myeloid Leukemia Management and Research in 2025. *CA Cancer J. Clin.* **2025**, *75*, 46–67. https://doi.org/10.3322/caac.21873
216. Piel, J. Metabolites from Symbiotic Bacteria. *Nat. Prod. Rep.* **2009**, *26*, 338–362. https://doi.org/10.1039/b703499g
217. Gerwick, W.H.; Moore, B.S. Lessons from the Past and Charting the Future of Marine Natural Products Drug Discovery and Chemical Biology. *Chem. Biol.* **2012**, *19*, 85–98. https://doi.org/10.1016/j.chembiol.2011.12.014
218. Wilson, M.C.; Mori, T.; Rückert, C.; Uria, A.R.; Helf, M.J.; Takada, K.; Gernert, C.; Steffens, U.A.E.; Heycke, N.; Schmitt, S.; Rinke, C.; Helfrich, E.J.N.; Brachmann, A.O.; Gurgui, C.; Wakimoto, T.; Kracht, M.; Crüsemann, M.; Hentschel, U.; Abe, I.; Matsunaga, S.; Kalinowski, J.; Takeyama, H.; Piel, J. An Environmental Bacterial Taxon with a Large and Distinct Metabolic Repertoire. *Nature* **2014**, *506*, 58–62. https://doi.org/10.1038/nature12959
219. Trindade, M.; van Zyl, L.J.; Navarro-Fernández, J.; Abd Elrazak, A. Targeted Metagenomics as a Tool to Tap into Marine Natural Product Diversity for the Discovery and Production of Drug Candidates. *Front. Microbiol.* **2015**, *6*, 890. https://doi.org/10.3389/fmicb.2015.00890
220. Fenical, W. Marine Microbial Natural Products: the Evolution of a New Field of Science. *J. Antibiot.* **2020**, *73*, 481–487. https://doi.org/10.1038/s41429-020-0331-4
221. McCauley, E.P.; Piña, I.C.; Thompson, A.D.; Bashir, K.; Weinberg, M.; Kurz, S.L.; Crews, P. Highlights of Marine Natural Products Having Parallel Scaffolds Found from Marine-Derived Bacteria, Sponges, and Tunicates. *J. Antibiot.* **2020**, *73*, 504–525. https://doi.org/10.1038/s41429-020-0330-5

 doi:10.20944/preprints202607.1303.v1

222. Carroll, A.R.; Copp, B.R.; Grkovic, T.; Keyzers, R.A.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2025**, *42*, 257–297. https://doi.org/10.1039/D4NP00067F
223. Veluchamy, C.; Nallakaruppan, N.; Nachiappan, K.; Sekaran, M.; Vartak, R.B.; Zambare, R.B.; Panneerselvam, S.; Chandrasekaran, R.; Sharma, A.; Thiagarajan, K. Marine Microbial Bioprospecting and Bioactive Bioproducts: Seven Decades of Discovery and Contemporary Perspectives. *Front. Mar. Sci.* **2025**, *12*, 1698327. https://doi.org/10.3389/fmars.2025.1698327
224. Yang, Z.; Hu, J.; Huang, Z.; Du, Y.; Zhou, B.; Hua, Y.; Emam, M.; Wang, H. Recent Advances in Marine Natural Products as Antibacterial Agents: Structural Elucidation, Pharmacological Activities, and Structure-Activity Relationship (2020–2024). *Mar. Med.* **2026**, *2*, 102–125. https://doi.org/10.64187/mm.2026.v2.i1.007
225. Abida, H.; Ruchaud, S.; Rios, L.; Humeau, A.; Probert, I.; De Vargas, C.; Bach, S.; Bowler, C. Bioprospecting Marine Plankton. *Mar. Drugs* **2013**, *11*, 4594–4611. https://doi.org/10.3390/md11114594
226. Deva Darshinii, B.; Anbarasu, K.; Devarajan, Y. Marine Biodiversity as a Reservoir of Innovative Biomaterials for Regenerative Medicine. *Regen. Eng. Transl. Med.* **2025**. Online ahead of print. https://doi.org/10.1007/s40883-025-00507-9
227. Gao, J.; Xu, S.; Zhou, X.; Liu, Y.; Wang, X.; Yang, B. Marine Fungal-Derived Natural Products against Prostate Cancer: A Comprehensive Review of Discoveries and Mechanisms. *Phytochemistry* **2026**, *247*, 114885. https://doi.org/10.1016/j.phytochem.2026.114885
228. Talha, M.; Roque-Borda, C.A. Enhanced Antibacterial Activity of Antimicrobial Peptide—Antibiotic Combinations against Multidrug-Resistant Bacteria. *FEMS Microbes* **2026**, *7*, xtag003. https://doi.org/10.1093/femsmc/xtag003
229. Ziemert, N.; Alanjary, M.; Weber, T. The Evolution of Genome Mining in Microbes – A Review. *Nat. Prod. Rep.* **2016**, *33*, 988–1005. https://doi.org/10.1039/c6np00025h
230. Lloyd, K.G.; Steen, A.D.; Ladau, J.; Yin, J.; Crosby, L. Phylogenetically Novel Uncultured Microbial Cells Dominate Earth Microbiomes. *mSystems* **2018**, *3*, e00055-18. https://doi.org/10.1128/mSystems.00055-18
231. Gavriilidou, A.; Kautsar, S.A.; Zaburannyi, N.; Krug, D.; Müller, R.; Medema, M.H.; Ziemert, N. Compendium of Specialized Metabolite Biosynthetic Diversity Encoded in Bacterial Genomes. *Nat. Microbiol.* **2022**, *7*, 726–735. https://doi.org/10.1038/s41564-022-01110-2
232. King, A.M.; Zhang, Z.; Glassey, E.; Siuti, P.; Clardy, J.; Voigt, C.A. Systematic Mining of the Human Microbiome Identifies Antimicrobial Peptides with Diverse Activity Spectra. *Nat. Microbiol.* **2023**, *8*, 2420–2434. https://doi.org/10.1038/s41564-023-01524-6
233. Chen, J.W.; Jia, Y.Y.; Sun, Y.; Liu, K.; Zhou, C.H.; Liu, C.; Li, D.H.; Liu, G.L.; Zhang, C.S.; Yang, T.; Huang, L.; Zhuang, Y.Y.; Wang, D.Z.; Xu, D.Y.; Zhong, Q.L.; Guo, Y.; Li, A.D.; Seim, I.; Jiang, L.; Wang, L.S.; Lee, S.M.Y.; Liu, Y.J.; Wang, D.T.; Zhang, G.Q.; Liu, S.S.; Wei, X.F.; Yue, Z.; Zheng, S.M.; Shen, X.C.; Wang, S.; Qi, C.; Chen, J.; Ye, C.; Zhao, F.; Wang, J.; Fan, J.; Li, B.T.; Sun, J.H.; Jia, X.D.; Xia, Z.Y.; Zhang, H.; Liu, J.N.; Zheng, Y.; Liu, X.; Wang, J.; Yang, H.M.; Kristiansen, K.; Xu, X.; Mock, T.; Li, S.Y.; Zhang, W.W.; Fan, G.Y. Global Marine Microbial Diversity and Its Potential in Bioprospecting. *Nature* **2024**, *633*, 371–379. https://doi.org/10.1038/s41586-024-07891-2
234. Medeiros, W.; Hidalgo, K.; Leão, T.; de Carvalho, L.M.; Ziemert, N.; Oliveira, V. Unlocking the Biosynthetic Potential and Taxonomy of the Antarctic Microbiome along Temporal and Spatial Gradients. *Microbiol. Spectr.* **2024**, *12*, e00244-24. https://doi.org/10.1128/spectrum.00244-24
235. Santos-Júnior, C.D.; Torres, M.D.T.; Duan, Y.; Rodríguez del Río, Á.; Schmidt, T.S.B.; Chong, H.; Fullam, A.; Kuhn, M.; Zhu, C.; Houseman, A.; Somborski, J.; Vines, A.; Zhao, X.-M.; Bork, P.; Huerta-Cepas, J.; de la Fuente-Nunez, C.; Coelho, L.P. Discovery of Antimicrobial Peptides in the Global Microbiome with Machine Learning. *Cell* **2024**, *187*, 3761–3778. https://doi.org/10.1016/j.cell.2024.05.013
236. Torres, M.D.T.; Brooks, E.F.; Cesaro, A.; Sberro, H.; Gill, M.O.; Nicolaou, C.; Bhatt, A.S.; de la Fuente-Nunez, C. Mining Human Microbiomes Reveals an Untapped Source of Peptide Antibiotics. *Cell* **2024**, *187*, 5453–5467. https://doi.org/10.1016/j.cell.2024.07.027

 doi:10.20944/preprints202607.1303.v1

237. Bertagnolio, S.; Dobreva, Z.; Centner, C.M.; Olaru, I.D.; Donà, D.; Burzo, S.; Huttner, B.D.; Chaillon, A.; Gebreselassie, N.; Wi, T.; Hasso-Agopsowicz, M.; Allegranzi, B.; Sati, H.; Ivanovska, V.; Kothari, K.U.; Balkhy, H.H.; Cassini, A.; Hamers, R.L.; Van Weezenbeek, K. on behalf of the WHO Research Agenda for AMR in Human Health Collaborators. WHO Global Research Priorities for Antimicrobial Resistance in Human Health. *Lancet Microbe* **2024**, *5*, 100902. https://doi.org/10.1016/S2666-5247(24)00134-4
238. Nussinov, R.; Tsai, C.-J.; Jang, H. Anticancer Drug Resistance: An Update and Perspective. *Drug Resist. Updat.* **2021**, *59*, 100796. https://doi.org/10.1016/j.drup.2021.100796
239. Ge, M.; Chen, X.-Y.; Huang, P.; Fleishman, J.S.; Yang, D.-H.; Wu, Z.-X.; Ke, Z.-F.; Chen, Z.-S. Understanding and Overcoming Multidrug Resistance in Cancer. *Nat. Rev. Clin. Oncol.* **2025**, *22*, 760–780. https://doi.org/10.1038/s41571-025-01059-1
240. Wei, J.-R.; Lu, M.-Y.; Wei, T.-H.; Fleishman, J.S.; Yu, H.; Chen, X.-L.; Kong, X.-T.; Sun, S.-L.; Li, N.-G.; Yang, Y.; Ni, H.-W. Overcoming Cancer Therapy Resistance: From Drug Innovation to Therapeutics. *Drug Resist. Updat.* **2025**, *81*, 101229. https://doi.org/10.1016/j.drup.2025.101229
241. Servillera, M.; Peña, M.; Cabeza, L.; Pula, H.J.; Prados, J.; Melguizo, C. Nudibranchs as Sources of Marine Natural Products with Antitumor Activity: A Comprehensive Review. *Mar. Drugs* **2025**, *23*, 319. https://doi.org/10.3390/md23080319
242. Azam, F.; Long, R.A. Sea Snow Microcosms. *Nature* **2001**, *414*, 495–498. https://doi.org/10.1038/35107174
243. Dang, H.; Lovell, C.R. Microbial Surface Colonization and Biofilm Development in Marine Environments. *Microbiol. Mol. Biol. Rev.* **2016**, *80*, 91–138. https://doi.org/10.1128/MMBR.00037-15
244. Wang, F.-Q.; Bartosik, D.; Sidhu, C.; Siebers, R.; Lu, D.-C.; Trautwein-Schult, A.; Becher, D.; Huettel, B.; Rick, J.; Kirstein, I.V.; Wiltshire, K.H.; Schweder, T.; Fuchs, B.M.; Bengtsson, M.M.; Teeling, H.; Amann, R.I. Particle-Attached Bacteria Act as Gatekeepers in the Decomposition of Complex Phytoplankton Polysaccharides. *Microbiome* **2024**, *12*, 32. https://doi.org/10.1186/s40168-024-01757-5
245. Alldredge, A.L.; Silver, M.W. Characteristics, Dynamics and Significance of Marine Snow. *Prog. Oceanogr.* **1988**, *20*, 41–82. https://doi.org/10.1016/0079-6611(88)90053-5
246. Verdugo, P.; Alldredge, A.L.; Azam, F.; Kirchman, D.L.; Passow, U.; Santschi, P.H. The Oceanic Gel Phase: A Bridge in the DOM–POM Continuum. *Mar. Chem.* **2004**, *92*, 67–85. https://doi.org/10.1016/j.marchem.2004.06.017
247. Bar-Zeev, E.; Berman-Frank, I.; Girshevitz, O.; Berman, T. Revised Paradigm of Aquatic Biofilm Formation Facilitated by Microgel Transparent Exopolymer Particles. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 9119–9124. https://doi.org/10.1073/pnas.1203708109
248. Turner, J.T. Zooplankton Fecal Pellets, Marine Snow, Phytodetritus and the Ocean's Biological Pump. *Prog. Oceanogr.* **2015**, *130*, 205–248. https://doi.org/10.1016/j.pocean.2014.08.005
249. Decho, A.W.; Gutierrez, T. Microbial Extracellular Polymeric Substances (EPSs) in Ocean Systems. *Front. Microbiol.* **2017**, *8*, 922. https://doi.org/10.3389/fmicb.2017.00922
250. Durkin, C.A. The Biology of Marine Snowflakes. *Annu. Rev. Mar. Sci.* **2026**, *18*, 327–350. https://doi.org/10.1146/annurev-marine-040523-021832
251. Boyd, P.W.; Claustre, H.; Levy, M.; Siegel, D.A.; Weber, T. Multi-Faceted Particle Pumps Drive Carbon Sequestration in the Ocean. *Nature* **2019**, *568*, 327–332. https://doi.org/10.1038/s41586-019-1098-2
252. Dang, H. Grand Challenges in Microbe-Driven Marine Carbon Cycling Research. *Front. Microbiol.* **2020**, *11*, 1039. https://doi.org/10.3389/fmicb.2020.01039
253. Turner, J.T. Zooplankton Fecal Pellets, Marine Snow and Sinking Phytoplankton Blooms. *Aquat. Microb. Ecol.* **2002**, *27*, 57–102. https://doi.org/10.3354/ame027057
254. Iversen, M.H. Carbon Export in the Ocean: A Biologist's Perspective. *Annu. Rev. Mar. Sci.* **2023**, *15*, 357–381. https://doi.org/10.1146/annurev-marine-032122-035153
255. Siegel, D.A.; DeVries, T.; Cetinić, I.; Bisson, K.M. Quantifying the Ocean's Biological Pump and Its Carbon Cycle Impacts on Global Scales. *Annu. Rev. Mar. Sci.* **2023**, *15*, 329–356. https://doi.org/10.1146/annurev-marine-040722-115226
256. Ploug, H.; Grossart, H.-P.; Azam, F.; Jørgensen, B.B. Photosynthesis, Respiration, and Carbon Turnover in Sinking Marine Snow from Surface Waters of Southern California Bight: Implications for the Carbon Cycle in the Ocean. *Mar. Ecol. Prog. Ser.* **1999**, *179*, 1–11. https://doi.org/10.3354/meps179001

 doi:10.20944/preprints202607.1303.v1

257. Simon, M.; Grossart, H.-P.; Schweitzer, B.; Ploug, H. Microbial Ecology of Organic Aggregates in Aquatic Ecosystems. *Aquat. Microb. Ecol.* **2002**, *28*, 175–211. https://doi.org/10.3354/ame028175
258. Azam, F.; Malfatti, F. Microbial Structuring of Marine Ecosystems. *Nat. Rev. Microbiol.* **2007**, *5*, 782–791. https://doi.org/10.1038/nrmicro1747
259. Stocker, R.; Seymour, J.R. Ecology and Physics of Bacterial Chemotaxis in the Ocean. *Microbiol. Mol. Biol. Rev.* **2012**, *76*, 792–812. https://doi.org/10.1128/mmbr.00029-12
260. Long, R.A.; Azam, F. Antagonistic Interactions among Marine Pelagic Bacteria. *Appl. Environ. Microbiol.* **2001**, *67*, 4975–4983. https://doi.org/10.1128/AEM.67.11.4975-4983.2001
261. Kiørboe, T.; Tang, K.; Grossart, H.-P.; Ploug, H. Dynamics of Microbial Communities on Marine Snow Aggregates: Colonization, Growth, Detachment, and Grazing Mortality of Attached Bacteria. *Appl. Environ. Microbiol.* **2003**, *69*, 3036–3047. https://doi.org/10.1128/AEM.69.6.3036-3047.2003
262. Grossart, H.-P.; Schlingloff, A.; Bernhard, M.; Simon, M.; Brinkhoff, T. Antagonistic Activity of Bacteria Isolated from Organic Aggregates of the German Wadden Sea. *FEMS Microbiol. Ecol.* **2004**, *47*, 387–396. https://doi.org/10.1016/S0168-6496(03)00305-2
263. Cordero, O.X.; Datta, M.S. Microbial Interactions and Community Assembly at Microscales. *Curr. Opin. Microbiol.* **2016**, *31*, 227–234. https://doi.org/10.1016/j.mib.2016.03.015
264. Datta, M.S.; Sliwerska, E.; Gore, J.; Polz, M.F.; Cordero, O.X. Microbial Interactions Lead to Rapid Micro-Scale Successions on Model Marine Particles. *Nat. Commun.* **2016**, *7*, 11965. https://doi.org/10.1038/ncomms11965
265. Cordero, O.X.; Stocker, R. A *Particularly* Useful System to Study the Ecology of Microbes. *Environ. Microbiol. Rep.* **2017**, *9*, 16–17. https://doi.org/10.1111/1758-2229.12490
266. Boeuf, D.; Edwards, B.R.; Eppley, J.M.; Hu, S.K.; Poff, K.E.; Romano, A.E.; Caron, D.A.; Karl, D.M.; DeLong, E.F. Biological Composition and Microbial Dynamics of Sinking Particulate Organic Matter at Abyssal Depths in the Oligotrophic Open Ocean. *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116*, 11824–11832. https://doi.org/10.1073/pnas.1903080116
267. Gralka, M.; Szabo, R.; Stocker, R.; Cordero, O.X. Trophic Interactions and the Drivers of Microbial Community Assembly. *Curr. Biol.* **2020**, *30*, R1176–R1188. https://doi.org/10.1016/j.cub.2020.08.007
268. Kost, C.; Patil, K.R.; Friedman, J.; Garcia, S.L.; Ralser, M. Metabolic Exchanges Are Ubiquitous in Natural Microbial Communities. *Nat. Microbiol.* **2023**, *8*, 2244–2252. https://doi.org/10.1038/s41564-023-01511-x
269. Li, F.; Burger, A.; Eppley, J.M.; Poff, K.E.; Karl, D.M.; DeLong, E.F. Planktonic Microbial Signatures of Sinking Particle Export in the Open Ocean's Interior. *Nat. Commun.* **2023**, *14*, 7177. https://doi.org/10.1038/s41467-023-42909-9
270. Guo, K.; Zhao, Z.; Breyer, E.; Baltar, F. Organic Matter Degradation by Oceanic Fungi Differs between Polar and Non-Polar Waters. *Nat. Commun.* **2025**, *16*, 7589. https://doi.org/10.1038/s41467-025-63047-4
271. Heitger, M.; Amano, C.; Reinthaler, T.; Papadatou, M.; Pokorny, L.; Alvarez-Salgado, X.A.; Herndl, G.J. Major Contribution of Particle-Associated Microbes to Deep-Sea Organic Carbon Degradation. *Limnol. Oceanogr.* **2026**, *71*, e70310. https://doi.org/10.1002/lno.70310
272. Nurkolis, F. Marine Bioactives: Pioneering Sustainable Solutions for Advanced Cosmetics and Therapeutics. *Pharmacol. Res.* **2025**, *218*, 107868. https://doi.org/10.1016/j.phrs.2025.107868
273. Zhang, T.; Ouyang, Z.; Zhang, Y.; Sun, H.; Kong, L.; Xu, Q.; Qu, J.; Sun, Y. Marine Natural Products in Inflammation-Related Diseases: Opportunities and Challenges. *Med. Res. Rev.* **2025**, *45*, 1375–1406. https://doi.org/10.1002/med.22109
274. Bhatnagar, I.; Kim, S.-K. Immense Essence of Excellence: Marine Microbial Bioactive Compounds. *Mar. Drugs* **2010**, *8*, 2673–2701. https://doi.org/10.3390/md8102673
275. Weiss, M.C.; Sousa, F.L.; Mrnjavac, N.; Neukirchen, S.; Roettger, M.; Nelson-Sathi, S.; Martin, W.F. The Physiology and Habitat of the Last Universal Common Ancestor. *Nat. Microbiol.* **2016**, *1*, 16116. https://doi.org/10.1038/nmicrobiol.2016.116
276. Malve, H. Exploring the Ocean for New Drug Developments: Marine Pharmacology. *J. Pharm. Bioallied Sci.* **2016**, *8*, 83–91. https://doi.org/10.4103/0975-7406.171700

 doi:10.20944/preprints202607.1303.v1

277. Svendsen, P.B.; Alfastsen, L.; Gram, L.; Henriksen, N.N.S.E.; Bentzon-Tilia, M.; Zhang, S.-D. Roles of Marine Microbial Natural Products. *Annu. Rev. Microbiol.* **2025**, *79*, 361–382. https://doi.org/10.1146/annurev-micro-040824-022431
278. Macedo, M.W.F.S.; Cunha, N.B.; Carneiro, J.A.; Costa, R.A.; Alencar, S.A.; Cardoso, M.H.; Franco, O.L.; Dias, S.C. Marine Organisms as a Rich Source of Biologically Active Peptides. *Front. Mar. Sci.* **2021**, *8*, 667764. https://doi.org/10.3389/fmars.2021.667764
279. Nawaz, M.Z.; Subin Sasidharan, R.; Alghamdi, H.A.; Dang, H. Understanding Interaction Patterns within Deep-Sea Microbial Communities and Their Potential Applications. *Mar. Drugs* **2022**, *20*, 108. https://doi.org/10.3390/md20020108
280. Wibowo, J.T.; Bayu, A.; Aryati, W.D.; Fernandes, C.; Yanuar, A.; Kijjoa, A.; Putra, M.Y. Secondary Metabolites from Marine-Derived Bacteria with Antibiotic and Antibiofilm Activities against Drug-Resistant Pathogens. *Mar. Drugs* **2023**, *21*, 50. https://doi.org/10.3390/md21010050
281. Han, J.-R.; Li, S.; Li, W.-J.; Dong, L. Mining Microbial and Metabolic Dark Matter in Extreme Environments: a Roadmap for Harnessing the Power of Multi-Omics Data. *Adv. Biotechnol.* **2024**, *2*, 26. https://doi.org/10.1007/s44307-024-00034-8
282. Phi, K.-H.; Heo, E.J.; Kwon, S.; Youn, U.J.; Lee, S. Bioactive Secondary Metabolites at the Ends of the Earth (2015–2025): Insights into Arctic and Antarctic Aquatic Sources. *Mar. Drugs* **2026**, *24*, 93. https://doi.org/10.3390/md24030093
283. Cloern, J.E.; Abreu, P.C.; Carstensen, J.; Chauvaud, L.; Elmgren, R.; Grall, J.; Greening, H.; Johansson, J.O.R.; Kahru, M.; Sherwood, E.T.; Xu, J.; Yin, K.D. Human Activities and Climate Variability Drive Fast-Paced Change across the World's Estuarine–Coastal Ecosystems. *Glob. Chang. Biol.* **2016**, *22*, 513–529. https://doi.org/10.1111/gcb.13059
284. Gobler, C.J.; Baumann, H. Hypoxia and Acidification in Ocean Ecosystems: Coupled Dynamics and Effects on Marine Life. *Biol. Lett.* **2016**, *12*, 20150976. https://doi.org/10.1098/rsbl.2015.0976
285. Zhu, Y.-G.; Zhao, Y.; Li, B.; Huang, C.-L.; Zhang, S.-Y.; Yu, S.; Chen, Y.-S.; Zhang, T.; Gillings, M.R.; Su, J.-Q. Continental-Scale Pollution of Estuaries with Antibiotic Resistance Genes. *Nat. Microbiol.* **2017**, *2*, 16270. https://doi.org/10.1038/nmicrobiol.2016.270
286. Wurtsbaugh, W.A.; Paerl, H.W.; Dodds, W.K. Nutrients, Eutrophication and Harmful Algal Blooms along the Freshwater to Marine Continuum. *WIREs Water* **2019**, *6*, e1373. https://doi.org/10.1002/wat2.1373
287. Glibert, P.M. Harmful Algae at the Complex Nexus of Eutrophication and Climate Change. *Harmful Algae* **2020**, *91*, 101583. https://doi.org/10.1016/j.hal.2019.03.001
288. Gobler, C.J. Climate Change and Harmful Algal Blooms: Insights and Perspective. *Harmful Algae* **2020**, *91*, 101731. https://doi.org/10.1016/j.hal.2019.101731
289. Maghsodian, Z.; Sanati, A.M.; Mashifana, T.; Sillanpää, M.; Feng, S.; Nhat, T.; Ramavandi, B. Occurrence and Distribution of Antibiotics in the Water, Sediment, and Biota of Freshwater and Marine Environments: A Review. *Antibiotics* **2022**, *11*, 1461. https://doi.org/10.3390/antibiotics11111461
290. Morin-Crini, N.; Lichtfouse, E.; Liu, G.; Balaram, V.; Ribeiro, A.R.L.; Lu, Z.; Stock, F.; Carmona, E.; Teixeira, M.R.; Picos-Corrales, L.A.; Moreno-Piraján, J.C.; Giraldo, L.; Li, C.; Pandey, A.; Hocquet, D.; Torri, G.; Crini, G. Worldwide Cases of Water Pollution by Emerging Contaminants. *Environ. Chem. Lett.* **2022**, *20*, 2311–2338. https://doi.org/10.1007/s10311-022-01447-4
291. Dai, Y.H.; Yang, S.B.; Zhao, D.; Hu, C.M.; Xu, W.; Anderson, D.M.; Li, Y.; Song, X.-P.; Boyce, D.G.; Gibson, L.; Zheng, C.M.; Feng, L. Coastal Phytoplankton Blooms Expand and Intensify in the 21st Century. *Nature* **2023**, *615*, 280–284. https://doi.org/10.1038/s41586-023-05760-y
292. El-Sharkawy, M.; Alotaibi, M.O.; Li, J.; Du, D.; Mahmoud, E. Heavy Metal Pollution in Coastal Environments: Ecological Implications and Management Strategies: A Review. *Sustainability* **2025**, *17*, 701. https://doi.org/10.3390/su17020701
293. Zhao, S.; Kvale, K.F.; Zhu, L.; Zettler, E.R.; Egger, M.; Mincer, T.J.; Amaral-Zettler, L.A.; Lebreton, L.; Niemann, H.; Nakajima, R.; Thiel, M.; Bos, R.P.; Galgani, L.; Stubbins, A. The Distribution of Subsurface Microplastics in the Ocean. *Nature* **2025**, *641*, 51–61. https://doi.org/10.1038/s41586-025-08818-1
294. Davies, J.; Davies, D. Origins and Evolution of Antibiotic Resistance. *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 417–433. https://doi.org/10.1128/MMBR.00016-10

 doi:10.20944/preprints202607.1303.v1

295. Zhang, Q.; Yu, Y.; Vélasquez, J.E.; van der Donk, W.A. Evolution of Lanthipeptide Synthetases. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 18361–18366. https://doi.org/10.1073/pnas.1210393109
296. Holohan, C.; Van Schaeybroeck, S.; Longley, D.B.; Johnston, P.G. Cancer Drug Resistance: An Evolving Paradigm. *Nat. Rev. Cancer* **2013**, *13*, 714–726. https://doi.org/10.1038/nrc3599
297. Cubillos-Ruiz, A.; Berta-Thompson, J.W.; Becker, J.W.; van der Donk, W.A.; Chisholm, S.W. Evolutionary Radiation of Lanthipeptides in Marine Cyanobacteria. *Proc. Natl. Acad. Sci. U.S.A.* **2017**, *114*, E5424–E5433. https://doi.org/10.1073/pnas.1700990114
298. Adamek, M.; Alanjary, M.; Ziemert, N. Applied Evolution: Phylogeny-Based Approaches in Natural Products Research. *Nat. Prod. Rep.* **2019**, *36*, 1295–1312. https://doi.org/10.1039/c9np00027e
299. Chevrette, M.G.; Gutiérrez-García, K.; Selem-Mojica, N.; Aguilar-Martínez, C.; Yáñez-Olvera, A.; Ramos-Aboites, H.E.; Hoskisson, P.A.; Barona-Gómez, F. Evolutionary Dynamics of Natural Product Biosynthesis in Bacteria. *Nat. Prod. Rep.* **2020**, *37*, 566–599. https://doi.org/10.1039/c9np00048h
300. Peng, Q.; Huang, W.; Zhang, X.; Pang, X.; Liu, Y.; Ruan, W.; Li, Q.; Ding, L.; Jin, H.; Yang, D.; Wang, J.; Wang, M.-W. Structurally Diverse New Metabolites from Three Hadal Trench-Derived Microorganisms. *ACS Omega* **2025**, *10*, 6201–6209. https://doi.org/10.1021/acsomega.4c11083
301. Barzkar, N.; Sukhikh, S.; Babich, O. Study of Marine Microorganism Metabolites: New Resources for Bioactive Natural Products. *Front. Microbiol.* **2024**, *14*, 1285902. https://doi.org/10.3389/fmicb.2023.1285902
302. Chevrette, M.G.; Handelsman, J. Needles in Haystacks: Reevaluating Old Paradigms for the Discovery of Bacterial Secondary Metabolites. *Nat. Prod. Rep.* **2021**, *38*, 2083–2099. https://doi.org/10.1039/d1np00044f
303. Khalifa, S.A.M.; Elias, N.; Farag, M.A.; Chen, L.; Saeed, A.; Hegazy, M.-E.F.; Moustafa, M.S.; Abd El-Wahed, A.; Al-Mousawi, S.M.; Musharraf, S.G.; Chang, F.-R.; Iwasaki, A.; Suenaga, K.; Alajlani, M.; Göransson, U.; El-Seedi, H.R. Marine Natural Products: A Source of Novel Anticancer Drugs. *Mar. Drugs* **2019**, *17*, 491. https://doi.org/10.3390/md17090491
304. Smanski, M.J.; Schlatter, D.C.; Kinkel, L.L. Leveraging Ecological Theory to Guide Natural Product Discovery. *J. Ind. Microbiol. Biotechnol.* **2016**, *43*, 115–128. https://doi.org/10.1007/s10295-015-1683-9
305. Miller, I.J.; Chevrette, M.G.; Kwan, J.C. Interpreting Microbial Biosynthesis in the Genomic Age: Biological and Practical Considerations. *Mar. Drugs* **2017**, *15*, 165. https://doi.org/10.3390/md15060165
306. Grenade, N.L.; Howe, G.W.; Ross, A.C. The Convergence of Bacterial Natural Products from Evolutionarily Distinct Pathways. *Curr. Opin. Biotechnol.* **2021**, *69*, 17–25. https://doi.org/10.1016/j.copbio.2020.10.009
307. Rodríguez del Río, Á.; Giner-Lamia, J.; Cantalapiedra, C.P.; Botas, J.; Deng, Z.; Hernández-Plaza, A.; Munar-Palmer, M.; Santamaría-Hernando, S.; Rodríguez-Herva, J.J.; Ruscheweyh, H.-J.; Paoli, L.; Schmidt, T.S.B.; Sunagawa, S.; Bork, P.; López-Solanilla, E.; Coelho, L.P.; Huerta-Cepas, J. Functional and Evolutionary Significance of Unknown Genes from Uncultivated Taxa. *Nature* **2024**, *626*, 377–384. https://doi.org/10.1038/s41586-023-06955-z
308. Jiang, Q.; Han, Y.; Ye, C.; Duan, Y.; Li, F.; Han, Z.; Santos-Júnior, C.D.; Luo, Z.; Dong, X. A Global Deep-Sea Small Protein Atlas Reveals a Reservoir of Noncanonical Antimicrobial Peptides. *bioRxiv* **2025**. https://doi.org/10.64898/2025.12.15.694180
309. Salamzade, R.; Kalan, L.R. Context Matters: Assessing the Impacts of Genomic Background and Ecology on Microbial Biosynthetic Gene Cluster Evolution. *mSystems* **2025**, *10*, e01538-24. https://doi.org/10.1128/msystems.01538-24
310. Mara, P.; Geller-McGrath, D.; Suter, E.; Taylor, G.T.; Pachiadaki, M.G.; Edgcomb, V.P. Plasmid-Borne Biosynthetic Gene Clusters within a Permanently Stratified Marine Water Column. *Microorganisms* **2024**, *12*, 929. https://doi.org/10.3390/microorganisms12050929
311. Wang, S.; Fan, L.; Pan, H.; Li, Y.; Qiu, Y.; Lu, Y. Antimicrobial Peptides from Marine Animals: Sources, Structures, Mechanisms and the Potential for Drug Development. *Front. Mar. Sci.* **2023**, *9*, 1112595. https://doi.org/10.3389/fmars.2022.1112595
312. Chen, P.Y.; Ye, T.; Li, C.Y.; Praveen, P.; Hu, Z.L.; Li, W.Y.; Shang, C.J. Embracing the Era of Antimicrobial Peptides with Marine Organisms. *Nat. Prod. Rep.* **2024**, *41*, 331–346. https://doi.org/10.1039/d3np00031a
313. Aoyama, K.; Okai, M.; Ogawa, N.; Fukumaru, R.; Ishida, M.; Inoue, K.; Takagi, T. A Coral Peptide with Bactericidal Activity against a Global Marine Pathogen, *Vibrio coralliilyticus*. *iScience* **2025**, *28*, 113286. https://doi.org/10.1016/j.isci.2025.113286

 doi:10.20944/preprints202607.1303.v1

314. Radjasa, O.K.; Vaske, Y.M.; Navarro, G.; Vervoort, H.C.; Tenney, K.; Linington, R.G.; Crews, P. Highlights of Marine Invertebrate-Derived Biosynthetic Products: Their Biomedical Potential and Possible Production by Microbial Associants. *Bioorg. Med. Chem.* **2011**, *19*, 6658–6674. https://doi.org/10.1016/j.bmc.2011.07.017
315. Ramesh, C.; Tulasi, B.R.; Raju, M.; Thakur, N.; Dufossé, L. Marine Natural Products from Tunicates and Their Associated Microbes. *Mar. Drugs* **2021**, *19*, 308. https://doi.org/10.3390/md19060308
316. Romano, G.; Almeida, M.; Varela Coelho, A.; Cutignano, A.; Gonçalves, L.G.; Hansen, E.; Khnykin, D.; Mass, T.; Ramšak, A.; Rocha, M.S.; Silva, T.H.; Sugni, M.; Ballarin, L.; Genevière, A.M. Biomaterials and Bioactive Natural Products from Marine Invertebrates: From Basic Research to Innovative Applications. *Mar. Drugs* **2022**, *20*, 219. https://doi.org/10.3390/md20040219
317. Devkar, H.U.; Thakur, N.L.; Kaur, P. Marine-Derived Antimicrobial Molecules from the Sponges and Their Associated Bacteria. *Can. J. Microbiol.* **2023**, *69*, 1–16. https://doi.org/10.1139/cjm-2022-0147
318. Díaz-Puertas, R.; Adamek, M.; Mallavia, R.; Falco, A. Fish Skin Mucus Extracts: An Underexplored Source of Antimicrobial Agents. *Mar. Drugs* **2023**, *21*, 350. https://doi.org/10.3390/md21060350
319. Tan, L.T. Impact of Marine Chemical Ecology Research on the Discovery and Development of New Pharmaceuticals. *Mar. Drugs* **2023**, *21*, 174. https://doi.org/10.3390/md21030174
320. Fan, S.; Qin, P.; Lu, J.; Wang, S.T.; Zhang, J.; Wang, Y.; Cheng, A.F.; Cao, Y.; Ding, W.; Zhang, W.P. Bioprospecting of Culturable Marine Biofilm Bacteria for Novel Antimicrobial Peptides. *iMeta* **2024**, *3*, e244. https://doi.org/10.1002/imt2.244
321. Shahidi, F.; Saeid, A. Bioactivity of Marine-Derived Peptides and Proteins: A Review. *Mar. Drugs* **2025**, *23*, 157. https://doi.org/10.3390/md23040157
322. Zhong, W.M.; Lin, Z.J.; Schmidt, E.W.; Agarwal, V. Discovery, Biosynthesis, and Bioactivities of Peptidic Natural Products from Marine Sponges and Sponge-Associated Bacteria. *Nat. Prod. Rep.* **2025**, *42*, 2034–2074. https://doi.org/10.1039/d5np00048c
323. Fan, S.; Lu, J.; Cui, H.; Ding, W.; Li, S.; Sun, J.; Li, Y.-X.; Zhang, W. Unlocking the Unexplored AMPSphere in Marine Rare Species. *Microbiome* **2026**, *14*, 100. https://doi.org/10.1186/s40168-025-02326-0
324. Lu, J.; Fan, S.; Shi, J.; Hu, X.; Ding, W.; Hao, J.; Zhang, W. Genomic and Chemical Analyses of 713 Marine Biofilm-Derived Bacterial Strains. *Appl. Environ. Microbiol.* **2026**, *92*, e02593-25. https://doi.org/10.1128/aem.02593-25
325. Wiederkehr, F.; Paoli, L.; Richter, D.; Racunica, D.; Ruscheweyh, H.-J.; Sperfeld, M.; O'Brien, J.; Miravet-Verde, S.; Streiff, A.B.; Ransome, J.; Chepkirui, C.; Priest, T.; Sintsova, A.; Salazar, G.; Bistolas, K.S.I.; Sawyer, T.; Labadie, K.; Mayer, K.-I.; Perdereau, A.; Reddy, M.M.; Moulin, C.; Boissin, E.; Bourdin, G.; Cailliau, J.; Iwankow, G.; Poulain, J.; Romac, S.; Tara Pacific Consortium Coordinators; Planes, S.; Allemand, D.; Agostini, S.; Bowler, C.; Douville, E.; Forcioli, D.; Galand, P.E.; Lombard, F.; Oliveira, P.H.; Thomas, O.P.; Vega Thurber, R.; Troublé, R.; Voolstra, C.R.; Wincker, P.; Ziegler, M.; Piel, J.; Sunagawa, S. Coral Microbiomes as Reservoirs of Unknown Genomic and Biosynthetic Diversity. *Nature* **2026**, *652*, 686–693. https://doi.org/10.1038/s41586-026-10159-6
326. Xu, D.-B.; Ye, W.-W.; Han, Y.; Deng, Z.-X.; Hong, K. Natural Products from Mangrove Actinomycetes. *Mar. Drugs* **2014**, *12*, 2590-2613. https://doi.org/10.3390/md12052590
327. Zain ul Arifeen, M.; Ma, Y.-N.; Xue, Y.-R.; Liu, C.-H. Deep-Sea Fungi Could Be the New Arsenal for Bioactive Molecules. *Mar. Drugs* **2020**, *18*, 9. https://doi.org/10.3390/md18010009
328. Hu, D.; Lee, S.M.-Y.; Li, K.; Mok, K.M. Secondary Metabolite Production Potential of Mangrove-Derived Streptomyces olivaceus. *Mar. Drugs* **2021**, *19*, 332. https://doi.org/10.3390/md19060332
329. Giddings, L.-A.; Newman, D.J. Extremophilic Fungi from Marine Environments: Underexplored Sources of Antitumor, Anti-Infective and Other Biologically Active Agents. *Mar. Drugs* **2022**, *20*, 62. https://doi.org/10.3390/md20010062
330. Lo Giudice, A.; Rizzo, C. Bacteria Associated with Benthic Invertebrates from Extreme Marine Environments: Promising but Underexplored Sources of Biotechnologically Relevant Molecules. *Mar. Drugs* **2022**, *20*, 617. https://doi.org/10.3390/md20100617
331. Zhang, J.-W.; Wang, R.; Liang, X.; Han, P.; Zheng, Y.-L.; Li, X.-F.; Gao, D.-Z.; Liu, M.; Hou, L.-J.; Dong, H.-P. Novel Gene Clusters for Natural Product Synthesis Are Abundant in the Mangrove Swamp Microbiome. *Appl. Environ. Microbiol.* **2023**, *89*, e00102-23. https://doi.org/10.1128/aem.00102-23

 doi:10.20944/preprints202607.1303.v1

332. Wilson, Z.E.; Brimble, M.A. Molecules Derived from the Extremes of Life. *Nat. Prod. Rep.* **2009**, *26*, 44–71. https://doi.org/10.1039/b800164m
333. Thornburg, C.C.; Zabriskie, T.M.; McPhail, K.L. Deep-Sea Hydrothermal Vents: Potential Hot Spots for Natural Products Discovery? *J. Nat. Prod.* **2010**, *73*, 489–499. https://doi.org/10.1021/np900662k
334. Guo, L.-L.; Wang, S.-L.; Zhu, F.-C.; Xue, F.; He, L.-S. Characteristics of Two Crustins from *Alvinocaris longirostris* in Hydrothermal Vents. *Mar. Drugs* **2021**, *19*, 600. https://doi.org/10.3390/md19110600
335. Wang, Y.; Zhang, J.; Sun, Y.; Sun, L. A Crustin from Hydrothermal Vent Shrimp: Antimicrobial Activity and Mechanism. *Mar. Drugs* **2021**, *19*, 176. https://doi.org/10.3390/md19030176
336. Cong, M.; Pang, X.; Zhao, K.; Song, Y.; Liu, Y.; Wang, J. Deep-Sea Natural Products from Extreme Environments: Cold Seeps and Hydrothermal Vents. *Mar. Drugs* **2022**, *20*, 404. https://doi.org/10.3390/md20060404
337. Dong, X.; Zhang, T.; Wu, W.; Peng, Y.; Liu, X.; Han, Y.; Chen, X.; Gao, Z.; Xia, J.; Shao, Z.; Greening, C. A Vast Repertoire of Secondary Metabolites Potentially Influences Community Dynamics and Biogeochemical Processes in Cold Seeps. *Sci. Adv.* **2024**, *10*, eadl2281. https://doi.org/10.1126/sciadv.adl2281
338. Yu, T.; Luo, Y.F.; Tan, X.Y.; Zhao, D.H.; Bi, X.C.; Li, C.J.; Zheng, Y.N.; Xiang, H.; Hu, S.N. Global Marine Cold Seep Metagenomes Reveal Diversity of Taxonomy, Metabolic Function, and Natural Products. *Genom. Proteom. Bioinform.* **2024**, *22*, qzad006. https://doi.org/10.1093/gpbjnl/qzad006
339. Hu, G.-A.; Sun, H.-Y.; Yin, Q.-J.; Wang, H.; Liu, S.-Y.; Wang, B.-G.; Wang, H.; Li, X.; Wei, B. Exploring the Biosynthetic Potential of Microorganisms from the South China Sea Cold Seep Using Culture-Dependent and Culture-Independent Approaches. *Mar. Drugs* **2025**, *23*, 313. https://doi.org/10.3390/md23080313
340. Kaari, M.; Manikkam, R.; Baskaran, A. Exploring Newer Biosynthetic Gene Clusters in Marine Microbial Prospecting. *Mar. Biotechnol.* **2022**, *24*, 448–467. https://doi.org/10.1007/s10126-022-10118-y
341. Paoli, L.; Ruscheweyh, H.-J.; Forneris, C.C.; Hubrich, F.; Kautsar, S.; Bhushan, A.; Lotti, A.; Clayssen, Q.; Salazar, G.; Milanese, A.; Carlström, C.I.; Papadopoulou, C.; Gehrig, D.; Karasikov, M.; Mustafa, H.; Larralde, M.; Carroll, L.M.; Sánchez, P.; Zayed, A.A.; Cronin, D.R.; Acinas, S.G.; Bork, P.; Bowler, C.; Delmont, T.O.; Gasol, J.M.; Gossert, A.D.; Kahles, A.; Sullivan, M.B.; Wincker, P.; Zeller, G.; Robinson, S.L.; Piel, J.; Sunagawa, S. Biosynthetic Potential of the Global Ocean Microbiome. *Nature* **2022**, *607*, 111–118. https://doi.org/10.1038/s41586-022-04862-3
342. Chen, B.; Zhang, Z.; Zhang, Q.; Xu, N.; Lu, T.; Wang, T.; Hong, W.; Fu, Z.; Penuelas, J.; Gillings, M.; Qian, H. Antimicrobial Peptides in the Global Microbiome: Biosynthetic Genes and Resistance Determinants. *Environ. Sci. Technol.* **2023**, *57*, 7698–7708. https://doi.org/10.1021/acs.est.3c01664
343. Li, L. Accessing Hidden Microbial Biosynthetic Potential from Underexplored Sources for Novel Drug Discovery. *Biotechnol. Adv.* **2023**, *66*, 108176. https://doi.org/10.1016/j.biotechadv.2023.108176
344. Wei, B.; Hu, G.-A.; Zhou, Z.-Y.; Yu, W.-C.; Du, A.-Q.; Yang, C.-L.; Yu, Y.-L.; Chen, J.-W.; Zhang, H.-W.; Wu, Q.; Xuan, Q.; Xu, X.-W.; Wang, H. Global Analysis of the Biosynthetic Chemical Space of Marine Prokaryotes. *Microbiome* **2023**, *11*, 144. https://doi.org/10.1186/s40168-023-01573-3
345. Wang, S.; Li, X.; Yang, W.; Huang, R. Exploring the Secrets of Marine Microorganisms: Unveiling Secondary Metabolites through Metagenomics. *Microb. Biotechnol.* **2024**, *17*, e14533. https://doi.org/10.1111/1751-7915.14533
346. Wu, K.; Xu, G.; Tian, Y.; Li, G.; Yi, Z.; Tang, X. Synthesis and Evaluation of Aquatic Antimicrobial Peptides Derived from Marine Metagenomes Using a High-Throughput Screening Approach. *Mar. Drugs* **2025**, *23*, 178. https://doi.org/10.3390/md23040178
347. Jiang, P.; Liang, Z.; Kovacevic, V.; Shi, J.; Milicevic, N.; Wang, F.; Liu, L.; Liu, Y.; Jiang, Y.; Han, M.; Lin, X.; Petronić, Č.; Stanojevic, N.; Wang, L.; Wang, S.; Cheng, H.; Li, J.; Chen, R.; Zhang, Y.; Li, Y.; Li, J.; Fang, X.; Yue, Z.; Xue, C.; Yin, P.; Chen, H. The Extreme Environment Microbiome Catalog (EEMC): a Global Resource for Microbial Diversity and Antimicrobial Discovery. *Nat. Commun.* **2026**, *17*, 4791. https://doi.org/10.1038/s41467-026-71145-0
348. Geller-McGrath, D.; Mara, P.; Taylor, G.T.; Suter, E.; Edgcomb, V.; Pachiadaki, M. Diverse Secondary Metabolites Are Expressed in Particle-Associated and Free-Living Microorganisms of the Permanently Anoxic Cariaco Basin. *Nat. Commun.* **2023**, *14*, 656. https://doi.org/10.1038/s41467-023-36026-w

 doi:10.20944/preprints202607.1303.v1

349. Nair, S.; Simidu, U. Distribution and Significance of Heterotrophic Marine Bacteria with Antibacterial Activity. *Appl. Environ. Microbiol.* **1987**, *53*, 2957–2962. https://doi.org/10.1128/aem.53.12.2957-2962.1987
350. Long, R.A.; Rowley, D.C.; Zamora, E.; Liu, J.; Bartlett, D.H.; Azam, F. Antagonistic Interactions among Marine Bacteria Impede the Proliferation of *Vibrio cholerae*. *Appl. Environ. Microbiol.* **2005**, *71*, 8531–8536. https://doi.org/10.1128/AEM.71.12.8531-8536.2005
351. Velicer, G.J. Social Strife in the Microbial World. *Trends Microbiol.* **2003**, *11*, 330–337. https://doi.org/10.1016/S0966-842X(03)00152-5
352. Mitri, S.; Foster, K.R. The Genotypic View of Social Interactions in Microbial Communities. *Annu. Rev. Genet.* **2013**, *47*, 247–273. https://doi.org/10.1146/annurev-genet-111212-133307
353. Granato, E.T.; Meiller-Legrand, T.A.; Foster, K.R. The Evolution and Ecology of Bacterial Warfare. *Curr. Biol.* **2019**, *29*, R521–R537. https://doi.org/10.1016/j.cub.2019.04.024
354. Gu, T.; Chen, Z.; Sun, J. Variability of Microbial Network Complexity and Stability along the Size-Fraction Particles in the Global Ocean. *Glob. Planet. Change* **2025**, *252*, 104859. https://doi.org/10.1016/j.gloplacha.2025.104859
355. Zhang, C.; Tian, J.; Shao, H.; Wang, M.; Zhou, C.; McMinn, A.; Liang, Y.; Wang, H. Contrasting Lifestyle of Free-Living and Particle-Attached Microbes Shaped Community Dynamics and Stability in the Seamount Environment. *Mol. Ecol.* **2026**, *35*, e70205. https://doi.org/10.1111/mec.70205
356. Hibbing, M.E.; Fuqua, C.; Parsek, M.R.; Peterson, S.B. Bacterial Competition: Surviving and Thriving in the Microbial Jungle. *Nat. Rev. Microbiol.* **2010**, *8*, 15–25. https://doi.org/10.1038/nrmicro2259
357. Ghoul, M.; Mitri, S. The Ecology and Evolution of Microbial Competition. *Trends Microbiol.* **2016**, *24*, 833–845. https://doi.org/10.1016/j.tim.2016.06.011
358. Debray, R.; Herbert, R.A.; Jaffe, A.L.; Crits-Christoph, A.; Power, M.E.; Koskella, B. Priority Effects in Microbiome Assembly. *Nat. Rev. Microbiol.* **2022**, *20*, 109–121. https://doi.org/10.1038/s41579-021-00604-w
359. Bäcker, M.; Doekes, H.M.; Garza, D.R.; Meijer, J.; van Vliet, S.; Allen, R.J.; Hogeweg, P.; Dutilh, B.E.; van Dijk, B. Spatial Structure: Shaping the Ecology and Evolution of Microbial Communities. *FEMS Microbiol. Rev.* **2026**, *50*, fuaf067. https://doi.org/10.1093/femsre/fuaf067
360. Saier, M.H., Jr. Cooperation and Competition Were Primary Driving Forces for Biological Evolution. *Microb. Physiol.* **2025**, *35*, 13–29. https://doi.org/10.1159/000544890
361. Alldredge, A.L.; Cohen, Y. Can Microscale Chemical Patches Persist in the Sea? Microelectrode Study of Marine Snow, Fecal Pellets. *Science* **1987**, *235*, 689–691. https://doi.org/10.1126/science.235.4789.68
362. Ganesh, S.; Parris, D.J.; DeLong, E.F.; Stewart, F.J. Metagenomic Analysis of Size-Fractionated Picoplankton in a Marine Oxygen Minimum Zone. *ISME J.* **2014**, *8*, 187–211. https://doi.org/10.1038/ismej.2013.144
363. Nadell, C.D.; Drescher, K.; Foster, K.R. Spatial Structure, Cooperation and Competition in Biofilms. *Nat. Rev. Microbiol.* **2016**, *14*, 589–600. https://doi.org/10.1038/nrmicro.2016.84
364. Hmelo, L.R. Quorum Sensing in Marine Microbial Environments. *Annu. Rev. Mar. Sci.* **2017**, *9*, 257–281. https://doi.org/10.1146/annurev-marine-010816-060656
365. Bianchi, D.; Weber, T.S.; Kiko, R.; Deutsch, C. Global Niche of Marine Anaerobic Metabolisms Expanded by Particle Microenvironments. *Nat. Geosci.* **2018**, *11*, 263–268. https://doi.org/10.1038/s41561-018-0081-0
366. Kragh, K.N.; Tolker-Nielsen, T.; Lichtenberg, M. The Non-Attached Biofilm Aggregate. *Commun. Biol.* **2023**, *6*, 898. https://doi.org/10.1038/s42003-023-05281-4
367. Yu, S.; Lu, X.; Lu, H. Marine Microbial Biofilms on Diverse Abiotic Surfaces. *Front. Mar. Sci.* **2025**, *12*, 1482946. https://doi.org/10.3389/fmars.2025.1482946
368. Douglas, G.M.; Tromas, N.; Gaudin, M.; Lypaczewski, P.; Bobay, L.-M.; Shapiro, B.J.; Chaffron, S. Co-Occurrence is Associated with Horizontal Gene Transfer across Marine Bacteria Independent of Phylogeny. *ISME J.* **2026**, *20*, wraf275. https://doi.org/10.1093/ismejo/wraf275
369. Mao, Z.; Jiang, M.; Zhao, Z.; Xu, S.; Wang, H.; Chen, K.; Duan, J.; Chen, Z.; He, D.; Xing, P.; Wu, Q.L. Biofilm-Forming Traits Enrich the Plasmid Diversity and Functional Potential in Particle-Attached Bacteria in Coastal Ecosystems. *Microbiol. Spectr.* **2026**. Ahead of Print. https://doi.org/10.1128/spectrum.00460-26
370. Zan, J.; Liu, Y.; Fuqua, C.; Hill, R.T. Acyl-Homoserine Lactone Quorum Sensing in the *Roseobacter* Clade. *Int. J. Mol. Sci.* **2014**, *15*, 654-669. https://doi.org/10.3390/ijms15010654

 doi:10.20944/preprints202607.1303.v1

371. Cude, W.N.; Prevatte, C.W.; Hadden, M.K.; May, A.L.; Smith, R.T.; Swain, C.L.; Campagna, S.R.; Buchan, A. *Phaeobacter* sp. Strain Y4I Utilizes Two Separate Cell-to-Cell Communication Systems To Regulate Production of the Antimicrobial Indigoidine. *Appl. Environ. Microbiol.* **2015**, *81*, 1417–1425. https://doi.org/10.1128/AEM.02551-14
372. Timmermans, M.L.; Picott, K.J.; Ucciferri, L.; Ross, A.C. Culturing Marine Bacteria from the Genus *Pseudoalteromonas* on a Cotton Scaffold Alters Secondary Metabolite Production. *MicrobiologyOpen* **2019**, *8*, e724. https://doi.org/10.1002/mbo3.724
373. Armes, A.C.; Buchan, A. Cyclic di-GMP Is Integrated Into a Hierarchal Quorum Sensing Network Regulating Antimicrobial Production and Biofilm Formation in Roseobacter Clade Member Rhodobacterales Strain Y4I. *Front. Mar. Sci.* **2021**, *8*, 681551. https://doi.org/10.3389/fmars.2021.681551
374. Armes, A.C.; Walton, J.L.; Buchan, A. Quorum Sensing and Antimicrobial Production Orchestrate Biofilm Dynamics in Multispecies Bacterial Communities. *Microbiol. Spectr.* **2022**, *10*, e02615-22. https://doi.org/10.1128/spectrum.02615-22
375. Liu, H.Y.; Prentice, E.L.; Webber, M.A. Mechanisms of Antimicrobial Resistance in Biofilms. *npj Antimicrob. Resist.* **2024**, *2*, 27. https://doi.org/10.1038/s44259-024-00046-3
376. Zhong, J.; Osborn, T.; Del Rosario Hernández, T.; Kyrysyuk, O.; Tully, B.J.; Anderson, R.E. Increasing Transposase Abundance with Ocean Depth Correlates with a Particle-Associated Lifestyle. *mSystems* **2024**, *9*, e00067-24. https://doi.org/10.1128/msystems.00067-24
377. Henriksen, N.N.S.E.; Lindqvist, L.L.; Wibowo, M.; Sonnenschein, E.C.; Bentzon-Tilia, M.; Gram, L. Role Is in the Eye of the Beholder—the Multiple Functions of the Antibacterial Compound Tropodithietic Acid Produced by Marine *Rhodobacteraceae*. *FEMS Microbiol. Rev.* **2022**, *46*, fuac007. https://doi.org/10.1093/femsre/fuac007
378. Svendsen, P.B.; Henriksen, N.N.S.E.; Jarmusch, S.A.; Andersen, A.J.C.; Smith, K.; Selsmark, M.W.; Zhang, S.-D.; Schostag, M.D.; Gram, L. Co-existence of Two Antibiotic-Producing Marine Bacteria: *Pseudoalteromonas piscicida* Reduce Gene Expression and Production of the Antibacterial Compound, Tropodithietic Acid, in *Phaeobacter* sp.. *Appl. Environ. Microbiol.* **2024**, *9*, e00588-24. https://doi.org/10.1128/aem.00588-24
379. Comstock, J.; Henderson, L.C.; Close, H.G.; Liu, S.; Vergin, K.; Worden, A.Z.; Wittmers, F.; Halewood, E.; Giovannoni, S.; Carlson, C.A. Marine Particle Size-Fractionation Indicates Organic Matter Is Processed by Differing Microbial Communities on Depth-Specific Particles. *ISME Commun.* **2024**, *4*, ycae090. https://doi.org/10.1093/ismeco/ycae090
380. Stephens, B.M.; Durkin, C.A.; Sharpe, G.; Nguyen, T.T.H.; Albers, J.; Estapa, M.L.; Steinberg, D.K.; Levine, N.M.; Gifford, S.M.; Carlson, C.A.; Boyd, P.W.; Santoro, A.E. Direct Observations of Microbial Community Succession on Sinking Marine Particles. *ISME J.* **2024**, *18*, wrad010. https://doi.org/10.1093/ismejo/wrad010
381. Bochdansky, A.B.; Clouse, M.A.; Herndl, G.J. Eukaryotic Microbes, Principally Fungi and Labyrinthulomycetes, Dominate Biomass on Bathypelagic Marine Snow. *ISME J.* **2017**, *11*, 362–373. https://doi.org/10.1038/ismej.2016.113
382. Rath, J.; Wu, K.Y.; Herndl, G.J.; DeLong, E.F. High Phylogenetic Diversity in a Marine-Snow-Associated Bacterial Assemblage. *Aquat. Microb. Ecol.* **1998**, *14*, 261–269. https://doi.org/10.3354/ame014261
383. Dang, H.; Lovell, C.R. Seasonal Dynamics of Particle-Associated and Free-Living Marine *Proteobacteria* in a Salt Marsh Tidal Creek as Determined Using Fluorescence In Situ Hybridization. *Environ. Microbiol.* **2002**, *4*, 287–295. https://doi.org/10.1046/j.1462-2920.2002.00295.x
384. Leu, A.O.; Eppley, J.M.; Burger, A.; DeLong, E.F. Diverse Genomic Traits Differentiate Sinking-Particle-Associated versus Free-Living Microbes throughout the Oligotrophic Open Ocean Water Column. *mBio* **2022**, *13*, e01569-22. https://doi.org/10.1128/mbio.01569-22
385. Orsi, W.D.; Smith, J.M.; Wilcox, H.M.; Swalwell, J.E.; Carini, P.; Worden, A.Z.; Santoro, A.E. Ecophysiology of Uncultivated Marine Euryarchaea Is Linked to Particulate Organic Matter. *ISME J.* **2015**, *9*, 1747–1763. https://doi.org/10.1038/ismej.2014.260
386. Jain, A.; Krishnan, K.P. Marine Group-II Archaea Dominate Particle-Attached as well as Free-Living Archaeal Assemblages in the Surface Waters of Kongsfjorden, Svalbard. *Antonie van Leeuwenhoek* **2021**, *114*, 633–647. https://doi.org/10.1007/s10482-021-01547-1

 doi:10.20944/preprints202607.1303.v1

387. Li, J.; Gu, L.; Bai, S.; Wang, J.; Su, L.; Wei, B.; Zhang, L.; Fang, J. Characterization of Particle-Associated and Free-Living Bacterial and Archaeal Communities along the Water Columns of the South China Sea. *Biogeosciences* **2021**, *18*, 113–133. https://doi.org/10.5194/bg-18-113-2021
388. van Wolferen, M.; Pulschen, A.A.; Baum, B.; Gribaldo, S.; Albers, S.-V. The Cell Biology of Archaea. *Nat. Microbiol.* **2022**, *7*, 1744–1755. https://doi.org/10.1038/s41564-022-01215-8
389. Du, H.; Liu, Y. Archaeasins as a Promising Resource for Developing Next-Generation Antibiotics Uncovered via Deep Learning. *Eng. Microbiol.* **2025**, *5*, 100241. https://doi.org/10.1016/j.engmic.2025.100241
390. Walker, M.C.; Eslami, S.M.; Hetrick, K.J.; Ackenhusen, S.E.; Mitchell, D.A.; van der Donk, W.A. Precursor Peptide-Targeted Mining of More Than One Hundred Thousand Genomes Expands the Lanthipeptide Natural Product Family. *BMC Genom.* **2020**, *21*, 387. https://doi.org/10.1186/s12864-020-06785-7
391. Castro, I.; Costa, H.; Turgeman-Grott, I.; Allers, T.; Mendo, S.; Caetano, T. The Lanthipeptide Biosynthetic Clusters of the Domain Archaea. *Microbiol. Res.* **2021**, *253*, 126884. https://doi.org/10.1016/j.micres.2021.126884
392. Galal, A.; Abou Elhassan, S.; Saleh, A.H.; Ahmed, A.I.; Abdelrahman, M.M.; Kamal, M.M.; Khalel, R.S.; Ziko, L. A Survey of the Biosynthetic Potential and Specialized Metabolites of Archaea and Understudied Bacteria. *Curr. Res. Biotechnol.* **2023**, *5*, 100117. https://doi.org/10.1016/j.crbiot.2022.11.004
393. Liang, H.; Song, Z.-M.; Zhong, Z.; Zhang, D.; Yang, W.; Zhou, L.; Older, E.A.; Li, J.; Wang, H.; Zeng, Z.; Li, Y.-X. Genomic and Metabolic Analyses Reveal Antagonistic Lanthipeptides in Archaea. *Microbiome* **2023**, *11*, 74. https://doi.org/10.1186/s40168-023-01521-1
394. Song, Z.-M.; Cai, C.; Gao, Y.; Lin, X.; Yang, Q.; Zhang, D.; Wu, G.; Liang, H.; Zhuo, Q.; Zhang, J.; Cai, P.; Jiang, H.; Liu, W.; Li, Y.-X. Decoding the Chemical Language of Ribosomally Synthesized and Post-Translationally Modified Peptides from the Untapped Archaea Domain. *Angew. Chem. Int. Ed.* **2025**, *64*, e202501074. https://doi.org/10.1002/anie.202501074
395. Torres, M.D.T.; Wan, F.; de la Fuente-Nunez, C. Deep Learning Reveals Antibiotics in the Archaeal Proteome. *Nat. Microbiol.* **2025**, *10*, 2153–2167. https://doi.org/10.1038/s41564-025-02061-0
396. Notomista, E.; Falanga, A.; Fusco, S.; Pirone, L.; Zanfardino, A.; Galdiero, S.; Varcamonti, M.; Pedone, E.; Contursi, P. The Identification of a Novel *Sulfolobus islandicus* CAMP-Like Peptide Points to Archaeal Microorganisms as Cell Factories for the Production of Antimicrobial Molecules. *Microb. Cell Fact.* **2015**, *14*, 126. https://doi.org/10.1186/s12934-015-0302-9
397. Chen, S.; Dai, Y.; Ke, J.; Luo, Y.; Wang, C.; Hao, Y.; Zhang, A.; Han, J.; Xiang, H. Halocin H4 Is Activated through Cleavage by Halolysin HlyR4. *Appl. Environ. Microbiol.* **2024**, *90*, e02284-23. https://doi.org/10.1128/AEM.02284-23
398. Duan, Y.; Santos-Júnior, C.D.; Schmidt, T.S.; Fullam, A.; de Almeida, B.L.S.; Zhu, C.; Kuhn, M.; Zhao, X.-M.; Bork, P.; Coelho, L.P. A Catalog of Small Proteins from the Global Microbiome. *Nat. Commun.* **2024**, *15*, 7563. https://doi.org/10.1038/s41467-024-51894-6
399. Poff, K.E.; Leu, A.O.; Eppley, J.M.; Karl, D.M.; DeLong, E.F. Microbial Dynamics of Elevated Carbon Flux in the Open Ocean's Abyss. *Proc. Natl. Acad. Sci. U.S.A.* **2021**, *118*, e2018269118. https://doi.org/10.1073/pnas.2018269118
400. Zhao, Z.; Klawonn, I.; Baltar, F.; Grossart, H.-P. Size-Fractionated Fungal Communities in the Sunlit Ocean. *Commun. Biol.* **2026**, *9*, 47. https://doi.org/10.1038/s42003-025-09314-y
401. Breyer, E.; Stix, C.; Kilker, S.; Roller, B.R.K.; Panagou, F.; Doebke, C.; Amano, C.; Saavedra, D.E.M.; Coll-García, G.; Steger-Mähnert, B.; Dachs, J.; Berrojalbiz, N.; Vila-Costa, M.; Sobrino, C.; Fuentes-Lema, A.; Berthiller, F.; Polz, M.F.; Baltar, F. The Contribution of Pelagic Fungi to Ocean Biomass. *Cell* **2025**, *188*, 3992–4002. https://doi.org/10.1016/j.cell.2025.05.004
402. Peng, X.; Amend, A.S.; Baltar, F.; Blanco-Bercial, L.; Breyer, E.; Burgaud, G.; Cunliffe, M.; Edgcomb, V.P.; Grossart, H.-P.; Mara, P.; Masigol, H.; Pang, K.-L.; Retter, A.; Roberts, C.; van Bleijswijk, J.; Walker, A.K.; Whitner, S. Planktonic Marine Fungi: A Review. *J. Geophys. Res. Biogeosci.* **2024**, *129*, e2023JG007887. https://doi.org/10.1029/2023JG007887
403. Bugni, T.S.; Ireland, C.M. Marine-Derived Fungi: a Chemically and Biologically Diverse Group of Microorganisms. *Nat. Prod. Rep.* **2004**, *21*, 143–163. https://doi.org/10.1039/b301926h

 doi:10.20944/preprints202607.1303.v1

404. Jin, L.; Quan, C.; Hou, X.; Fan, S. Potential Pharmacological Resources: Natural Bioactive Compounds from Marine-Derived Fungi. *Mar. Drugs* **2016**, *14*, 76. https://doi.org/10.3390/md14040076
405. Youssef, F.S.; Ashour, M.L.; Singab, A.N.B.; Wink, M. A Comprehensive Review of Bioactive Peptides from Marine Fungi and Their Biological Significance. *Mar. Drugs* **2019**, *17*, 559. https://doi.org/10.3390/md17100559
406. Ameen, F.; AlNAdhari, S.; Al-Homaidan, A.A. Marine Fungi Showing Multifunctional Activity against Human Pathogenic Microbes and Cancer. *PLoS ONE* **2022**, *17*, e0276926. https://doi.org/10.1371/journal.pone.0276926
407. Gao, Y.; Wang, J.; Meesakul, P.; Zhou, J.; Liu, J.; Liu, S.; Wang, C.; Cao, S. Cytotoxic Compounds from Marine Fungi: Sources, Structures, and Bioactivity. *Mar. Drugs* **2024**, *22*, 70. https://doi.org/10.3390/md22020070
408. Breyer, E.; Baltar, F. The Rise of Marine Fungi: Drug Discovery's Blue Frontier. *Clin. Transl. Med.* **2026**, *16*, e70623. https://doi.org/10.1002/ctm2.70623
409. Kharbush, J.J.; Close, H.G.; Van Mooy, B.A.S.; Arnosti, C.; Smittenberg, R.H.; Le Moigne, F.A.C.; Mollenhauer, G.; Scholz-Böttcher, B.; Obreht, I.; Koch, B.P.; Becker, K.W.; Iversen, M.H.; Mohr, W. Particulate Organic Carbon Deconstructed: Molecular and Chemical Composition of Particulate Organic Carbon in the Ocean. *Front. Mar. Sci.* **2020**, *7*, 518. https://doi.org/10.3389/fmars.2020.00518
410. Siebers, R.; Schultz, D.; Farza, M.S.; Brauer, A.; Zühlke, D.; Mücke, P.A.; Wang, F.; Bernhardt, J.; Teeling, H.; Becher, D.; Riedel, K.; Kirstein, I.V.; Wiltshire, K.H.; Hoff, K.J.; Schweder, T.; Urich, T.; Bengtsson, M.M. Marine Particle Microbiomes during a Spring Diatom Bloom Contain Active Sulfate-Reducing Bacteria. *FEMS Microbiol. Ecol.* **2024**, *100*, fiae037. https://doi.org/10.1093/femsec/fiae037
411. Pelve, E.A.; Fontanez, K.M.; DeLong, E.F. Bacterial Succession on Sinking Particles in the Ocean's Interior. *Front. Microbiol.* **2017**, *8*, 2269. https://doi.org/10.3389/fmicb.2017.02269
412. Enke, T.N.; Datta, M.S.; Schwartzman, J.; Cermak, N.; Schmitz, D.; Barrere, J.; Pascual-García, A.; Cordero, O.X. Modular Assembly of Polysaccharide-Degrading Marine Microbial Communities. *Curr. Biol.* **2019**, *29*, 1528–1535. https://doi.org/10.1016/j.cub.2019.03.047
413. Lindemann, S.R. Microbial Ecology: Functional 'Modules' Drive Assembly of Polysaccharide-Degrading Marine Microbial Communities. *Curr. Biol.* **2019**, *29*, R330–R332. https://doi.org/10.1016/j.cub.2019.03.056
414. Buesseler, K.O.; Boyd, P.W. Shedding Light on Processes that Control Particle Export and Flux Attenuation in the Twilight Zone of the Open Ocean. *Limnol. Oceanogr.* **2009**, *54*, 1210–1232. https://doi.org/10.4319/lo.2009.54.4.1210
415. Giering, S.L.C.; Sanders, R.; Lampitt, R.S.; Anderson, T.R.; Tamburini, C.; Boutrif, M.; Zubkov, M.V.; Marsay, C.M.; Henson, S.A.; Saw, K.; Cook, K.; Mayor, D.J. Reconciliation of the Carbon Budget in the Ocean's Twilight Zone. *Nature* **2014**, *507*, 480–483. https://doi.org/10.1038/nature13123
416. Cavan, E.L.; Laurenceau-Cornec, E.C.; Bressac, M.; Boyd, P.W. Exploring the Ecology of the Mesopelagic Biological Pump. *Prog. Oceanogr.* **2019**, *176*, 102125. https://doi.org/10.1016/j.pocean.2019.102125
417. Wenley, J.; Currie, K.; Lockwood, S.; Thomson, B.; Baltar, F.; Morales, S.E. Seasonal Prokaryotic Community Linkages Between Surface and Deep Ocean Water. *Front. Mar. Sci.* **2021**, *8*, 659641. https://doi.org/10.3389/fmars.2021.659641
418. Lloyd, C.C.; Brown, S.; Balmonte, J.P.; Hoarfrost, A.; Ghobrial, S.; Arnosti, C. Particles Act as 'Specialty Centers' with Expanded Enzymatic Function throughout the Water Column in the Western North Atlantic. *Front. Microbiol.* **2022**, *13*, 882333. https://doi.org/10.3389/fmicb.2022.882333
419. Herndl, G.J.; Bayer, B.; Baltar, F.; Reinthaler, T. Prokaryotic Life in the Deep Ocean's Water Column. *Annu. Rev. Mar. Sci.* **2023**, *15*, 461–483. https://doi.org/10.1146/annurev-marine-032122-115655
420. Miller, L.C.; Close, H.G.; Grabb, K.C.; Huffard, C.L.; Li, F.; Karl, D.M.; Smith, K.L.; DeLong, E.F.; Benitez-Nelson, C.R.; Drazen, J.C.; Popp, B.N. Transformations of Particulate Organic Matter from the Surface to the Abyssal Plain in the North Pacific as Inferred from Compound-Specific Stable Isotope and Microbial Community Analyses. *Deep-Sea Res. Part I* **2025**, *225*, 104597. https://doi.org/10.1016/j.dsr.2025.104597
421. Hansell, D.A. Recalcitrant Dissolved Organic Carbon Fractions. *Annu. Rev. Mar. Sci.* **2013**, *5*, 421–445. https://doi.org/10.1146/annurev-marine-120710-100757

 doi:10.20944/preprints202607.1303.v1

422. Dittmar, T.; Lennartz, S.T.; Buck-Wiese, H.; Hansell, D.A.; Santinelli, C.; Vanni, C.; Blasius, B.; Hehemann, J.-H. Enigmatic Persistence of Dissolved Organic Matter in the Ocean. *Nat. Rev. Earth Environ.* **2021**, *2*, 570–583. https://doi.org/10.1038/s43017-021-00183-7
423. Zhao, Z.; Baltar, F.; Herndl, G.J. Linking Extracellular Enzymes to Phylogeny Indicates a Predominantly Particle-Associated Lifestyle of Deep-Sea Prokaryotes. *Sci. Adv.* 2020, *6*, eaaz4354. https://doi.org/10.1126/sciadv.aaz4354
424. Amano, C.; Zhao, Z.; Sintes, E.; Reinthaler, T.; Stefanschitz, J.; Kisadur, M.; Utsumi, M.; Herndl, G.J. Limited Carbon Cycling due to High-Pressure Effects on the Deep-Sea Microbiome. *Nat. Geosci.* **2022**, *15*, 1041–1047. https://doi.org/10.1038/s41561-022-01081-3
425. Zhao, Z.; Amano, C.; Reinthaler, T.; Baltar, F.; Orellana, M.V.; Herndl, G.J. Metaproteomic Analysis Decodes Trophic Interactions of Microorganisms in the Dark Ocean. *Nat. Commun.* **2024**, *15*, 6411. https://doi.org/10.1038/s41467-024-50867-z
426. Zhao, Z.; Amano, C.; Reinthaler, T.; Orellana, M.V.; Herndl, G.J. Substrate Uptake Patterns Shape Niche Separation in Marine Prokaryotic Microbiome. *Sci. Adv.* **2024**, *10*, eadn5143. https://doi.org/10.1126/sciadv.adn5143
427. Fernandez, V.I.; Blitvić, N.; Keegstra, J.M.; Stocker, R. Stochastic Resilience Enables Particle Foraging in Oligotrophic Marine Environments. *Proc. Natl. Acad. Sci. U.S.A.* **2026**, *123*, e2508238123. https://doi.org/10.1073/pnas.2508238123
428. Li, X.; Zhao, X.; Dang, H.; Zhang, C.; Fernández-Urruzola, I.; Liu, Z.; Wenzhöfer, F.; Glud, R.N. High Variability in Organic Carbon Sources and Microbial Activities in the Hadopelagic Waters. *Limnol. Oceanogr.* **2023**, *68*, 1704–1718. https://doi.org/10.1002/lno.12379
429. Sogin, M.L.; Morrison, H.G.; Huber, J.A.; Welch, D.M.; Huse, S.M.; Neal, P.R.; Arrieta, J.M.; Herndl, G.J. Microbial Diversity in the Deep Sea and the Underexplored "Rare Biosphere". *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12115–12120. https://doi.org/10.1073/pnas.0605127103
430. Voser, T.M.; Campbell, M.D.; Carroll, A.R. How Different are Marine Microbial Natural Products Compared to Their Terrestrial Counterparts? *Nat. Prod. Rep.* **2022**, *39*, 7–19. https://doi.org/10.1039/d1np00051a
431. Raman, A.S. Combatting Superbugs Using the Evolutionary Record of Microbial Warfare. *Cell Host Microbe* **2024**, *32*, 1037–1039. https://doi.org/10.1016/j.chom.2024.06.001
432. Lai, Q.; Yao, S.; Zha, Y.; Zhang, H.; Zhang, H.; Ye, Y.; Zhang, Y.; Bai, H.; Ning, K. Deciphering the Biosynthetic Potential of Microbial Genomes Using a BGC Language Processing Neural Network Model. *Nucleic Acids Res.* **2025**, *53*, gkaf305, https://doi.org/10.1093/nar/gkaf305
433. Census of Marine Life. International Census of Marine Microbes (ICoMM). 2010, http://www.coml.org/international-census-marine-microbes-icomm/ (accessed on 9 May 2026).
434. Amann, R.I.; Ludwig, W.; Schleifer, K.H. Phylogenetic Identification and In Situ Detection of Individual Microbial Cells without Cultivation. *Microbiol. Rev.* **1995**, *59*, 143–169. https://doi.org/10.1128/mr.59.1.143-169.1995
435. Steen, A.D.; Crits-Christoph, A.; Carini, P.; DeAngelis, K.M.; Fierer, N.; Lloyd, K.G.; Thrash, J.C. High Proportions of Bacteria and Archaea across most Biomes Remain Uncultured. *ISME J.* **2019**, *13*, 3126–3130. https://doi.org/10.1038/s41396-019-0484-y
436. Colarusso, E.; Giordano, A.; Chini, M.G.; Bifulco, G.; Lauro, G. Marine Natural Products in Preclinical Cancer Studies: Ten Years of Advanced Total Synthesis. *Mar. Drugs* **2025**, *23*, 430. https://doi.org/10.3390/md23110430
437. Guryanova, S.V.; Ovchinnikova, T.V. Multifaceted Marine Peptides and Their Therapeutic Potential. *Mar. Drugs* **2025**, *23*, 288. https://doi.org/10.3390/md23070288
438. Yao, M.; Shaheen, H.M.U.; Zuo, C.; Xiong, Y.; He, B.; Ye, Y.; Yan, W. Natural Products from Marine Microorganisms with Agricultural Applications. *Mar. Drugs* **2025**, *23*, 438. https://doi.org/10.3390/md23110438
439. Gaudêncio, S.P.; Pereira, F. Dereplication: Racing to Speed Up the Natural Products Discovery Process. *Nat. Prod. Rep.* **2015**, *32*, 779–810. https://doi.org/10.1039/c4np00134f

 doi:10.20944/preprints202607.1303.v1

440. Gaudêncio, S.P.; Bayram, E.; Lukić Bilela, L.; Cueto, M.; Díaz-Marrero, A.R.; Haznedaroglu, B.Z.; Jimenez, C.; Mandalakis, M.; Pereira, F.; Reyes, F.; Tasdemir, D. Advanced Methods for Natural Products Discovery: Bioactivity Screening, Dereplication, Metabolomics Profiling, Genomic Sequencing, Databases and Informatic Tools, and Structure Elucidation. *Mar. Drugs* **2023**, *21*, 308. https://doi.org/10.3390/md21050308
441. Han, T.; He, Q.; Zhai, G.; Cai, X. Antimicrobial Discovery from Underexplored Environments: Unlocking Specialized Metabolism. *Curr. Opin. Microbiol.* **2026**, *91*, 102745. https://doi.org/10.1016/j.mib.2026.102745
442. Sedeek, A.M.; Hassan, M.; Elsayed, T.R.; Ramadan, M.A. Recent Strategies and Methodological Advances for Microbial Natural Product Research in the Post-Genomics Era. *Arch. Microbiol.* **2026**, *208*, 43. https://doi.org/10.1007/s00203-025-04570-2
443. Scherlach, K.; Hertweck, C. Mining and Unearthing Hidden Biosynthetic Potential. *Nat. Commun.* **2021**, *12*, 3864, https://doi.org/10.1038/s41467-021-24133-5
444. Hemmerling, F.; Piel, J. Strategies to Access Biosynthetic Novelty in Bacterial Genomes for Drug Discovery. *Nat. Rev. Drug Discov.* **2022**, *21*, 359–378. https://doi.org/10.1038/s41573-022-00414-6
445. Kim, N.; Ma, J.; Kim, W.; Kim, J.; Belenky, P.; Lee, I. Genome-Resolved Metagenomics: A Game Changer for Microbiome Medicine. *Exp. Mol. Med.* **2024**, *56*, 1501–1512. https://doi.org/10.1038/s12276-024-01262-7
446. Mirete, S.; Sánchez-Costa, M.; Díaz-Rullo, J.; González de Figueras, C.; Martínez-Rodríguez, P.; González-Pastor, J.E. Metagenome-Assembled Genomes (MAGs): Advances, Challenges, and Ecological Insights. *Microorganisms* **2025**, *13*, 985. https://doi.org/10.3390/microorganisms13050985
447. Qayyum, H.; Ishaq, Z.; Ali, A.; Kayani, M.U.R.; Huang, L. Genome-Resolved Metagenomics from Short-Read Sequencing Data in the Era of Artificial Intelligence. *Funct. Integr. Genomics* **2025**, *25*, 124, https://doi.org/10.1007/s10142-025-01625-x
448. Saleem, N.; Kumar, N.; El-Omar, E.; Willcox, M.; Jiang, X.-T. Harnessing Machine Learning Approaches for the Identification, Characterization, and Optimization of Novel Antimicrobial Peptides. *Antibiotics* **2025**, *14*, 1263. https://doi.org/10.3390/antibiotics14121263
449. Clements, A.E.; Fieldhouse, M.R.; Walker, A.S. Harnessing Artificial Intelligence for Antimicrobial Discovery and Optimization. *Curr. Opin. Microbiol.* **2026**, *91*, 102724, https://doi.org/10.1016/j.mib.2026.102724
450. Jayawardena, A.; Hung, A.; Qiao, G.; Hajizadeh, E. Advances in Computational and Data-Driven Methodologies for Accelerating Antimicrobial Peptide Design and Discovery. *Prog. Polym. Sci.* **2026**, *177*, 102119, https://doi.org/10.1016/j.progpolymsci.2026.102119
451. Pandi, A.; Adam, D.; Zare, A.; Trinh, V.T.; Schaefer, S.L.; Burt, M.; Klabunde, B.; Bobkova, E.; Kushwaha, M.; Foroughijabbari, Y.; Braun, P.; Spahn, C.; Preußer, C.; Pogge von Strandmann, E.; Bode, H.B.; von Buttlar, H.; Bertrams, W.; Jung, A.L.; Abendroth, F.; Schmeck, B.; Hummer, G.; Vázquez, O.; Erb, T.J. Cell-Free Biosynthesis Combined with Deep Learning Accelerates De Novo-Development of Antimicrobial Peptides. *Nat. Commun.* **2023**, *14*, 7197, https://doi.org/10.1038/s41467-023-42434-9
452. Li, X.; Hao, Y.; Teng, D.; Mao, R.; Yang, N.; Wang, J. Review on Microbial Recombination Expression of Antimicrobial Peptides. *Chem. Eng. J.* **2025**, *525*, 170733, https://doi.org/10.1016/j.cej.2025.170733
453. Seshadri, K.; Abad, A.N.D.; Nagasawa, K.K.; Yost, K.M.; Johnson, C.W.; Dror, M.J.; Tang, Y. Synthetic Biology in Natural Product Biosynthesis. *Chem. Rev.* **2025**, *125*, 3814–3931, https://doi.org/10.1021/acs.chemrev.4c00567
454. Lynch, M.D.J.; Neufeld, J.D. Ecology and Exploration of the Rare Biosphere. *Nat. Rev. Microbiol.* **2015**, *13*, 217–229. https://doi.org/10.1038/nrmicro3400
455. Jousset, A.; Bienhold, C.; Chatzinotas, A.; Gallien, L.; Gobet, A.; Kurm, V.; Küsel, K.; Rillig, M.C.; Rivett, D.W.; Salles, J.F.; van der Heijden, M.G.A.; Youssef, N.H.; Zhang, X.; Wei, Z.; Hol, W.H.G. Where Less May Be More: How the Rare Biosphere Pulls Ecosystems Strings. *ISME J.* **2017**, *11*, 853–862. https://doi.org/10.1038/ismej.2016.174
456. Subramani, R.; Sipkema, D. Marine Rare Actinomycetes: A Promising Source of Structurally Diverse and Unique Novel Natural Products. *Mar. Drugs* **2019**, *17*, 249. https://doi.org/10.3390/md17050249
457. Pascoal, F.; Costa, R.; Magalhães, C. The Microbial Rare Biosphere: Current Concepts, Methods and Ecological Principles. *FEMS Microbiol. Ecol.* **2021**, *97*, fiaa227. https://doi.org/10.1093/femsec/fiaa227

 doi:10.20944/preprints202607.1303.v1

458. Silva, S.G.; Paula, P.; da Silva, J.P.; Mil-Homens, D.; Teixeira, M.C.; Fialho, A.M.; Costa, R.; Keller-Costa, T. Insights into the Antimicrobial Activities and Metabolomes of *Aquimarina* (*Flavobacteriaceae*, *Bacteroidetes*) Species from the Rare Marine Biosphere. *Mar. Drugs* **2022**, *20*, 423. https://doi.org/10.3390/md20070423
459. Parra, J.; Beaton, A.; Seipke, R.F.; Wilkinson, B.; Hutchings, M.I.; Duncan, K.R. Antibiotics from Rare Actinomycetes, beyond the Genus *Streptomyces*. *Curr. Opin. Microbiol.* **2023**, *76*, 102385. https://doi.org/10.1016/j.mib.2023.102385
460. Litchman, E.; Villéger, S.; Zinger, L.; Auguet, J.-C.; Thuiller, W.; Munoz, F.; Kraft, N.J.B.; Philippot, L.; Violle, C. Refocusing the Microbial Rare Biosphere through a Functional Lens. *Trends Ecol. Evol.* **2024**, *39*, 923–936. https://doi.org/10.1016/j.tree.2024.06.005
461. Mesquita, A.; Cerqueira, D.; Rocha, M.; Silva, D.; Martins, C.; Souza, B. A Review on Rare and Symbiotic Actinobacteria: Emerging Biotechnological Tools Against Antimicrobial Resistance. *J. Basic Microbiol.* **2025**, *65*, e70036. https://doi.org/10.1002/jobm.70036
462. Chakraborty, D.; Jousset, A.; Wei, Z.; Banerjee, S. Rare Taxa in the Core Microbiome. *Trends Microbiol.* **2025**, *33*, 727–737. https://doi.org/10.1016/j.tim.2025.03.002
463. Beck, M.L.; Song, S.; Shuster, I.E.; Miharia, A.; Walker, A.S. Diversity and Taxonomic Distribution of Bacterial Biosynthetic Gene Clusters Predicted to Produce Compounds with Therapeutically Relevant Bioactivities. *J. Ind. Microbiol. Biotechnol.* **2023**, *50*, kuad024. https://doi.org/10.1093/jimb/kuad024
464. González-Salazar, L.A.; Quezada, M.; Rodríguez-Orduña, L.; Ramos-Aboites, H.; Capon, R.J.; Souza-Saldívar, V.; Barona-Gomez, F.; Licona-Cassani, C. Biosynthetic Novelty Index Reveals the Metabolic Potential of Rare Actinobacteria Isolated from Highly Oligotrophic Sediments. *Microb. Genom.* **2023**, *9*, 000921. https://doi.org/10.1099/mgen.0.000921
465. Bickhart, D.M.; Kolmogorov, M.; Tseng, E.; Portik, D.M.; Korobeynikov, A.; Tolstoganov, I.; Uritskiy, G.; Liachko, I.; Sullivan, S.T.; Shin, S.B.; Zorea, A.; Pascal Andreu, V.; Panke-Buisse, K.; Medema, M.H.; Mizrahi, I.; Pevzner, P.A.; Smith, T.P.L. Generating Lineage-Resolved, Complete Metagenome-Assembled Genomes from Complex Microbial Communities. *Nat. Biotechnol.* **2022**, *40*, 711–719. https://doi.org/10.1038/s41587-021-01130-z
466. Li, Q.-M.; He, L.-S.; Wang, Y. Small Proteins from Prokaryotes in the Marine Water Column. *iScience* **2026**, *29*, 114585. https://doi.org/10.1016/j.isci.2025.114585
467. Storz, G.; Wolf, Y.I.; Ramamurthi, K.S. Small Proteins Can No Longer Be Ignored. *Annu. Rev. Biochem.* **2014**, *83*, 753–777. https://doi.org/10.1146/annurev-biochem-070611-102400
468. Scheidler, C.M.; Kick, L.M.; Schneider, S. Ribosomal Peptides and Small Proteins on the Rise. *ChemBioChem* **2019**, *20*, 1479–1486. https://doi.org/10.1002/cbic.201800715
469. Orr, M.W.; Mao, Y.; Storz, G.; Qian, S.-B. Alternative ORFs and Small ORFs: Shedding Light on the Dark Proteome. *Nucleic Acids Res.* **2020**, *48*, 1029–1042. https://doi.org/10.1093/nar/gkz734
470. Ren, X.; Liu, Z.H.; Zhang, P. Small Open Reading Frame-Encoded Peptides (SEPs) as Hidden Treasures: A Review. *Expert Opin. Drug Discov.* **2026**, *21*, 73–100. https://doi.org/10.1080/17460441.2025.2603517
471. Coelho, L.P.; Santos-Júnior, C.D.; de la Fuente-Nunez, C. Challenges in Computational Discovery of Bioactive Peptides in 'Omics Data. *Proteomics* **2024**, *24*, 2300105. https://doi.org/10.1002/pmic.202300105
472. Ma, Y.; Guo, Z.; Xia, B.; Zhang, Y.; Liu, X.; Yu, Y.; Tang, N.; Tong, X.; Wang, M.; Ye, X.; Feng, J.; Chen, Y.; Wang, J. Identification of Antimicrobial Peptides from the Human Gut Microbiome Using Deep Learning. *Nat. Biotechnol.* **2022**, *40*, 921–931. https://doi.org/10.1038/s41587-022-01226-0
473. Fang, Y.; Ma, Y.; Yu, K.; Dong, J.; Zeng, W. Integrated Computational Approaches for Advancing Antimicrobial Peptide Development. *Trends Pharmacol. Sci.* **2024**, *45*, 1046–1060. https://doi.org/10.1016/j.tips.2024.09.011
474. Wan, F.; Wong, F.; Collins, J.J.; de la Fuente-Nunez, C. Machine Learning for Antimicrobial Peptide Identification and Design. *Nat. Rev. Bioeng.* **2024**, *2*, 392–407. https://doi.org/10.1038/s44222-024-00152-x
475. Brizuela, C.A.; Liu, G.; Stokes, J.M.; de la Fuente-Nunez, C. AI Methods for Antimicrobial Peptides: Progress and Challenges. *Microb. Biotechnol.* **2025**, *18*, e70072. https://doi.org/10.1111/1751-7915.70072
476. Lin, C.; Xiong, S.; Cui, F.; Zhang, Z.; Shi, H.; Wei, L. Deep Learning in Antimicrobial Peptide Prediction. *J. Chem. Inf. Model.* **2025**, *65*, 7373–7392, https://doi.org/10.1021/acs.jcim.5c00530

 doi:10.20944/preprints202607.1303.v1

477. Szymczak, P.; Zarzecki, W.; Wang, J.; Duan, Y.; Wang, J.; Coelho, L.P.; de la Fuente-Nunez, C.; Szczurek, E. AI-Driven Antimicrobial Peptide Discovery: Mining and Generation. *Acc. Chem. Res.* **2025**, *58*, 1831–1846. https://doi.org/10.1021/acs.accounts.0c00594
478. Torres, M.D.T.; Zeng, Y.; Wan, F.; Maus, N.; Gardner, J.; de la Fuente-Nunez, C. A Generative Artificial Intelligence Approach for Peptide Antibiotic Optimization. *Nat. Mach. Intell.* **2026**, *8*, 841–856, https://doi.org/10.1038/s42256-026-01237-5
479. Reen, F.J.; Romano, S.; Dobson, A.D.W.; O'Gara, F. The Sound of Silence: Activating Silent Biosynthetic Gene Clusters in Marine Microorganisms. *Mar. Drugs* **2015**, *13*, 4754-4783. https://doi.org/10.3390/md13084754
480. Rutledge, P.J.; Challis, G.L. Discovery of Microbial Natural Products by Activation of Silent Biosynthetic Gene Clusters. *Nat. Rev. Microbiol.* **2015**, *13*, 509–523. https://doi.org/10.1038/nrmicro3496
481. Zhang, X.; Hindra; Elliot, M.A. Unlocking the Trove of Metabolic Treasures: Activating Silent Biosynthetic Gene Clusters in Bacteria and Fungi. *Curr. Opin. Microbiol.* **2019**, *51*, 9–15. https://doi.org/10.1016/j.mib.2019.03.003
482. Atanasov, A.G.; Zotchev, S.B.; Dirsch, V.M.; the International Natural Product Sciences Taskforce; Supuran, C.T. Natural Products in Drug Discovery: Advances and Opportunities. *Nat. Rev. Drug Discov.* **2021**, *20*, 200–216. https://doi.org/10.1038/s41573-020-00114-z
483. Covington, B.C.; Xu, F.; Seyedsayamdost, M.R. A Natural Product Chemist's Guide to Unlocking Silent Biosynthetic Gene Clusters. *Annu. Rev. Biochem.* **2021**, *90*, 763–788. https://doi.org/10.1146/annurev-biochem-081420-102432
484. Zhou, Z.-Y.; Guan, Y.-T.; Li, Z.-Y.; Wu, X.-W.; Xin, J.-X.; Wang, H.; Wei, B. Towards the Targeted Activation of Silent Biosynthetic Gene Clusters by Chemical Elicitors. *Biotechnol. Adv.* **2026**, *89*, 108870. https://doi.org/10.1016/j.biotechadv.2026.108870
485. Kloosterman, A.M.; Medema, M.H.; van Wezel, G.P. Omics-Based Strategies to Discover Novel Classes of RiPP Natural Products. *Curr. Opin. Biotechnol.* **2021**, *69*, 60–67, https://doi.org/10.1016/j.copbio.2020.12.008
486. Wang, Z.; Yu, J.; Wang, C.; Hua, Y.; Wang, H.; Chen, J. The Deep Mining Era: Genomic, Metabolomic, and Integrative Approaches to Microbial Natural Products from 2018 to 2024. *Mar. Drugs* **2025**, *23*, 261. https://doi.org/10.3390/md23070261
487. Sahayasheela, V.J.; Lankadasari, M.B.; Dan, V.M.; Dastager, S.G.; Pandian, G.N.; Sugiyama, H. Artificial Intelligence in Microbial Natural Product Drug Discovery: Current and Emerging Role. *Nat. Prod. Rep.* **2022**, *39*, 2215–2230. https://doi.org/10.1039/d2np00035k
488. Zhang, Z.; Zhou, Y.; Xie, S.; Liu, R.-Z.; Huang, Z.; Kumar, P.S.; Feng, G.; Yuan, F.; Zhang, L. NRPStransformer, an Accurate Adenylation Domain Specificity Prediction Algorithm for Genome Mining of Nonribosomal Peptides. *J. Am. Chem. Soc.* **2025,** *147*, 32662–32670, https://doi.org/10.1021/jacs.5c08076
489. Sagar, K.; Priti, K.; Chandra, H. Artificial intelligence in metagenome-assembled genome reconstruction: Tools, pipelines, and future directions. *J. Microbiol. Methods* **2026**, *241*, 107390, https://doi.org/10.1016/j.mimet.2026.107390
490. Terlouw, B.R.; Huang, C.; Meijer, D.; Cediel-Becerra, J.D.D.; He, R.; Rothe, M.L.; Jenner, M.; Zhou, S.; Zhang, Y.; Fage, C.D.; Tsunematsu, Y.; van Wezel, G.P.; Robinson, S.L.; Alberti, F.; Alkhalaf, L.M.; Chevrette, M.G.; Challis, G.L.; Medema, M.H. PARAS: High-Accuracy Machine Learning of Substrate Specificity in Nonribosomal Peptide Synthetases. *JACS Au* **2026**, *6*, 2315–2336, https://doi.org/10.1021/jacsau.5c01636
491. Wang, X.-W.; Wang, T.; Liu, Y.-Y. Artificial Intelligence for Microbiology and Microbiome Research. *Cell Syst.* **2026**, *17*, 101531, https://doi.org/10.1016/j.cels.2026.101531

 doi:10.20944/preprints202607.1303.v1

492. Sunagawa, S.; Coelho, L.P.; Chaffron, S.; Kultima, J.R.; Labadie, K.; Salazar, G.; Djahanschiri, B.; Zeller, G.; Mende, D.R.; Alberti, A.; Cornejo-Castillo, F.M.; Costea, P.I.; Cruaud, C.; d'Ovidio, F.; Engelen, S.; Ferrera, I.; Gasol, J.M.; Guidi, L.; Hildebrand, F.; Kokoszka, F.; Lepoivre, C.; Lima-Mendez, G.; Poulain, J.; Poulos, B.T.; Royo-Llonch, M.; Sarmento, H.; Vieira-Silva, S.; Dimier, C.; Picheral, M.; Searson, S.; Kandels-Lewis, S.; *Tara* Oceans coordinators; Bowler, C.; de Vargas, C.; Gorsky, G.; Grimsley, N.; Hingamp, P.; Iudicone, D.; Jaillon, O.; Not, F.; Ogata, H.; Pesant, S.; Speich, S.; Stemmann, L.; Sullivan, M.B.; Weissenbach, J.; Wincker, P.; Karsenti, E.; Raes, J.; Acinas, S.G.; Bork, P. Structure and Function of the Global Ocean Microbiome. *Science* **2015**, *348*, 1261359. https://doi.org/10.1126/science.1261359
493. Keller-Costa, T.; Lago-Lestón, A.; Saraiva, J.P.; Toscan, R.; Silva, S.G.; Gonçalves, J.; Cox, C.J.; Kyrpides, N.; da Rocha, U.N.; Costa, R. Metagenomic Insights into the Taxonomy, Function, and Dysbiosis of Prokaryotic Communities in Octocorals. *Microbiome* **2021**, *9*, 72, https://doi.org/10.1186/s40168-021-01031-y
494. Chen, N.; Liu, L.; Wang, J.; Mao, D.; Lu, H.; Shishido, T.K.; Zhi, S.; Chen, H.; He, S. Novel Gene Clusters for Secondary Metabolite Synthesis in Mesophotic Sponge-Associated Bacteria. *Microb. Biotechnol.* **2025**, *18*, e70107, https://doi.org/10.1111/1751-7915.70107
495. Finking, R.; Marahiel, M.A. Biosynthesis of Nonribosomal Peptides. *Annu. Rev. Microbiol.* **2004**, *58*, 453–488, https://doi.org/10.1146/annurev.micro.58.030603.123615
496. Bharti, R.; Grimm, D.G. Current Challenges and Best-Practice Protocols for Microbiome Analysis. *Brief. Bioinform.* **2021**, *22*, 178–193, https://doi.org/10.1093/bib/bbz155
497. van Dijk, E.L.; Jaszczyszyn, Y.; Naquin, D.; Thermes, C. The Third Revolution in Sequencing Technology. *Trends Genet*. **2018**, *34*, 666–681, https://doi.org/10.1016/j.tig.2018.05.008
498. Waschulin, V.; Borsetto, C.; James, R.; Newsham, K.K.; Donadio, S.; Corre, C.; Wellington, E. Biosynthetic Potential of Uncultured Antarctic Soil Bacteria Revealed through Long-Read Metagenomic Sequencing. *ISME J.* **2022**, *16*, 101–111, https://doi.org/10.1038/s41396-021-01052-3
499. Agustinho, D.P.; Fu, Y.; Menon, V.K.; Metcalf, G.A.; Treangen, T.J.; Sedlazeck, F.J. Unveiling Microbial Diversity: Harnessing Long-Read Sequencing Technology. *Nat. Methods* **2024**, *21*, 954–966, https://doi.org/10.1038/s41592-024-02262-1
500. Sánchez-Navarro, R.; Nuhamunada, M.; Mohite, O.S.; Wasmund, K.; Albertsen, M.; Gram, L.; Nielsen, P.H.; Weber, T.; Singleton, C.M. Long-Read Metagenome-Assembled Genomes Improve Identification of Novel Complete Biosynthetic Gene Clusters in a Complex Microbial Activated Sludge Ecosystem. *mSystems* **2022**, *7*, e00632-22, https://doi.org/10.1128/msystems.00632-22
501. Kim, C.; Pongpanich, M.; Porntaveetus, T. Unraveling Metagenomics through Long-Read Sequencing: A Comprehensive Review. *J. Transl. Med.* **2024**, *22*, 111, https://doi.org/10.1186/s12967-024-04917
502. Berg, M.; Reiter, T.; Emerson, J.; Brown, C.T.; Roux, S. Comparison of short-read and long-read metagenome assemblies in a natural soil community highlights systematic bias in recovery of high-diversity populations. *NAR Genom. Bioinform.* **2025**, *7*, lqaf163, https://doi.org/10.1093/nargab/lqaf163
503. Bižić-Ionescu, M.; Ionescu, D.; Grossart, H.-P. Organic Particles: Heterogeneous Hubs for Microbial Interactions in Aquatic Ecosystems. *Front. Microbiol.* **2018**, *9*, 2569, https://doi.org/10.3389/fmicb.2018.02569
504. Baumas, C.; Bizic, M. A Focus on Different Types of Organic Matter Particles and Their Significance in the Open Ocean Carbon Cycle. *Prog. Oceanogr.* **2024**, *224*, 103233, https://doi.org/10.1016/j.pocean.2024.103233
505. Kapellos, G.E.; Eberl, H.J.; Kalogerakis, N.; Doyle, P.S.; Paraskeva, C.A. Bacterial Clustering Amplifies the Reshaping of Eutrophic Plumes around Marine Particles: A Hybrid Data-Driven Model. *PLoS Comput. Biol.* **2024**, *20*, e1012660, https://doi.org/10.1371/journal.pcbi.1012660
506. Parra, J.; Macias-Contreras, M.I.; Guillén Matus, D.G.; Duncan, K.R. Ecological Context for Bacterial Natural Products. *Nat. Prod. Rep.* **2026**, Online ahead of print. https://doi.org/10.1039/d6np00018e
507. Aboul-Ella, H.; Aboul-Ella, H.; De Zoysa, M. Marine Antimicrobial Peptides: From Ocean Biodiversity to Genome Mining, Multi-Omics Discovery, and Biotechnological Innovation in the Battle Against Antimicrobial Resistance. *Probiotics Antimicro. Prot.* **2026**, Online ahead of print. https://doi.org/10.1007/s12602-026-10959-2
508. Magalhães, R.; Mil-Homens, D.; Cruz, S.; Oliveira, M. Marine Antimicrobial Peptides: Emerging Strategies Against Multidrug-Resistant and Biofilm-Forming Bacteria. *Antibiotics* **2025**, *14*, 808. https://doi.org/10.3390/antibiotics14080808

 doi:10.20944/preprints202607.1303.v1

509. Xuma, C.; Bourles, A.; Colot, J.; Guentas, L.; Matsui, M. Marine Bacteria as a Source of Antibiotics Against *Staphylococcus aureus*: Natural Compounds, Mechanisms of Action, and Discovery Strategies. *Mar. Drugs* **2026**, *24*, 44. https://doi.org/10.3390/md24010044
510. Falanga, A.; Lombardi, L.; Franci, G.; Vitiello, M.; Iovene, M.R.; Morelli, G.; Galdiero, M.; Galdiero, S. Marine Antimicrobial Peptides: Nature Provides Templates for the Design of Novel Compounds against Pathogenic Bacteria. *Int. J. Mol. Sci.* **2016**, *17*, 785. https://doi.org/10.3390/ijms17050785
511. Patra, A.; Das, J.; Agrawal, N.R.; Kushwaha, G.S.; Ghosh, M.; Son, Y.-O. Marine Antimicrobial Peptides-Based Strategies for Tackling Bacterial Biofilm and Biofouling Challenges. *Molecules* **2022**, *27*, 7546. https://doi.org/10.3390/molecules27217546
512. Kim, T.; Tabassum, N.; Javaid, A.; Hassan, M.I.; Khan, F. Marine-derived Peptides As Anti-biofilm and Anti-virulence Agents: Mechanistic Insights and Applications Against Microbial Pathogens. *Probiotics Antimicro. Prot.* Online ahead of print. **2026**, https://doi.org/10.1007/s12602-026-10962-7
513. Saini, Y.; Wani, M.Y.; Hameed, S. Antifungal Peptides for Biofilm Disruption: Mechanisms, Design Strategies, and Translational Outlook. *Microb. Pathog.* **2026**, *217*, 108601, https://doi.org/10.1016/j.micpath.2026.108601
514. Huan, Y.; Kong, Q.; Mou, H.; Yi, H. Antimicrobial Peptides: Classification, Design, Application and Research Progress in Multiple Fields. *Front. Microbiol.* **2020**, *11*, 582779, https://doi.org/10.3389/fmicb.2020.582779
515. Talapko, J.; Meštrović, T.; Juzbašić, M.; Tomas, M.; Erić, S.; Horvat Aleksijević, L.; Bekić, S.; Schwarz, D.; Matić, S.; Neuberg, M.; Škrlec, I. Antimicrobial Peptides—Mechanisms of Action, Antimicrobial Effects and Clinical Applications. *Antibiotics* **2022**, *11*, 1417. https://doi.org/10.3390/antibiotics11101417
516. Beyer, L.I.; Thoma, J.; Alarcon, L.A.; Unksov, I.N.; Karlsson, R.; Inda-Díaz, J.S.; Tietze, A.A. Marine-Inspired Antimicrobial Peptides Disrupt Gene Expression at the DNA Level. *ACS Infect. Dis.* **2026**, *12*, 447–459, https://doi.org/10.1021/acsinfecdis.5c01000
517. Andersson, D.I.; Hughes, D.; Kubicek-Sutherland, J.Z. Mechanisms and Consequences of Bacterial Resistance to Antimicrobial Peptides. *Drug Resist. Updates* **2016**, *26*, 43–57, https://doi.org/10.1016/j.drup.2016.04.002
518. Rodríguez-Rojas, A.; Baeder, D.Y.; Johnston, P.; Regoes, R.R.; Rolff, J. Bacteria Primed by Antimicrobial Peptides Develop Tolerance and Persist. *PLoS Pathog.* **2021**, *17*, e1009443, https://doi.org/10.1371/journal.ppat.1009443
519. Tajer, L.; Paillart, J.-C.; Dib, H.; Sabatier, J.-M.; Fajloun, Z.; Abi Khattar, Z. Molecular Mechanisms of Bacterial Resistance to Antimicrobial Peptides in the Modern Era: An Updated Review. *Microorganisms* **2024**, *12*, 1259. https://doi.org/10.3390/microorganisms12071259
520. Lu, Y.; Zhang, B.; Wang, Z.; He, Y.; Ge, H.; Ma, H.; Cui, P. From Host-Derived Pressures to the Environmental Anti-Antimicrobial Peptides Resistome: Mechanisms, Reservoirs and Implications for Therapeutic Peptide Design. *Mar. Drugs* **2026**, *24*, 76. https://doi.org/10.3390/md24020076
521. Tabarzad, M.; Torshabi, M.; Haeri, A.; Fathi, F.; Mortazavi, S.M. Peptide-Based Antibiotics: Structure-Driven Strategies to Tackle Toxicity and Resistance of Antimicrobial Peptides. *Bioorg. Med. Chem.* **2026**, *133*, 118486, https://doi.org/10.1016/j.bmc.2025.118486
522. Fathi, F.; Alizadeh, B.; Tabarzad, M.V.; Tabarzad, M. Important Structural Features of Antimicrobial Peptides towards Specific Activity: Trends in the Development of Efficient Therapeutics. *Bioorg. Chem.* **2024**, *149*, 107524, https://doi.org/10.1016/j.bioorg.2024.107524
523. Ding, X.; Li, Y. Engineering Bispecific Peptides for Precision Immunotherapy and Beyond. *Int. J. Mol. Sci.* **2025**, *26*, 10082. https://doi.org/10.3390/ijms262010082
524. Qiu, J.; Wu, D.; Xu, C.; Zhuang, Y.; Lu, Y.; Sun, A.; Lu, X.; Han, J.; Ni, L. Current Advances and Emerging Prospects of Specifically Targeted Antimicrobial Peptides: A Comprehensive Review. *Int. J. Biol. Macromol.* **2025**, *322*, 147037, https://doi.org/10.1016/j.ijbiomac.2025.147037
525. Sreepathi, B.; Bhukkal, H.; Saraf, S.A.; Awasthi, S. Engineering Rules for Optimizing Antimicrobial Peptides from Sequence to Translation. *Chem. Eng. J.* **2026**, *530*, 173238, https://doi.org/10.1016/j.cej.2026.173238

 doi:10.20944/preprints202607.1303.v1

526. Xian, W.; Hennefarth, M.R.; Lee, M.W.; Do, T.; Lee, E.Y.; Alexandrova, A.N.; Wong, G.C.L. Histidine-Mediated Ion Specific Effects Enable Salt Tolerance of a Pore-Forming Marine Antimicrobial Peptide. *Angew. Chem. Int. Ed.* **2022**, *61*, e202108501, https://doi.org/10.1002/anie.202108501
527. Costerton, J.W.; Stewart, P.S.; Greenberg, E.P. Bacterial Biofilms: A Common Cause of Persistent Infections. *Science* **1999**, *284*, 1318–1322, https://doi.org/10.1126/science.284.5418.1318
528. Stewart, P.S.; Costerton, J.W. Antibiotic Resistance of Bacteria in Biofilms. *Lancet* **2001**, *358*, 135–138, https://doi.org/10.1016/S0140-6736(01)05321-1
529. Hall-Stoodley, L.; Costerton, J.W.; Stoodley, P. Bacterial Biofilms: From the Natural Environment to Infectious Diseases. *Nat. Rev. Microbiol.* **2004**, *2*, 95–108, https://doi.org/10.1038/nrmicro821
530. Hall, C.W.; Mah, T.-F. Molecular Mechanisms of Biofilm-Based Antibiotic Resistance and Tolerance in Pathogenic Bacteria. *FEMS Microbiol. Rev.* **2017**, *41*, 276–301, https://doi.org/10.1093/femsre/fux010
531. Ramage, G.; Kean, R.; Rautemaa-Richardson, R.; Williams, C.; Lopez-Ribot, J.L. Fungal Biofilms in Human Health and Disease. *Nat. Rev. Microbiol.* **2025**, *23*, 355–370, https://doi.org/10.1038/s41579-025-01147-0
532. Arciola, C.R.; Campoccia, D.; Montanaro, L. Implant Infections: Adhesion, Biofilm Formation and Immune Evasion. *Nat. Rev. Microbiol.* **2018**, *16*, 397–409, https://doi.org/10.1038/s41579-018-0019-y
533. Su, Y.; Yrastorza, J.T.; Matis, M.; Cusick, J.; Zhao, S.; Wang, G.; Xie, J. Biofilms: Formation, Research Models, Potential Targets, and Methods for Prevention and Treatment. *Adv. Sci.* **2022**, *9*, 2203291, https://doi.org/10.1002/advs.202203291
534. Mishra, A.; Aggarwal, A.; Khan, F. Medical Device-Associated Infections Caused by Biofilm-Forming Microbial Pathogens and Controlling Strategies. *Antibiotics* **2024**, *13*, 623. https://doi.org/10.3390/antibiotics13070623
535. Kjaerulff, L.; Nielsen, A.; Mansson, M.; Gram, L.; Larsen, T.O.; Ingmer, H.; Gotfredsen, C.H. Identification of Four New *agr* Quorum Sensing-Interfering Cyclodepsipeptides from a Marine *Photobacterium*. *Mar. Drugs* **2013**, *11*, 5051-5062. https://doi.org/10.3390/md11125051
536. Doiron, K.; Beaulieu, L.; St-Louis, R.; Lemarchand, K. Reduction of Bacterial Biofilm Formation Using Marine Natural Antimicrobial Peptides. *Colloid Surf. B-Biointerfaces* **2018**, *167*, 524–530, https://doi.org/10.1016/j.colsurfb.2018.04.051
537. Wang, K.-L.; Dou, Z.-R.; Gong, G.-F.; Li, H.-F.; Jiang, B.; Xu, Y. Anti-Larval and Anti-Algal Natural Products from Marine Microorganisms as Sources of Anti-Biofilm Agents. *Mar. Drugs* **2022**, *20*, 90. https://doi.org/10.3390/md20020090
538. Caudal, F.; Roullier, C.; Rodrigues, S.; Dufour, A.; Artigaud, S.; Le Blay, G.; Bazire, A.; Petek, S. Anti-Biofilm Extracts and Molecules from the Marine Environment. *Mar. Drugs* **2024**, *22*, 313. https://doi.org/10.3390/md22070313
539. Sukmarini, L.; Atikana, A.; Hertiani, T. Antibiofilm Activity of Marine Microbial Natural Products: Potential Peptide- and Polyketide-Derived Molecules from Marine Microbes toward Targeting Biofilm-Forming Pathogens. *J. Nat. Med.* **2024**, *78*, 1–20, https://doi.org/10.1007/s11418-023-01754-2
540. Almutairi, F.A.; Edrada-Ebel, R.A. Marine Fungal Metabolites: A Promising Source for Antibiofilm Compounds. *Molecules* **2025**, *30*, 4266. https://doi.org/10.3390/molecules30214266
541. Khan, M.A.; Zhu, L.; Zhu, H. Peptide-Based Approaches to Quorum-Sensing Disruption: Emerging Trends and Applications in Antimicrobial Therapy. *Bioorg. Med. Chem.* **2026**, *133*, 118496, https://doi.org/10.1016/j.bmc.2025.118496
542. Prakash, S.; Bharathi, S.; Soundara Rajan, Y.A.P.A.; Nisha, R.G.; Mohanasundaram, S.; Alagendran, S.; Kannapiran, E.; Ramasubburayan, R. Harnessing Marine Bacteria-Derived Compounds as Anti-Quorum Sensing Agents: a Spotlight on Sources, Mechanisms and Emerging Technologies. *Bioorg. Chem.* **2026**, 170, 109463, https://doi.org/10.1016/j.bioorg.2025.109463
543. Rangel, M.; Correia de Santana, C.J.; Pinheiro, A.; dos Anjos, L.; Barth, T.; Rodrigues Pires Júnior, O.; Fontes, W.; Castro, M.S. Marine Depsipeptides as Promising Pharmacotherapeutic Agents. *Curr. Protein Pept. Sci.* **2017**, *18*, 72–91, https://doi.org/10.2174/1389203717666160526122130
544. Semreen, M.H.; El-Gamal, M.I.; Abdin, S.; Alkhazraji, H.; Kamal, L.; Hammad, S.; El-Awady, F.; Waleed, D.; Kourbaj, L. Recent Updates of Marine Antimicrobial Peptides. *Saudi Pharm. J.* **2018**, *26*, 396–409, https://doi.org/10.1016/j.jsps.2018.01.001

 doi:10.20944/preprints202607.1303.v1

545. Al-Khayri, J.M.; Asghar, W.; Khan, S.; Akhtar, A.; Ayub, H.; Khalid, N.; Alessa, F.M.; Al-Mssallem, M.Q.; Rezk, A.A.-S.; Shehata, W.F. Therapeutic Potential of Marine Bioactive Peptides against Human Immunodeficiency Virus: Recent Evidence, Challenges, and Future Trends. *Mar. Drugs* **2022**, *20*, 477. https://doi.org/10.3390/md20080477
546. Sukmarini, L. Antiviral Peptides (AVPs) of Marine Origin as Propitious Therapeutic Drug Candidates for the Treatment of Human Viruses. *Molecules* **2022**, *27*, 2619. https://doi.org/10.3390/molecules27092619
547. do Amaral, S.C.; Xavier, L.P.; Vasconcelos, V.; Santos, A.V. Cyanobacteria: A Promising Source of Antifungal Metabolites. *Mar. Drugs* **2023**, *21*, 359. https://doi.org/10.3390/md21060359
548. Ribeiro, R.; Costa, L.; Pinto, E.; Sousa, E.; Fernandes, C. Therapeutic Potential of Marine-Derived Cyclic Peptides as Antiparasitic Agents. *Mar. Drugs* **2023**, *21*, 609. https://doi.org/10.3390/md21120609
549. Yang, H.; Zhang, Q.; Zhang, B.; Zhao, Y.; Wang, N. Potential Active Marine Peptides as Anti-Aging Drugs or Drug Candidates. *Mar. Drugs* **2023**, *21*, 144. https://doi.org/10.3390/md21030144
550. Yang, G.; Lin, M.; Kaliaperumal, K.; Lu, Y.; Qi, X.; Jiang, X.; Xu, X.; Gao, C.; Liu, Y.; Luo, X. Recent Advances in Anti-Inflammatory Compounds from Marine Microorganisms. *Mar. Drugs* **2024**, *22*, 424. https://doi.org/10.3390/md22090424
551. Zhang, X.; Zhuang, H.; Wu, S.; Mao, C.; Dai, Y.; Yan, H. Marine Bioactive Peptides: Anti-Photoaging Mechanisms and Potential Skin Protective Effects. *Curr. Issues Mol. Biol.* **2024**, *46*, 990-1009. https://doi.org/10.3390/cimb46020063
552. Lee, H.; Nihan, K.; Kwon, Y.R. Cyanobacterial Peptides in Anticancer Therapy: A Comprehensive Review of Mechanisms, Clinical Advances, and Biotechnological Innovation. *Mar. Drugs* **2025**, *23*, 233. https://doi.org/10.3390/md23060233
553. Debnath, I.; Ghosh, S.; Duttagupta, N.; Mondal, S.; Debata, J.; Nandi, S.; Bhattacharjee, S.; Dutta, R.; Jha, S.K.; Banik, N.; Bhowmik, M.; Chatterjee, A.; Roy, S.; Sil, A.; Gangopadhyay, A.; Ghosh, A.; Patra, S.; Das, S.; Das, D.; Mahato, P.; Khan, B. Unexplored Marine-Derived Microbial Metabolites as Next-Generation Antiparasitic Agents: Phytochemistry, Mechanistic Insights, and Translational Prospects. *Pharmacogn. Res.* **2026**, *18*, 279–294, https://doi.org/10.5530/pres.20260146
554. Saisavoey, T.; Boonserm, P.; Sangtanoo, P.; Srimongkol, P.; Karnchanatat, A. Antioxidant Peptide from *Synechococcus* Marine Microalgae with Therapeutic Potential against Human Colon Adenocarcinoma. *Future Foods* **2026**, *13*, 100895, https://doi.org/10.1016/j.fufo.2025.100895
555. Tiwari, V.; Elste, J.; Wang, C.; Zhang, F. Marine Derived Natural Products: Emerging Therapeutics Against Herpes Simplex Virus Infection. *Biomolecules* **2026**, *16*, 100. https://doi.org/10.3390/biom16010100
556. Xu, X.; Peng, J.; Shi, H. Isolation, Structures, and Mechanisms of Anti-Tumor Peptides from Marine Organisms: A Review. *Protein Pept. Lett.* **2026**, *33*, 422–438, https://doi.org/10.2174/0109298665451278260413074905
557. Zakariya, M.; Montuori, E.; Kopp, G.; Coppola, A.; Giordano, D.; Bruno, S.; Lauritano, C. Antioxidant, Anti-Inflammatory and Anticancer Peptides from Extreme Marine Environments. *Antioxidants* **2026**, *15*, 615. https://doi.org/10.3390/antiox15050615
558. Offret, C.; Desriac, F.; Le Chevalier, P.; Mounier, J.; Jégou, C.; Fleury, Y. Spotlight on Antimicrobial Metabolites from the Marine Bacteria *Pseudoalteromonas*: Chemodiversity and Ecological Significance. *Mar. Drugs* **2016**, *14*, 129. https://doi.org/10.3390/md14070129
559. Desriac, F.; El Harras, A.; Simon, M.; Bondon, A.; Brillet, B.; Le Chevalier, P.; Pugnière, M.; Got, P.; Destoumieux-Garzón, D.; Fleury, Y. Alterins Produced by Oyster-Associated *Pseudoalteromonas* Are Antibacterial Cyclolipopeptides with LPS-Binding Activity. *Mar. Drugs* **2020**, *18*, 630. https://doi.org/10.3390/md18120630
560. Rahmani, A.; Parizadeh, L.; Baud, M.; Francois, Y.; Bazire, A.; Rodrigues, S.; Fleury, Y.; Cuny, H.; Debosse, E.; Cabon, J.; Louboutin, L.; Bellec, L.; Danion, M.; Morin, T. Potential of Marine Strains of *Pseudoalteromonas* to Improve Resistance of Juvenile Sea Bass to Pathogens and Limit Biofilm Development. *Probiotics Antimicro. Prot.* **2025**, *17*, 640–654, https://doi.org/10.1007/s12602-023-10180-5
561. Andryukov, B.G.; Mikhaylov, V.V.; Besednova, N.N.; Zaporozhets, T.S.; Bynina, M.P.; Matosova, E.V. The Bacteriocinogenic Potential of Marine Microorganisms. *Russ. J. Mar. Biol.* **2018**, *44*, 433–441. https://doi.org/10.1134/S1063074018060020

 doi:10.20944/preprints202607.1303.v1

562. Fernando, I.P.S.; Jayawardena, T.U.; Wu, J. Marine Proteins and Peptides: Production, Biological Activities, and Potential Applications. *Food Innov. Adv.* **2023**, *2*, 69–84, https://doi.org/10.48130/FIA-2023-0009
563. Cui, Y.; Li, X.; Sun, Y.; Liu, Y.; Zhang, W.; Jiang, Y.; Zhou, Y.; Liu, J.; Gong, B.; Wu, Y.; Li, S.; Zhuang, L.; Cong, W.; Zhang, J. Separation, Characterization, AI Screening, and Bioactivities of Marine Bioactive Peptides: A Review. *Food Chem.* **2025**, *495*, 146312, https://doi.org/10.1016/j.foodchem.2025.146312
564. Bowman, J.P. Bioactive Compound Synthetic Capacity and Ecological Significance of Marine Bacterial Genus *Pseudoalteromonas*. *Mar. Drugs* **2007**, *5*, 220-241. https://doi.org/10.3390/md504220
565. Antunes, J.; Pereira, S.; Ribeiro, T.; Plowman, J.E.; Thomas, A.; Clerens, S.; Campos, A.; Vasconcelos, V.; Almeida, J.R. A Multi-Bioassay Integrated Approach to Assess the Antifouling Potential of the Cyanobacterial Metabolites Portoamides. *Mar. Drugs* **2019**, *17*, 111. https://doi.org/10.3390/md17020111
566. Liu, D.; Shu, H.; Zhou, J.; Bai, X.; Cao, P. Research Progress on New Environmentally Friendly Antifouling Coatings in Marine Settings: A Review. *Biomimetics* **2023**, *8*, 200. https://doi.org/10.3390/biomimetics8020200
567. Arroussi, M.; Al-Athel, K.; ulhaq Toor, I.; Zhang, R. Interspecies electron transfer of mixed-species biofilms in microbial corrosion of metals: mechanisms and mitigation strategies. *World J. Microbiol. Biotechnol.* **2025**, *41*, 375, https://doi.org/10.1007/s11274-025-04599-x
568. Miftah, J.A.; Hanif, N.; Tan, L.T.; Mulijani, S.; Mubarik, N.R. The Next Generation of Integrated Eco-Friendly Anti-Biofouling and Anti-Biocorrosion Marine Natural Products. *Chem. Biodivers.* **2025**, *22*, e02263, https://doi.org/10.1002/cbdv.202502263