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Review Article

Harnessing the Antimicrobial Potential of Red Sea Coral-Associated Bacteria: Current Insights and Future Directions

Samar S Al-Harbi*, Shahira A Hassoubah and Bothaina A Alaidaroos

Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia

***Corresponding Author:** Samar S Al-Harbi, Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia.

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Abstract

The global escalation of antimicrobial resistance (AMR) has intensified the search for new bioactive molecules, particularly from marine environments. Coral reefs are among the planet's most biodiverse ecosystems, harboring intricate microbiomes in which coral-associated bacteria (CAB) play pivotal roles in host nutrition, immunity, and pathogen exclusion. Genera such as *Bacillus, Streptomyces, Pseudoalteromonas,* and *Endozoicomonas* synthesize a chemically diverse array of secondary metabolites, including polyketides, lipopeptides, alkaloids, and terpenes, which display broad-spectrum antibacterial, antifungal, cytotoxic, and anti-inflammatory activities.

These metabolites not only defend corals against pathogens and biofouling but also hold promise as drug leads against multidrug-resistant organisms, including methicillin-resistant *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. Investigations, particularly from the Red Sea, continue to reveal novel compounds such as aqabamycins, actinosporins, and saadamycin, underscoring the remarkable chemical richness of CAB and the Red Sea's status as an underexplored reservoir of antimicrobial scaffolds.

This review first surveys bioactive natural products from terrestrial and marine origins to provide context for CAB-derived chemistry. It then synthesizes the latest findings on the diversity, biosynthesis, and antimicrobial modes of action of CAB metabolites, with a special focus on Red Sea isolates. By highlighting both ecological function and pharmaceutical potential, we emphasize the enormous yet largely untapped capacity of CAB to yield next-generation therapeutics and advocate for intensified bioprospecting, genome-guided discovery, and pharmacological evaluation to help curb the AMR crisis.

Keywords: Coral Reef; Coral-Associated Bacteria (CAB); Red Sea; Antimicrobial Compounds; Antimicrobial Resistance (AMR); Marine Natural Products

Introduction

Coral reefs rank among the planet's most productive and biologically intricate marine habitats, underpinning vital ecological, economic, and cultural services. They act as high-diversity refugia of unique chemicals and genetic resources, yet anthropogenic pressures, from coastal development to climate-driven warming, are rapidly eroding their resilience [1]. Within this global context, the Red Sea stands out as a natural laboratory: its exceptional temperature and salinity gradients, combined with relative geographic isolation, have fostered a reservoir of

distinctive marine life and metabolites. Recent surveys reveal that many Red Sea organisms, particularly their resident microbes, synthesize compounds not observed elsewhere, highlighting the basin's promise for biodiscovery.

Corals are now recognized as *holobionts,* multicellular hosts intricately allied with complex assemblages of bacteria, archaea, fungi, protists, and viruses. Far from being passive passengers, these microbial partners mediate nutrient cycling, modulate the coral immune system, and outcompete invading pathogens [2]. Among them, coral-associated bacteria (CAB) perform some of the most consequential roles. CAB generates chemically diverse secondary metabolites, including polyketides, lipopeptides, alkaloids, and terpenoids that confer antibacterial, antiviral, antifouling, antiparasitic, and even anticancer activities [3-5]. Genera such as *Bacillus*, *Pseudoalteromonas*, *Streptomyces,* and *Endozoicomonas* routinely dominate these microbial consortia, occupying ecological niches on coral mucus, tissue, or skeleton and suppressing opportunistic microbes through competitive exclusion and chemical interference [6,7].

Meanwhile, humanity faces an accelerating crisis of antimicrobial resistance: terrestrial antibiotics are losing efficacy against drug-resistant pathogens at a pace that threatens modern medicine itself [8-10]. This shortfall has pivoted attention toward marine-derived natural products, where intense ecological competition has driven the evolution of novel bioactive chemistry. CAB from the Red Sea is especially compelling; compounds such as aqabamycins and actinosporins, first isolated from Red Sea actinomycetes, exhibit potent, structurallyunique antibacterial profiles [11]. Importantly, mounting evidence shows that many metabolites once attributed solely to coral hosts are synthesized by their symbiotic microbes, underscoring the microbiome's central role in reef chemical defense and its untapped pharmacological potential.

Collectively, these insights motivate a dedicated review of antimicrobial agents produced by Red Sea CAB. Here, we synthesize current knowledge on their taxonomy, chemistry, and ecological functions, and discuss how this emerging resource can be harnessed to counteract AMR and infectious disease.

Overview of antimicrobial compounds

Antimicrobial compounds are substances, either naturally occurring, semi-synthetic, or fully synthetic, that inhibit the growth of or eliminate microorganisms at concentrations that are effective within living systems. These agents may target a wide spectrum of pathogens, including bacteria, viruses, fungi, and protozoa.

The rapid rise of antimicrobial resistance (AMR) has intensified global efforts to identify alternative antimicrobial agents. While synthetic antibiotics have long dominated clinical and agricultural use, their diminishing efficacy and the growing threat of resistance have driven renewed interest in natural sources. Bioactive molecules derived from plants, microorganisms, and other biological systems are gaining recognition for their potential to manage infectious diseases while potentially reducing the likelihood of resistance development [12].

Advances in genomics, metabolomics, and molecular biology, coupled with innovative screening platforms and computational tools such as machine learning, have significantly improved the process of identifying new antimicrobial leads. The use of cost-effective model organisms and high-throughput technologies has also accelerated the discovery of promising compounds and novel drug targets.

Despite decades of drug discovery, nature remains a largely untapped reservoir of chemically diverse antimicrobial agents. Microorganisms continue to be a prolific source of novel compounds with distinct structural classes and mechanisms of action. This highlights the need for continued exploration and bioprospecting in natural environments, especially in unique ecosystems like coral reefs, where microbial symbionts offer promising avenues for future antimicrobial development.

Applications of natural bioactive products

The term "bioactive" combines the Greek root bio ("life") with the Latin activus ("dynamic"). In practical terms, it denotes any molecule capable of triggering a measurable biological or physiological response in living systems, beneficial or adverse, depending on its chemistry, dose, and uptake [13]. Medical dictionaries further refine the idea, describing bioactive materials as those that can elicit, or actively participate in, a reaction within host tissue.

Bioactive compounds, both essential and non-essential, occur throughout natural food webs and are now recognized as important modifiers of human health [14]. Their broad utility

spans pharmacology, plant science, geomedicine, and the food industry, motivating efforts to map new sources, optimize synthetic routes, and scaleup production. Historically, such molecules have underpinned traditional remedies for pain, inflammation, and neurological conditions [15] and today support the development of food additives, functional foods, and nutraceuticals. A recurring obstacle is their oftenlow natural abundance, which necessitates intensive harvesting or sophisticated extraction from complex matrices such as plant tissues or microbial cultures [16].

A large share of these molecules belongs to the realm of secondary metabolites (SMs), small chemicals derived from primary metabolic pathways yet dispensable for routine growth or reproduction. Despite their "non-essential" label, SMs act as signalling agents, enzyme modulators, structural components, or ecological defences, mediating interactions between organisms and their environment. Because of this functional versatility, bioactive substances influence many facets of health maintenance and disease prevention. Diverse classes of proteins, polysaccharides, lectins, polyphenols, triterpenes, peptides, and more have demonstrated antimicrobial, antiviral, antioxidant, and anti-inflammatory properties, along with protective effects against chronic disorders such as cancer [17], inflammatory diseases, and neurodegeneration [15]. This breadth of activity underscores their value as both therapeutic leads and functional ingredients, sustaining continued exploration of natural sources, including the coral-associated bacteria highlighted in this review.

Mechanisms of action of antimicrobial compounds

Microbial cells rely on well-coordinated processes such as nutrient uptake, biomolecule synthesis, and division to maintain viability and propagate during colonization or infection. Antimicrobial compounds exert their effects by interrupting these essential cellular processes, thereby inhibiting growth or causing cell death. Understanding the molecular mechanisms behind these actions is fundamental to both antimicrobial therapy and the development of new strategies to overcome resistance.

Antimicrobial agents are broadly categorized based on their target site and mode of action. The mode of action may either be bactericidal, leading to microbial death, or bacteriostatic, halting growth without direct killing. Common targets include the cell wall, ribosomes, nucleic acids, metabolic enzymes, and the cytoplasmic membrane [18]. A summary of these mechanisms is presented in Table 1.

One of the most well-known classes of antibiotics, the β-lactams (e.g., penicillin), disrupt bacterial cell wall biosynthesis by inhibiting penicillin-binding proteins (PBPs), particularly transpeptidases. These enzymes are responsible for cross-linking the peptidoglycan matrix, which provides structural integrity to bacterial cells. Inhibition leads to weakened cell walls and eventual lysis [9,10]. Similarly, vancomycin, a glycopeptide antibiotic, binds to the terminal D-Ala-D-Ala residues of peptidoglycan precursors, thereby preventing polymerization and cross-linking. Modified analogs of vancomycin have been developed to overcome resistance in vancomycin-insensitive strains. Agents such as aminoglycosides and chloramphenicol target protein synthesis by binding to bacterial ribosomes. Aminoglycosides interfere with the initiation complex and cause misreading of mRNA, resulting in the production of non-functional or toxic proteins. Chloramphenicol acts at the 50S subunit, inhibiting peptidyl transferase activity and stalling peptide bond formation, effectively halting protein synthesis [11]. These drugs are particularly useful in treating infections caused by both Gram-positive and Gram-negative bacteria, including ocular and respiratory tract pathogens.

Another notable class of antimicrobials includes bacteriocins, ribosomally synthesized peptides produced by bacteria to inhibit closely related species. In Gram-negative bacteria, environmental stressors can alter membrane lipopolysaccharides, rendering the cells more susceptible to bacteriocin action. These peptides attach to the bacterial membrane, creating pores that collapse the proton motive force, disturb ion gradients, and disrupt ATP synthesis. This membrane depolarization ultimately leads to cell leakage, metabolic arrest, and lysis. The specific mechanism may vary by bacteriocin type, but membrane disruption is a unifying feature.

Natural sources of antimicrobial compounds

Natural environments, including terrestrial, aquatic, and even aerial ecosystems, harbor a vast diversity of organisms capable of producing bioactive compounds with antimicrobial properties. These compounds are derived from a wide range of biological sources, including plants, animals, microorganisms, and marine

Mechanism of Action	Description	Examples of Bacterial Genera	Reported Metabolites	Target Microorganisms
Cell Wall Inhibition	Blocks peptidoglycan formation, resulting in bacterial cell rupture	*Bacillus, Streptomyces*	Bacilysin, Actinomycin-D	*Staphylococcus aureus, Escherichia coli*
Protein Synthesis Inhibition	Disrupts ribosomal function to prevent protein formation	*Pseudovibrio, Micromonospora*	Tetracenomycin, Lankacidin	*Bacillus subtilis,* MRSA
DNA/RNA Synthesis Inhibition	Interferes with replication or transcription processes	*Salinispora, Streptomyces*	Salinosporamide A, Rifamycin	*Pseudomonas aeruginosa, Klebsiella spp.*
Cell Membrane Disruption	Compromises membrane integrity, leading to leakage of cell contents	*Vibrio, Pseudoalteromonas*	Brominated alkaloids, Alterochromides	*Candida albicans, Escherichia coli*
Quorum Sensing Inhibition	Blocks microbial communication systems and biofilm development	*Ruegeria, Pseudovibrio*	Tropodithietic acid, Indole derivatives	*Pseudomonas aeruginosa, a Biofilm-forming bacterium*
Enzyme Inhibition	Targets enzymes crucial for microbial survival and growth	*Actinobacteria, Bacillus*	Protease inhibitors, β-lactamase inhibitors	*Enterococcus faecalis, Staphylococcus aureus*
Reactive Oxygen Species (ROS) Generation	Generates oxidative damage to proteins, DNA, and membranes	*Pseudoalteromonas, Shewanella*	Marine alkaloids, Phenazine-like compounds	Broad-spectrum

Table 1: Mechanisms of Action of Antimicrobial Agents from Coral-Associated Bacteria.

organisms [19]. Historically, nature has served as a cornerstone for drug discovery, offering structurally diverse molecules with therapeutic potential across a broad spectrum of diseases. The contribution of natural products to modern medicine remains substantial. A comprehensive survey by Newman and Cragg [20] revealed that between January 1981 and September 2019, a total of 1881 new drugs were globally approved for clinical use, of which 75% (1418) were either natural products, derived from natural products, or inspired by their chemical structures. This highlights the enduring importance of natural sources in pharmaceutical development.

Among these, marine environments have emerged as particularly promising reservoirs of novel bioactive compounds due to their extreme conditions and biodiversity. Microorganisms isolated from unique ecological niches such as coral reefs, deep-sea sediments, and marine sponges have been shown to produce a wide range of antimicrobial agents, including polyketides, peptides, and alkaloids with potent activity against drug-resistant pathogens.

In parallel, plants continue to be explored for phytochemicals such as alkaloids, terpenoids, flavonoids, and phenolic compounds, many of which exhibit antibacterial, antifungal, and antiviral activities. Fungi, especially endophytic species, also serve as prolific producers of antibiotics and immunomodulators. Meanwhile, certain animals, such as amphibians and marine invertebrates, contribute antimicrobial peptides (AMPs) as part of their innate defense systems.

Together, these diverse natural sources not only enrich the chemical space for therapeutic exploration but also serve as critical templates for semi-synthetic modification, combinatorial

biosynthesis, and structure-activity relationship (SAR) optimization in drug discovery pipelines. Continued exploration of these resources, particularly underexplored environments such as the Red Sea coral ecosystem, holds immense potential for uncovering next-generation antimicrobial agents.

Overall, these diverse mechanisms of action reflect the sophisticated strategies employed by antimicrobial compounds and underscore their therapeutic relevance. A deeper understanding of these interactions not only informs clinical use but also facilitates the rational design of next-generation antimicrobials in response to evolving resistance.

Class of Secondary Metabolite	Representative Compounds	Source	Reference
Polyketides	Erythromycin, Ateramide A	Marine *actinomycetes, Salinispora sp*.	[21]
Non-ribosomal Peptides	Gramicidin S, Tyrocidine A, Surfactins	*Bacillus, Pseudomonas*, marine isolates	[22]
RiPPs	Bottromycin	*Actinomycetes*	[23]
Saccharides	Streptomycin	*Streptomyces griseus*	[24]
Terpenes	Geosmin	Various soil and marine bacteria	[25]
Alkaloids	Violacein	Chromobacterium, marine *Pseudoalteromonas*	[26]
Other Compounds	Clavulanic acid	*Streptomyces clavuligerus*	[27]

Table 2: Representative Secondary Metabolite Types.

Antimicrobial compounds from microorganisms

Bacterial-derived antimicrobials

Microorganisms, particularly bacteria, are prolific producers of bioactive secondary metabolites such as polyketides, terpenes, peptides, alkaloids, and shikimate derivatives [12]. Advances in molecular biology, genomics, and bioinformatics have enhanced the discovery of novel antibacterial agents from bacterial sources [12]. Bacteria utilize two primary biosynthetic routes for antimicrobial compound production: polyketide synthase (PKS) and non-ribosomal peptide synthase (NRPS) pathways. Other gene clusters also contribute to the synthesis of ribosomally synthesized and post-translationally modified peptides (RiPPs), alkaloids, terpenes, and saccharides [3]. Notably, *Bacillus subtilis* produces diverse secondary metabolites including lipopeptides (surfactins, iturins, fengycins), polyketides, non-ribosomal peptides, and macrolides with antimicrobial and surfactant properties [28]. These compounds have potential uses in agriculture, pharmaceuticals, and biocontrol.

Burkholderia species are another important source of antimicrobial agents, producing polyenes, bacteriocins, and nitrogen-containing heterocycles with antibacterial, antifungal, and anticancer properties [29]. Similarly, *Xenorhabdus* spp. generate compounds active against a broad spectrum of pathogens, including bacteria, fungi, and protozoa, yet remain underexplored [30].

Additionally, bacterial volatile nitrogenous compounds have demonstrated antioxidant, antimicrobial, antifungal, algicidal, and anticancer activities, highlighting the multifunctionality of bacterial metabolites [31].

Fungal-derived antimicrobials

Fungi are an essential source of pharmacologically active compounds, contributing to human health through the production of antibiotics, anticancer agents, and enzymes. Edible fungi such as *Agaricus blazei Murrill* are rich in polysaccharides, terpenes, sterols, and amino acids, offering antioxidant, antiviral, antitumor, and hepatoprotective effects.

Filamentous fungi like *Fusarium* spp. are known for their metabolic diversity and capacity to produce structurally diverse antimicrobial compounds with broad-spectrum activity against

pathogens, including *Bacillus cereus*, *Streptococcus pyogenes*, and *Candida albicans* [32]. Their secondary metabolites hold promise for the development of novel antimicrobial therapies.

Antimicrobial compounds from plants

Plants synthesize a vast array of primary and secondary metabolites with therapeutic potential. While primary metabolites support basic physiological functions, secondary metabolites such as alkaloids, flavonoids, phenolics, terpenoids, and glycosides play defensive and ecological roles, and often exhibit antimicrobial, antiviral, and antioxidant properties.

Due to their structural complexity and low abundance in nature, the large-scale extraction of plant-based bioactives poses significant challenges. However, plant cell culture techniques offer an alternative for consistent production [33]. Historical examples include the isolation of morphine from *Papaver somniferum* in 1806 [33], and the therapeutic use of *Bridelia* species in African and Southeast Asian traditional medicine for treating infections, metabolic disorders, and hypertension [34].

Modern studies also highlight flavonoids from *Scutellaria barbata* with anti-HIV and anti-inflammatory activities [35], and essential oils from *Cinnamomum osmophloeum* rich in cinnamaldehyde, effective against drug-resistant bacteria such as MRSA and *E. coli*.

Marine organisms as a source of antimicrobial compounds

Marine ecosystems represent a largely untapped reservoir of biologically active natural products with remarkable chemical and structural diversity. Unlike terrestrial environments, marine organisms are exposed to unique ecological pressures that have driven the evolution of diverse chemical defense mechanisms. As a result, marine natural products often exhibit novel scaffolds and bioactivities, making them highly valuable in drug discovery efforts. Over the past five decades, more than 20,000 new compounds have been isolated from marine sources, with over 300 marine-derived patents granted to date [36]. Several marine natural products have progressed into clinical or preclinical development, highlighting their translational potential.

Antimicrobial compounds from marine invertebrates and algae

Marine invertebrates, particularly sponges (phylum *Porifera*), are prolific producers of bioactive secondary metabolites. These compounds are often synthesized by symbiotic microorganisms residing within host tissues. The discovery of nucleosides spongothymidine and spongouridine from the sponge *Cryptotethya crypta* in the 1950s, precursors to the antiviral agents cytarabine and vidarabine, pioneered marine-based drug development [37]. Since then, over 5,000 unique metabolites have been identified from sponges and their microbial consortia, with ongoing discoveries reported annually. Marine macroalgae, including green, brown, and red seaweeds, are also significant producers of antimicrobial and bioactive compounds. These include polyphenols, terpenoids, sulfated polysaccharides, and pigments, which exhibit antioxidant, antiviral, anticoagulant, and anti-inflammatory properties [38]. The efficacy of these compounds is often governed by structural characteristics such as molecular weight, degree of sulfation, and charge distribution.

Echinoderms, including sea stars, sea cucumbers, and sea urchins, contribute additional chemical diversity. Sea stars produce steroidal glycosides and glycolipids, sea cucumbers are rich in triterpenoid saponins and sulfated polysaccharides, and sea urchins yield bioactive compounds with antimicrobial and antioxidant effects [39].

Marine microorganisms as emerging sources of antimicrobial agents

Marine-derived microorganisms, including bacteria, fungi, cyanobacteria, and diatoms, constitute an underexplored but highly promising source of novel antimicrobial agents. Adaptation to extreme oceanic conditions, such as high salinity, pressure, and low nutrient availability, has driven the evolution of unique biosynthetic pathways in these organisms [40]. Consequently, marine microbes produce structurally distinct and often more potent secondary metabolites than their terrestrial counterparts.

Among them, marine *Actinobacteria* and *Proteobacteria* are well recognized for synthesizing antibiotics, lipopeptides, and polyketides with potent activity against multidrug-resistant pathogens. Likewise, marine fungi have yielded chemically

diverse antibacterial and antifungal compounds not typically observed in terrestrial species [16]. Importantly, marine microbial fermentation provides a scalable and sustainable platform for producing these bioactives, facilitating their progression into therapeutic development.

Marine Bacteria: A goldmine for bioactive compounds

Marine bacteria are prolific producers of structurally diverse antimicrobial metabolites. Early discoveries date back to the 1940s–50s, with the first marine bacterial metabolites reported in the 1960s and their antibiotic properties recognized by the 1970s. Since the 1990s, research has revealed a wide array of antibacterial compounds effective against drug-resistant pathogens such as MRSA and vancomycin-resistant enterococci (VRE), including lanthipeptides, lipopeptides, and various classes of small molecules.

Actinobacteria contribute significantly to the chemical diversity of marine-derived metabolites. The range of identified compounds spans peptides, quinones, macrolactones, terpenoids, esters, and siderophores [41], reflecting marine bacteria's adaptive metabolic flexibility under extreme environmental pressures. The known taxonomic diversity of marine bacteria has expanded considerably since 1996, when only seven genera were classified as truly marine. Ongoing discoveries continue to reveal novel taxa associated with fish, algae, and marine invertebrates, highlighting their ecological versatility and biotechnological promise.

A notable example is Bacicyclin, a cyclic peptide isolated from *Bacillus sp*., the mussel *Mytilus edulis*, which exhibited strong antibacterial activity against *E. faecalis* and *S. aureus* [42]. These findings underscore the immense potential of marine bacteria as sources of new antimicrobial leads.

A summary of recently identified antimicrobial compounds from marine microorganisms is provided in Table 3.

Marine bacteria	Compound	Activity	Reference
Actinomycetes	Fijimicyns and Lynamicyns	Antimicrobial	[43]
Lactobacillus lactis subsp.	Nisin	Antibacterial	[44]
Bacillus sp.	Macrolactins	Antimicrobial	[43]
Bacillus amyloliquefaciens	Propanoic acid, ethyl ester Cyclopropane, 1,1-dichloro-2,2-dimethyl-3-(2-methylpropyl)- Phenol, 3,5-bis(1,1-dimethylethyl)	Antimicrobial	[45]
Streptomyces sp. ZZ745	Bagremycins	Antimicrobial	[46]
Micrococcus luteus	fatty acids 9,12-Octadecadienoic acid, methyl ester; 9,12-Octadecadienoic acid (Z,Z); Octadecanoic acid; a nitrogen containing compound 2-(Dimethylamino) ethyl vaccenoate	Antimicrobial	[47]
Nocardiopsis terra	Antimycin A4	Antimicrobial	[48]
Streptomyces sp.	2-Alkyl-4-hydroxyquinolines	Antifungal	[49]
Psychrobacter sp.	Not determined	Antimicrobial	[50]
Pediococcus sp.	oleic acid	Antimicrobial	[51]
Mytilus edulis	Bacicyclin	Antibacterial	[42]
Salinispora tropica	Salinosporamide A	Anticancer	[52]
Pseudoalteromonas sp.	Alterochromides, Brominated compounds	Antimicrobial, Antifouling	[53]

Vibrio sp.	Andrimid, Holomycin	Antibacterial	[54]
Marinobacter sp.	Benzoic acid derivatives	Antibacterial	[55]
Streptomyces albus	Albofungin	Antibacterial, Antifungal	[56]

Table 3: Bioactive Compounds Derived from Marine Bacteria with Reported Antimicrobial and Therapeutic Activities.

Red Sea: A unique reservoir of antimicrobial resources

The Red Sea, bordered by the Arabian Peninsula and northeastern Africa, is characterized by high salinity, intense solar radiation, low nutrient availability, and distinct reef ecosystems. These extreme environmental conditions have fostered a unique microbial community that can produce structurally novel and functionally potent bioactive metabolites.

Between 2009 and 2011, over 230 natural marine products were reported from the Red Sea region, with nearly half displaying antimicrobial activity. The microbial diversity of this ecosystem extends across various ecological niches, from coral reefs and sediments to host-associated symbionts, presenting a rich source for bioprospecting.

Novel Antimicrobials from red sea-derived marine bacteria

Recent studies have highlighted the Red Sea as a promising source of novel antimicrobial compounds from marine bacteria. For instance, Vibrio sp. WMBA, isolated from soft coral near Aqaba, Jordan, produced eight maleimide derivatives aqabamycins AG, that showed antibacterial activity against *Bacillus subtilis*, *Micrococcus luteus*, *E. coli*, and *Proteus vulgaris* [12]. In another study, *Streptomyces coelicolor* LY001, associated with the sponge *Callyspongia siphonella* off the coast of Jizan, yielded chlorinated phenylpropanoic acid derivatives with antibacterial effects against *S. aureus* and *E. coli* [57]. Further discoveries include Actinosporin A, an O-glycosylated angucycline from *Actinokineospora* sp. EG49 found in *Spheciospongia vagabunda*, and Saadamycin, a potent antifungal agent from Streptomyces sp. associated with *Aplysina fistularis*, which exhibited superior activity against *Aspergillus* and *Candida* species [4].

These examples underscore the biotechnological significance of the Red Sea microbiota, offering novel scaffolds for antimicrobial drug development. Continued exploration of this biodiverse marine ecosystem is crucial for addressing the global challenge of antimicrobial resistance.

Description of coral reef ecosystems

Coral reefs, often referred to as the "rainforests of the sea," are among the most ecologically diverse and economically valuable ecosystems. Despite occupying less than 0.1% of the ocean surface, they support approximately 25% of all marine species. This biodiversity, along with their roles in coastal protection and livelihood support for over 500 million people globally, underscores their ecological and socioeconomic importance. Shallow coral reefs have been extensively studied, but mesophotic coral ecosystems (MCEs) remain less explored. MCEs, located in deeper, light-penetrated zones, represent over 80% of potential reef habitat and harbor unique communities of light-dependent corals and associated fauna. While similar in structure to shallow reefs, upper mesophotic zones differ in species composition and density.

Coral reefs are characterized by high biodiversity, complex ecological interactions, and efficient nutrient cycling. However, anthropogenic pressures such as overfishing, pollution, and coastal development are increasingly threatening their stability and resilience.

Biodiversity of coral reefs in the red sea

The Red Sea's coral reefs are notable biodiversity hotspots, hosting species with potential thermal resilience. Over 260 species from 59 genera of reef-building Scleractinia corals, along with numerous soft corals and gorgonians, have been documented, with significant levels of endemism. Approximately 23% of species are considered rare or geographically restricted to the central-northern Red Sea.

Recent surveys report 94 genera and 359 Scleractinia species, with notable contributions from zooxanthellate corals. While some species are broadly distributed, others are exclusive to the Red Sea, reflecting high biogeographic uniqueness. Soft coral diversity is also significant, particularly in the Alcyoniidae family, represented by genera such as *Sarcophyton* and *Sinularia*.

The Red Sea's steep latitudinal gradient and variable environmental conditions offer a natural laboratory for studying coral adaptation to climate change. Despite this, reefs in areas like the Gulf of Aqaba face mounting pressures from urbanization, pollution, and climate impacts, necessitating robust conservation strategies.

Microbial diversity in coral ecosystems

Recent metagenomic studies have revealed the complex and dynamic microbial communities associated with corals. These communities, comprising bacteria, archaea, fungi, and dinoflagellates (e.g., *Symbiodinium*), contribute significantly to coral health, functioning as part of the coral holobiont.

Microbiome composition varies by coral species, geography, and environmental conditions. Changes in microbial communities often indicate coral stress responses to environmental shifts such as increased temperature, nutrient loading, acidification, and disease. Coral-associated microbes can be mutualistic, pathogenic, or play other ecological roles essential for host resilience [58]. Environmental stressors can induce a shift from beneficial to pathogenic microbial consortia, characterized by enrichment of genes associated with virulence, chemotaxis, lipid metabolism, and secondary metabolite production. Delgadillo-Ordoñez., *et al*. [59] found that *Proteobacteria* dominate coral microbiomes (49.8%), followed by *Firmicutes* (11.9%), *Actinobacteria* (10.4%), and *Bacteroidetes* (10%). Bacterial abundance and diversity differ across coral compartments. Mucus supports high microbial loads, enriched with members of the Cytophagales-Flavobacteria-Bacteroidetes (CFB) group and *Gammaproteobacteria* and *Alphaproteobacteria* classes. These microbes play crucial roles in nutrient cycling, defense, and coral adaptation to environmental fluctuations.

Symbiotic relationships in coral microbiomes

Symbiotic interactions between corals and associated microorganisms play a vital role in maintaining the health and stability of coral reef ecosystems. These relationships facilitate key processes such as nutrient exchange, signaling, and genetic interactions, significantly contributing to coral resilience. Coral-associated bacterial communities are involved in biogeochemical cycling, metabolic functions, and defense against pathogens [60].

Among the most prominent symbionts are *Endozoicomonas* spp., which are widely distributed in corals from shallow to deep marine environments. These bacteria assist in synthesizing amino acids and vitamins for the coral host [61], and their genomic distinctiveness across coral species highlights specialized symbiotic interactions. Genomic evidence further suggests that *Endozoicomonas* can detect and influence host responses, emphasizing their functional significance.

Coral-associated bacteria also play crucial roles in nitrogen and sulfur cycling, phosphorus utilization, carbon metabolism, and trace metal regulation, which enhance coral tolerance to environmental stressors. Some taxa are involved in the metabolism of dimethylsulfoniopropionate (DMSP), with implications for sulfur cycling and microbial defense [62].

Understanding these coral-microbe symbioses is essential for developing strategies to support reef health, especially under climate stress. For instance, inoculation with nitrogen-fixing bacteria has been proposed to enhance coral thermal resilience. However, environmental changes or anthropogenic pressures can disrupt these associations, leading to microbial dysbiosis and coral disease.

Antimicrobial compounds from marine bacteria associated with coral reef organisms

Coral reefs are among the most biodiverse ecosystems, harboring a multitude of microbial species with significant biotechnological potential. Each square centimeter of coral surface can host thousands of microbial taxa, with microbial abundance exceeding that of surrounding seawater by an order of magnitude [43].

The class Anthozoa, within phylum Cnidaria, comprises many coral species that host dense and diverse bacterial communities. These coral-associated bacteria (CAB) contribute to host development and immunity. However, most studies on CAB-derived metabolites focus on shallow reef systems, while the deep-

sea coral microbiome remains largely uncharacterized [3]. Figure 3 illustrates that most bioactive compounds identified to date originate from shallow-water corals, particularly those in genera such as *Sinularia*, *Junceella*, *Acropora*, *Antipathes*, and *Galaxea*. Despite limited sampling, deep-sea CABs may harbor novel and biotechnologically valuable metabolites.

The coral surface mucus layer (SML) is considered a hotspot for antimicrobial compound production. Many CABs within the SML secrete antibiotics to outcompete other microbes and protect the coral from pathogens [6]. These symbiont-derived antimicrobials form a crucial part of the coral's innate immune defense, preventing microbial imbalance, disease, bleaching, and mortality [7]. Despite this, the chemical nature of most CAB-derived antimicrobial compounds remains unidentified, highlighting a promising direction for future drug discovery research. A significant proportion of the coral-associated bacterial (CAB) isolates exhibited antimicrobial or antibiofilm activity [3], (Figure 1).

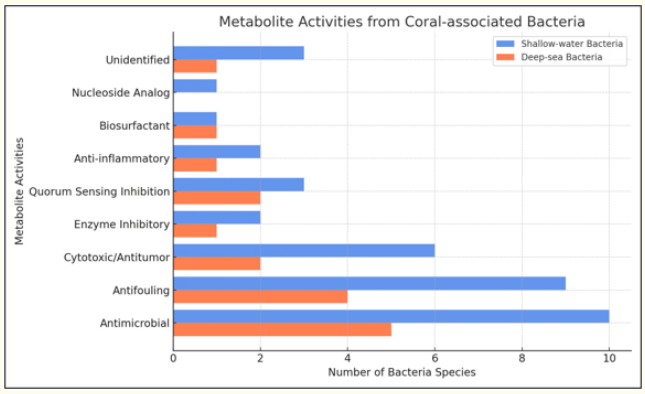

Figure 1: Distribution of coral-associated bacteria based on metabolite activity and origin.

Antibacterial potential of coral-associated bacteria

Coral-associated bacteria have demonstrated remarkable antibacterial potential, attracting increasing scientific attention. Zhang., *et al*. [63] reported that 51% of isolates from the black coral *Antipathes dichotoma* exhibited antagonistic activity against marine bacteria and coral fungal pathogens. Such antimicrobial agents are not only crucial for maintaining coral health but also show promise for therapeutic and industrial applications [3].

Notably, *Bacillus amyloliquefaciens* SCSIO 00856, isolated from a gorgonian coral, produced macrolactin V effective against *S. aureus*, *B. subtilis*, and *E. coli* along with four additional antimicrobial compounds [64]. Similarly, Atencio., *et al*. [65] isolated 39 *Pseudoalteromonas* strains from Panamanian octocorals, all exhibiting antibacterial and antifungal activity.

Streptomyces sp. OUCMDZ-1703, recovered from unidentified soft corals in the South China Sea, synthesized novel polyketides (strepchloritides A and B) with antibacterial and anticancer properties, as well as known compounds such as aerugine and watasemycin A [66]. *B. amyloliquefaciens* also produced antifungal metabolites during coculture with *Aspergillus fumigatus* [67].

Other applications of coral-associated bacteria (CAB)

Coral-associated bacteria (CAB) have emerged as prolific producers of secondary metabolites with diverse biotechnological applications. Several studies have highlighted their roles in pharmacology, antifouling, and enzyme inhibition. For instance, *Streptomyces* species isolated from soft corals in the South China Sea produce cytotoxic compounds such as carboxamides, ethenones, and thiazole derivatives that effectively inhibit MCF-7 breast cancer cells [66]. Similarly, *Pseudoalteromonas* species biosynthesize bioactive pigments with antibacterial, antifouling, and anti-algal properties [6].

A strain of *Vibrio neocaledonicus* isolated from coral in the South China Sea yielded three enzyme-inhibiting metabolites: indole, 4-hydroxybenzaldehyde (4HBA), and 1H-indole-3-carboxaldehyde (I3CA). These compounds inhibit key enzymes such as xanthine oxidase (XO), alpha-glucosidase (AG), and acetylcholinesterase (AChE), which are implicated in diseases like gout, diabetes, and Alzheimer's. Indole also showed venom-neutralizing activity [68]. *Vibrio* sp. and an unidentified alphaproteobacterium from the octocoral *Dendronephthya* sp. significantly reduced the larval settlement of the fouling tubeworm *Hydroides elegans*, demonstrating potent antifouling capabilities. Additionally, *Pseudoalteromonas* sp. CGH2XX, isolated from *Lobophytum crissum*, produces pseudoalteromone A, a compound with cytotoxicity against MOLT-4 leukemia cells and anti-inflammatory activity via neutrophil elastase inhibition.

Deep-sea CAB strains such as *Streptomyces cyaneofuscatus* M-27 and *S. carnosus* M-40, isolated from marine invertebrates in the Avilés Canyon, produce a suite of bioactive compounds including anthracyclines (e.g., daunomycin, cosmomycin B), antifungals (maltophilins), and anti-inflammatory agents with antituberculosis potential. A novel strain, *Saccharopolyspora jiangxiensis* IMA1, isolated from coral reefs, produces metabolites with strong antimicrobial activity against *Vibrio* pathogens and antioxidant effects. These metabolites also show cytotoxicity against MCF-7 breast cancer cells [5]. Furthermore, El-Gendy., *et al*. [4] reported the isolation of 51 *Streptomyces* strains from *Sarcophyton convolutum* soft coral, exhibiting broad-spectrum bioactivities. These include antibacterial, antifungal, antiviral (anti-HCV), antibiofilm (against MRSA and *Pseudomonas*), and anti-proliferative effects on liver and colon carcinoma cell lines.

Collectively, these findings underscore the immense potential of CAB-derived metabolites for biomedical, environmental, and industrial applications.

Challenges and future directions in coral-associated bacteria research

Despite their promising bioactive potential, several challenges hinder the full exploitation of coral-associated bacteria for drug discovery. A significant barrier is the difficulty in cultivating many of these microorganisms under standard laboratory conditions. It is estimated that over 99% of marine microbes are "unculturable" using conventional techniques, limiting access to their metabolic repertoire [69]. Although recent advances in metagenomics, single-cell genomics, and synthetic biology have enabled the partial reconstruction and heterologous expression of biosynthetic gene clusters from uncultured microbes, translating these discoveries into functional and scalable systems remains complex.

Moreover, horizontal gene transfer within coral holobionts presents concerns regarding genetic stability, biosafety, and the potential spread of antimicrobial resistance genes. Compounding these technical barriers are broader environmental issues: climate change, ocean acidification, and anthropogenic pollution are driving the degradation of coral reefs worldwide. These stressors not only threaten coral survival but also disrupt the structure and function of their associated microbiomes, risking the loss of microbial diversity and the extinction of yet-undiscovered bioactive compounds.

Looking ahead, future research on CAB must embrace integrative, multi-omics approaches linking genomics, transcriptomics, metabolomics, and advanced bioinformatics to comprehensively map the biosynthetic potential of these microbes and overcome cultivation limitations. At the same time, efforts must align with sustainable and ethically responsible bioprospecting practices. Frameworks such as the Nagoya Protocol guide fair and equitable access to marine genetic resources while emphasizing conservation and benefit-sharing. By combining technological innovation with ecological stewardship, CAB research can unlock new frontiers in marine drug discovery while safeguarding the biodiversity upon which it depends.

Future perspectives and research gaps

Despite increasing recognition of coral-associated bacteria (CAB) as a promising reservoir of novel bioactive compounds, several critical research gaps hinder their effective translation into pharmaceutical applications. A major limitation lies in the limited exploration of coral ecosystems, particularly deep-sea, mesophotic, and remote reef systems, which are likely to host distinct microbial communities with unique biosynthetic gene clusters (BGCs). These underexplored niches may represent untapped sources of structurally diverse and pharmacologically potent metabolites.

Current research is predominantly confined to in vitro antimicrobial assays, which, while valuable, fall short of establishing clinical relevance. There is an urgent need for comprehensive in vivo studies, including assessments of toxicity, pharmacokinetics, bioavailability, and efficacy in relevant disease models. Without this translational step, many CAB-derived compounds remain at the level of preclinical promise. Technological advances in multi-omics approaches such as metagenomics, transcriptomics, and metabolomics are beginning to shed light on the metabolic potential of uncultured or difficult-to-cultivate CAB [70]. Moreover, synthetic biology is poised to play a transformative role by enabling the heterologous expression of complex biosynthetic pathways in tractable microbial hosts. This not only circumvents cultivation barriers but also allows for pathway optimization and scalable production.

To fully realize the biomedical potential of CAB, interdisciplinary research integrating marine ecology, microbial genomics, natural product chemistry, and pharmacology is essential. Collaborative

efforts, supported by open-access databases and standardized screening platforms, will accelerate the identification and development of CAB-derived therapeutics.

Conclusion

Natural products have long played a pivotal role in drug development, with over half of current pharmaceuticals derived from or inspired by bioactive natural compounds. Among microbial sources, bacteria, particularly those producing secondary metabolites, stand out as prolific producers of structurally diverse and pharmacologically active molecules. However, the growing threat of antimicrobial resistance underscores the urgent need for novel therapeutic agents with enhanced efficacy and reduced side effects.

Marine environments, especially unique ecosystems like the Red Sea, offer an underexplored reservoir of microbial biodiversity shaped by extreme conditions such as high salinity, intense UV radiation, and low nutrient availability. Corals, particularly within the class Anthozoa (phylum Cnidaria), harbor dense and diverse communities of associated bacteria. These coral-associated bacteria (CAB) have demonstrated potential in producing antimicrobial compounds that may not only protect their hosts from pathogens but also offer promising candidates for human therapeutic development.

Despite this potential, the specific antimicrobial metabolites of CAB remain largely under characterized. Continued exploration of coral microbiomes holds significant promise for the discovery of new bioactive compounds and the development of next-generation antimicrobials.

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