Review:

A Review of Marine Bacterial Intracellular and Extracellular Bioactive Compounds as Novel Antibacterial and Anti-Inflammation Agents

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Abstract: *Unique and varied bioactive compounds produced by the ocean have drawn attention and served as a focus for creating antibacterial and anti-inflammatory agents. As part of the approach for locating these research sources, databases such as PubMed, Science Direct, MDPI, Google Scholar, Springer Link, Web of Science, Scopus, and Wiley Online Library were used to identify completed studies. Numerous intriguing bioactive compounds have so far been isolated from marine bacteria. A crucial resource in the ongoing search for novel peptides, proteins, lipids, nucleosides, enzymes, alkaloids, polyketides, and terpenoids is the diversity of marine bacterium strains. This review summarizes several bacterial intracellular and extracellular bioactive compounds that have been applied as antibacterial and anti-inflammatory agents in 2016–2024, which we present in the form of structures, species sources, and evaluations of these compounds' antibacterial and anti-inflammatory activities. Therefore, this review article can be used as a recommendation for utilizing biomaterials from marine bacteria that are promising in the future for industrial-scale production of antibacterial and anti-inflammatory agents.*

Keywords: *antibacterial; anti-inflammation; bioactive compounds; marine bacteria*

■ INTRODUCTION

The word "antibiotic" derives from the Greek word "antibiosis", which means "against life" [1-2]. In the past, people used to think of antibiotics as chemical substances produced by one type of bacteria but poisonous to another [2]. Based on this description, antibiotics were initially generally defined as compounds produced by a bacterium or other organisms [3] that at low quantities could stop the growth of or kill other bacteria [4]. However, in recent times, this definition has been expanded to encompass antimicrobial substances manufactured partially or entirely synthetically. Some antibiotics can only prevent other bacteria from growing, while others can destroy them [5]. Bactericidal and bacteriostatic substances prevent bacteria growth [6]. Antibiotics are classified as antiviral, antifungal, and antibacterial to correspond with the types of microbes they antagonize, even though they are commonly called "antibacterial" [7-8].

Most antibacterial medications used in medicine are made from natural materials or closely resemble them [2,9]. A total of 98 small-scale commercial combinations of antibacterial medications with identifiable structural motifs derived from nature were present between 1981 and 2005 [10]. Selection necessitated by bacteria leads to random chromosomal changes, which allow the bacteria to "adapt" to life in the presence of particular antibacterial chemicals [11-12]. Resistance to bactericidal drugs develops faster because of the rapid expansion of the genetic material encoding adherence [13]. The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and epidemic-level *Pseudomonas* resistant to fluoroquinolones in 2010 marked the turning point of bacterial infections [14-15].

Since the majority of antibiotic classes were discovered between 1940 and 1960, a period known as the "golden age" of antibiotic research [16], it is believed that the chemical arsenal available for treating human microbiological infections is sufficient. The development of germ resistance to antibiotics has, however, been fast. Microbes are subjected to selective pressure by antimicrobial agents, which causes random selection and chromosomal alterations that increase their susceptibility to environmental factors such as antibiotics, disinfectants, and chemical compounds [17-19]. Resistance-producing genetic material quickly replicates and spreads [20]. Additionally, antimicrobial drug persistence is greatly accelerated by the excessive and inappropriate use of antimicrobial medicines [21-22]. Antibiotic-resistant bacteria are categorized as agents that are detrimental to human health by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) [23-24]. These organizations also predict that by 2050, antimicrobial resistance might be responsible for up to 100 trillion US dollars of global economic losses or 10 million fatalities annually [25].

The marine environment covers 70% of the planet's surface. It has a much greater phylogenetic diversity than the various types of bacteria that have evolved to withstand particular environmental conditions (such as low light, high pressure, high acidity, low temperature, and varying oxygen content and salinity), which lead to the production of primary and secondary metabolites with unique structures and complex bioactivity [26-28]. Bioactive compounds produced by microorganisms, particularly bacteria, are thought to be interesting due to their structural variety and potential [29-30]. Numerous new pharmaceutical compounds can be made from sediments and bacteria produced by marine species [31]. Related marine bacteria secrete biologically active substances used as nutrients (such as carbon) from the host to defend themselves from potentially dangerous environmental components [32]. This review covered recent and trending topics such as intracellular and extracellular bioactive compounds with antibacterial and anti-inflammatory activity from marine bacteria.

■ METHODS USED FOR LITERATURE COLLECTION

Online databases like PubMed, Science Direct, MDPI, Google Scholar, Springer Link, Web of Science, Scopus, Research Gate, and Wiley Online Library were used to conduct the literature search for this review. In addition, the selection of articles used exclusion and inclusion criteria using articles written in English. We also followed several steps recommended by PRISMA, such as writing a structured summary of each article,

assessing studies and research methods, identifying the limitations of each study, drawing conclusions, and looking for implications of the main findings. Reviews are arranged based on the order of topics. This paper reviews the latest developments in marine bacterial intracellular and extracellular bioactive compounds as antibacterial and anti-inflammatory agents. The search approach is centered on principal keywords that are utilized in different combinations, such as bioactive compounds of marine bacteria, antibacterial and anti-inflammatory marine bacteria, and the structure of bioactive marine bacteria [33].

■ DIFFERENT MARINE BACTERIA PHYLA PRODUCE ANTIMICROBIAL AND ANTI-INFLAMMATION AGENT

Marine environments, particularly the ocean, are rich sources of diverse microorganisms, including bacteria with unique metabolic capabilities. Marine bacteria have evolved to produce bioactive compounds as a survival strategy against competing microorganisms or as a defense mechanism against predators. These compounds can exhibit antimicrobial and anti-inflammatory properties, making them potentially valuable for therapeutic and pharmaceutical applications [34-35]. These marine bacteria phyla have evolved unique biosynthetic pathways to produce a wide range of bioactive compounds, many exhibiting antimicrobial and anti-inflammatory properties [36-39]. Some marine bacterial phyla generate antibacterial and anti-inflammatory including the mechanism of action of every compound, as shown in Table 1. These compounds can potentially be developed into new therapeutic agents or serve as lead compounds for drug discovery efforts.

■ INTRACELLULAR BIOACTIVE COMPOUNDS OF MARINE BACTERIA

Peptides

The class of proteins known as antimicrobial peptides exhibits broad-spectrum antimicrobial action and is well-known to be effective against various infections. Numerous antimicrobial peptides (AMPs) exhibit an immediate and direct antibacterial effect by disrupting the physical integrity of the microbial membrane and/or by crossing the membrane to reach the cytoplasm of bacteria and act on intracellular targets [39]. These chemicals partially resolved the microbial resistance conundrum, which restricted the use of many effective antimicrobial medicines [52]. AMPs are a new treatment option for cancer patients since they also have antibacterial and anticancer capabilities. AMPs are currently mostly used in medicine to treat inflammation, wound healing, and infections caused by harmful microorganisms [53-54]. Despite these promising findings, only a few studies have focused peptide sources on exophytic bacteria derived from marine biota. In recent years, other studies have also reported using various proteins and/or peptides from marine microorganisms as antibacterial and anticancer agents [55-56]. Our group has shown that protein hydrolysates obtained from different sources of microsymbiont marine algae could effectively inhibit pathogenic bacteria and HeLa

Table 1. Marine bacterial phyla generate antibacterial and anti-inflammatory compounds

Phyla	Marine bacteria species	Mechanism of action	Ref.
Proteobacteria	*Pseudoalteromonas* sp.	Antimicrobial and antitumor compounds: proteins, polypeptides, and pigments	[40-41]
	Vibrio sp.	Antimicrobial and anti-inflammatory compounds: android and brindle	[42-43]
Actinobacteria	*Salinispora* sp.	Antimicrobial and anticancer compounds: salinosporamide A and salinosporamide K	[44-45]
	Streptomyces sp.	Antimicrobial, anticancer, antiviral compounds: lantimycins and streptonigrin	[46]
Firmicutes	*Bacillus* sp.	Antimicrobial compounds: surfactants, iturins and fengycin	[47-49]
Bacteroidetes	*Flavobacterium* sp.	Antimicrobial compounds: flavocyclomycin	[50]
Cyanobacteria	*Lyngba* sp., *Oscillatoria* sp.	Antimicrobial and anti-inflammatory compounds: dolastatin, curacin, and lyngbyatoxin	[51]

cancer cell lines [57-58]. These findings collectively indicate the potential of intracellular bioactive compounds of aquatic bacteria and peptide-based approaches in combating various diseases, including cancer, antibacterial, and anti-inflammatory. Further research could lead to the development of new and effective therapeutic agents for these health conditions. The structure of antibacterial peptide compounds from marine bacteria based on the results of previous studies is summarized in Table 2.

Lipid

The antimicrobial lipid classes that have been studied the most over the years include sterols, fatty acids, diacylglycerols (DAG), monoacylglycerols (MAG), and terpene derivatives [65]. The efficacy of these lipids against different microorganisms is dependent on both the medium's pH and their chemical makeup [66]. The structure-activity relationship between free fatty acids (non-esterified) and bacteria is dependent on the acyl chain length, stereochemistry, degree of unsaturation, and esterified form of the fatty acids [67]. In Gram-positive bacteria, long-chain fatty acids (C12 or above) are effective at low concentrations and under pH dependence [68-69], but short-chain fatty acids (C6 or below) are effective at high concentrations and pH dependence [70]. It has also been observed that unsaturated isomers are more potent against Gram-negative bacteria and that *cis*-isomers are more active than trans-isomers [71]. Table 3 displays the composition of the antibacterial lipid molecules produced by various marine bacteria.

Table 2. Structure of antibacterial peptide compounds from marine bacteria

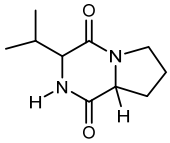
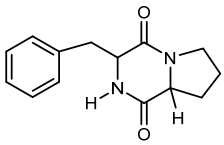
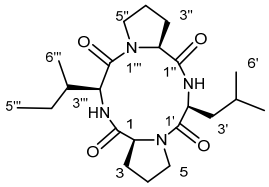
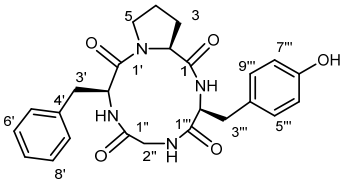
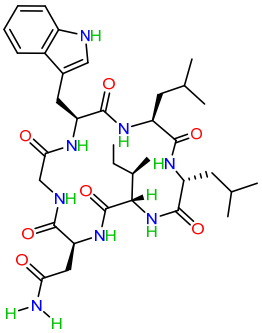
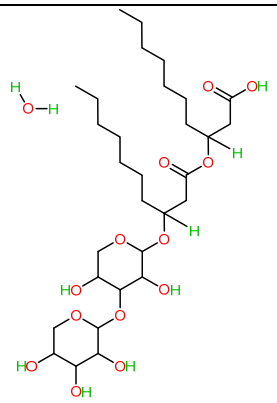
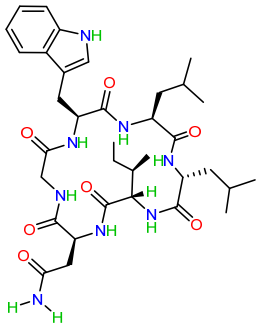
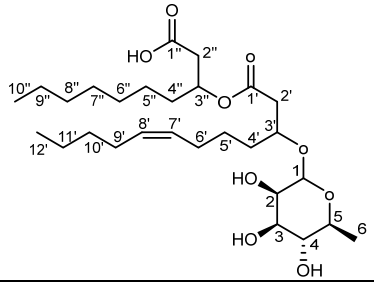
Peptide Compounds	Structure	Marine bacteria species	Mechanism of action	Ref.
Diketopiperazine: cyclo-(L-valiyl-D-proline)		*R. japonica* strain KMM 9513	Effective against methicillin-resistant *S. aureus*	[59]
			Antitumor, antiviral	
		S. rochei	Anticancer	[60]
cyclo-(L-phenylalanyl-D-proline)				
Tetrapeptides: cyclo-(Leu-Pro-Ile-Pro)		*B. amyloliquefaciens* GAS 00152	Antitumor, antibacterial	[61]
cyclo-(Tyr-Pro-Phe-Gly)		*Ruegeria* sp.	Effective against *S. aureus* ATCC 25923, *E. coli* ATCC 25922	[62]
			Antitumor, antihelminth	[63]
Desotamide		*Streptomyces* sp. NRRL 21611, *Streptomyces* sp. JAMM992, *S. scopuliridis* SCSIO Z	Effective against *S. aureus*, MRSE pneumoniae, *Mycobacterium* sp.	[64]

Table 3. Structure of antibacterial lipid compounds from marine bacteria

Lipid Compounds	Structure	Marine bacteria	Mechanism of action	Ref.
Glycolipid glycosyltransferase		*S. saprophyticus* SBPS 15,	Effective against methicillin-resistant *E. coli*, *K. pneumonia*, *V. cholerae*, and *P. aeruginosa*	[75]
		Candidatus Pelagibacter sp. HTCC7211	Effective against Gram-positive bacteria	[76]
Desotamide		*Streptomyces* sp. NRRL 21611, *Streptomyces* sp. JAMM992, *S. scopuliridis* SCSIO Z	Effective against *S. aureus*, MRSE, *S. pneumoniae*, and *Mycobacterium* sp.	[64]
Rhamnolipids		*P. fluorescence*	Effective against *S. aureus*, *E. faecalis*, *S. agalactiae*, *E. coli*, and *P. aeruginosa*	[77]

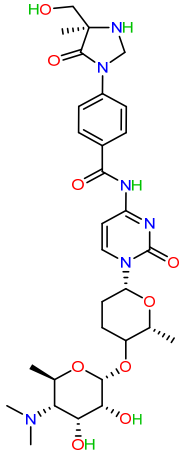
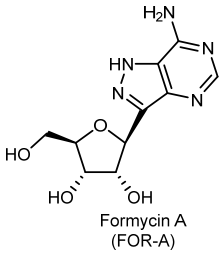
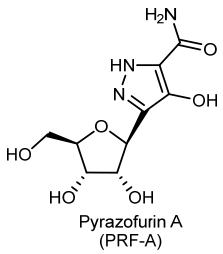
Nucleosides

Marine microorganisms are capable of producing a variety of nucleosides with unusual structures and biological characteristics [72]. The discovery of these remarkable biological characteristics in marine nucleosides has sparked a great deal of research into the synthesis of their various analogs and the ongoing evaluation of their biological factors, such as analgesic, anti-inflammatory, antibacterial, and anticancer activities [73]. The search for novel analogs of natural nucleosides with potential biological properties has accelerated the field of nucleoside chemistry research [74]. Based on earlier research findings, the composition and structure of antibacterial nucleoside compounds in various marine bacteria are outlined in Table 4.

Enzymes

The enzymes generated by marine microorganisms have numerous applications in the bioindustry. Utilizing microorganisms with elevated yields and production rates is crucial in manufacturing industrial enzymes. Enzymes such as amylase, casein, lipase, gelatinase, and DNase are found in microbes isolated from severe maritime environments. These enzymes are thermally stable, resistant to a wide range of pH values and other harsh conditions required for industrial applications and may have biological applications related to human health [80]. According to the research findings, enzymes produced by marine bacteria with a score of 4 or higher were selected for 16S rRNA molecular analysis. About 161 bacterial isolates

Table 4. Structure of antibacterial nucleoside compounds from marine bacteria

Nucleoside compounds	Structure	Marine bacteria	Mechanism of action	Ref.
Rocheicoside A		*S. rochei* 06CM016	Effective against *E. faecium* DSM 13590: vancomycin resistant; *E. coli* O157:H7 RSKK 234: streptomycin, sulfisoxazole and tetracycline-resistant; *S. aureus*: MRSA; *P. aureginosa* ATCC 27853	[78]
Formycin A	 Formycin A (FOR-A)	*N. interforma, S. kaniharaensis* SF-557	Antiviral and antitumor activities	[79]
Pyrazofurin A	 Pyrazofurin A (PRF-A)	*S. candidus* NRRL 3601, *S. lavendulae*	Antitumor activities	[79-80]

produced 68.7% of amylase, 88.3% of lipase, and 68.7% of protease in their secretions. Phylogenetic analysis led to the discovery of 4 major phyla: actinobacteria, proteobacteria, firmicutes, and bacteroidetes [81-82]. Several types of antibacterial enzymes contained in several marine bacteria are shown in Table 5.

■ EXTRACELLULAR BIOACTIVE COMPOUNDS OF MARINE BACTERIA

Alkaloid

Natural products are small molecules that are isolated from biological sources. They have long been recognized for their tremendous promise in human medicine, and in recent years, their popularity has continued to expand [9]. In the field of pharmaceutical development, natural product discovery has overtaken (combinatorial) chemistry thanks to the advent of novel technologies like more precise analytical methods or enhanced genome mining algorithms [84]. The most common antibacterial substances in marine environments are alkaloids [85]. A class of compounds known as marine alkaloids has shown promise in medicine [86]. Table 6 lists a few kinds of marine bacteria with a particular antibacterial alkaloid.

Polyketides

One of the most important problems in contemporary biotechnology is still discovering new antibiotics, as dangerous microorganisms quickly become resistant to them [91]. The latter leads to a growing number of incurable or difficult-to-treat

bacterial infections, which may eventually be among the leading causes of death. This is why it is so important for modern medicine to discover novel antibacterial compounds [92]. Polyketide-based natural antimicrobial marine products are a diverse class with various structural modifications, including antiviral, antibacterial, anticancer, and other effects [93]. Table 7 summarizes the composition of antibacterial polyketide chemicals in different marine bacteria based on findings from earlier research.

Table 5. Structure of antibacterial enzyme compounds from marine bacteria

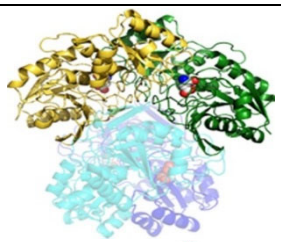
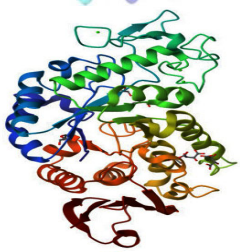
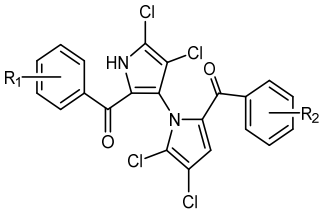
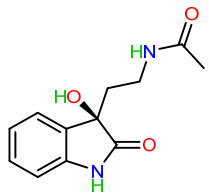
Enzyme compounds	Structure	Marine bacteria	Mechanism of action	Ref.
L-Asparaginase		*Streptomyces* sp.	Effective against MRSA, *E. coli,* and tumor therapy	[81-82]
Amylase		*V. alginolyticus*	Effective against Gram-positive bacteria	[83]
Protease		*V. harveyi, V. costicola*	Effective against MRSA, *E. coli, and anticancer*	[83]

Table 6. Structure of antibacterial alkaloid compounds from marine bacteria

Alkaloid compounds	Structure	Marine bacteria	Mechanism of action	Ref.
Marinopyrrole A		*Streptomyces* sp.	Effective against MRSA	[87]
Bacilsubteramide A		*B. subterraneus* 11593, *Micromonospora* sp. A258	Effective against MRSA and Gram-positive bacteria, anti-allergic bioactivities	[88]

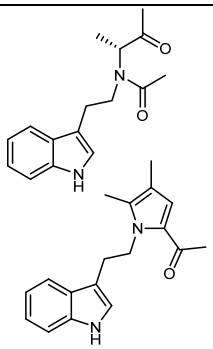
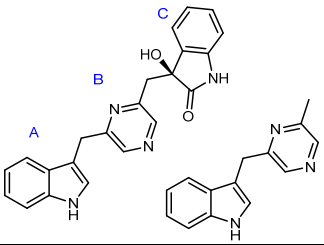
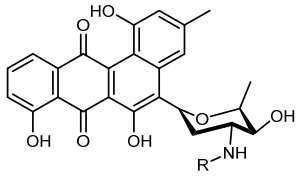
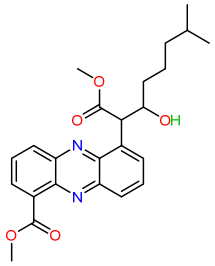
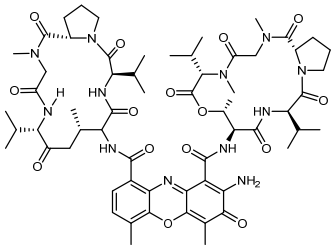
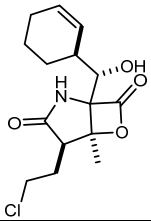
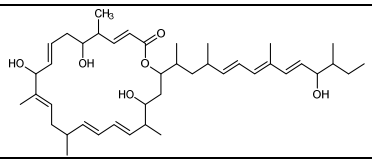
Alkaloid compounds	Structure	Marine bacteria	Mechanism of action	Ref.
Streptoindoles A–D		*Streptomyces* sp. ZZ1118	Inhibiting the growth of MRSA and *E. coli*	[89]
Indole pyrazine A and B		*Acinetobacter* sp. ZZ1275	Antimicrobial activities against MRSA and *E. coli*	[90]

Table 7. Structure of antibacterial polyketides compounds from marine bacteria

Polyketides compounds	Structure	Marine bacteria	Mechanism of action	Ref.
N-acetyl-*N*-demethylmayamycin		*Streptomyces* sp. 182SMLY	Effective against MRSA, induced apoptosis in the glioma cells	[94]
Streptophenazines		*Streptomyces* sp. 182SMLY	Effective against MRSA	[95]
Actinomycins D		*Streptomyces* sp. ZZ338	Effective against MRSA, *E. coli*, inhibiting the proliferation of glioma cells	[96]
Salinosporamide A		*S. tropica*	Potential anticancer, antimalarial, antibacterial MRSA, *M. tuberculosis*, and anti-inflammatory properties	[44,97]

Polyketides compounds	Structure	Marine bacteria	Mechanism of action	Ref.
Macrobrevin		*B. amyloliquefacien*	Antagonistic activities against MRSA, VRE, *V. parahaemolyticus*, *P. aeruginosa*, *K. pneumoniae*, *S. pyogenes*	[98]

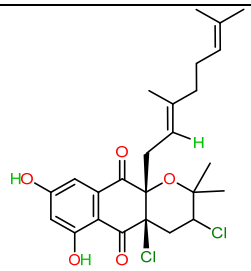
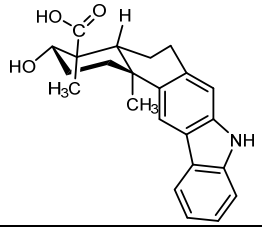
Terpenoid

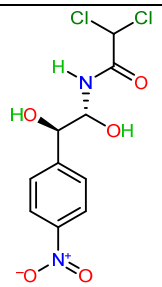
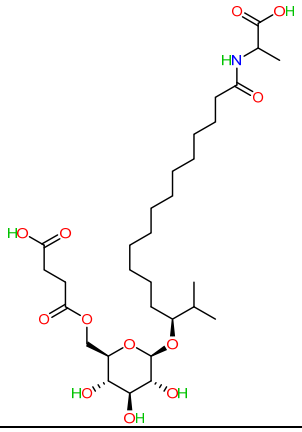
Numerous organisms that produce bioactive natural chemicals are part of the vast biological diversity seen in the marine environment [99]. Many different structural groups and biological roles of chemicals can be found in marine microorganisms [43]. Natural compounds with antibacterial properties are influenced by a variety of biotic and abiotic factors found in the marine environment, including temperature, nutrition, salinity, interactions with other microbes, and other factors [100]. Marine bacteria use terpenoids as important metabolites [101]. Table 8 displays the antibacterial terpenoids structural composition in marine microorganisms.

■ ANTIBACTERIAL ACTIVITY OF MARINE BACTERIA

Marine environments are rich reservoirs of diverse microorganisms, a vast and largely unexplored source of microbial diversity, including bacteria that have evolved unique metabolic capabilities and biosynthetic pathway [106]. These marine bacteria have demonstrated remarkable potential for producing bioactive compounds with antibacterial properties, offering promising avenues for combating bacterial infections, particularly those caused by multidrug-resistant pathogen [43]. Marine bacteria produce a wide range of bioactive compounds with antibacterial properties [107]. These compounds have attracted significant attention due to their potential applications in combating bacterial infections, particularly those caused by drug-resistant pathogens [108]. The following are important details regarding marine bacteria's antimicrobial activity. First is diverse sources. Antibacterial compounds-producing marine bacteria have been isolated from sediments, saltwater, marine invertebrates (such as sponges, corals, and tunicates), and algae [109-110]. Second, diversity in structure. The antibacterial substances generated by marine bacteria have a noteworthy diversity in structure, encompassing peptides, polyketides, terpenoids, alkaloids, and additional categories of natural products [111]. Third, mechanisms of action. Marine bacterial antibacterial

Table 8. Structure of antibacterial terpenoid compounds from marine bacteria

Terpenoids compounds	Structure	Marine bacteria	Mechanism of action	Ref.
Napyradiomycin		*S. aculeolatus*	Effective against methicillin-resistant *S. aureus*, exhibited moderate cytotoxicity against four human cancer cell lines SF-268	[102]
Dixiamycin A		*Streptomyces* sp.	Effective against herpes simplex virus–1 (HSV-1) *in vitro* *S. aureus*, *Acinetobacter* sp., and MRSA	[103]

Terpenoids compounds	Structure	Marine bacteria	Mechanism of action	Ref.
Chloroxiamycin		*Streptomyces* sp.	Effective against *S. aureus*, *E. coli* and MRSA	[104]
Ieodoglucomide A		*B. licheniformis*	Effective against *S. aureus*, *E. coli* and MRSA	[105]

compounds can act through various mechanisms, such as disrupting cell membranes, inhibiting cell wall synthesis, interfering with protein synthesis, or targeting essential enzymes and cellular processes in bacterial cells [30,112-113]. Fourth, broad-spectrum antibacterial activity. Numerous marine bacterial compounds have been shown to be effective against Gram-positive and Gram-negative bacteria, including those resistant to several drugs [114]. Fifth, novel chemical scaffolds. Marine bacterial metabolites are appealing prospects for the creation of novel antibacterial drugs because they frequently have distinct chemical structures and scaffolds that differ from those of conventional antibiotics [108]. Sixth, biofilm inhibition. Some marine bacterial compounds have been identified to suppress the production of biofilms, which is a major cause of antibiotic resistance and persistent infections. These compounds also have antibacterial qualities [19,115].

The composition of the cell wall is a major factor in determining how susceptible or resistant bacteria are to various antimicrobial agents [116]. It is noteworthy that several antimicrobial chemicals derived from marine bacteria possess broad-spectrum activity, which enables them to target both Gram-positive and Gram-negative bacteria efficiently [30]. This wide range of activity can be explained by their capacity to target conserved cellular structures or processes, such as those that interfere with vital enzymes, disturb membrane integrity, or impede protein synthesis, which is shared by both species of bacteria [117]. Bacteria are often classified as Gram-positive or Gram-negative depending on the unique components of their cell walls [113]. Unlike Gram-positive bacteria, which have a thick peptidoglycan layer encircling their cytoplasmic membrane, Gram-negative bacteria have an outer membrane and a thin peptidoglycan layer covering their cytoplasmic membrane [118-121].

Cell wall permeability is a crucial factor in target intracellular inhibition, and these discrepancies have wider implications for antibacterial efficacy [122]. The peptidoglycan coating of Gram-positive bacteria [123] allows antibacterial substances to pass through it efficiently (e.g., *S. aureus* and *E. faecium*). Many times, the chemical characteristics necessary for piercing the glycolipid layer are highly distinct and peculiar to the membranes of Gram-negative bacteria (e.g., *E. coli* and

P. aeruginosa) [124-125]. In reality, the development of specialized Gram-positive antibiotics has been successful, while the development of Gram-negative antibiotics has not [126-127]. The structure of the Gram-positive cell wall depicts the thick peptidoglycan layer, which also contains wall-associated teichoic acids and membrane-associated lipoteichoic acids, as shown in Fig. 1 [127]. In addition, the structure of the Gram-negative cell wall includes the peptidoglycan layer, periplasmic space, and outer membrane. The external leaflet of the outer membrane is predominately lipopolysaccharides. The outer membrane and peptidoglycan are linked together by Braun's lipoprotein, as shown in Fig. 2 [128].

The antibacterial activity of substances made by marine bacteria is frequently assessed using a variety of techniques, such as the following. The first method is disk diffusion assay. In this method, sterile disks containing the marine bacterial extract or purified compound are placed on an agar plate and inoculated with the test bacterial strain. After incubation, the zone of inhibition around the disk is measured, indicating the compound's ability to inhibit bacterial growth [129]. The second method is a well diffusion assay. It is a good diffusion assay and comparable to the disk diffusion assay, but it uses wells punched into the agar plate to disseminate the marine bacterial extract or chemical compound that is dispensed into the wells [130-131]. The third method is minimum inhibitory concentration (MIC) determination. This method involves preparing serial dilutions of the marine bacterial extract or compound in a liquid growth medium, followed by inoculation with the test bacterial strain. The MIC is defined as the lowest concentration of the compound that inhibits visible bacterial growth after incubation [121]. The fourth method is minimum bactericidal concentration (MBC) determination. This method is comparable to that of determining MIC in that it involves plating the contents of the MIC wells onto fresh agar plates and looking for signs of bacterial growth. The MBC is the lowest concentration of the compound that kills the bacterial [132].

Time-kill assays technique entails subjecting the test bacterial strain to various marine bacterial chemical concentrations for a predetermined amount of time. Colony-forming units (CFUs) are counted and plated to assess the amount of viable bacterial cells in samples that are taken at regular intervals. Understanding the kinetics of the antibacterial action is possible using this method [133]. Biofilm inhibition and eradication tests assess

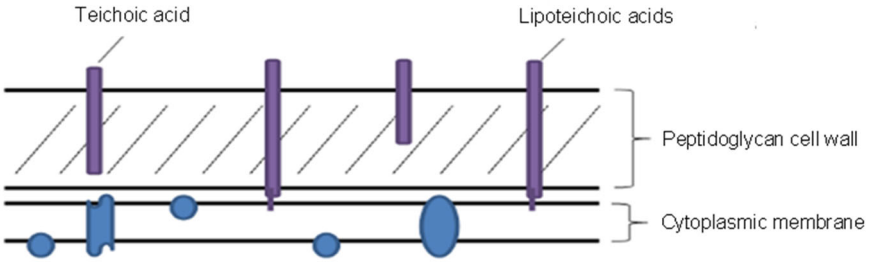


Fig 1. The Gram-positive cell wall structure depicts the thick peptidoglycan layer, which also contains wall-associated teichoic acids and membrane-associated lipoteichoic acids [127]

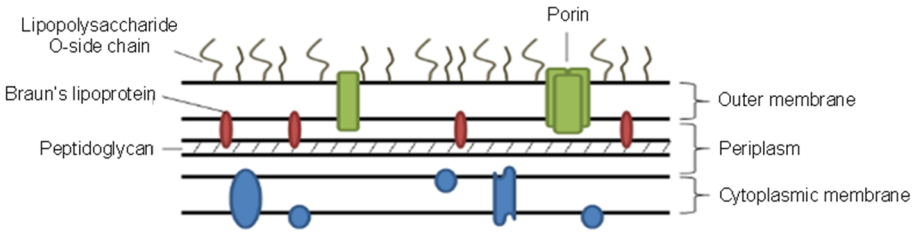


Fig 2. The Gram-negative cell wall structure includes the peptidoglycan layer, periplasmic space, and outer membrane. The external leaflet of the outer membrane is predominately lipopolysaccharides. Braun's lipoprotein links the outer membrane and peptidoglycan together [128]

whether marine bacterial chemicals can disrupt and break up pre-existing biofilms or prevent new ones from forming. It is possible to use a variety of quantitative and qualitative techniques, including microscopic procedures, metabolic activity tests, and crystal violet staining [133].

The purpose of combination studies is to ascertain whether the marine bacteria component, when coupled with other antibiotics or antimicrobial agents, demonstrates synergistic antibacterial action [133]. Numerous biochemical, molecular, and microscopic techniques can be used to shed light on the specific mechanisms by which the chemicals found in marine bacteria exert their antibacterial effects. These mechanisms may include the disruption of membranes, the inhibition of cell wall formation, or interference with protein synthesis [134]. It is significant to remember that these techniques can be adjusted and improved in accordance with the particular needs of the experiment, the characteristics of the marine bacterial compound, and the target species or strain of bacteria. Furthermore, *in vivo* investigations employing suitable models might be conducted to assess the antibacterial effectiveness and toxicity of a promising marine bacterial agent.

■ ANTI-INFLAMMATORY ACTIVITIES OF MARINE BACTERIA

Marine bacteria frequently have a substantial and varied supply of biologically active compounds with suspected anti-inflammatory properties, contributing to the exploration of novel therapeutic agents for various inflammatory conditions [92,111]. These microorganisms showed promising anti-inflammatory properties through different pathways [43]. *In vitro* and *in vivo* models of inflammation, such as cell-based assays, animal models of inflammatory disorders, and clinical investigations, have all demonstrated the anti-inflammatory properties of marine bacterial metabolites [135]. These bioactive substances have demonstrated possible beneficial effects in the treatment of inflammatory diseases and disorders such as rheumatoid arthritis, asthma, inflammatory bowel diseases, and neurodegenerative disorders [136]. Although these bacteria have evolved to survive in unique and frequently unpleasant settings, they have produced a diverse range of secondary metabolites with a variety of biological actions, including the ability to reduce inflammation [137]. These marine bacterial metabolites' distinct chemical structures and modes of action present exciting prospects for the creation of novel anti-inflammatory medications and treatment approaches [43]. One significant anti-inflammatory activity of marine bacteria is the inhibition of pro-inflammatory mediators [136]. Studies have identified marine bacteria-derived compounds that can modulate cytokine production, such as tumor necrosis factor (TNF)-alpha and interleukins, which play crucial roles in the inflammatory response [138]. Marine bacteria help to lessen inflammation and related tissue damage by preventing the release of these pro-inflammatory chemicals [139].

In many disorders, oxidative stress and inflammation are significant factors. An immune defense process known as inflammation is triggered by noxious stimuli such as mechanical trauma, burns, microbial infections, allergies, and other noxious stimuli [140-141]. The recommended carrageenan-induced paw edema method was used to measure the anti-inflammatory activity [140,142-143]. Marine microorganisms are highly favored in drug development research due to their potential for producing bioactive compounds. Antimycin-type depsipeptides (Fig. 3), namely urauchimycin D (1) and somalimycin (2), were isolated from a mutant strain of *Streptomyces somaliensis* SCSIO ZH66. These compounds were found to suppress the production of interleukin-5 in splenocytes induced by ovalbumin in mice. Among the depsipeptides, compound 1 exhibited strong inhibitory activity with an IC_{50} value of 0.57 μM, while compound 2 showed milder effects (> 10 μM). Additionally, these depsipeptides displayed minimal cytotoxicity against human umbilical vein endothelial cells, with LD_{50} values of 62.6, 34.6, and 192.9 μM, respectively. The (+)- and (−)-actinoxocine (3a, 3b) were isolated from a marine-derived *Streptomyces* sp. and showed inhibition on TNFα protein release in LPS- and Pam3CSK4-induced RAW 264.7 mouse macrophages, respectively [144]. The

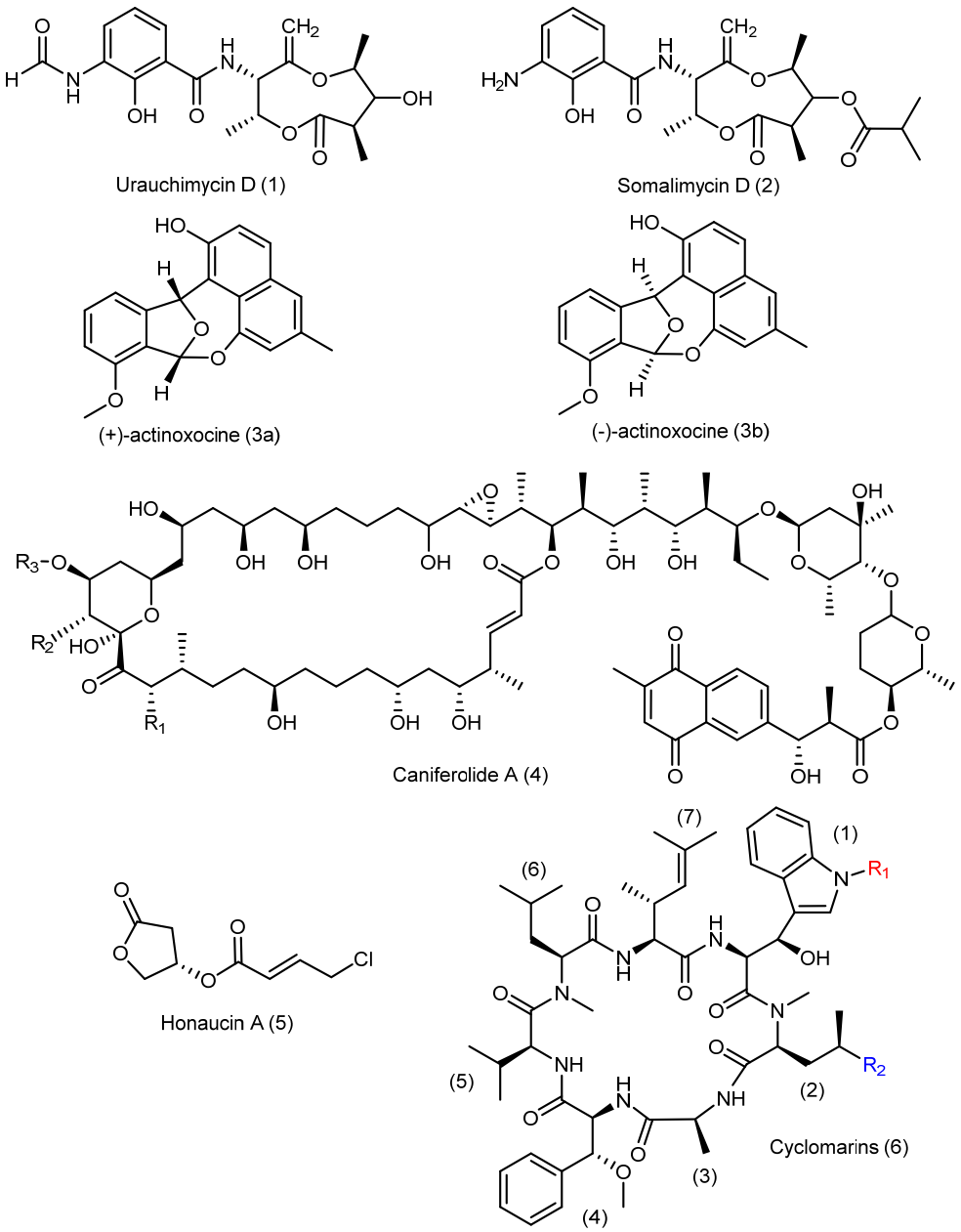


Fig 3. Structures of anti-inflammatory compounds from marine bacteria

macrolide caniferolide A (4) from *S. caniferus* could block NFκBp65 translocation to the nucleus and showed inhibition on the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNFα), the release of NO, and the activities of iNOS, JNK, and p38 in LPS induced BV2 microglial cells [145].

Honaucin A (5), isolated from a marine-polyketides cyanobacterium, has been found to inhibit mouse ear edema [146]. The crude pigment extracts of marine *Brevibacterium* sp. were an effective compound for anti-inflammatory activity using carrageenan-induced paw edema on Wistar male rats [38]. Cyclomarins (6) was isolated from a marine *Streptomyces* sp. have been found to have interesting lead structures for developing drugs against tuberculosis and malaria [147]. These findings demonstrate the potential of marine-derived compounds as promising candidates for developing anti-inflammatory agents, which could have significant

implications for treating various inflammatory conditions and diseases.

■ DISCUSSION

Marine environments are the source of all life, and it is thought that this "primordial soup" is where the earliest forms of life first emerged [148]. With its varied bacteria, the marine environment evolves specific adaptation mechanisms due to thriving in a different type of climate [127,149]. These mechanisms may be helpful for their defense, and the outcomes of these adaptations may benefit humans in various ways [150]. One such marine bacterial defense strategy against predators is the production of bioactive metabolites [151]. This means that marine bacteria are probably a very promising source for new antibiotic and anti-inflammation manufacturers [147-150]. Considering their distinct living environments and metabolic processes, these investigations indicate that marine bacteria have great potential for creating novel physiologically active substances [151]. The fight against the threat posed by the rise in infections caused by antibiotic-resistant organisms includes the hunt for new antibiotics and anti-inflammation as a key component. A key strategy in the fight against the threat posed by the growth in diseases brought on by drug-resistant microbes is the search for novel antibiotics and anti-inflammation [152]. According to literature reviews, most antibiotics and anti-inflammations used today are synthesized from relatively few scaffold molecules. Antimicrobial and anti-inflammation drugs for harmful bacteria are undoubtedly becoming more prevalent. However, the rate of finding and creating new, potent antibacterial and anti-inflammation substances is slowing down.

■ CONCLUSION

Marine bacteria are important providers of structurally diverse and distinctive intracellular such as peptides, lipids, nucleosides, enzymes, and extracellular bioactive compounds such as alkaloids, polyketides, and terpenoids. We highlighted the diversity of marine bacteria, which has helped researchers identify novel antibacterial and anti-inflammatory agents and supports the notion that research holds great promise for developing biomaterials in the future for large-scale industrial production of antibacterial and anti-inflammatory agent applications.

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■ CONFLICT OF INTEREST

The authors declare no conflict of interest.

■ AUTHOR CONTRIBUTIONS

The study was designed by Harningsih Karim, Ahyar Ahmad, and Anita. Ahyar Ahmad, Arief Azis, Ananda Ramadani, and Harningsih Karim collected the data. Ahyar Ahmad and Hasnah Natsir conducted the data analysis and interpretation, while Harningsih Karim, Anita, and Paulina Taba wrote the manuscript. Anita, Suriati Eka Putri, and Sarlan prepared figure/table. Ahyar Ahmad, Hasnah Natsir, Siti Halimah Larekeng, and Paulina Taba revised the manuscript. All authors discussed the results and contributed to the final manuscript.

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