Research in Marine Sciences
Volume 10-Issue 3-2025
Pages 932-955

Review paper

Marine ecosystem: A resource of bacteria producing bioactive metabolites

Chandan Deosthali[1], Ashish Jain[2], Nitinkumar Patil[2], and Pranali Shete[2,*]

[1]School of Health Sciences and Technology, UPES, Dehradun, 248007, India

[2]Smt. Chandibai Himathmal Mansukhani College, Ulhasnagar – 421003, Maharashtra, India

Received: 2025-08-10 *Accepted: 2025-09-14*

Abstract

The intricate physical and chemical divergence exhibited by marine ecosystem significantly supports a rich biological community, rendering it an ideal source for identifying bioactive compounds with wide-ranging industrial applications. Marine flora and fauna have been already explored extensively for procuring secondary metabolites. The marine microorganisms, especially those from extreme environments, hold immense potential by virtue of their ability to produce unique bioactive metabolites. In order to acclimatize to extreme conditions, microbes synthesize novel and complex metabolites, which are beneficial not only for humans, but also for the environment. To date, noticeable bioactives are recovered from marine microbes including enzymes, peptides, polysaccharides and secondary metabolites against ailments like bacterial infections, cancer, inflammation and other degenerative diseases. The revolutionization of molecular biology with the manifestation of taq polymerase makes the quest prevailing. A unique advantage of marine microorganisms, due to the standard cultivation method and advanced biotechnological processes, is their capacity to produce consistent and economical yields of metabolites. Methodologies like strain improvement and genetic engineering can further modulate the recovered microbial metabolites, expanding the application avenues even

* Corresponding Author's Email: pranalikale2@gmail.com
ORCID: 0000-0002-3157-7449

further. Thus, the present review collates and explores bioactives produced by diverse marine microorganisms.

Keywords: Marine Bioactive; Marine Microorganisms; Biotechnological Processes; Extremophiles.

1. Introduction

The earth is manifested as an infinite resource of metabolites that can be exploited by humankind. The communal harmony of biological communities across different ecosystems on earth has molded diverse bioactive metabolites having the potential of human aid (Rigogliuso *et al*., 2023). The term bioactive compounds refer to the natural substances that impart biological activity on a living organism, which can have contrasting outcomes depending on the substance and its bioavailability (Guaadaoui *et al*., 2014). The fact that bioactives originate from biological platforms, concerns like biocompatibility and eco-friendly nature gets resolved. Bioactive metabolites have widespread applications in the healthcare industry as anti-microbial, anti-tumor, anti-inflammatory, anti-diabetic, and osteogenic agents. Besides healthcare, textile, cosmetic, and food industries have also reaped benefits from several natural bioactives (Nawaz *et al*., 2020). Along with plants and animals, which serve as an excellent resource of bioactives, microbes are also becoming a compelling choice for the same. The discovery of Penicillin from *Penicillium notatum* has already created a major breakthrough in the field of antibiotics. Similarly, isolation of thermostable *Taq* polymerase from an extremophilic marine organism *Thermophilus aquaticus* has revolutionized molecular biology (Hegemann *et al.,* 2023; Raghu *et al.,* 2023).

Harsh ecosystems are represented by extreme physical and chemical parameters, which make them and their biodiversity alluring and exclusive (Choudhary *et al.,* 2024). The marine ecosystem is one such ecosystem, exemplified by multiple extreme parameters at the same time. Standard extreme physical parameters associated with marine ecosystems include high pressure, high/low temperatures, variable pH etc (Stief *et al.,* 2023).

Analogous to physical parameters, chemical parameters are equally non-conducive, some of which include the presence of different salts, heavy metals, oils, recalcitrant compounds and effluents etc., (Zhang *et al.,* 2021; Deosthali *et al.,* 2024). For each marine habitat, the permutation and combinations of these physical and chemical parameters shape the microbial community in terms of not only diversity but also exclusivity (Voser *et al.,* 2022).

Besides shaping the microbial diversity, the parameters also contribute towards evolving the ore of microbial bioactive compounds as survival strategies. For instance, one can recover high pressure, high salt or high temperature tolerating bioactives that can have immense scope from food industry to therapeutics. Moreover, one can also aim in unearthing bioactives, which may have amalgamated all the above properties targeting multitasking metabolites (Jagannathan *et al.,* 2021; Ameen *et al.,* 2021).

934 Marine ecosystem: A resource of bacteria producing bioactive metabolites

With the marine ecosystem proclaiming the majority of the earth's surface, it probably becomes the highest contributor to microbial diversity, which indirectly expands the bioactive metabolite repertoire (Hosseini *et al.,* 2022). Despite this fact, marine expeditions targeted towards microbial explorations are relatively low. Moreover, characterization and bioprospection of the microbial bioactives are quite negligible and have been given creditable consideration only recently (Ameen *et al.,* 2021). Recent expeditions have contributed to several therapeutically important bioactives described in Figure 1.

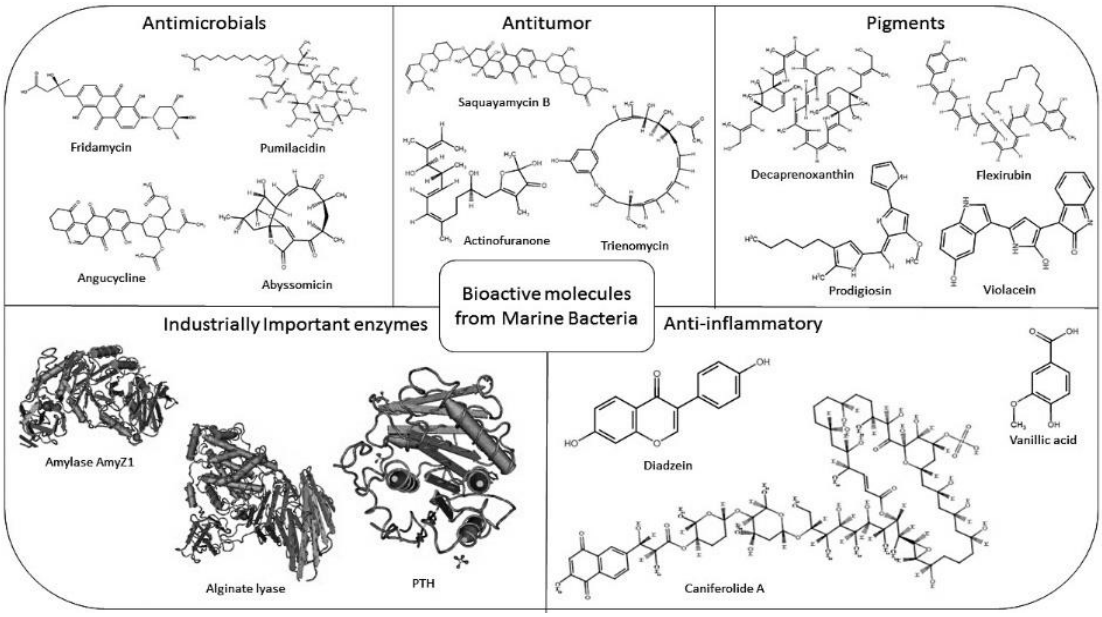

Figure 1. Important Bioactive Compounds, drawn by ChemAxon (2017) using Marvin 17.21.0

A significant advantage of microbial bioactives is - employing biotechnology one can aim not only at constant but also recurring yield. The fact that manipulating microbes using current strain improvement techniques is feasible, the bioactive yield can be expanded in terms of diversity along with productivity (Wang *et al.,* 2021). Marine microorganisms can produce bioactive metabolites such as actinomycetes, fungi, bacteria, cyanobacteria, algae and some symbiotic associations (Ameen *et al.,* 2021). Across bacteria, prominent phyla in the order of fruitful bioactives outcome include Firmicutes, Actinobacteria, Proteobacteria, Planctomycetes and Bacteroidetes (Paul *et al.,* 2021).

Currently plants serve as a major resource of bioactive compounds. Among the promising bioactives procured from plants are the phenolics and terpenes. They have received considerable attention and have been contributing significantly in the healthcare and food industry (Roy *et al.,* 2022). The modern extraction methods employing ultrasound and microwave techniques amalgamating with conventional methods have undoubtedly made plants as a preferred choice for bioactives (Yusoff *et al.,* 2022). However, occurrence of redundancy, constraints regarding escalating yields, pest infestations and fluctuating yield consistency are concerns which remain unavoidable (Chaloner *et al.,* 2021). Thus, microorganisms are currently preferred to ensure constancy in yield qualitatively and quantitatively.

The present review collates different bioactive metabolites derived from marine microorganisms with special attention given to their explored applications. Bioactive metabolites can be broadly classified depending upon the nature of the compound, its application or source from which it is obtained. Here we have tried to culminate bioactives based on their applications concerning human aid.

2. Antimicrobials

Although significant advancements have been made in managing infectious diseases, they persist as a formidable challenge to global health. According to WHO, infections by antimicrobial resistant organisms have led to 4.95 million deaths in 2019 (Murray *et al.,* 2022). The gravity of the situation intensifies with the backdrop of evolving antimicrobial resistance along with multidrug resistance and a consistent decline in the availability of new effective drugs. Both these factors have created immense pressure to develop new and effective drugs. As nosocomial infections are major culprits in developing multiple drug resistance bacteria, addressing them is the current demand. Most of the health care associated infections are caused due to ESKAPE organisms, which stand for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp*. Key antibiotics regularly used in ICU to treat or prevent microbial infections include aminoglycosides for Gram – negative bacteria, second–to fourth–generation cephalosporins, beta-lactamase inhibiters, fluoroquinolones, carbapenems, and co-trimoxazole. Whereas the one's used to treat Gram positive infections are ampicillin, Cotrimoxazole, Vancomycin, Linezolid, Aminoglycosides, High Level Gentamicin and Fluoroquinolones (Chakraborty *et al.,* 2023).

A yearly report released in 2021 by ICMR, India, shows a trend in isolation frequency of top 10 pathogens and antibiotic resistance. A steady increase in isolation frequency of antimicrobial resistant (AMR) in *K. pneumoniae* and *A. baumannii* was observed from 2016 until 2021 with no significant increase in isolation frequency of other isolates. Over the last seven years, the resistance of *E. coli* towards imipenem, a carbapenem class of antibiotics, has increased steadily from 14% to 36%, and that of *K. pneumoniae* has increased from 35% to 57%. Levofloxacin, a third generation fluoroquinolone antibiotic, is used to treat *A. baumannii* infections. However, in the past seven years, *A. baumannii* has shown an increase in resistance from 66.7% to 86.1% towards levofloxacin, currently the most effective drug against it. There is no significant increase in resistance in *P. aeruginosa*, on the contrary there is an increase in susceptibility percentage over a wide array of antibiotics. The drugs available for MRSA have improved susceptibility throughout the last seven years. However, there has been a significant decrease in susceptibility of *S. aureus* against cefoxitin and erythromycin with percent decrease of 14.2% and 8.2%, respectively. A 10% increase in resistance was observed in *E. faecium* against ampicillin, vancomycin, and teicoplanin throughout the last seven years, while, insignificant change in susceptibility was observed in *E. faecalis*. Thus, it becomes crucial to ponder for drugs that can resolve the concerned resistance (ICMR, 2021).

936 Marine ecosystem: A resource of bacteria producing bioactive metabolites

Microbial secondary metabolites have always been exploited for their antimicrobial properties. Apart from harboring conventional antimicrobials, they are anticipated to be a rich reservoir of novel and structurally diverse forms. Predominant marine bacteria belonging to phylum *Actinobacteria, Firmicutes* and *Proteobacteria* have contributed significantly as a resource of antimicrobials. For instance, novel antibiotic Fridamycin belonging to the Aquayamycin group of antibiotics have been discovered from *Actinokineospora spheciospongiae sp. nov* and *Streptomyces sp.* strain DSD011 both of which are marine microbes. The prior bacterium was procured from a marine sponge *Spheciospongia vagabunda* recovered from Red sea, while the later one was isolated from marine sediments of Uaydahon Island. Moreover, Fridamycin A and D derived from *Streptomyces sp.* strain DSD011, exhibited potent bactericidal effects against methicillin-resistant *Staphylococcus aureus*, with a minimum inhibitory concentration of 500 µg/ml and 62.5 µg/ml, respectively. Whereas, Fridamycin H procured from *Actinokineospora spheciospongiae sp. Nov* displayed significant activity against sleeping sickness causative agent *Trypanosoma brucei* strain TC221 (Tawfike *et al.,* 2019; Sabido *et al.,* 2020).

In another exploration, a class of polyketide antibiotic called Abyssomicin was isolated from marine microbes *Streptomyces koyangensis* SCSIO 5802 and *Verrucosispora* sp. MS100137 recovered from deeper layers of the Southern China sea. Both Abyssomicin F and G showed significant antimicrobial activity against MRSA whereas Abyssomycin Y showed antiviral activity against Influenza A virus (Huang *et al.,* 2018; Zhang *et al.,* 2020). *Streptomyces sp*., which is an excellent source of several secondary metabolites, is also extensively explored from several marine ecosystems. Bioactive molecules like Angucycline, Dentigerumycin, pyrrolo[1–a] pyrazine-1,4-dione hexahydro-3-(2-methylpropyl)-, 3-methylpyridazine, n-hexadecanoic acid, indazol-4-one, octadecanoic acid, 3a-methyl-6-(4-methylphenyl) sul, and 2-Alkyl-4-hydroxyquinolines have been isolated from *Streptomyces pratensis* NA-ZhouS1, *Streptomyces sp.* JB5, *Streptomyces sp.* S2A, *Streptomyces sp*. Al-Dhabi-90, and *Streptomyces sp.* MBTG13, respectively.

Shin, *et al.* (2018), reported the production of Dentigerumycin from *Bacillus sp.* GN1 as well (Akhter *et al.,* 2018; Siddharth and Vittal 2018; Al-Dhabi *et al.,* 2019; Kim *et al.,* 2019). *Bacillus pumilus* showed production of a biosurfactant compound called Pumilacidin along with another uncharacterized 10 kDa compound which was found to be active against *S. aureus* and *L. monocytogenes*, respectively (Saggese *et al.,* 2018). A marine actinomycete namely *Micromonospora carbonacea* LS276 was isolated from Ling Shui Bay, Hainan Province of China. The actinomycete was capable of producing Tetrocarcin Q, a novel spirotetronate displaying a distinctive sugar residue at C-9 position. *B. subtilis* ATCC 63501 was inhibited at minimum inhibitory concentration of 12.5 µM of Tetrocarcin Q (Gong *et al.,* 2018). The other marine bioactive compounds showing antimicrobial activity are summarized in Table 1.

Table 1. Marine Bioactive Compounds – Antimicrobials

Sr. no.	Metabolite	Source Name	Sampling Site	Reference
1	Janthinopolyenemycins A and B	*Janthinobacterium* spp. ZZ145 and ZZ148	East China Sea	Anjum *et al.* (2018)
2	Imaqobactin	*Variovorax* sp. RKJM285	Nunavut, Canada	Robertson *et al.* (2018)
3	Linear Aminolipids	*Aequorivita* sp.	Edmonson Point, Antarctica	Chianese *et al.* (2018)
4	Sealutomicin A	*Nonomuraea* sp. strain MM565M-173N2	Sanriku coast, Japan	Igarashi *et al.* (2021)
5	Fatty acids	*Brevibacillus antibioticus* sp. TGS2-1T	Nakdong, Republic of Korea	Choi *et al.* (2019)
6	4-Hydroxy-pyran-2-one and 3-hydroxy-N-methyl-2-oxindole	*Salinispora arenicola*	St. Peter and St. Paul Archipelago, Brazil	da Silva *et al.* (2019)

3. Antitumor

An uncontrolled growth, incursion and metastasis or progression of cells is termed as cancer. Cancer can be induced by various factors like carcinogenic chemicals, environmental pollutants, ionizing radiations, hereditary or a combination of all (Chang *et al.,* 2011). A total of 851,678 deaths were reported in the year 2020 due to cancer in India (Sung *et al.,* 2021). The Contemporary cancer treatment strategies encompass surgical intervention, chemotherapy, radiotherapy, targeted molecular therapies, immunotherapy, and endocrine therapy. The choice of antineoplastic agents is determined by the tumor's histological type and its stage of progression. Altretamine, Carboplatin, Cladribine, Decitabine, Ifosfamide, Mercaptopurine, Raltitrexed, Streptozocin, and Vinorelbine are the few examples of drugs, which are in the forefront for cancer treatment. It is but obvious the available miniscule number of drugs cannot be justified for the diverse types of reported cancers. Moreover, a majority of these drugs are also harmful against other normal fast-growing cells making them cause several adverse side effects. Furthermore, resistance is another concern, which arises due to consistent use of analogous drugs. Resistance towards anticancer drugs can arise from multiple reasons like, mutations in genetic code, upregulation of drug efflux, and other molecular and cellular mechanisms (Wang *et al.,* 2019; Anand *et al.,* 2022).

Various cellular transport systems such as ABC transporter are overexpressed in tumor cells that can expel the drugs like doxorubicin and imatinib. Alterations in epigenetic codes also lead to resistance development in cancer cells (National Cancer Institute, 2016). The increased resistance towards antitumor drugs along with the restricted repertoire of drugs can lead to relapse of cancer. The increasing death rate, cost of commercially available drugs and decreased efficacy of current anticancer agents, has resulted in desperate search

for novel, efficient, non-toxic and relatively affordable antitumor drugs. With these concerns, explorations of several ecosystems including marine habitats were undertaken for screening microbes with anticancer metabolite producing potential. For example, Yang *et al.* (2019) isolated an actinomycete called *Nonomuraea sp.* AKA32 from Sagami Bay, Japan. It was capable of producing a novel odorous polyketide called Azakamycin along with Actinofuranone C and N-formylanthranilic acid. All the three metabolites showed cytotoxicity against B16 melanoma, Caco-2 and HepG2 cell lines. Peng *et al*. (2018) procured another aromatic polyketide metabolite belonging to angucycline group of antibiotics called Saquayamycin. The metabolite was extracted from *Streptomyces sp.* OC1610.4, isolated from the tidal flats in Xiaoshi Island, Weihai, China. Saquayamycin B exhibited cytotoxicity against plc-prf-5, Hep-G2 and SMMC-7721 cell lines with IC_{50} values of 0.244, 0.135 and 0.033 μM, respectively. It also triggered apoptosis in the SMMC-7721 cell line, which was confirmed using DAPI staining. Following promising in vitro results, in vivo studies of saquayamycin are in progress and anticipated to yield positive results.

In another study, Wang in 2019 purified an ansamycin antibiotic named Trienomycin from the bacteria dwelling in deep sea called *Ochrobactrum sp.* OUCMDZ-2164. It showed anticancer effects against MCF-7 cell lines, derived from breast tissue of a patient suffering from metastatic breast adenocarcinoma (Wang, 2019). The cytotoxic activity of Trienomycin can be corroborated by the studies done by He *et al.* (2021). They investigated the in vivo efficacy of Trienomycin against PANC-1 cell lines xenografted in BALB/c nude mice. STAT3 pathway, which is responsible for the growth and progression of tumor, was inhibited by Trineomycin, successfully retarding the growth of PANC-1 cell line (He *et al.,* 2021).

Bacterial exopolysaccharides (EPS) are polymers that exhibit not only diverse physio-chemical properties but also widespread applications. Ramamoorthy and team, extracted EPS from *Bacillus thuringiensis* RSK CAS4 isolated from an ascidian called *Didemnum granulatum* residing in Campbell Bay, India. The EPS, mainly composed of fructose (43.8%), showed a CTC_{50} of 115 μg/ml against A-549 lung cancer cell line, along with CTC_{50} of 320μg/ml against the HEp-2 liver cancer cell line. This suggest its potential as an anticancer metabolite, exhibiting lower toxicity to normal cells with a CTC_{50} of 480 μg/ml, (Ramamoorthy *et al.,* 2018).

On the similar lines, Wang *et al.,* (2019) extracted EPS11 from a marine *Bacillus sp*. 11 isolated from marine samples cumulated from the Yap Trench, Western Pacific. The in vitro anticancer mechanism of EPS11 was studied against Huh7.5 cell lines and it's in vivo efficacy to suppress metastasis was studied in C57BL/6 mice suffering from highly metastatic B16F-10 melanoma. In Huh7.5 cell lines EPS11 remarkably down-regulated the expression of CD99 which is a fundamental protein required for adhesion, cancer metastasis and death of a cell. While in animal, models EPS11 revealed significant reduction of root nodule formation resulting in decreased metastasis and colonization of melanoma cells in lungs.

Alshawwa *et al.* (2022) extracted a novel exopolysaccharide EPSR5 from a Red Sea bacteria *Kocuria sp*. strain AG5. EPSR5 showed highest and lowest IC_{50} of 1691.00 ± 44.20 µg/ml and 453.46±21.80 µg/ml against MCF-7 and HepG-2 cell lines respectively. In another study, a novel β-glycosidic sulphated exopolysaccharide, was extracted from a marine bacterium, *Bacillus subtilis* strain AG4, isolated from marine sediment of Red sea. The EPSR4 exhibited antioxidant, anti-inflammatory along with anti-tumor and anti-alzheimer activity. EPSR4 exhibited an IC_{50} of 244 ± 6.9 µg/ml against the T-24 bladder cancer cell line. However, it displayed its potent cytotoxic activity on HepG-2 and A-549 cell lines with IC_{50} values of 123 ± 4.3 µg/ml and 148 ± 5.8 µg/ml, respectively (Abdel-Wahab *et al.,* 2022).

Alike to secondary metabolites and EPS several amino acid lytic enzymes are also known to show antitumor activity. Their mechanism of action primarily entails limiting the availability of essential amino acids necessary for the proliferation of malignant cells. Among the forefront lies the glutaminase enzyme, for instance extracellular glutaminase, produced by *B. subtilis* strain JK 79 isolated from Parangipettai coastal area of Tamil Nadu, India, was examined for antitumor activity. It was observed that it exhibited cytotoxic activity against leukemic cell lines, like K562, U937 and Jurkart with IC_{50} values of 231µg/ml, 480 µg/ml and 500 µg/ml respectively. It also showed cytotoxic activity against other cell lines like MCF-7, OV1063 and HCA-7 (Jambulingam and Sudhakar, 2019). Similarly, two other studies exploited the cytotoxic nature of L-glutaminase against various cancer cell lines like MCF-7, HepG-2, NFS-60, as well as LS174T and HCT116, which are colorectal cancer cell lines (Mostafa *et al.,* 2021; Orabi *et al.,* 2020).

Another novel enzyme called GH107 Endo-α-(1, 4)-Fucoidanase was extracted from a gram-negative bacterium called *Formosa haliotis* by Vuillemin *et al.*, (2020). This enzyme producing bacterium originated from marine benthic regions of Mie coast, Japan exhibited in vitro and in vivo anti-tumour activity (Torres *et al.,* 2020). A pure cytotoxic compound (PCC) was extracted from Bacillus sp. CU-3, isolated from Masan Bay, Korea. The cytotoxicity of PCC was checked against 12 different human tumor cell lines, in which the highest cytotoxic activity was seen against MDA-MB-231 cell line with IC50 value of 18.6µg/ml followed by IC50 value of 17.5 µg/ml against NCI-H23 cell line (Jeong, 2018). Other compounds showing antitumor activity extracted from marine microorganisms are listed in Table 2.

Table 2. Marine Bioactive Compounds – Antitumor

Sr. no.	Metabolite	Source Name	Sampling Site	Reference
1	Prodigiosin	*Serratia marcescens* TKU011	Taiwan	Nguyen *et al.* (2019)
2	Natural pyrrole-derivative	*Streptomyces sp*. MN41	Caspian Sea	Norouzi *et al.* (2019)

4. Anti-inflammatory

A dynamic adaptive mechanism of the body, which is triggered by a tissue injury or an infection, wherein components of blood are delivered to the infected/injured area to establish homeostasis, is called inflammation (Medzhitov 2008). However, excess inflammation can cause harm to a body and thus anti-inflammatory substances are required to reduce the painful symptoms of inflammation. Gloria Hettige reported a case of 52-year-old women with chronic inflammation, diagnosed with granulosa cell tumor, chronic fatigue, glandular fever, eczema, hypertension, arm and shoulder bursitis, weight gain and chronic constipation (Hettige, 2020) presence of excess inflammatory mediators play a crucial role in causing organ specific acute or chronic injury thus inducing diseases such as pancreatitis, atherosclerosis, non-alcoholic fatty-liver disease, pulmonary fibrosis, cystic fibrosis, COPD, glomerulonephritis, ulcerative colitis, and Crohn disease (Chen *et al.,* 2018). In order to curb the symptoms of inflammation several commercially, synthetic, steroidal or non-steroidal anti-inflammatory compounds are recommended. These however are associated with severe adverse effects on prolonged use. For instance, currently available non-steroidal anti-inflammatory drugs (NSAIDs) such as Diclofenac, Ibuprofen, Ketorolac, Celecoxib, Rofecoxib and Valdecoxib exert detrimental effect on cardiovascular system (atrial fibrillation and thromboembolic events), gastric system, and hepatic system (hepatotoxicity). Among the steroidal anti-inflammatories commonly used are cortisone and prednisone. They are used to treat rheumatic conditions however, they come with substantial adverse effects including, weight gain, swelling, blurry vision, increased acne, increased risk of high blood pressure, glaucoma, diabetes and cataract, reduced sleep, increased susceptibility to infection, and muscle weakness (Ghlichloo and Gerriets 2019; Metropolis India 2023). Thus, explorations of several marine ecosystems for procuring effective safer anti-inflammatory drugs are being carried out.

In search of such compounds, Zhang *et al.* (2019) successfully recovered optical isomers of a ring C-modified angucyclinone called (+)- and (-)-actinoxocine from *Streptomyces pratensis* KCB-132. The bacterium was obtained from marine sediment of Kiaochow Bay, China and the compound demonstrated anti-inflammatory reaction on RAW 264.7 mouse macrophages when stimulated by Pam3CSK4 and lipopolysaccharide. In addition, (+)-actinoxocine also inhibited release of TNF-α in LPS induced macrophages, whereas, (-)-actinoxocine exhibited activity in Pam3CSK4 stimulated assay. This study gave insight about how just a small structural change can lead to inhibition of inflammation via two different pathways.

In another study, Alvariño *et al.* (2019) isolated *Streptomyces caniferus* from the coastal region of Spain and examined its potential to treat Alzeimer's disease. The isolated *Streptomyces caniferus* produced an anti-inflammatory compound called caniferolide A. This neuro anti-inflammatory compound was capable of blocking NFκB-p65 translocation and significantly reduced pro-inflammatory cytokines including TNF-α, IL-1β and IL-6 in

LPS activated BV2 microglial cells. Caniferolide A was also able to decrease ROS, which in turn impeded Aβ-activation of microglia.

One more anti-inflammatory active enzyme displaying novel fibrinolytic and serralysin-like activity was extracted from *Pseudomonas aeruginosa* KU1 by Kumar *et al.* (2020). The bacterium was isolated from Ezhara beach, Kerala, India and the in-silico studies showed high binding affinity towards bradykinin, a pro-inflammatory substance. It is predicted that the enzyme can exhibit a strong bradykininase activity thus reducing inflammation. In yet another study, Mangamuri, *et al.* (2022) isolated *Streptomonospora arabica* VSM-25 from depths of Bay of Bengal. Five bioactive compounds were screened from *S. arabica,* out of which Vanillic acid and Diadzein displayed 67.74% and 62.67% of inhibition in albumin denaturation, respectively. The results were compared with commercially available Diclofenac sodium, which showed a lower effect compared to Vanillic acid. Thus, vanillic acid extracted from marine *S. arabica* can serve as a suitable candidate as an anti-inflammatory agent. The EPSR5 extracted by Alshawwa *et al.,* (2022) from marine bacteria isolated from the Red Sea, showed anti-inflammatory activity along with anti-tumor activity. The IC_{50} value against Lipoxygenase (LOX) and Cyclooxygenase (COX-2) was found to be 15.39 and 28.06 µg/ml. LOX and COX-2 are associated with a number of inflammatory diseases. Table 3 comprises other few examples of anti-inflammatory compounds derived from marine microorganisms.

Table 3. Marine Bioactive Compounds - Anti-inflammatory

Sr. no.	Metabolite	Source Name	Sampling Site	Reference
1	Gallic acid	*Streptomyces canarius*	Alexandria, Egypt	Neveen *et al.* (2020)
2	EPS-A28	*Alteromonas* sp. PRIM-28	Malpe, India	Sahana and Rekha 2019

5. Pigments

Pigments i.e. chromogenic compounds play a vital role in our day-to-day life. They are significantly employed in industries such as food, pharmaceutical, textile, agriculture and cosmetics etc., (Pailliè-Jiménez *et al.,* 2020). Synthetic pigments are commercially economical compared to their natural counterparts but are loaded with concerns like toxicity, carcinogenicity, non-biodegradable and teratogenic in nature (Ramesh *et al.,* 2019). Commercially available paints/pigments contain harmful substances such as aluminum, amines, ammonia, antimony, barium, cadmium, chromium, and strontium, etc (IARC 2012). On the other hand, natural pigments originating from microorganisms can not only be considered as safe alternatives, but also be manipulated to give higher yields. Besides, many microbial pigments have an additional functional character such as antioxidant, antibacterial and used in food industries not only just act as a coloring agent

but also have health benefits and are pharmacologically active compounds (Sen *et al.,* 2019).

Jeong *et al.* (2022), isolated yellow pigment producing Gram negative bacterium, *Erythrobacter* sp. SDW2 from coastal seawater of Jeju Island in Korea. This yellow pigment was characterised as xanthophyll. Decaprenoxanthin diglucoside and Decaprenoxanthin, belonging to class xanthophyll, were extracted from *Arthrobacter* sp. 40 isolated from Fildes Peninsula, King George Island, and Antarctica. Vila *et al.* (2019) also reported flexirubin producing *Zobellia* sp. P7 as well as zeaxanthin producing *Flavobacterium* sp. P33.

Liu *et al.* (2020) reported the production of 2,2′-Dihydroxy-astaxanthin from novel organism *Brevundimonas scallop* Zheng & Liu isolated from scallop *Chlamys nobilis*, Nanao Island of Guangdong Province, China. Setiyono *et al.* (2019) isolated sulfur containing carotenoid producing bacteria *Erythrobacter flavus* strain KJ5 which forms a symbiotic relationship with coral *Acropora nasuta* found in Indonesia. The pigments were identified as caloxanthin sulfate, nostoxanthin sulfate, and a novel zeaxanthin sulfate. Batbatan *et al.* (2022) reported isolation of marine pigmented heterotrophic bacteria, *Pseudoalteromonas rubra* and *Meridianimaribacter flavus* from mesophotic depth at Benham Bank Seamount. These isolates were capable of producing astaxanthin and zeaxanthin pigments respectively.

Another red colored pigment called prodigiosin, is a linear derivative of the prodiginines group of pigments. It shows an extensive array of activities such as antimalarial, antibacterial, antitumor and can be used as food colorant (Darshan and Manonmani 2015). Setiyono *et al.* (2020), isolated *Pseudoalteromonas rubra* from seawater of Alor Island in Indonesia. This strain was capable of producing prodigiosin which showed a good antimicrobial as compared to other commercially available antimicrobials against clinical isolate of *S. aureus*. In the same year, Ramesh *et al.* (2020) reported prodigiosin producing bacteria *Zooshikella* sp. and an actinomycete *Streptomyces* sp. isolated from the southern coast of Andaman Island. Abdelfattah *et al.* (2019), isolated prodigiosin from marine sponge associated *Actinomycete* RA2 from *Spheciospongia mastoidea* sponge, in seabed south of Sinai, Egypt. The prodigiosin isolated showed attenuation of gastric ulcers in rats.

A naturally occurring bis-indole pigment called violacein acts as an antibacterial agent by disrupting the membrane integrity of bacteria. Marine bacteria such as *Pseudoalteromonas byunsanensis, Pseudoalteromonas luteoviolacea* and *Iodobacter* sp 7MAnt capable of producing violacein were isolated from Arabian sea, Coral reefs and Antarctic Peninsula respectively (Wu *et al.,* 2017; Jayasree *et al.,* 2021; Atalah *et al.,* 2020). Marine bacteria also produce melanin, a cosmetologically important pigment. *Pseudomonas stutzeri* and Antarctic *Streptomyces fildesensis* are the two examples which are studied for production of melanin from marine bacteria (Silva *et al.,* 2019, Manirethan *et al.,* 2020, Kurian *et al.,* 2018). Few other examples of pigments extracted from marine microorganisms are described in Table 4.

Table 4. Marine Bioactive Compounds – Pigments

Sr. no.	Metabolite	Source Name	Sampling Site	Reference
1	1H-Purine-2,6-dione,3,7-dihydro-1,3,7-trimethyl-	*Micromonospora chalcea* strain 1464-217L	Pramuka Island, Indonesia	Mesrian *et al.* (2021)
2	5-Methoxypyrrolidin-2-one	*Micromonospora tulbaghiae* strain TVU1		
3	Actinomycin X2	*Streptomyces cyaneofuscatus*	Nanji Island, China	Chen *et al.* (2021)
4	β-carotene	*Vibrio owensii* TNKJ.CR.24-7	Tanjung Gelam, Indonesia	Sibero *et al.* (2019)
5	Medermycin-Type Naphthoquinones	*Streptomyces* sp. XMA39	China	Jiang *et al.* (2018)
6	Pyocyanin	*Pseudomonas aeruginosa*	Not available	Li *et al.* (2018)
7	Carotenoid	*Planococcus plakortidis BMS5*	Bordi, India	Joshi *et al.* (2023)

6. Enzymes

For many years, humans have employed enzymes for commercial purposes in diverse industries. These efficient biocatalysts display attributes like sensitivity, selectivity and environment compatibility. The only hindrance speculated towards their potential application is their instability to a wide array of pH and temperature. This limitation can be resolved by exploring marine microbial enzymes. Extremophilic bacteria procured from marine ecosystems can be resourceful in delivering enzymes, which are stable across a range of pH and temperature.

Amylase, which is responsible for hydrolysis of starch molecules and results in formation of simple sugars play a significant role in not only digestion but also in food, paper, textile and detergent industries (Farooq *et al.,* 2021). A novel α-amylase, AmyZ1, was isolated from *Pontibacillus sp.* ZY, Yongxing Island in the South China Sea, which showed high activity against a variety of raw starches. It was found to be stable over a temperature range of 25 to 50 ℃ (Fang *et al.,* 2019). In contrast, Ding *et al.* (2021) was successful in isolating low temperature and salt tolerating amylase, namely, SdG5A. The enzyme was procured from a marine bacterium, *Saccharophagus degradans* 2-40T and expressed maximum activity at 4 ℃ in 3 Molar NaCl.

Another study reported by Elmansy *et al.* (2018) showed production of thermostable and halotolerant α-amylase from *Bacillus sp.* NRC22017 isolated from Alexandria coast, Egypt. A study conducted on previously isolated halophilic bacteria namely *Oceanobacilluscaeni* S-11(T), *Virgibacillusdokdonesis* DSW-10(T), *Planococcusplakortidis* DSM 23997(T), *Halomonaspiezotolerans* NBT06E8 (T), *Kocuriaflava* HO-9041(T), and *Halolactibacillusmiurensis* DSM 17074(T), showed the production of amylase along with protease and lipase (Joshi *et al.,* 2022).

Cellulose is a major constituent of plant biomass, which is degraded by enzyme, specifically produced by microorganisms, called Cellulase. Cellulase is being employed in a wide array of industries including health care, textile, paper, foods and beverages and detergents (Balla *et al.,* 2022). Maharsiwi *et al.* (2020) were able to isolate sponge associated marine bacteria including *Bacillus, Pseudomonas, Mycobacterium and Brachybacterium* from Seribu island of Indonesia. Tsudome *et al.* (2023) were able to isolate cellulase--producing bacteria from deep sea off the Noma- misaki, Japan. They used nanofibrous cellulose plates and isolated a novel bacterium *Marinagarivorans cellulosilyticus sp*., which degraded pectin and xylan along with cellulose. While the emphasis on isolating cellulolytic bacteria has primarily been on mangrove ecosystems, it is equally important to explore oceanic environments for these bacteria, given their robustness and tolerance to extreme conditions.

Laccase belongs to the oxidase group of enzymes that catalyze the oxidation of a wide array of phenolic and non-phenolic aromatic compounds (Bhardwaj and Rathod, 2024). Bisaccia and her team successfully isolated a novel strain of *Halomonas* sp. from the Antarctic marine ecosystem. The laccase purified from *Halomonas* M68 showed good activity in acidic pH along with thermal stability across the temperature range with optimal between 40 to 50 ℃ and retaining 40% of its maximum activity at 10 ℃. The effect of salinity and organic solvents on its activity was studied, which revealed that it can tolerate up to 1 M NaCl concentrations by maintaining its activity at 80% (Bisaccia *et al.,* 2023). Zhang *et al.* (2022) studied the ability of cold adapted laccase purified from antarctic sea ice dwelling psychrophilic bacteria *Psychrobacter sp*. NJ228. Another study conducted in the cypermethrin polluted marine water near Manao Bay, Ancud, Chiloé, Northern Patagonia, revealed the presence of bacterial consortia capable of producing laccase and biosurfactant enabling the bioremediation of cypermethrin (Aguila-Torres *et al.,* 2020). Study conducted along the west coast of India specifically at Alang, Diu and Sikka in Gujarat, lead to isolation of early colonizing potent bacteria, *Pseudomonas* sp. ESPS40. The bacteria were capable of degrading malachite green using enzyme laccase and tyrosinase (Kumar *et al.,* 2023).

Rise of plastic debris in the last two decades in the marine ecosystem is of great concern. Gao and Sun isolated five plastic degrading bacterias from marine environments. Out of these 5 isolates a consortium of three potent bacteria namely *Exiguobacterium sp.*, *Halomonas sp.*, *Ochrobactrum sp.* was designed to carry out efficient polyethylene

terephthalate degradation. They successfully purified PET degrading enzymes such as lipases, esterases, cutinases and hydrolases (Gao and Sun, 2021).

Another study reported *Streptomyces sp.* SM14 associated with marine sponge located at a depth of 15 m in Kilkieran Bay, Galway, Ireland, capable of producing Polyethylene Terephthalate Hydrolase (Almeida *et al.,* 2019). *Microbulbifer* sp. capable of producing industrially important enzymes, agarase and cellulase have been studied (Li *et al.,* 2020; Tanaka *et al.,* 2021). Alginate lyase can be used to prepare alginate oligosaccharides, which have been shown to stimulate growth of human endothelial cells. It has a potential use in pharmaceutical industry wherein it can be combined with some antibiotics to treat pulmonary cystic fibrosis in which pathogenic bacteria in lungs (Kim *et al.,* 2011; Xue *et al.*, 2019) can use it to degrade alginate produced. An alkaline, thermostable, halotolerant and bifunctional alginate lyase (AlgH) was isolated from *Marinimicrobium sp.* H1 obtained from rotten kelp samples on the coast in Weihai City, Shandong province, China (Yan *et al.,* 2019). Alginate lyase, Aly1281 was isolated from marine mangrove soil dwelling bacteria *Pseudoalteromonas carrageenovora* ASY5, from Xiamen, China showed its maximum activity at 50 ℃ and pH 8 (Zhang *et al.,* 2020). Other industrially important enzymes are listed in Table 5.

Table 5. Marine Bioactive Compounds - Industrially important enzymes

Sr. no.	Metabolite	Source Name	Sampling Site	Reference
1	β-glucosidase	*Alteromonas* sp. L82.	Mariana Trench, U.S.A	Sun *et al.* (2018)
2	Esterase	*Acetomicrobium hydrogeniformans*	Alaska, U.S.A	Kumagai *et al.* (2018)
3	β-galactosidase	*Alteromonas* sp. ML52	Mariana Trench, U.S.A	Sun *et al.* (2018)
4	CAZymes	*Paraglaciecola hydrolytica* S66T	Zealand, Denmark	Schultz-Johansen *et al.* (2018)
5	Carboxylic ester hydrolase	*Pseudomonas aestusnigri* VGXO14T	Germany	Bollinger *et al.* (2020)

The above review describes different geographical locations explored for marine bacterial bioactives. However, these locations are miniscule in magnitude compared to global marine space. Figure 2 collates several explored habitats and the corresponding bioactives recovered, indirectly highlighting habitats which await exploration. Figure 3 highlights few of the prominent marine microorganisms explored for their bioactive compounds.

Figure 2. Bioactives obtained from various locations

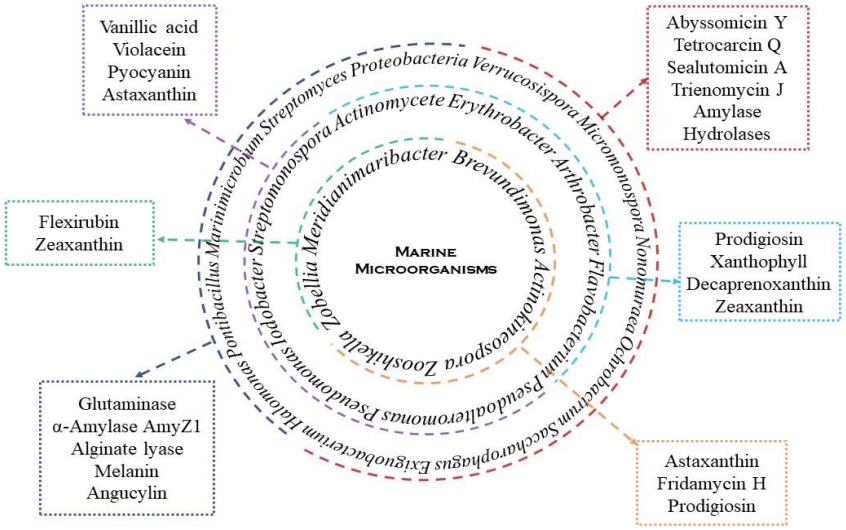

Figure 3. Prominent Microorganisms Explored for Bioactive Compounds

Conclusion

The marine ecosystem permutates with microbial diversity in generating a unique pool of bioactives, which hold potential for resolving several human health concerns. The rise in degenerative diseases along with development of resistance to existing pool of treatments intensifies the gravity of health concerns. Furthermore, considering the escalating demand for natural products, harnessing well-equipped marine microbes for bioactives can be a preferred choice. Several revolutionary antimicrobials, enzymes and secondary metabolites have already been recovered from marine microbes and scientists predict this repertoire is minuscule compared to the available resource. The review presented a glimpse of recently

explored marine microbes for bioactives like anti-microbials, therapeutics, pigments and enzymes with special attention to the locations of marine bacteria.

Conflict of interest

The authors have no competing interests to declare that are relevant to the content of this article.

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