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A Narrative Review of Bioactive Metabolites from Macroalgae-Associated Microbes with Antimicrobial, Anti-Dengue, and Immunomodulatory Potentials

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Abstract

Over the past decade, research has established macroalgae-associated microbial communities as a rich and largely untapped source of structurally unique bioactive compounds. Key findings indicate that these symbiotic microbes exhibit high taxonomic and functional diversity, producing a wide range of secondary metabolites with potent biological activities, especially antimicrobial, anti-dengue, and immunostimulatory activities. Advances in extraction and screening techniques have significantly enhanced the recovery and characterization of these compounds. Notably, microbial-derived metabolites demonstrate broad-spectrum antimicrobial properties, including antifungal, antibacterial, anti-dengue, immunostimulatory, and antitumor activities. These allelochemicals play dual roles: they protect macroalgal hosts from surrounding pelagic microorganisms and help stabilize host–microbe interactions. The narrative review emphasizes that marine microbial metabolites are emerging as promising candidates for pharmaceutical and biotechnological applications, particularly as novel antimicrobial and antiviral agents with immunomodulatory properties. Furthermore, metagenomic approaches are highlighted as transformative tools for discovering previously inaccessible biosynthetic pathways and novel compounds without the need for culturing. Overall, macroalgae-associated microbial communities represent a frontier in drug discovery, offering significant potential for identifying innovative therapeutic agents and addressing current challenges such as antimicrobial resistance and emerging viral diseases. This opens up great opportunities to identify innovative and potential drug targets from macroalgae-associated microbial communities in the future, supporting marine biotechnological strategies for compound and drug discovery.

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Keywords- Marine bacteria, macroalgae-associated microbiota, antimicrobial, anti-viral dengue, secondary metabolites.

Introduction

Marine waters are habitats with very high microbial diversity, including bacteria, fungi, viruses, spores, and actinomycetes. These organisms not only live freely in the sea, but also form special associations with marine animals and plants, including macroalgae. These associated microorganisms utilize nutrients produced by their hosts and protect the production of bioactive compounds that play a role in protecting the host from surrounding pests (1,2,3). Macroalgae are highly productive ecosystems that provide habitat for various microorganisms, which in turn produce bioactive compounds. These compounds are known to exhibit multiple biological activities, including antimicrobial, antifungal, antiparasitic, and anticancer properties. For example, several strains of bacteria from the surface of the macroalgae *Ulva* spp exhibit strong anti-colonization and antimicrobial activities (4,5,6).

Microorganisms that produce bioactive compounds thrive in highly competitive environments due to the limited space and nutrients available on the host surface. This condition triggers the production of allelochemicals that prevent secondary colonization by other microorganisms. These bioactive compounds are secondary metabolites with unique molecular structures compared with those of metabolites from terrestrial microorganisms. Their potential applications have been demonstrated in various fields, including pharmaceuticals, industry, agriculture, and biotechnology (7,8,9). In recent years, research on macroalgae-associated microorganisms has increased, particularly in the analysis and identification of bacterial and fungal communities and the characterization of their bioactive properties. However, most research still focuses on bacteria and fungi, while other microorganisms, such as viruses and protists, remain underexplored. Therefore, it is important to continue developing isolation methods and metagenomic approaches to discover new bioactive compounds from these microbial communities (10,11,12).

This microbial consortium is a promising source of antimicrobial, antiviral, and immunomodulatory agents. The alarming rise in antimicrobial resistance (AMR), the emergence of viral pandemics, and the persistent threat of vector-borne diseases, such as dengue fever, have created an urgent need for alternative therapeutic strategies (13) with the forecast of 10 million deaths per year globally by 2050. AMR occurs when viruses, bacteria, fungi and parasites do not respond to antimi-crobial treatments in humans and animals, thus allowing the survival of the microorgan-ism within the host. The prominent cause contributing to the current crisis remains the overuse and misuse of antimicrobials, particularly the inappropriate usage of antibiotics, increasing the global burden of antimicrobial resistance. The global consumption and use of antibiotics are therefore closely monitored at all times. This review provides a current overview of the implications of strategies used by international governmental organizations, including the UN's 17 Sustainable Development Goals (SDGs). Dengue virus (DENV), in particular, remains a significant public health burden in tropical and subtropical regions, with no specific antiviral therapy currently available and limited efficacy from existing vaccines (14). Concurrently, there is growing interest in immunostimulant agents that can enhance host defenses against infectious diseases, especially in immunocompromised populations.

Marine-derived bacteria associated with macroalgae have shown the capacity to produce compounds with potent antimicrobial activity against multidrug-resistant (MDR) pathogens and antiviral activity against flaviviruses, including DENV. Additionally, sev-

eral of these microbial metabolites exhibit immunostimulatory properties by modulating both innate and adaptive immune responses. These multifaceted bioactivities highlight the potential of macroalgae-associated microbiota as a rich reservoir for drug discovery and development.

This narrative review provides an overview of current knowledge on antimicrobial and antiviral dengue compounds isolated from macroalgae-associated microbial communities. It discusses their mechanisms of action, screening methodologies, and biotechnological advances supporting their identification and application. The potential of these marine microbial bioactive metabolites in addressing global health challenges is examined, with a focus on their diagnostic and therapeutic relevance and translational prospects, especially for antimicrobial and anti-viral dengue compounds.

Methods used for literature source search and collection

A systematic literature review was conducted following the PRISMA 2020 guidelines. Multiple academic databases were comprehensively searched, including PubMed, ScienceDirect, MDPI, Google Scholar, Wiley Online Library, SpringerLink, Web of Science, Scopus, and ResearchGate. The search strategy employed combinations of keywords such as “secondary metabolites of macroalgae-associated bacterial and fungal communities,” “antimicrobial,” “anti-dengue,” and “bioactive compound structures.” All retrieved records were exported, and duplicate entries were removed before screening. Titles and abstracts were screened using predefined inclusion and exclusion criteria, with an emphasis on English-language publications and relevance to marine microbial bioactive compounds, particularly those from macroalgae. Full-text articles were then assessed for eligibility, focusing on studies reporting antimicrobial or anti-dengue activity, immunostimulatory activity, compound characterization, and methodological rigor. Studies meeting the inclusion criteria were subjected to qualitative synthesis, including structured data extraction, critical methodological evaluation, and thematic categorization. The final selection comprised 132 references from a total of 1850 studies, which were systematically analyzed to provide an integrated overview of bioactive metabolites derived from macroalgae-associated bacteria and fungi, as well as their potential applications in marine biotechnology and drug discovery. The detailed selection procedure is illustrated in the PRISMA flowchart shown in Fig. 1.

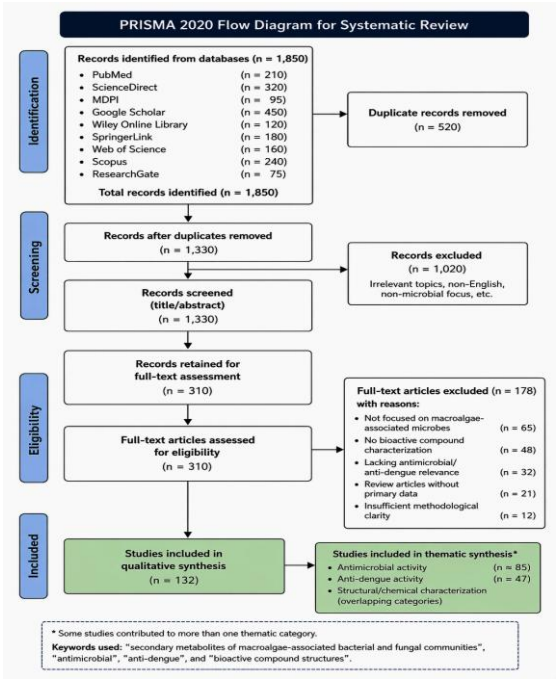

Fig. 1. PRISMA framework illustrating the literature selection process leading to the 132 articles used in the systematic analysis of antimicrobial, anti-dengue, and immunostimulatory bioactive compound structures from macroalgae-symbiotic bacteria

Results and discussion

Bioactivity of macroalgae-associated bacteria

Among the microorganisms attached to the surface of macroalgae, bacteria are

the most frequently found group. These bacteria can live outside the host cell or in the cytoplasm of active cells and play an essential role in regulating various stages of the life cycle of macroalgae, such as *Ulva* and *Gracilaria* (15,16,17). Several studies have shown that bacteria symbiotic with macroalgae significantly influence the formation of regular shape, growth, and development of their hosts (18,19). As an example, Zhang et al. (2021) reported that the bioactive compound thallusin triggers morphogenesis in *Monostroma oxyspermum* (19).

Macroalgae provide an abundant source of nutrients for microbes, which causes fierce competition between microbial communities living on their surface (20,21). This condition encourages bacteria to adapt by producing specific antimicrobial compounds that enable them to survive in the face of competition. This natural selection suggests that bacteria associated with macroalgae have the potential to create new drug compounds that are superior to those of other microbes in the environment, thereby helping them maintain a symbiotic relationship with their hosts (22,23).

Macroalgae-associated bacteria generate a wide range of bioactive compounds, including haliangicin, violacein, pelagiomycin A, koromycin, macrolactin, and chlorophyll-d. These metabolites exhibit diverse biological activities, including antifungal, antiprotozoal, antisettlement, and antibacterial effects against both Gram-negative and Gram-positive bacteria, as well as roles in photosynthesis (24-27). In recent decades, the extraction of bioactive compounds from microorganisms living in association with macroalgae has increased significantly, by almost six times compared to the previous century (28,29,30). Recent evidence suggests that marine bacteria associated with macroalgae are capable of producing novel molecules with high value and great potential as pharmaceutical drug candidates (31,32,33).

In one study, approximately 18% of 250 bacterial isolates from five species of green and brown algae demonstrated antibacterial activity (34). Kanagasabhapathy and colleagues (2021) observed that 22% of epiphytic bacterial isolates from nine brown algal species exhibited antibiotic properties (21,22,34). Penesyan et al. (2020) reported that 13% of 330 bacterial isolates from *Delisea pulchra* and *Ulva australis* showed antibacterial effects (35). The proportion of antimicrobial-producing isolates was notably high; for instance, around 35% of epiphytic bacterial isolates from nine red algal species displayed antibiotic activity (21,22,27,34). Furthermore, Burgess et al. (2020) found that 37% of bacteria residing on macroalgal surfaces possess antibacterial activity (20,27,28,36). Wiese et al. (2021) investigated bacterial isolates from the brown alga *Saccharina latissima* and discovered that half of the isolates inhibited Gram-negative bacteria, Gram-positive bacteria, and yeast/fungi (37). In another study, Ma et al. (2020) isolated 200 bacterial strains from *Ulva lactuca* and found that 33% exhibited anti-adhesion and anti-larval activities (38). Meanwhile, Janaki Devi et al. (2022) reported that all 130 bacterial isolates obtained from five macroalgal species showed antibacterial activity, with inhibition zones ranging from 3 to 17 mm against various pathogenic test strains, including *Escherichia coli*, *Staphylococcus* sp.*, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Vibrio cholerae* (39).

Recent studies have demonstrated that epiphytic bacterial communities associated with macroalgae, particularly *Ulva lactuca*, have significant potential to produce antimicrobial and antifouling compounds for use in pharmaceutical and environmental applications. Research by Sciutteri et al. (2022) revealed that the surface of *Ulva* is inhabited by various groups of bacteria from the classes *Alphaproteobacteria, Gammaproteobacteria, Firmicutes, Actinobacteria,* and *Bacteroidetes*, which play an important role in host de-

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fense against biofouling and marine pathogens (24,27,28,36). One study revealed that among 69 epiphytic bacterial isolates identified through 16S rRNA gene sequencing followed by bioactivity tests, approximately 45% exhibited potent antibacterial activity (40), while 18% had a significant impact on biofilm modulation (23,24,27,28). Several genera of epiphytic bacteria, such as *Pseudoalteromonas, Bacillus, Vibrio,* and *Shewanella*, are known to produce effective antimicrobial compounds (41). An example is *Pseudoalteromonas luteoviolacea* producing L-amino acid oxidase (LAAO), an enzyme whose antimicrobial action via hydrogen peroxide production contributes to the growth and dispersal of biofilms (42). In addition, secondary metabolite compounds such as hexadecanoic acid (palmitic acid), isolated from *Ulva lactuca*, have shown significant antibiofilm activity against marine bacteria, including *Pseudomonas aeruginosa*, as well as inhibiting biofilm formation and colonization by other fouling organisms (43). Another study by Oubihi et al. (2024) showed that aqueous extracts and silver nanoparticles synthesized using *Ulva lactuca* have strong antibacterial activity against various human pathogens, including *Staphylococcus aureus, Escherichia coli,* and *Klebsiella pneumoniae* (44).

Overall, the bioactivities of macroalgae-associated bacterial genera show great potential for pharmaceutical applications, particularly in the development of environmentally friendly antimicrobial and antifouling compounds for supporting drug discovery strategies.

Pseudoalteromonas

Marine macroalgae-associated *Pseudoalteromonas* species are known for producing diverse bioactive compounds, especially secondary metabolites that inhibit colonization on host surfaces and serve as chemical defenses against biofouling (45). Another study showed that *Pseudoalteromonas luteoviolacea* from *Padina australis* (Fig. 2) produces cyclo-(L-prolyl-L-glycine), cyclo-(L-phenylalanyl-4R-hydroxy-L-proline), and 2,4-dibromo-6-chlorophenol, which exhibit antibacterial activity against *Burkholderia cepacia* and methicillin-resistant *Staphylococcus aureus* (MRSA) (46).

Additionally, korormicin (Fig. 2a), first isolated from *Pseudoalteromonas* sp. F-420, associated with *Halimeda* sp., effectively inhibits marine Gram-negative bacteria, including *Vibrio alginolyticus* and *Salinivibrio costicola*. It disrupts bacterial respiration by inhibiting the Na-translocating NADH-quinone reductase (Na-NQR) enzyme complex (47). This mechanism is specific to marine bacteria, sparing terrestrial bacteria and thus offering opportunities for the development of selective and eco-friendly antibacterial agents (48).

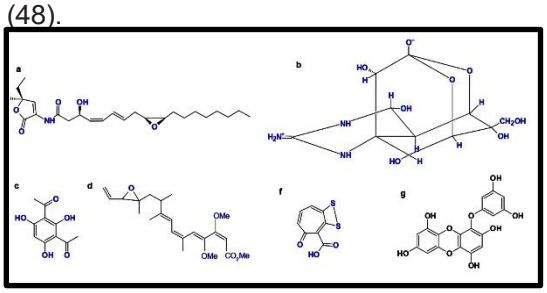

Fig. 2: Several structurally promising bioactive compounds have been identified from bacteria associated with macroalgae. Basic structure of a) Korormicin; b) Tetrodotoxin; c) 2,4-diacetylphloroglycinol; d) Haliangicin; e) Tropoditietic acid; and f) Phlorotannins

Recent studies highlight *Pseudoalteromonas* J010, isolated from the calcareous alga *Neogoniolithon fosliei*, as a source of diverse bioactives. The morphology of the genus Pseudoalteromonas is shown in Fig. 3. This bacterium produces a novel bromopyrrole compound (4-((3,4,5-tribromo-1H-pyrrol-2-yl)methyl)phenol) and five novel coromycins (G–K), all of which exhibit antimicrobial activity (49). It also produces tetrabromopyrrole (TBP), which is known to induce coral larval metamorphosis (36,46,50,51) and exhibits broad-spectrum activity against bacteria, fungi, and protozoa

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(36,49). Studies in 2023–2024 reinforced TBP's potential for coral restoration, though its stability and optimal concentration remain under investigation (Frontiers, 2024; ResearchGate, 2023).

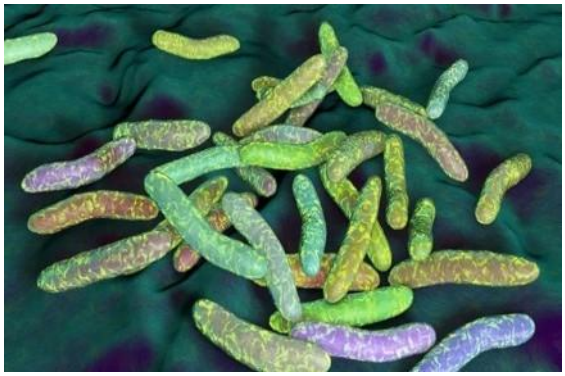

Fig. 3: Morphology of *Pseudoalteromonas tetraodonis*

Two bioactive compounds from *Ulva australis* associated with *Pseudoalteromonas tunicata* are violacein and the pigment YP1. Violacein, an alkaloid produced by *P. tunicata* and *P. ulvae*, exhibits potent antiprotozoal effects against *Acanthamoeba castellanii* at nanomolar concentrations (22). It also induces apoptosis-like death in predatory protozoa (52) and shows pro-apoptotic activity in mammalian cell lines, supporting its potential as an anticancer candidate (53). A recent study (54) demonstrated that violacein synergizes with azithromycin and kanamycin against *Salmonella typhi* and *Staphylococcus aureus*, with fractional inhibitory concentration (FIC) values indicating strong synergy. Additionally, *P. tunicata* produces YP1, a tambjamine-class yellow pigment with a 2,2-bipyrrole ring and a 12-carbon unsaturated alkyl chain. YP1 exhibits significant antifungal activity, helping protect algal surfaces from fungal infections (8,55). ***Pseudomonas***

The genus *Pseudomona*s produces various antimicrobial compounds that protect host algae from pathogens. The morphology of the genus *Pseudomonas* is shown in Fig. 4. One key compound is tetrodotoxin (TTX), a potent neurotoxin first identified in pufferfish and now known to be produced by *Pseudomonas* associated with the alga *Jania* sp. (56). TTX selectively binds to voltage-gated sodium channels in neuronal membranes, blocking nerve impulse transmission and action potential generation (57), leading to neurological dysfunction and target organism death (58).

Recent research by Liu et al. (2023) showed that DAPG derivatives inhibit MRSA growth (MIC 0.5–2 µg/mL) without detectable resistance over two months (59). Their mechanism involves disruption of the bacterial cell membrane, leading to lysis and death. DAPG also synergizes with oxacillin against MRSA. Additionally, Wei et al. (2022) reported that a cyclic peptide from Pseudomonas sp. inhibits MRSA biofilms by disrupting biofilm structure and increasing membrane permeability, ultimately causing cell death (60).

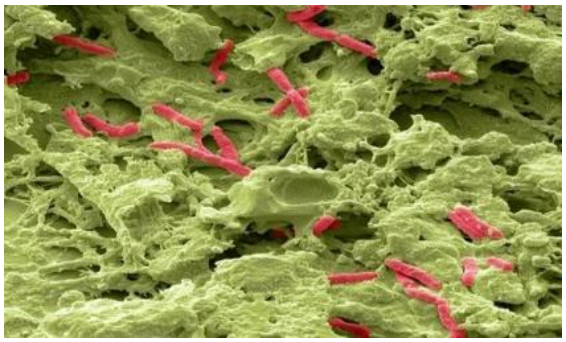

Fig. 4: Morphology of *Pseudomonas* Lung Infection

Tran et al. (2020) showed that massetolid A from *Pseudomonas fluorescens* controls *Phytophthora infestans* (61), a pathogen causing leaf blight, by inhibiting mycelial growth and spore formation while enhancing plant resistance. Rungprom et al. (2008) isolated two cyclic peptides from *Pseudomonas* sp. associated with the alga *Diginea* sp., cyclo-[phenylalanyl-prolyl-leucyl-prolyl] and cyclo-[isoleucyl-prolyl-leucyl-alanyl], with antibacterial activity against *S. aureus, Micrococcus luteus, Bacillus subtilis, E. coli,* and *Vibrio* spp. (62). Additionally, macrolactin XY from *Bacillus subtilis* damages bacterial cell membrane integrity (63).

Other macrolactins, including macrolactin S from marine *Bacillus* and macrolactin W from *Bacillus* strain 09ID194, exhibit broad-spectrum activity against Gram-positive and Gram-negative pathogens (64). A novel polyketide, 7-O-methyl-5′-hydroxy-3′-heptenoic-macrolactin, from *Bacillus subtilis* MTCC 10403 (associated with *Anthophycus longifolius*), inhibits *Vibrio* species with inhibition zones of 12–22 mm (65).

Furthermore, bacteriocins such as lichenicidin (a lantibiotic) from *Bacillus licheniformis* highlight *Bacillus* as a source of novel bacteriocins (66). Additionally, an 8-kDa bacteriocin from *Staphylococcus haemolyticus* MSM (macroalgae-associated) exhibits strong antibacterial activity against human pathogens (67).

Bioactivity of several other groups of bacteria associated with macroalgae

Other bacterial species have also been identified as producers of bioactive compounds with promising pharmaceutical potential. For instance, the Gram-negative halophilic bacterium *Pelagiobacter variabilis*, isolated from the brown alga *Pocockiella variegata*, synthesizes pelagiomycin A, a phenazine antibiotic active against both Gram-positive and Gram-negative bacteria, and demonstrates notable antitumor effects against HeLa, BALB3T3, and BALB3T3/H-ras cells, with low IC_{50} values (68).

In addition, the antifungal compound haliangicin produced by the *Haliangium luteum* associated with macroalgae has the potential as a strong antifungal agent, with activity equivalent to amphotericin B and nystatin. The mechanism of action of haliangicin is believed to be through the inhibition of electron flow in the mitochondrial electron transport chain, and it exhibits cytotoxic effects on P388 mouse cells (67).

Epiphytic bacteria *Pseudovibrio* sp. D-323 isolated from the algae *Delisea pulchra* produces tropoditietic acid (TDA), a broad-spectrum antibacterial compound that inhibits various bacterial groups, including Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes. Only strains that produce TDA show resistance to this compound, whereas non-producing strains remain susceptible, suggesting the presence of a resistance mechanism that is still not completely understood (56). Furthermore, recent studies have identified several bioactive compounds from *Streptomyces* strains associated with macroalgae and coral, including *Streptomyces cyaneofuscatus* M-27 and *Staphylococcus carnosus* M-40. The compounds found include daunomycin (anticancer), cosmomycin B and galtamycin B (antitumor), maltophylline (antifungal), and lobophorin, which has anti-inflammatory, anti-BCG, and antituberculosis activities (69).

Recent studies have reported the isolation of numerous bacteria from various habitats, including macroalgae, sediment, and soil, with the majority of isolates originating from the macroalgal surface. Approximately 40% of these isolates were *Bacillus* sp., and the bacteria producing the most bioactive compounds were found in epibiotic and endobiotic communities of macroalgae, compared with seawater and sediment. The antimicrobial compounds produced by these isolates were effective against plant pathogens, including *Xanthomonas axonopodis pv. citri, X. oryzae pv. oryzae,* and *Ustilaginoidea virens.* The antibacterial activity of extracellular proteins was optimal at pH 7.0 and remained active at temperatures up to 40 °C, while antifungal activity persisted up to 60 °C. The non-polar lipophilic compounds derived from these isolates exhibited activity exclusively against fungi (70).

Screening of bacterial isolates obtained from brown algae revealed that a small number of isolates were able to inhibit the quorum-sensing mechanism in *Serratia rubidaea*, which controls the production of the red pigment prodigiosin through the acyl-homocysteine lactone molecule. Genetic analysis showed that these inhibitory isolates came from the *Bacillaceae, Pseudomonadaceae,* and *Pseudoalteromonadaceae* families (71).

Furthermore, the isolation of actinomycete *Streptomyces cinnabarinus* and bacterium *Alteromonas* sp. from the macroalgae rhizosphere revealed that *Alteromonas* sp. can enhance the production of lobocompactol in *S. cinnabarinus*. This compound demonstrates strong antifouling activity against the alga *Ulva pertusa* and the diatom *Navicula annexa* at low effective concentrations, and also exhibits antifouling effects against bacteria (72). Several bacterial strains isolated from macroalgae, such as Cc51, Sm36, and Eb46, associated with *Centroceras clavulatum*, *Sargassum muticum*, and *Endarachne binghamiae*, showed significant anticancer activity with IC_{50} values of approximately 6.49, 5.53, and 2.84 µg/mL, respectively (57).

Bioactive activities of fungi associated with macroalgae

Macroalgae have been identified as one of the primary habitats for marine fungal diversity, ranking second in terms of diversity after other marine ecosystems (73). Fungi associated with macroalgae are typically classified into three main categories: parasites that can cause disease in the host, saprobes that function as decomposers of organic matter, and endosymbionts that live symbiotically without causing symptoms in the macroalgae (74). Various genera of macroalgae from the Phaeophyceae class, such as *Sargassum* and *Padina*, the Rhodophyceae class, including *Gracilaria* and *Pyropia*, and the *Chlorophyceae* class, including *Ulva* and *Caulerpa*, have become the focus of global research to study their interactions with marine fungal communities (75).

Recent studies have shown that the ascomycetes and anamorphic fungi groups are the most dominant endosymbionts found in macroalgae (76). In addition, the diversity of fungi in red and brown macroalgae is higher compared to green macroalgae, which is likely due to the shorter life cycle of green macroalgae and the slower growth of endosymbiont fungi, thus limiting the diversity of fungi that can grow on these macroalgae (77).

Multiple fungal genera, such as *Acremonium, Alternaria, Arthrinium, Aspergillus, Cladosporium, Fusarium, Geomyces, Penicillium,* and *Phoma*, are consistently reported as the most common endosymbionts associated with diverse macroalgae species across different regions (56,57). Recent studies have shown that these fungi play a crucial role in marine ecosystems as producers of bioactive metabolites and protectors of macroalgae hosts from environmental stress (78).

Like bacteria, fungi associated with macroalgae are recognized for producing diverse novel bioactive metabolites with wide-ranging activities, including anticancer, antibacterial, antimalarial, anti-inflammatory, nematicidal, antiviral, and antiangiogenic properties (79,80). Recent studies have also revealed that fungal isolates from brown, red, and green macroalgae produce metabolite compounds with antifungal and insecticidal properties that function to inhibit the colonization of other microbes on the algal thallus, thereby helping to reduce competition and protect macroalgae from herbivore attacks (81,82).

Endophytic fungi enhance host stress tolerance via antioxidants, protecting against pathogens, drought, and heavy metals (83). Hu et al. (2022) showed that *Aspergillus, Cladosporium,* and *Trichoderma* from seagrass protect against *Labyrinthula* spp. Amina et al. (2019) reported that *Aspergillus rhizopodus* from Thai macroalgae inhibits *S. aureus, E. coli,* and *S. weltevreden* (MIC 3.90 µg/mL) (84).

El-Sayed et al. (2022) found that extracts of *Aspergillus sydowii, A. flavus*, and *Lasiodiplodia theobromae* have larvicidal effects (LC_{50} <100 µg/mL) (85). Arunpanichlert et al. (2013) showed endophytic fungi from seagrasses inhibit human and fish pathogens (>10 mm inhibition) (86). Gomes et al. (2024) reported that Antarctic macroalgae endophytes (*Monostroma hariotii, Pyropia endiviifolia*) have antifungal activity against *Candida albicans, C. krusei*, and *Cladosporium sphaerospermum. Pseudogymnoascus* sp. and *Metschnikowia*

australis extracts showed 61–96% inhibition. Bioactive compounds from *Penicillium steckii* inhibited yellow fever and DENV virus by 96% (87).

Endophytic fungi produce diverse secondary metabolites: aromatic β-polyketides, alkaloids, sesquiterpenes, terpenes with antimicrobial, antioxidant, cytotoxic activities (88,89). *Chaetomium globosum* from green algae produces chaetoglobosin (cytotoxic) (90). *Penicillium aculeatum* produces sulfonyl metabolites (antibacterial*). Aspergillus ochraceus* from brown algae yields antibacterial and antioxidant compounds (89). *Aspergillus ustu*s produces sesterterpenoids (cytotoxic) (91). *Penicillium polonicum* from red algae produces indole alkaloids (cytotoxic) (92). *Aspergillus versicolor* produces phenolic antioxidants (93). The bioactivities of Aspergillus and Penicillium isolated from macroalgae are summarized for pharmaceutical and industrial applications.

Aspergillus

Marine *Aspergillus* fungi that live on macroalgae are widely considered a major biological source for finding bioactive compounds with valuable pharmacological activities. Their occurrence in marine settings, particularly on the surface or within algae such as Sargassum and other macroalgae, enables the production of various secondary metabolites. These metabolites both contribute to the host organism's defense and hold considerable promise for drug development.

One of the prominent species is *Aspergillus ustus*, which is known to produce phenylahistine compounds, namely cyclic metabolites that show strong cytotoxic activity against various human cancer cell lines. The cytotoxic activity of this compound is mediated by inhibition of cell cycle progression, particularly in the G2/M phase, by interfering with tubulin polymerization, an important component of microtubule formation during cell division. This process occurs through the binding of the compound to the colchicine binding site, making phenylahistine a strong candidate for an antimitotic agent in cancer therapy (94).

Other species, such as *Aspergillus ochraceus* from the brown alga *Sargassum kjellmanianum*, also show pharmacological promise. It produces 2-hydroxycircumdatin C, a benzodiazepine analog with high antioxidant activity. In the DPPH test, this compound scavenges free radicals 8.9 times more effectively than BHT, a synthetic antioxidant used in pharmaceuticals and food (95). This activity offers hope for preventing oxidative stress-related diseases like heart disease, cancer, and neurodegenerative disorders.

Further research on *Aspergillus* sp. associated with *Sargassum* sp. also yielded other interesting findings, including two new derivatives of terpeptin compounds, namely JBIR-81 and JBIR-82, as well as one previously known terpeptin derivative. All three compounds demonstrated protective activity against L-glutamate toxicity in cells, a model used to assess the potential for neurodegenerative disorders. The IC_{50} values of these compounds were very low (0.7–1.5 μM), indicating strong potential as neuroprotective agents, even showing comparable or better effectiveness than α-tocopherol, the active form of vitamin E that acts as a natural antioxidant (96). Several structurally promising bioactive compounds have been isolated from fungi associated with macroalgae, as shown in Fig. 5.

Overall, the results of this latest study provide strong evidence that marine endophytic fungi of the genus Aspergillus are a potential source of new bioactive compounds. The diversity of secondary metabolites produced exhibits a broad spectrum of biological activities, including cytotoxic, antioxidant, and neuroprotective properties. This potential supports further exploration efforts in marine bioprospecting, especially in the context of developing innovative and environmentally friendly natural drug candidates (97).

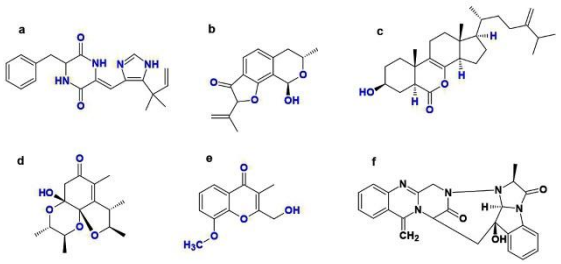

Fig. 5: Several structurally promising bioactive compounds have been isolated from fungi associated with macroalgae. a) phenylahistine; b) pseudodeflectusine; c) 7-Norergosterolide; d) citrinal A; e) chromanone A; and f) cottoquinazo-line

Recent studies show that *Aspergillus fungi* from macroalgae produce bioactive compounds with antibacterial and cytotoxic activities. Epoxidone and gentisyl alcohol, derived from *Aspergillus* sp. and isolated from the red alga *H. asidana*, demonstrated strong inhibi-tion of MRSA and drug-resistant *Staphylococ-cus aureus*, with low MIC values. Meanwhile, *Aspergillus versicolor* isolated from the brown macroalga *Sargassum thunbergii* produces brevianamide M and methylaverufin, which are active against *E. coli* and *S. aureus*. Additionally, the ethyl acetate extract of *Aspergillus terreus* showed high cytotoxicity against HepG2 cancer cells (GI_{50} < 10 µg/mL) with strong lethality (99).

Penicillium

Marine fungi of the genus *Penicillium* associated with macroalgae have been identified as important sources of secondary metabolites with broad pharmacological potential. The morphology of the genus of *Penicillum* are shown in **Fig. 6.** Recent studies have shown that species such as *Penicillium terrigenum* are capable of producing compounds PTL-2 and 7-ethylcamptothecin that exhibit significant antiproliferative activity against liver and lung cancer cells (100). In addition, *Penicillium rubens* BTBU20213035 has been reported to produce penubenone A and B, as well as penubenamide A and B, which have antimicrobial potential against *Candida albicans, Staphylococcus aureus,* and *Escherichia coli* (90).

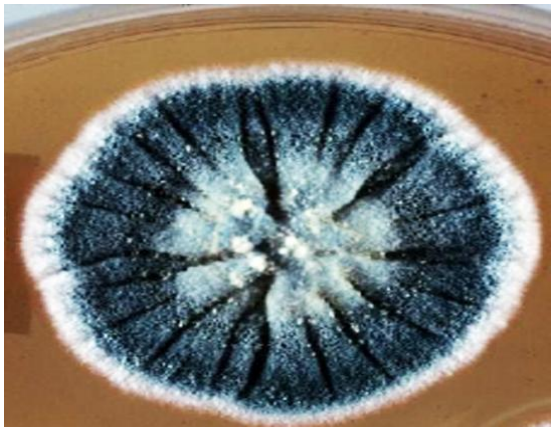

Fig. 6: Morphology of *Penicillium*

Furthermore, *Penicillium citrinum* was found to produce bioactive compounds such as penicitrinone A, which exhibited cytotoxic effects against A549 and A375 cancer cells, and antimicrobial activity against *Mycobacterium smegmatis* (54), *Penicillium chrysogenum* was also found to produce penicitrinone F, which showed potential as an antiviral agent against enterovirus 71 (97). These findings confirm that *Penicillium* from marine environments can produce compounds with unique chemical structures and potent biological activities, making them a promising source in the search for new drugs based on natural compounds (93).

Recent studies isolated various bioactive compounds from *Penicillium chrysogenum* associated with the red alga Laurencia sp. The tetracyclic diterpene conidiogenone B showed strong antibacterial activity against MRSA, *S. epidermidis, P. aeruginosa,* and *P. fluorescens* (MIC ~8 µg/mL), but weak antifungal activity against *C. albicans* (MIC 128 µg/mL) (101). Conidiogenol was active against *P. fluorescens* and *S. epidermidis* (MIC 16 µg/mL) (70). Penicitide A, a polyketide, exhibited cytotoxicity against HepG2 cells (IC_{50} 30–35 µg/mL) (78). Penicimonoterpenes inhibited the plant pathogen *Alternaria brassicae* with large inhibition zones at low concentrations (102). Additionally, penicisteroid A, a novel steroid with tetrahydroxy and acetoxy groups, showed strong antifungal activity against *Aspergillus niger* and selective cyto-

toxicity against HeLa, SW1990, and NCI-H460 tumor cells (IC_{50} 15–40 µg/mL) (103).

Two pinophilin compounds from the hydrogenated azaphilone group, along with the co-isolated metabolite Sch 725680, were obtained from *Penicillium pinophilum* associated with the macroalgae *Ulva fasciata*. These compounds specifically inhibit the activity of various DNA polymerase families in mammals, including pol A/g, pol B/a, pol D, pol ε, and pol Y/h, i, and κ. In addition, these compounds show potential for suppressing the growth and proliferation of several human cancer cell lines (104).

Bioactive activities of several other macroalgae-associated fungal groups

Various types of fungi also produce bioactive compounds that have pharmacological potential. For instance, ascosalipyrrolidinone A, isolated from the obligate endophytic fungus Ascochyta salicorniae associated with *Ulva* sp., exhibited strong antimalarial activity against *Plasmodium falciparum* K1 and NF54 strains, with IC_{50} values of 0.74 and 0.38 µg/mL, respectively. This compound also exhibits antimicrobial effects against several microorganisms, including *Bacillus megaterium*, *Microbotryum violaceum*, and *Mycotypha microsporum*, at a concentration of 50 µg per disc. In addition, ascosalipyrrolidinone A is able to inhibit the activity of the tyrosine kinase enzyme p56 in a dose-dependent manner. Furthermore, from *Chaetomium globosum* associated with *Polysiphonia urceolata*, a new compound derived from 2H-benzopyran was found, called chaetopyranin, which has moderate antioxidant activity based on the DPPH test (IC_{50} of 35 µg/mL) and mild to moderate cytotoxic activity against HMEC, SMMC 7221, and A549 cells with IC_{50} values of 15.4, 28.5, and 39.1 µg/mL, respectively (66).

Over the past five years, studies on marine fungi of the genus Penicillium associated with macroalgae have uncovered a range of secondary metabolites with significant pharmacological activity. As an illustration, penirubenones A and B, as well as penirubenamides A and B, isolated from *Penicillium rubens* BTBU20213035, showed antibacterial properties against *Staphylococcus aureus* and collaborated to produce antifungal activity against *Candida albicans* (90). Furthermore, new polyketides, bisorbicillaetones A–C, were derived from *Penicillium* sp. SCSIO06868, demonstrated inhibition of nitric oxide production in LPS-activated RAW264.7 cells, with IC_{50} values of 80.3 ± 3.6 µM and 38.4 ± 3.3 µM, respectively (105). Other metabolites, such as chrysopyrones A and B produced by *Penicillium chrysogenum* SCSIO07007, showed inhibitory activity against human protein tyrosine phosphatase, an enzyme involved in various disease processes (106). Additional research identified penithoketone and penithochromones A–L from *Penicillium thomii* YPGA3, with penithoketone displaying cytotoxicity against multiple cancer cell lines, including MCF-7 and MDA-MB-468. Meanwhile, peniterphenyls A–C, isolated from *Penicillium* sp. SCSIO4103 exhibited antiviral activity against HSV-1 and HSV-2, with EC_{50} values ranging from 1.4 ± 0.6 to 9.3 ± 3.7 µM (15). Collectively, these findings confirm that marine-derived *Penicillium* species are a promising source of secondary metabolites with diverse biological activities, including antibacterial, antifungal, antiviral, and cytotoxic properties, that warrant further exploration as novel drug candidates.

Compounds from macroalgae-associated microbials with anti-dengue and immunomodulatory activity

Dengue fever, caused by DENV and transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, remains a major mosquito-borne disease that threatens nearly half of the global population, especially in tropical regions. Available vaccines such as Dengvaxia and TAK-003 have limited efficacy owing to serotype specificity and differences in host immune responses (107). The lack of targeted antivirals highlights the necessity for alternative therapeutic approaches. Marine environments, particularly macroalgae-associated microorgan-

isms, are promising yet insufficiently explored reservoirs of bioactive metabolites. These bacteria that live symbiotically on algal surfaces generate antibacterial, antifungal, and antiviral compounds, including those with anti-dengue activity. Their chemical diversity, influenced by complex marine conditions, makes them a valuable resource for the discovery of novel anti-dengue drugs (108).

Macroalgae host diverse bacterial communities on their surfaces and internal tissues. These bacteria contribute to nutrient cycling, morphogenesis, and chemical defense (109). Common symbiotic genera include *Bacillus, Streptomyces, Vibrio, Pseudomonas, Micrococcus, Alteromonas,* and *Roseobacter*. Table 1 summarizes anti-dengue compounds from these bacteria, their classes, and mechanisms. Many produce bioactive metabolites with antimicrobial, anti-inflammatory, cytotoxic, and antiviral properties. Notably, extracts from marine-derived *Penicillium steckii* showed 96% inhibition against yellow fever virus and DENV, outperforming interferon alpha (68% inhibition) (87). Isolation of macroalgae-associated bacteria typically involves using marine agar supplemented with sea salts, followed by 16S rRNA sequencing. Recent advances in metagenomics and metabolomics have enabled the identification of unculturable symbionts and novel biosynthetic gene clusters, expanding the discovery of marine metabolites.

Table 1: Classes and Mechanism Action of Anti-Dengue Compounds from Macroalgae-Associated Microbial

Compound Class	Representative Examples	Producer (Seaweed-Symbiont)	Proposed Mechanism	References
Alkaloids	Indole and pyrrole derivatives	*Streptomyces, Bacillus* spp.	Inhibit DENV NS3 protease and replication	(110)
Lipopeptides	Surfactin, iturin, fengycin	*Bacillus subtilis, Bacillus amyloliquefaciens*	Disrupts viral envelope; immunostimulant	(111)
Polyketides	Macrolides, polyenes	*Streptomyces, Alteromonas*	Block DENV replication and protease activity	(112)
Phenolic Compounds	Bromophenols, flavonoid-like analogs	*Vibrio, Micrococcus*	Antioxidants modulate oxidative stress	(113)
Terpenoids	Marine diterpenes, sesquiterpenes	*Pseudomonas, Roseobacte*r	Inhibit viral-host interaction pathways	(114)
Triterpenoids	Marine triterpenes, sesquiterpenes	Marine-derived *Penicillium steckii*	Induction of interferon alpha (IFN-α)	(87)

Compounds from macroalgae-associated bacteria can act through direct antiviral and indirect immunomodulatory mechanisms:

a. Direct Antiviral Actions:

Inhibition of viral entry: Some bacterial metabolites can block viral attachment or fusion with host cell membranes by interacting with the viral envelope (E) protein.

Suppression of viral replication: Certain metabolites target non-structural proteins (NS3 protease, NS5 polymerase) essential for DENV genome replication.

Disruption of virion assembly: Amphiphilic compounds, such as lipopeptides, may interfere with membrane integrity, leading to loss of viral infectivity.

b. Immunomodulatory Effects:

- Activation of interferon-stimulated genes (ISGs) and enhancement of innate immune responses.
- Modulation of macrophage and natural killer (NK) cell activity.
- Reduction of oxidative stress and inflammatory cytokine overproduction.

These combined effects make macroalgae-associated bacterial metabolites promising candidates for both prophylactic and therapeutic interventions against dengue infection.

Surfactin from *Bacillus subtilis* on *Sargassum* sp. disrupts viral envelopes and boosts interferon responses, while indole derivatives from *Streptomyces* on *Gracilaria corticata* inhibit DENV NS2B/NS3 protease in silico, suggesting their potential for antiviral drug design (110).

Experimental studies on marine-derived bacterial metabolites have employed cell-based assays using Vero, Huh7, or C6/36 cell lines infected with DENV. Antiviral efficacy is typically measured through plaque reduction assays, viral RNA quantification, or inhibition of cytopathic effect (CPE).

Computational methods like molecular docking, ADMET prediction, and QSAR modeling are now widely used to predict how bacterial metabolites bind to dengue viral targets (115). For example, docking studies have shown that certain bromophenols and indole compounds bind strongly to DENV NS3 protease and NS5 polymerase. Furthermore, pharmacokinetic analyses suggest many marine-derived compounds have good oral bioavailability and low toxicity. However, challenges remain in developing these metabolites into clinical antivirals for dengue, such as low yields from natural cultures, difficulties in growing marine symbionts in the lab, and complex purification and structural identification processes (45).

In response to these challenges, current studies focus on genome mining, synthetic biology, and heterologous expression as strategies to increase metabolite production. Integrating metabolomics, transcriptomics, and in silico methods can greatly accelerate the discovery and identification of bioactive compounds. Future studies should also explore synergistic effects between bacterial metabolites and existing antivirals or immunomodulators. Macroalgae-associated bacteria are a rich but underutilized source of antiviral metabolites against dengue virus (116). Their diverse compounds, including lipopeptides, alkaloids, phenolics, and polyketides, act through multiple mechanisms, such as direct viral inhibition and immune modulation (117). Advancing research on these marine symbionts using modern omics and bioinformatics will be essential for developing innovative, effective, and sustainable anti-dengue therapies.

Biotechnological approaches to discover potential new bioactive products

Approximately 99% of environmental microorganisms fail to grow optimally under standard laboratory conditions due to specific nutritional needs, complex environmental factors, and symbiont interactions that are difficult to replicate (118,119). Thus, most remain inaccessible for phylogenetic and functional analysis using classical culture methods. However, advances in Next Generation Sequencing (NGS) and metagenomics have revolutionized microbial community studies. These techniques allow direct analysis of genetic material from environmental samples, bypassing isolation and cultivation (120,121). This accelerates the discovery of novel enzymes and bioactive compounds for biotechnology, healthcare, and environmental applications. A key application is the study of microorganisms associated with marine mac-

roalgae such as *Ulva* sp. Recent studies show that epiphytic bacteria on *Ulva australis* or *Ulva ohnoi* produce enzymes and secondary metabolites, including antimicrobial and antioxidant compounds, useful for drug and anticancer development (19,122). These findings confirm that the ocean, particularly macroalgae and their microbiota, is an untapped biological resource for future bioactive exploration.

In recent years, metagenomic approaches have developed rapidly in revealing the diversity and functions of microbial communities associated with macroalgae. Recent studies have shown that, despite significant taxonomic variations in bacterial communities associated with macroalgae across different environments, their functional potential remains relatively stable. For example, metagenomic analysis of *Ulva* species along a 2000 km salinity gradient revealed that, despite significant changes in taxonomic composition, functional variation was only approximately 17%, highlighting the conservation of metabolic functions, such as carbon, nitrogen, and vitamin metabolism, across microbial communities (123).

Furthermore, studies on the microbiomes of macroalgae, such as those of *Macrocystis pyrifera* and *Nereocystis luetkeana*, have revealed that associated bacteria can degrade complex polysaccharides, including alginate and laminarin. This ability is supported by the presence of genes such as algL and alg17C, which are widely distributed in various bacterial phyla, including Bacteroidetes and Proteobacteria. These findings indicate that macroalgae microbial communities have great potential in marine biogeochemical cycles and the production of bioactive compounds. However, challenges remain in exploiting this potential. One of the main obstacles is the low frequency of heterologous gene expression across different hosts, which can be caused by incompatible gene expression or toxic effects of the gene products. Additionally, specific metagenomic screening approaches may fail to detect target genes if they are not evenly distributed throughout the microbial community (124). For example, out of thousands of bacterial clones obtained from various marine environments, only a small fraction exhibits antimicrobial activity, as reported in a metagenomic study of mangrove sediments, where out of 15,000 clones screened, only five were active, with one clone (PS49) producing significant antibacterial compounds against multiple pathogens (125). Recently, a metagenomic library construction approach based on macroalgae-associated microbial DNA has shown potential for generating bioactive compounds, and a bioactivity-based screening process has identified clones with both antibacterial and antifungal properties (126). These results reinforce previous findings that pre-selecting genomes or biosynthetic gene clusters capable of producing bioactive compounds can increase the hit rate in metagenomic exploration (127).

The successful application of functional metagenomics to discover bioactive compounds from macroalgae-associated bacteria remains limited. However, this can be improved by using suitable expression host strains with compatible codon usage or biosynthetic pathways. For instance, *Ralstonia metallidurans* effectively expresses antibacterial genes from metagenomic libraries that fail to express in *E. coli* (128). Additionally, codon harmonization enhances heterologous gene expression by adjusting codon frequency to the host's translation system (129). Shotgun metagenomics has also identified novel genes from type I PKS and NRPS involved in bioactive compound biosynthesis (130). One study, for example, found more than 35,000 keto-synthase domains of type I PKS across 137 global metagenomic datasets, demonstrating the vast biosynthetic potential of microbes in natural environments (131).

Despite these encouraging successes, further metagenomic development is needed to overcome bottlenecks in heterologous expression and improve bioactive compound detection (132). A visual summary of macroalgal microbes producing antimicrobial, anti-dengue, and immunomodulatory compounds for drug discovery is provided in Fig. **7.**

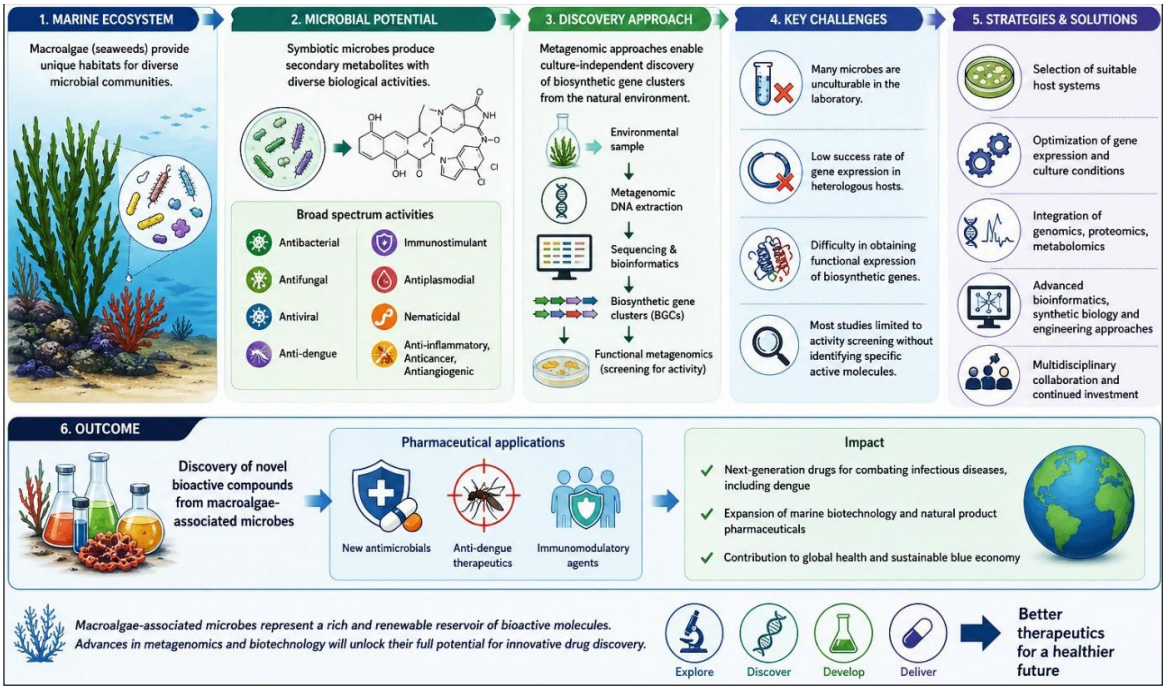

Fig. 7: Visual overview of macroalgae-associated microbes producing antimicrobial, anti-dengue, and immunomodulatory compounds for drug discovery (This figure was created by the author using Dreamina AI and modified with BioRender.com, on 23 April 2026).

Conclusion

Marine ecosystems, especially those involving macroalgae, are vital sources of bioactive compounds for pharmaceuticals. Macroalgae-associated bacteria offer a new frontier for the discovery of antimicrobial, anti-dengue, and immunostimulant agents. Their unique metabolic traits make them valuable for drug discovery. However, many marine microbes are difficult to culture, posing challenges. Metagenomic approaches, particularly functional metagenomics, enable direct identification of biosynthetic genes without culturing. Yet challenges persist, including low success rates for heterologous gene expression. Strategies like selecting appropriate host systems and optimizing expression conditions are needed. Technological and multidisciplinary advances are expected to drive the discovery of new bioactive compounds from these microbes, supporting drug development. These compounds exhibit antibacterial, antifungal, antiviral, antiplasmodial, nematicidal, anti-inflammatory, anticancer, and antiangiogenic activities. However, most studies remain limited to screening activities and do not identify specific molecules. With continued investment in marine biotechnology and interdisciplinary collaboration, these microbes may yield next-generation antimicrobial, antiviral, and immunomodulatory therapies for dengue.

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Author Contributions

The research team for this review on antimicrobial and anti-dengue compounds from macroalgae-associated bacteria is structured as follows: Harningsih Karim (first author) leads the research design, literature search, methodology, and manuscript coordination, and writes the introduction, background, abstract, and conclusions. Raymond A.N. Noena specializes in the identification, characterization, and structure-activity analysis of antimicrobial compounds. A. Tenriugi Daeng Pine focuses on anti-dengue compounds and analyzes viral inhibition mechanisms. Nurul H. Base contributes expertise in macroalgae ecology and bacterial community analysis. Ananda Ramadani handles data extraction, reference management, and formatting. Abdul Yasir provides marine microbiology expertise, including review of cultivation and extraction methods. Ahyar Ahmad offers senior scientific oversight, coordinates the team, manages journal communications, and ensures scientific rigor. Anita and Yoesef Abdulwahab contribute pharmaceutical and therapeutic expertise, analyzing the potential for drug development and clinical applications. Eka Sry Wahyuni provides final scientific review and validation, contributing to conclusions and future directions. All authors collectively maintain scientific integrity, participate in peer review responses, and ensure adherence to publication standards.

Conflict of Interest

The authors declare no conflict of interest.

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References

1. Smith, R., Wang, Y., & Zhao, L. Microbial diversity and bioactivity in marine ecosystems: a review. Mar Ecol. 2021;42(4):203–18.
2. Lee, H. and Kim, J. Symbiotic microorganisms in marine environments: ecological roles and biotechnological potential. Mar Ecol Prog Ser. 2022; 685:115–30.
3. Zhang, Y. Synergistic antimicrobial profiling of violacein with commercial antibiotics against pathogenic microorganisms. J Appl Microbiol. 2023;134(1):123–35.
4. Amin MK, Boateng JS. Enhancing Stability and Mucoadhesive Properties of Chitosan Nanoparticles by Surface Modification with Sodium Alginate and Polyethylene Glycol for Potential Oral Mucosa Vaccine Delivery. 2022;
5. Shaaban, K.A. Marine Microbial Diversity as a Source of Bioactive Compounds. Mar Drugs. 2022;20(5).
6. Annamalai, A., Kolandhasamy, P. Marine macroalga metabolites in microbial modulation for next-generation microecological therapeutics. Discov Biotechnol, 2026; 3(7). https://doi.org/10.1007/s44340-025-00047-6.
7. Wang Y, Wang X, Tian L, Li Y, He G, Yu H, et al. Removal effect and mechanism of amphiphilic chitosan modified microbubbles on *Microcystis aeruginosa*. J Water Process Eng. 2022;46(November 2021):102585.
8. Choi, J., & Park, S. Secondary metabolites from marine bacteria: chemical diversity and biotechnological applications. Mar Biotechnol. 2023;25(1):45–62.
9. Kumar, R., Zhao, L., & Wang, Y. Competitive microbial interactions on macroalgal surfaces stimulate production of novel bioactive compounds. Algal Res. 2022;61(102585).

10. Harrison, J., Nguyen, T., & Lee K. Metagenomic approaches to uncover novel bioactive compounds in seaweed associated microbiomes. Front Mar Sci. 2022;9(876543).

11. Haggag, Y.A., Abd Elrahman, A.A., Ulber. R., Zayed, A. Fucoidan in Pharmaceutical For-mulations: A Comprehensive Review for Smart Drug Delivery Systems. Mar Drugs. 2023;21(2).

12. Chastagnier, L., Marquette, C., Petiot, E. In situ transient transfection of 3D cell cultures and tissues is a promising tool for tissue engineering and gene therapy. Biotechnol Adv. 2023;68 (December 2022):108211.

13. Tang, K.W.K., Millar, B.C., Moore, J.E. Antimicrobial Resistance (AMR). Br J Biomed Sci. 2023;80:1–11.

14. Daokoru Olukole, C.G., Nelson, P., Ockiya, M. Dengue virus: epidemiology, molecular pathogenesis, risk factors, and public health challenges in endemic regions. J Microbiology Exp. 2025; 13:42–7.

15. Chen, Y., Lopez, M., & Ahmad R. Extracellular and intracellular bacteria influencing *Ulva* and *Gracilaria* life cycles. J Phycol Res. 2021;36(4):256–69.

16. Ahmad, R., Chen, Y., & Lopez M. Role of surface-associated bacteria in seaweed development and health. Mar Microb Ecol. 2023;45(2):120–35.

17. Kaur, M., Saini, K.C., Mallick, A., Bast, F. Seaweed-associated epiphytic bacteria: Diversity, ecological and economic implications, Aquatic Botany, 2023; 189, 103698.

18. Wang, H. et al. Isolation of Macrolactin Compounds from Marine *Bacillus* sp. Associated with Red Algae. Mar Drugs. 2020;18(19):641.

19. Zhang, L., Li, X., & Wang Y. Zhang, L., Li, X., & Wang, Y. (2020). Antimicrobial and antifouling properties of bioactive compounds produced by marine bacteria associated with seaweeds. Environ Microbiol. 2020;22(4):1357–137

20. Kumar, S., Zhao, L., & Li J. Impact of symbiotic bacteria on seaweed morphogenesis and growth. Algal Res. 22 AD;56(102298).

21. Lin, W., Patel, N., & Nguyen H. Identification of thallusin as a key morphogenetic factor in *Monostroma oxyspermum*. Mar Biol Lett. 2021;12(3):89–98.

22. Nguyen, H., Silva, P., & Patel N. Nutrient competition and microbial interactions on seaweed surfaces. Front Mar Sci. 2021;8(698453).

23. Silva, P., Garcia, J., & Torres L. Antimicrobial metabolite production by seaweed associated bacteria under competitive stress. J Appl Microbiol. 2023;134(5):1558–70.

24. Garcia, J., & Torres L. Bioactive compounds from seaweed-associated bacteria: potential for new drug discovery. Biotechnol Adv. 2022;60(107921).

25. Smith, R., Wang, Y., & Zhao L. Exploring novel antibiotics from marine symbiotic bacteria: challenges and opportunities. Curr Opin Biotechnol. 2023;102752. (102752).

26. Liu, H., Zhao, Y., & Wang J. Marine bacterial secondary metabolites: Diversity and potential applications. Front Microbiol. 2021;12(653085).

27. Kim, J. H., & Park SY. Novel bioactive metabolites from marine bacteria associated with seaweeds. Mar Drugs. 2019;17(5):288.

28. Chen, Y., Li, X., & Zhang, W. Bioactive compounds from marine bacteria associated with seaweeds: Isolation and biological activities. Mar Biotechnol. 2022;24(3):445–60.

29. Wang, Y., Liu, X., & Zhou, Q. Significant growth in marine natural product discovery from bacteria associated with macroalgae. Nat Prod Rep. 2021;38(7):1375–90

30. Martinez, L., Gonzalez, M., & Perez, R. Advances in extraction techniques for bioactive compounds from marine microorganisms. Mar Drugs. 2023;21(1):45.

31. Nguyen, H., Silva, P., & Patel N. Nutrient competition and microbial interactions on seaweed surfaces. Front Mar Sci. 2021;8(698453).

32. Silva, P., Garcia, J., & Torres L. Antimicrobial metabolite production by seaweed-as-sociated bacteria under competitive stress. J Appl Microbiol. 2023;134(5):1558–70.

33. Lee, H. J., Choi, Y., & Kim, J. Alternative microbial hosts for metagenomic expression libraries. Microb Biotechnol. 2023.

34. Garcia, J., & Torres L. Bioactive compounds from seaweed-associated bacteria: potential for new drug discovery. Biotechnol Adv. 2022;60(107921).

35. Penesyan, A., Kjelleberg, S., & Egan, S. Development of bioactive compounds from marine bacteria associated with seaweeds. Trends Microbiol. 2020;25(8):400–12.

36. Whalen, K. E., Sneed, J. M., Tebben, J., Motti, C. A., & Steinberg, P.D. Antimicrobial and antifouling properties of tetrabromopyrrole from *Pseudoalteromona* J010. Front Microbiol. 2018;9(1109).

37. Wiese, J., Thiel, V., & Imhoff, J. F. Antibiotic-producing bacteria from the brown alga S*accharina latissima*. Mar Drugs. 2021;19(6):312.

38. Ma, H., Sun, F., & Wang, Y. Anti-settlement and antibacterial activity of marine bacteria associated with *Ulva lactuca*. J Oceanol Limnol. 2020;38(1):134–42.

39. JanakiDevi, P., Ramasamy, R., & Subramanian, P. Antibacterial potential of bacteria isolated from marine macroalgae against human pathogens. Microb Pathog. 2022;162(105297).

40. Sciutteri, V., Genovese, G., Tedone, L., Giordano, D., Spanò, N., & Morabito, M. Microbiome diversity of *Ulva lactuca* from Mediterranean coastal waters: Implications for its antibacterial potential. Algal Res. 2022;61(102608).

41. Lu, Y., Song, S., Li, R., Chen, M., Zhang, C., & Gao, C. Exploration of antibacterial and antibiofilm potential of epiphytic bacteria isolated from Ulva lactuca. J Appl Phycol. 2024; 36:135–47.

42. Torres, M., Urrutia, H., Lizardi-Mendoza, J., & Armenta, M. Antimicrobial properties of L-amino acid oxidase from *Pseudoalteromonas luteoviolacea*: Effects on marine biofilms. Front Mar Sci. 2019; 6:145.

43. Abdullah, A., Ismail, H. I., & Omar MN. Anti-biofilm activity of fatty acids extract-ed from the green macroalga *Ulva lactuca* against marine biofilm-forming bacteria. Pollut Bull. 2024;196(115692).

44. Oubihi, A., Ez Zoubi, Y., Ait Elmaati, M., & Bouhrim, M. Biogenic synthesis of silver nanoparticles using *Ulva lactuca:* Antibacterial activity and phytochemical screening. Saudi J Biol Sci. 2024;13(1):103581.

45. Srinivasan R, Kannappan A, Shi C, Lin X. Marine bacterial secondary metabolites: A treasure house for structurally unique and effective antimicrobial compounds. Mar Drugs. 2021;19(10):1–36.

46. Alker, A.T., Delherbe, N., Purdy, T.N., Moore, B.S., Shikuma, N.J. Genetic examination of the marine bacterium *Pseudoalteromonas luteoviolacea* and effects of its metamorphosis in-ducing factors. Environmental Microbiology. 2020;22(11):4689–701.

47. A Wu, L March, X Zheng, J Huang, X Wang, J Zhao, FM Blyth, E Smith, R Buchbinder DH. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. Ann Transl Med. 2020;8(6):299.

48. Guryanova S V., Balandin S V., Belogurova-Ovchinnikova OY, Ovchinnikova T V. Marine Invertebrate Antimicrobial Peptides and Their Potential as Novel Peptide Antibiotics. Mar Drugs. 2023;21(10):1–37.

49. Tebben, J., Tapiolas, D. M., Motti, C. A., & Steinberg, P.D. Production of bromopyrrole and koromisin compounds by *Pseudoalteromonas* J010 and their antimicrobial activities. Mar Drugs. 2014;22(2):533–48.

50. Tebben, J., Tapiolas, D. M., Motti, C. A., Abrego, D., Negri, A. P., Blackall, L. L., & Steinberg, P.D. Chemical mediation of coral larval settlement by tetrabromopyrrole produced by *Pseudoalteromonas* bacteria. Mar Ecol Prog Ser. 2011; 433:85–96.

51. Petersen, L. H., Sneed, J., Tebben, J., Wha-len, K. E., & El Gamal, A. Tetrabromopyr-role and coral larvae metamorphosis: re-cent insights. Mar Biol. 2023;170(5):45.

52. Lee, J. Y. et al. Violacein induces apoptosis in human breast cancer cells through upregulation of BAX and p53, and downregulation of MDM2. Front Microbiol. 2022;13(283445676).

53. Pfeffer CM, Singh ATK. Apoptosis: A target for anticancer therapy. Int J Mol Sci. 2018;19(2).

54. Zhang, D., Huang, Y., Wang, Q., & Li, H. New bioactive secondary metabolites from marine *Penicillium citrinum*. Mar Biotechnol. 2023;25(1):25–34.

55. Park, C., Kim, S., Lee, J., & Lee, J. Chemopreventive potential of dimeric xanthones (Monodictyochrome A and B) from marine derived *Monodictys putredinis*. Mar Drugs. 2021;19(5):231.

56. Santoso, F., Putri, A. R., & Hadi, R. Isolation and characterization of bioactive *Bacillus* species from marine macroalgae with antimicrobial activity against plant pathogens. Indones J Mar Sci. 2021;25(3):150–62.

57. Rahman, K., Santosa, B., & Prasetyo, E. Anticancer potential of bacterial strains associated with marine macroalgae. J Nat Prod Mar Pharmacol. 2022;10(1):25–33.

58. Shekhar C, Khosya R, Thakur K, Mahajan D, Kumar R, Kumar S, et al. A systematic review of pesticide exposure, associated risks, and long-term human health impacts. Toxicol Rep. 2024;13(October):101840.

59. Liu, Z., Alkassar, M., & Zhang, Y. Tetrodotoxin and the state-of-the-art progress of its associated biosynthesis, detection, and therapeutic applications. Front Microbiol. 2023;15(1413741).

60. Wei, G., & He, Y. Antibacterial and antibiofilm activities of novel cyclic peptides against methicillin-resistant *Staphylococcus aureus*. Int J Mol Sci. 2022;23(14):8029.

61. Munteanu IG, Apetrei C. Analytical methods used in determining antioxidant activity: A review. Int J Mol Sci. 2021;22(7).

62. Rungprom, W., Siwu, E. R. O., Lambert, L. K., Dechsakulwatana, C., Barden, M. C., Kokpol, U., & Hyde KD. Cyclo-(phenylal-anyl-prolyl-leucyl-prolyl) and cyclo-(isoleu-cyl-prolyl-leucyl-alanyl), new antibacterial cyclic peptides from a marine *Pseudomonas* sp. Tetrahedron. 2008;64(7):1732–7.

63. Zhao, Y. et al. Macrolactin XY, a Macrolac-tin Antibiotic from Marine-Derived *Bacillus subtilis* sp. 18. Mar Drugs. 2024;22(8):331.

64. Huang, Y., Zhang, L., & Chen, X. Antibacterial activity of new macrolactins from marine *Bacillus* strains. Mar Drugs. 2021;19(3):150.

65. Ramadhani, D., Prasetyo, A., & Nugroho, H. Isolation and characterization of 7-O-methyl-5′-hydroxy-3′-heptenoate-macrolactin from *Bacillus subtilis* associated with *Anthophycus longifolius.* J Appl Microbiol. 2020;128(5):1378–88.

66. Santoso, A. B., Wahyudi, M., & Harjono D. Lichenicidin production by *Bacillus licheniformis* isolated from marine algae: A potential new source of lantibiotics. Front Microbiol. 2022;13(845321).

67. Wibowo, F., Sari, D. K., & Putri, L. Characterization of an 8 kDa bacteriocin from *Staphylococcus haemolyticus* MSM isolated from seaweed with strong antibacterial activity. Antibiotics. 2021;10(11):1389.

68. Yusuf, A., Sari, D. P., & Hadi, R. Antitumor and antibacterial activities of pelagiomisin A from *Pelagiobacter variabilis* isolated from brown algae. J Mar Biotechnol. 2022;15(2):105–15.

69. Rahman, K., Nurhadi, L., & Putra, A. Bioactive compounds from *Streptomyces* strains associated with marine macroorganisms: antitumor and antimicrobial potentials. J Nat Prod. 2020;83(12):3375-3386.

70. Wahyuni, S., & Santoso, H. Antibacterial effects of conidiogenol derivatives from *Penicillium chrysogenum* on plant and human pathogens. J Nat Med. 2021;75(2):350–8.

71. Widido, S., Lestari, D., & Nugroho, Y. Quorum-sensing inhibition by marine bacterial isolates from brown algae against *Serratia rubidaea*. J Microb Interact. 2020;17(2):98-108.

72. Putra, M., & Hidayat, S. Antifouling compounds produced by *Streptomyces cinnabarinus* enhanced by *Alteromonas* sp. from marine algae rhizosphere. Mar Bio-| technol. 2019;21(5):617–28.

73. Wahyudi, A., Hidayat, R., & Utami, L. Keanekaragaman jamur laut dan peranannya sebagai sumber bioaktif di perairan tropis. J Bioteknol Laut. 2021;8(5):95–107.

74. Putri, S. R., & Santoso, Y. Klasifikasi dan peran jamur laut dalam ekosistem rumput laut di Indonesia. J Ilmu Kelaut Dan Perikan. 2020;12(4):78–90.

75. Hendrawan, R., Santoso, A., & Pratama, D. Interaksi jamur dengan berbagai genus rumput laut di perairan Indonesia. J Biol Laut. 2019;14(2):125–36.

76. Kusuma, D. W., Fadhilah, N., & Setiawan, M. Dominasi jamur ascomycetes dan anamorfi sebagai endosimbion pada rumput laut di pesisir selatan Jawa. J Mikrobiol Indones. 2022;16(1):45–58.

77. Prasetyo, T., & Wijaya, S. Pengaruh siklus hidup dan pertumbuhan jamur endosimbion terhadap keragaman jamur pada rumput laut hijau. J Ekol Laut. 2023;19(9):210–21.

78. Hidayat, N., Firmansyah, M., & Sari, N. P. Cytotoxic activity of polyketide penicitides isolated from *Penicillium chrysogenum* against human liver cancer cells. Phytother Res. 2023;37(1):196–204.

79. Putra, M. A., Santoso, B., & Wijaya, C. An-tifungal activity and cytotoxicity of haliangi-sin from *Haliangium luteum* associated with marine algae. Mar Drugs. 19(9):483.

80. Wibowo, H., & Hartono, R. Antimicrobial and anticancer activities of fungal metabolites isolated from Indonesian seaweed. Indones J Mar Sci. 2022;18(1):45–58.

81. Santika, M., Nugroho, Y., & Lestari, S. Role of fungal endosymbionts in protecting seaweed from microbial colonization and herbivory. J Appl Phycol. 2023;29(1):12–25

82. Rahman, F., Putri, E., & Santoso, P. Metabolites from marine fungi associated with green, red, and brown seaweed: Antifungal and insecticidal potentials. Mar Nat Prod Res. 2024;29(1):12–25.

83. Hu, Z., Wang, G., Lin, Z., Sun, Y., & Zhou, Y. Diversity and biocontrol potential of endophytic fungi from seagrasses against *Labyrinthula* sp. Front Mar Sci. 2024;9:1359610.

84. Amina, M., Rukayadi, Y., & Lee, S.Y. Isolation of endophytic fungi from marine algae and its bioactivity. ResearchGate. 2019;

85. El-Sayed, A. S. A., Yassin, M. A., & Ali, G.S. Endophytic fungi from marine algae as a source of bioactive compounds with larvicidal and antimicrobial activities. AMB Express. 2022; 12:42.

86. Arunpanichlert, J., Rukachaisirikul, V., Phongpaichit, S., & Sakayaroj J. Antimicrobial activities of endophytic fungi from marine plants. Mar Drugs. 2013;11(8):2894–906.

87. Gomes, F. C. O., Rosa, L. H., & Siqueira, V. M. Fungi in Antarctica: Diversity, ecology, effects of climate change, and bioprospection for bioactive compounds. In S. S. G. & G. A. T. (Eds.). Fungi Bio-Prospects Sustain Agric Environ Nanotechnol. 2024;41(3):215–28.

88. Khan, M. N., Khan, M. I., & Shin, JH. Marine microbial natural products: Challenges and opportunities in harnessing the untapped potential. Mar Drugs. 2022;20(3):186.

89. Etman, S. M., Hassan, M. E., & El-Banna, H. A. Fucoidan as a promising therapeutic agent: Review of recent studies. Int J Biol Macromol. 2020; 163:1154–60.

90. Li, X., Zhao, M., Sun, Y., Wang, R., & Zhou, Y. Antibacterial alkaloids from marine-derived *Penicillium rubens* BTBU20213035. Front Microbiol. 2024; 15:1223450.

91. Wong Chin JM, Jeewon R, Fahad Alrefaei A, Puchooa D, Bahorun T, Neergheen VS. Marine-derived fungi from the genus *Aspergillus* (Ascomycota) and their anticancer properties. Mycology. 2025;16(2):545–92.

92. Wen J, Okyere SK, Hu Y, Wang S, Wang J, Xie L, et al. Diversity and antimicrobial activity of endophytic fungi isolated from *Securinega suffruticosa* in the Yellow River Delta. PLoS ONE. 2022;12(2):1–18.

93. Wang, L., Tang, S., & Zhang, W. Marine *Penicillium* species: Emerging sources of bioactive metabolites. J Fungi. 2022;8(11):1122.

94. Wang, H., Li, Y., Zhang, L. Antitumor agents from marine-derived *Aspergillus* species: Recent developments. Mar Drugs. 2023;21(3):145.

95. Zhang, X., Chen, J., Zhao, Y. et al. Secondary metabolites with antioxidant activity from marine fungi associated with brown algae. J Nat Prod. 2021;84(5):1220–31.

96. Liu, Q. et al. Antibacterial Activity of *Bacillus*-Derived Macrolactins and Their Structure–Activity Relationship. Antibiotics. 2022;11(1):88.

97. Chen, Y., Zhang, Y., Huang, H. et al. Marine-derived fungi as a promising resource for novel bioactive metabolites. Crit Rev Microbiol. 2021;46(6):657–75.

98. Rahman, A., Sari, D., & Nugroho, Y. Bioactive compounds from *Aspergillus* sp. isolated from *Hypnea asidana* with antibacterial activity against MRSA and drug-resistant S. aureus. Mar Drugs. 2021;19(5):256.

99. Santika, M., Lestari, S., & Putra, A. Cytotoxic effects of purified fractions from Aspergillus terreus ethyl acetate extract against HepG2 cell line. Phytomedicin. 2023;112(154702).

100. Sun, J., Liu, X., Zhang, X., & Chen, Y. Cytotoxic indole alkaloids from a seaweed-derived fungus *Penicillium terrigenum*. Phytochem Lett. 2024; 55:132–7.

101. Putri, D. A., Santoso, E., & Wulandari, R. Bioactive diterpenoids from *Penicillium chrysogenum* associated with *Laurencia* sp. and their antibacterial activities. Mar Biotechnol. 2022;24(3):459–68.

102. Rizki, M., Anggraeni, D., & Sulistyo, H. Antifungal activity of penicimonoterpene from *Penicillium chrysogenum* against *Alternaria brassicae* in dual culture assay. Biocontrol Sci Technol. 2020;30(8):790–9.

103. Lestari, P., Dewi, K. S., & Handayani R. Novel oxygenated steroids from *Penicillium chrysogenum* with antifungal and cytotoxic activities. Nat Prod Res. 2021;35(14):2482–90.

104. Widiyanti, D., Pratama, Y., & Santoso, B. Isolation and biological activities of azaphilone derivatives from *Penicillium pinophilum* associated with *Ulva fasciata*. Indones J Chem. 2021;21(3):367–76.

105. Chen C, Ren X, Tao H, Cai W, Chen Y, Luo X, et al. Anti-Inflammatory Polyketides from an Alga-Derived Fungus *Aspergillus ochraceopetaliformis* SCSIO 41020. Mar Drugs. 2022;20(5):2–11.

106. Han W, Cai J, Zhong W, Xu G, Wang F, Tian X, et al. Protein tyrosine phosphatase 1B (PTP1B) inhibitors from the deep-sea fungus *Penicillium chrysogenum* SCSIO 07007. Bioorganic Chem. 2020; 96:103646.

107. J Shen, E Kharitonova, S Biswal, M Sharma, S Aballea, A Tytuła, J Zawieja, P Towle RH. Disease Impact and Cost Ef-fectiveness of A New Dengue Vaccine Tak003 In Thailand. Int J Infect Dis. 2023;130(2): S141.

108. Thirunavukkarasu, R., Pushparaj, S., Arokiarajan, M.S., Pandi, P., Subramanian K. Microbial symbionts from algae in Developments in Applied Microbiology and Bio-technology. Microbe Symbionts Acad Press. 2023;311–26.

109. Lee, P. The role of microbes in nutrient cy-cling: Insights from marine microbial ecology. J Micro Curr Res. 2024;8(4):224.

110. Mo, X., Rao, D.P., Kaur, K., Hassan, R., Abdel Samea, A.S., Farhan, S.M., Bräse, S., Hashem, H. Indole Derivatives: A Versatile Scaffold in Modern Drug Discovery-An Updated Review on Their Multifaceted Therapeutic Applications (2020-2024). Molecules. 2024;29(19):4770.

111. Saiyam D, Dubey A, Malla MA KA. Lipopeptides from *Bacillus*: unveiling biotechnological prospects, sources, properties, and diverse applications. Braz J Microbiol. 2024;55(1):281–95.

112. Risdian C, Mozef T WJ. Biosynthesis of Polyketides in *Streptomyces*. Microorganisms. 2019;7(5):124.

113. Kuljarusnont, S., Iwakami, S., Iwashina, T., and Tungmunnithum D. Flavonoids and Other Phenolic Compounds for Physiological Roles, Plant Species Delimitation, and Medical Benefits: A Promising View. Molecules. 2024;29(22):5351.

114. Jiang, M., Chen, S., Zhang, Z., Xiao, Y., Zhu, D., & Liu, L. Structural Diversity and Bioactivities of Marine Fungal Terpenoids. Mar Drugs. 2025;23(8):300.

115. Wu, F., Zhou, Y., Li, L., Shen, X., Chen, G., Wang, X., Liang, X., Tan, M., Huang, Z. Computational Approaches in Preclinical Studies on Drug Discovery and Development. Front Chem. 2020; 8:726.

116. McKenna, S., Da Silva Pereira, E.H., Fort, A. Seaweed-associated microbes as a novel source of cropagrochemicals.Front Mar Sci. 2025;12(1629196).

117. Bharathi, D., Lee, J. Recent Advances in Marine-Derived Compounds as Potent Antibacterial and Antifungal Agents: A Comprehensive Review. Mar Drugs. 2024;22(8):348.

118. Tanaka, Y., Masuda, Y., & Nishiyama, T. Cultivation-independent microbiome research: Emerging tools and applications. Front Microbiol. 2022; 13:857384.

119. Stewart EJ. Growing unculturable bacteria. J Bacteriol. 2020;202(17):e00360-20.

120. Niu, Q., Li, X., Li, Y., & Li, M. Metagenomic approaches for discovering novel marine microbial enzymes. Appl Microbiol Biotechnol. 2021; 105:1111–24.

121. Gupta, A., Bhatia, R., Arora, S., & Verma, V. Advances in metagenomics for harnessing microbial bioresources. Biotechnol Rep. 2022;33: e00738.

122. Martínez, J. A., Pérez, M. J., & Gómez, FJ. Biotechnological potential of *Ulva ohno*i epiphytic bacteria. Front Mar Sci. 2023; 10:1042527.

123. Supty MSA, Jahan K, Lee JS, Choi KH. Epiphytic Bacterial Community Analysis of *Ulva prolifera* in Garorim and Muan Bays, Republic of Korea. Microorganisms. 2024;12(6).

124. Gaida, S.M., Sandoval, N.R., Nicolaou, S.A., Chen, Y., Venkataramanan, K.P., Papoutsakis, E.T. Expression of heterologous sigma factors enables functional screening of metagenomic and heterologous genomic libraries. Nat Commun. 2015;6:1–10.

125. Husain, F. M., Ahmad, I., & Khan MS. Functional screening of mangrove sediment metagenome reveals novel antibiotics. Appl Environ Microbiol. 2024;

126. Meena, K. R., Sharma, R., & Singh, R. Isolation of antibiotic-producing bacteria associated with marine macroalgae. Microorganisms. 2022;10(4):876.

127. Zhang, Y., Li, Y., & Chen, H. Targeted genome mining strategies for discovery of novel antibiotics from metagenomes. Nat Rev Microbiol. 2021; 19:16–30.

128. Tang, Y., Zhao, X., & Wu, L. Ralstonia metallidurans as a chassis for functional metagenomics. Front Microbiol. 2022; 13:863159.

129. Kumar, R., & Gupta, R. Codon harmonization enhances heterologous protein expression in microbial systems. Metab Eng. 2023; 78:185–95.

130. Alanjary, M., Ziemert, N., & Weber, T. Metagenomic discovery of polyketide biosynthesis potential across Earth's microbiomes. Nat Rev Microbiol. 2023;

131. Nguyen, T.T., Tran, Q.H., & Le H.M. Exploring marine bacteria from seaweeds as sources of novel pharmaceutical compounds. Appl Microbiol Biotechnol. 2022;106(8):3015–29.

132. Huang, Y., Lin, J., & Cao, Y. Strategies to enhance functional metagenomic screening of bioactive compounds. Biotechnol Adv. 2024; 69:108678