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Antimicrobial lead compounds from marine plants

Jaya Vikas Kurhekar

Department of Microbiology, Sangli, Maharashtra, India

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17.1 Introduction

The Earth is home to an estimated 10 million species, of which a large chunk belongs to marine environment. Marine environment occupies a large section on the surface of earth which provides umpteen kinds of habitats that support marine life, which primarily depend on the salt present in marine water. Marine environment is a home to a very wide diversity of flora and fauna, which includes an array of genetically diverse coastline and under seawater plant species, animal species and microbial species, their habitats, ecosystems, and supporting ecological processes. Marine habitats spread as coastline or coastal habitats and as open sea habitats. Coastal habitats occupy merely 7% of the total ocean area, yet most marine life exists in this zone. Open sea habitats extend into the deep ocean, beyond the continental shelf. Marine sea columns have been classified into pelagic and demersal zones, away from ocean bottom while close to the open surface and those near the bottom or on the bottom of the ocean, respectively. Demersal habitats are stationary, compared with pelagic habitats as they depend on the ocean currents and tend to be transient and ephemeral. Marine habitats are shaped by the species that inhabit them such as kelp, mangroves, and sea grasses, which are the base of ecosystems formed for other life.

Lot of natural medicinal therapy research today is directed toward marine products, derived from marine species, which have proved to be a potent source of structurally widely diverse and yet highly bioactive antimicrobial secondary metabolites. Particularly important are flavones and flavonols, terpenoids, alkaloids, peptides, carbohydrates, fatty acids, polyketides, polysaccharides, phenolic compounds, and steroids. These are housed in the varied species of phylum Porifera, algae including diatoms, Chlorophyta, Euglenophyta, Dinoflagellata, Chrysophyta, cyanobacteria, Rhodophyta, and Phaeophyta, bacteria, fungi, and weeds, which have been exploited by mankind for their inherent indigenous biological antimicrobial compounds, produced under the extreme stressful underwater conditions of temperature,

atmospheric pressure, light, and nutrition. The present study aims at presenting a brief review of these bioactive marine compounds possessing antimicrobial potency [1].

Some of these marine species live in a stressful habitat, under cold, lightless, and high-pressure conditions. These factors have resulted in the development of unique metabolisms, which provide the opportunity to produce metabolites that differ from the terrestrial ones, offering a wonderful resource for discovery of new compounds with interesting biological activities, including antimicrobial and antiviral properties [2].

Significant oceanic resources, such as marine flora constituting halophytes, cyanobacteria, actinobacteria, bacteria, microalgae, fungi, seaweeds, and mangroves, make up more than 90% of oceanic biomass. Taxonomically diverse, largely productive, biologically active, and chemically unique, they are a storehouse of antimicrobial and prohuman health promoting drugs. Marine flora is rich in medicinally potent chemicals such as sulfated polysaccharides and polyphenols, which possess antioxidant, immunostimulatory, and antitumour pharmacological activities. They probably control carcinogenesis by inducing apoptosis, activating macrophages and preventing oxidative damage of DNA. They may prove as cheaper, safer, and potent medicinal remedies to challenge the dreadful human disease [3].

17.1.1 Bioactive compounds in marine plants with various molecular targets in bacteria

17.1.1.1 Flavonoids (Bioflavonoids)

Flavones and flavonols (*flavus*—Latin for yellow) are present in plant and fungi as secondary metabolites and are naturally yellow in color. Chemical structure has a 15-carbon skeleton, with two phenyl rings (A and B) and one heterocyclic ring (C); abbreviated as C6—C3—C6. They are anthoxanthins (flavones and flavonols), ketone-containing polyhydroxy polyphenol compounds. More than 5000 natural flavonoids are studied from flora and fauna, classified according to their chemical structure. Flavonoids have been shown to have a wide range of biological and pharmacological activities such as antibacterial [4], antiviral, antifungal [5], antimicrobial, antidiarrheal activities [6], antiinflammatory [7], and antioxidant [8]. Flavonoids show antibacterial potency, synergism with antibiotics along with suppression of virulence factors in bacteria [9].

17.1.1.2 Terpenoids/Isoprenoids/modified terpenes

Terpenoids are organic chemicals derived from terpenes, which can also be termed as modified terpenes, in which either methyl groups are removed or transferred or oxygen atoms are added. Simple terpenoids and unusual terpenoids are found in ample amount in flora growing in marine environment. Isopentenyl pyrophosphate and dimethylallyl pyrophosphate condense to produce geranyl pyrophosphate, which is a precursor to all terpenes and terpenoids.

Cytochrome P450s modify the structure of terpenes and this property is found to be due to enzymes terpenoid synthase encoded by genes of 17 plant species genomes [10]. Sesterterpenoids, sesquiterpenoids, and meroterpenoids found to be antimicrobial and antiviral are more commonly found in marine environments. Marine sesterterpenoids exhibiting prominent antimicrobial and antiviral bioactivities occur in marine sponges [11]. Seven different types of sesterterpenes sulfates were isolated from tropical sponge belonging to *Dysidea* sp., of which most were found strong isocitrate lyase inhibitors showing potent antibacterial effect against *Bacillus subtilis* and *Proteus vulgaris* [12]. Hyrtiosol is a bioactive sesterterpenoid isolated from *Hyrtios erectus*, which is a marine sponge inhibiting HIV integrase (IN), which binds to viral DNA at a new binding site for inhibitor, observed to bind to HIV N-terminal domain at Ser17, Trp19, and Lys34, having potential application in anti-HIV research [13]. Terpenes possess 1,4-benzoquinone supposed to be responsible for antimicrobial and antiviral properties. Puupehanol, a novel sesquiterpene-dihydroquinone derivative, and chloropuupehenone and puupehenone are responsible for antifungal activity in marine sponge *Hyrtios* sp. extract [14]. Puupehenone proved most inhibitory against *Candida krusei* and *Cryptococcus neoformans*. Nakijiquinones G-I from Okinawan marine sponges, belonging to family *Spongilidae*, were found to be a sesquiterpenoid quinone with antimicrobial potency [15]. Novel sesquiterpenoid hydroquinones from *Dysidea arenaria*, a marine sponge, were found moderately inhibitory for enzyme HIV reverse transcriptase (RT) [16]. Peyssonioic acids A and B, novel sesquiterpene hydroquinones, with a novel carbon skeleton, isolated from crustose marine red alga *Peyssonnelia* sp [17] were found inhibitory for bacterial pathogen *Pseudoalteromonas bacteriolytica* in marine algae and *Lindra thalassiae*, a fungal pathogen of marine algae.

Sesquiterpenoid hydroquinones such as tiomanene and acetylmajapolene A and B isolated from Malaysian *Laurencia* sp. showed antimicrobial activity probably because of incorporation of halogens occasionally [18]. 10-Hydroxykahukuene B,

a brominated metabolite, isolated from the red marine alga *Laurencia mariannensis* [19] was found antimicrobial. Meroterpenoids isolated from marine sponges were found to have antimicrobial activities. They include the following:

- a) Fascioquinols series A–F are bioactive antimicrobial meroterpenes isolated from Southern Australian marine sponge *Fasciospongia* sp. found in deepwater [20]. Fascioquinol A produces acid-mediated hydrolysis/cyclization products fascioquinols B, C, and D. Fascioquinol A and B exhibited antibacterial potency against Gram-positive organisms, especially *Staphylococcus aureus* and *Bacillus subtilis*.
- b) Meroterpenes, alisiaquinones A-C, and alisiaquinol isolated from deepwater sponge *New Caledonian* [21] showed activity against two enzymes—plasmodium kinase Pfnek-1 and protein farnesyltransferase, significant in control of malaria. They were active against chloroquine-sensitive and chloroquine-resistant *Plasmodium falciparum* strains. Marine algae Brazilian brown algae *Dictyota pfaffi* and *Dictyota menstrualis* showed the presence of diterpenes 8,10,18-trihydroxy-2,6-dolabelladiene and (6R)-6-hydroxydichotoma-4,14-diene-1,17-dial, which are found to have antiviral potency. Diterpenes 8,10,18-trihydroxy-2,6-dolabelladiene and (6R)-6-hydroxydichotoma-4,14-diene-1,17-dial inhibited replication of Herpes Simplex type-1 (HSV-1) in Vero cells. Marine Brazilian brown algae *Dictyota pfaffi* and *Dictyota menstrualis* possessed dolabellane diterpene dolabelladienetriol, which is a noncompetitive inhibitor of enzyme HIV RT [22]. Marine brown alga *Sargassum macrocarpum* methanol extract showed the presence of diterpene sargafuran, which proved bactericidal against *Propionibacterium acnes*. Marine antibacterial diterpenes, dehydroxy-chlorofusarielin B, a polyoxygenated decalin derivative from *Aspergillus* sp., exhibited anti-*S. aureus* and methicillin- and multidrug-resistant *S. aureus* activities [23].

17.1.1.3 Alkaloids

Alkaloids are a vast group of heterogeneous natural nitrogenous metabolites, thickly interwoven with human affairs. Morphine takes the credit of being the first alkaloid, isolated from opium poppy *Papaver somniferum*, in 1804, by Friedrich Sertürner, a German chemist [24]. Alkaloids are bitter, natural, organic compounds with basic structure containing nitrogen atoms along with carbon, hydrogen, oxygen, sulfur, sometimes chlorine, bromine, and phosphorus. Alkaloids may include weakly acidic [25] or neutral [26] or few synthetic compounds, similar in structures [27]. Alkaloids are produced by pro- and eukaryotes and are known to have antimalarial-like quinine and antibacterial-like chelerythrine [28] activities.

Marine macroalgae are rich sources of alkaloids, though few marine alkaloids of algal origin like those using phenylethylamine as precursors have been extracted from plants of terrestrial origin. Halogenated alkaloids from green algae (marine specific) and indole derivatives from red algae are specific. Algae of marine origin possess 44 types of alkaloids, 41 indole, 1 naphthyridine, and 1 phenylethylamine derivatives. Halogenated ones possess 25 bromine, 7 chlorine, and 5 sulfur components [29].

Marine fauna is a rich source of alkaloids, rather unique chemicals that inhibit enzyme enoyl-ACP reductase, a clinically relevant enzyme target from the type II fatty acid pathway of several pathogenic microorganisms. Several compounds related to bromopyrrole alkaloids have also been isolated from marine bacteria. A strain of marine *Streptomyces* is known to have A and B marinopyrroles, which are axially chiral and densely halogenated metabolites possessing an uncommon bispyrrole structure [30], significant because of their potent antibiotic properties against MRSA or methicillin-resistant *S. aureus*. A, B, C.

Marine sponges are very potent reservoirs of antimicrobially active natural sources of nitrogen-containing heterocyclic alkaloids like 1H-benzo [de] [1,6]-naphthyridine. Bromotyrosine alkaloids ceratinadins from Okinawan marine sponge belonging to *Pseudoceratina* sp., show N-imidazolyl-quinolinone moiety and antifungal potency [31]. A and B pseudoceratins, two bicyclic bromotyrosine-derived metabolites from *Pseudoceratina purpurea* [32], showed significant anti *Candida albicans* fungal activity. Two pyrroloiminoquinone alkaloids of class discorhabdin from sponge *Sceptrella* sp. from Gageodo, Korea [33] showed antibacterial potency, especially against enzyme sortase A, with a key role in anchoring of cell wall protein responsible for *S. aureus* virulence. 19-oxofasciospongine A and fasciospongine C (sulfated sesterterpene alkaloids) and 25-hydroxyhalisulfate 9 (sesterterpene sulfate), found recently and known sesterterpene sulfates halisulphates 7 and 9, have been extracted from marine sponge *Fasciospongia* sp. organic extract [34], showed strong inhibitory hyphae - formation efficiency against *Streptomyces 85E*. Chinese marine sponge *Iotrochota baculifera* showed the presence of sulfated alkaloids baculiferins A-O and O-sulfated pyrrole alkaloids [35]. Of these, Baculiferins C, E – H, K–N efficiently inhibited HIV IIIB, by binding to targets viral infectivity factor (Vif), cellular deoxycytidine deaminase APOBEC3G and recombinant gp41, a trans-membrane protein. Caribbean sponge *Monanchora unguifera* shows the presence of guanidine alkaloids which are polycyclic with significant antimicrobial and antiviral properties [36] and batzelladine alkaloids like batzelladines K, L, M, N; 16 β -hydroxycrambescidin 359, ptilomycalin A, batzelladine C,

crambescidine 800, and dehydrobatzelladine C with significant inhibitory activities against HIV and opportunistic pathogens of Acquired Immuno Deficiency Syndrome (AIDS). Merobatzelladines A, B isolated from this marine sponge is antibacterial [37]. Marine sponge *Aaptos aaptos* possesses alkaloid 4-methylaaptamine which shows inhibition against HSV-1 replication and antiherpetic activity [38]. Four aaptamines from *A. aaptos* show inhibitory activity against enzyme sortase A which is involved in *S. aureus* virulence and anchoring of cell wall protein [39]. Topsentin and hamacanthin are antimicrobial bisindole alkaloids isolated from marine sponge *Spongisorites* sp [40]. Dysideanins A and B from marine sponge *Dysidea* sp. are found to have antimicrobial potency [41]. 5-hydroxyindole-type alkaloids from *Hyrrios* sp. Sponges from tropical regions exhibited inhibitory potency against isocitrate lyase in *C. albicans* [42]. A family of alkaloids isonitrile-containing indole alkaloids, such as hapalindoles, have fused pentacyclic and hexacyclic carbon skeletons from cyanobacteria, are contemplated for use in pharmaceuticals. Fischambiguines A and B, ambiguine P, ambiguine Q nitrite, ambiguine G nitrite were isolated and identified from *Fischerella ambigua* [43]. Fischambiguine B showed anti-*Mycobacterium tuberculosis* activity. Diketopiperazine alkaloids are marine antimicrobial alkaloids. A marine halotolerant fungal strain - *Alternaria raphani* from sea salt fields showed the presence of cerebrosides, alternarosides A, B, C, and diketopiperazine alkaloid, alternarosin A [44], which show weak antibacterial activity against *Escherichia coli*, *Bacillus subtilis* and *C. albicans*. Caboxamycin produced by deep-sea *Streptomyces* sp. NTK937 showed inhibitory activity against Gram-positive bacteria [45].

17.1.1.4 Peptides

Marine antimicrobial peptides are present in all living species and build up their defense mechanisms. They probably act as humoral natural humoral defense in invertebrates, also termed as “natural antibiotics” [46]. Cyclodepsipeptides are marine peptides found in sponges exhibiting antiviral and antimicrobial potencies [47]. Cyclic peptides family includes unique N-terminal polyketide-derived molecules and diverse types of unusual amino acid residues.

Cyclic depsipeptides Papuamides from marine sponges have shown in vitro cytoprotective activity for HIV, preventing entry of the virus. Antiviral cyclic depsipeptides - mirabamides A, B, C, D are isolated from sponge *Siliquariaspongia mirabilis* [48], probably preventing HIV fusion. Mirabamides are composed of 4-chloromoproline in 1, 2, 3 positions, β -methoxytyrosine 4'-O- α -L-rhamnopyranoside (unusual glycosylated amino acid) in 1, 2, 4 positions and rare N-terminal aliphatic hydroxy acid. Mirabamide A, C, D is found to inhibit HIV acting at entry stage of HIV. Mirabamides A, B, C inhibit *Bacillus subtilis* and *C. albicans*. Alternaramide, a cyclic depsipeptide from the marine fungus *Alternaria* sp. SF-5016 [49] exhibited weak anti *S. aureus* and anti *Bacillus subtilis* activity. Homophymine A, a cyclodepsipeptide from marine sponge *Homophymia* sp [50]. showed anti - HIV cytoprotective potency. Homophymine A is composed of 11 amino acids, an amide-linked-3-hydroxy-2, 4, 6-trimethyloctanoic acid molecules; four Dextro, two Levo, one N-methyl amino acids and four unusual amino acid residues. Callyaerins A, B, C, D, E, F and H are antiviral and antimicrobial peptides from marine sponge *Callyspongia aerizusa* [51]. Theonellamides are bicyclic peptides from marine sponges which show antifungal activities [52]. Aminolipopeptides, Trichoderins A, A1 and B, are marine antimicrobial peptides from sponge - derived fungus of *Trichoderma* sp. They show antimycobacterial activity versus dormant and active marine bacilli [53], especially against *Mycobacterium tuberculosis*, *M. Smegmatis* and *M. bovis*. Anthranilic acid and dehydroamino acid units, sclerotides A and B, components of cyclic hexapeptides obtained from marine halotolerant *Aspergillus sclerotiorum* PT06-1 [54] exhibited antibacterial and antifungal activities. *Aspergillus sclerotiorum* PT06-1 was found to contain cyclic tripeptides scleraotiotides A-K of aspochracin nature [55]. Sclerotiotides A, B, F, I showed antifungal activity for *C. albicans*. Maribasins A and B cyclic lipopeptides, from marine *Bacillus marinus* B-9987 showed broad-spectrum activity against phytopathogens [56]. Two antifungal lipopeptides on eof which is the rare 6-Abu fengycin lipopeptides from marine *Bacillus amyloliquefaciens* SH-B10 [57] showed remarkable inhibitory potency against five phyto-fungal pathogens, suggesting bio-control and sustainable agricultural practices. Tauramamide, lipopeptide from marine bacteria *Brevibacillus laterosporus* PNG276 [58] along with ethyl ester 3, showed selective inhibitory activity against pathogenic species of *Enterococcus*. Thiopeptides and depsipeptides are marine bacterial antimicrobial peptides found in *Nocardiopsis* sp. TP-1161 [59], possessing a unique aminoacetone group. Unnarmicine A and C, marine depsipeptides from *Photobacterium* MBIC06485 [60] selectively killed two *Pseudovibrio* species, commonly existing in marine environment. Hybrid forms of marine peptide polyketide-nonribosomal antimicrobial agents from *Myxobacteria* have been isolated. One example is halophilic myxobacterium *Paraliomyxa miuraensis*, producing miuraenamides A and B which are hybrid cyclic polyketide-peptide antimicrobial agents [61]. Two rare hybrid polyketide-nonribosomal linear peptide antibiotics, Ariakemicins A and B found in marine gliding bacterium *Rapidithrix* species [62], are found to be composed of two Ω -amino-(Ω -3)-methyl carboxylic acids with diene or triene units, threonine and δ -isovanilloylbutyric acid and inhibited particularly Gram-positive bacterial growth. Nonribosomal peptides from marine Brazilian

cyanobacterial isolates are antimicrobial [63], while from *Brevibacillus laterosporus* Lh-1 exhibit antimicrobial activity for fungi and Gram-positive and Gram-negative bacteria [64].

17.1.1.5 Carbohydrates

Carbohydrates are biomolecules present in abundance, in the form of cellulose and chitin, glycogen and starch acting as great energy sources and cellular recognition molecules, at cell surface [65]. They are structurally complex with dynamic properties, structural fluctuations, large diversity of units due to umpteen enantiomers, various glycosidic bonds and modifications after polymerization. The diverse classes of carbohydrate classes consist of negatively charged neutral and neutral saccharides of different lengths [66]. Marine carbohydrate compounds are chemically diverse with glycosidic domains and exhibit various biological properties and functions which may help in their implementation in bioactive products. Many are the known applications of substances obtained from marine species. Their activities include antioxidant, antiinflammatory, anticoagulant, antitumor, and antimicrobial potencies. This may utilize them for their nutritional and therapeutic potential, though they are the most poorly explored but promising molecules. Many of them are being clinically tried out for possible potential for antiviral therapies [67]. Their biological roles include significant pharmacological potencies like antiinflammatory [68], antiviral [69], cellular interactions [70], and pathogen recognition [71].

17.1.1.5.1 Neutral and acidic polysaccharides

- a) **Laminaran:** Laminarans are marine glycans, brown algal polysaccharides existing in chains made up of 3-linked β -D-glucose (Glc) residues with less than 10% of single β -D-Glc residues branches attached to C-6 of backbone Glc residues [72], Type G with chains terminated by D-Glc residues, and Type M - with chains ending with D-mannitol (Man) residues [73].

They show antiinflammatory activity [74]. Laminaran enhances release of few inflammation mediators, thus being immunostimulatory and antiinflammatory [75]. Laminaran, a marine glycan inhibits both Gram-positive and Gram-negative marine bacteria such as *Vibrio parahaemolyticus*, *Listeria monocytogenes*, and *Salmonella typhimurium*. It prevents HIV virulence by decreasing its adsorption in human lymphocytes, reducing the efficiency of HIV enzyme reverse transcriptase, thus preventing HIV replication and multiplication [76].

- b) **Alginic acid:** It is a marine polysaccharide extracted from brown algae, with a broad spectrum of medicinal, food, biotechnological, and industrial applications [77].

Brown algae *Sargassum wightii* species show alginic acid with antioxidant and antiinflammatory activities, reducing many cyclooxygenase, lipoxygenase, and myeloperoxidase enzyme activities, C-reactive protein levels, rheumatoid factor and ceruloplasmin along with lipid peroxidation reduction and enhanced enzyme activity [78]. The antioxidant activity of alginic acid is because of its metal chelating capacity, scavenging of free radicals, reducing tissue ferric ions and enhancing antimicrobial potency [79]. It controls *Listeria monocytogenes* growth, responsible for serious food infections [80].

17.1.1.5.2 Sulfated polysaccharides

- a) **Fuoidan:** Fuoidan is found in Brown algae. It has a complex structure, with a backbone of alternating α -L-Fuc residues with 3 - and 4 - glycosidic linkages or 3-linked α -L-fucose (Fuc), which case can be replaced by acetyl groups or sulfate groups or Fuc or glycosyl unit side chains [81], with monosaccharides like Glc, Galactose (Gal), Xylose, Mannose [82].

Biological activities of Fuoidan are because of its polysaccharide nature, consisting of 3-linked α -L-Fuc units [83]. Fuc units in Fuoidan backbone can occur in α -1, 2 linkage, in addition to α -1, 3, α -1, 4 bonds [84]. Fuoidan has a wide spectrum of applications with reference to its biomedical features [85]. Fuoidan shows antiinflammatory effects, selection inhibition, complement inhibition and enzyme inhibitory activities because of its pleiotropic properties [86]. Three brown algae *Sargassum polycystum*, *Sargassum mclurei*, *Turbinara ornate* Fuoidan has shown anti-HIV potency, probably due to blocking of first HIV entry steps in target cells [87]. Alga *Padina tetrastratica* synthesizes silver nanoparticles (AgNPs) with the help of fuoidan as a coating material [88], which probably increases activity against antibiotic resistant bacterial strains. Antibiotics along with fuoidan in nanoparticles show synergistic effect.

- b) **Carrageenan/Agaran:** Carrageenans are extracted from red seaweeds. They are sulfated galactans, made up of linear chains of alternating A units and B units (4-linked α -D-Gal or α -D-3, 6-anhydrogalactose (AnGal) and 3-linked β -D-Gal), forming repeating disaccharide building units [89].

Commercially used carrageenans are kappa (κ), iota (ι) and lambda (λ), alias carrageenan 4-sulfate (DA-G4S), carrageenan 2,4-disulfate (DA2S-G4S) and carrageenan 2,6,2-trisulfate (D2S,6S-G2S), respectively (IUPAC) and carrageenans ν and μ which are biological precursors of ι - and κ -carrageenans [90] (Campo et al.), which show emulsifying, gelling, thickening, stabilizing characteristics which offer protective effects for food [91], pharmaceutical and cosmetic products [92]. Oligosaccharides derived from Carrageenan show scavenging activity for hydroxyl radicals, DPPH radicals and reducing power [93]. λ and ι carrageenans show strong inhibitory action against Dengue virus type 2 and 3 (DENV-2 and DENV-3) [94]. λ -Carrageenan reduces the infectivity of Bovine Herpes virus type 1 and Suid Herpes virus type 1 ((BoHV-1 and SuHV-1) viruses. ι -carrageenan inhibits Influenza A (H1N1) virus infection [95]. λ -carrageenan oligosaccharide (P32) particularly inhibits early post-adsorption replication of RABV strains, viral internalization and fusion mediated by glycoproteins. P32 from λ -carrageenan is a possible agent for developing anti-RABV drugs [96].

- c) **Sulfated Polymannuronate:** SPM or Sulfated polymannuronate or sulfated polymannuroguluronate from brown algae is a sulfated polysaccharide composed of 4-linked β -D-ManA, molecular weight 10,000 D with sulfation at C-2 or C-3, another form propylene glycol mannuronate sulfate being used for medical purpose. SPM takes credit of being first marine sulfated polysaccharide exhibiting anti-HIV property. Oligosaccharides derived from SPM interact with gp120, targeting HIV [97]. SPM is known to bind specifically at CD4 on lymphocytes.
- d) **Glycosaminoglycans:** GAGs or Glycosaminoglycans are heterogeneous linear sulfated glycans with repeating building units of disaccharides UroA - uronic acid (glucuronic acid (GlcA) or iduronic acid (IdoA)) or Gal and hexosamine (glucosamine or *N*-acetylgalactosamine or its substituted sulfated derivatives [98].

GAGs in animals include Heparin, heparan sulfate (HS), chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate (KS) and hyaluronan (HA), with varying sulfation patterns and alternating monosaccharides. Even same class of GAG of marine or terrestrial origin, has structural difference [99] because of sequence domains or occurrence in extracellular matrix or on surface of cells, giving them diverse medicinal and biological and functions.

- e) **Fucosylated Chondroitin Sulfate:** FCS or Fucosylated Chondroitin Sulfate, a marine GAG, in sea cucumber (Echinodermata, Holothuroidea), is made up of CS backbone with branches made of α -L-Fuc units attached to C-3 of GlcA residues, lateral units showing different sulfation patterns [99].

It is found to be antiinflammatory [100] and that from *Thelenota ananas*, sea cucumber inhibits replication of many strains of HIV, strongly binding recombinant HIV-1 gp120 protein, while not inhibiting reverse transcriptase [101]. FCS displays antiviral action against HIV [102].

17.1.1.5.3 N-acetylated sugars

Chitin and Chitosan: Chitin is present in organism's exoskeletons like crustaceans and insects. It is biopolymer and found abundance in marine environment, structurally made up of GlcNAc, GlcN units linked by β -1, 4 glycosidic bonds. GlcNAc is strongly *N*-acetylated due to the presence of more than 70% of total monosaccharides, decreasing its water solubility. Chitin has 4-linked *N*-acetyl Glucosamine (GlcNAc 2-acetamido-2-deoxy-D- β -glucose) units and partly glucosamine, GlcN (2-amino-2-deoxy- β -D-glucose) units. In case of less than 50% GlcNAc content or DA - degree of *N*-acetylation, the polymer is called Chitosan. Chitosan, a cationic polysaccharide, is made up of repeating units with chitin glycosidic linkages, but less than 50% levels of GlcNAc. Their interactions and hydrophobicity depends on number and positions of acetyl groups [103]. Due to non-toxicity, it can be biomedically applied for special functions like antipathogenic activity [104], decided by its molecular weight, extent of deacetylation and substitution, pH, length of substituents and their positions in GlcN units [103].

ChNP or Chitosan nanoparticles exhibit antifungal activity [105]. ChNP inhibits *Pseudomonas aeruginosa*, *S. aureus*, *E. coli*, *Klebsiella pneumonia*, clinically important pathogens and antibiofilm potency [106].

17.1.1.5.4 Triterpene Glycosides

Triterpene Glycosides are amphiphilic with a sugar molecule (mono- or oligosaccharide) linked to a functional group (terpene or flavonoid or other natural molecules) with a glycosidic bond [68]. They are highly diverse in nature.

Marine Glycosides have been observed in starfish [107], sea cucumber [108], algae [109], sponge [110] and corals [111].

Melophlus sponge shows the presence of a tetramic acid glycoside - Aurantioside K with wide spectrum antifungal action against *C. albicans* strains, yeast *Cryptococcus neoformans*, *Aspergillus niger*, *Penicillium* sp., *Rhizopus sporangia*

and *Sordaria* sp [112]. Variegatusides - Triterpene glycosides from Holothuriida, *Stichopus variegatus* sea cucumber shows antifungal activity [113].

17.1.1.5.5 Glycoproteins

Glycoproteins are a big class of biomolecules, present in cell membranes. Glycoprotein glycoconjugates have a protein backbone to which different monosaccharides are covalently attached. Glycoproteins contain *N*-linked sugar chains (GlcNAc group at reducing end attached to amide group of asparagine residue of polypeptide backbone) and *O*-linked sugar chains (GalNAc at reducing end, attached to hydroxyl group of Serine (Ser) or Threonine (Thr) groups of polypeptide backbone) [114].

Glycoproteins act as receptors capturing ligands into cells like transport proteins responsible for ingestion of nutrients, structures mediating molecular recognition, molecular signaling and cellular interactions [99].

Mannose-specific Lectin from Green alga *Halimeda renschii* showed strong activity against influenza virus due to high affinity binding to hemagglutinins on envelopes of viruses [115].

17.1.1.5.6 Glycolipids

Glycolipids, amphipathic in nature, are a diverse and large lipid group, containing a hydrophilic portion with carbohydrate units, from which its prefix “glyco” is derived. The lipid portion is the hydrophobic tail, with aliphatic chains of fatty acids [116]. Glycosphingolipids are a class of glycolipids, which constitute cell membranes in marine or terrestrial organisms [117]. Their action is because of variations in sugar chains, based on which they are classified as cerebrosides, ceramide oligohexosides, globosides and gangliosides.

Marine algae show three types of glycolipids; MGDG – Mono Galactosyl Di Glyceride, DGDG – Di Galactosyl Di Glyceride and SQDG – Sulfono Quinovosyl Dipalmitoyl Glyceride, found in chloroplasts of algae. MGDG, DGDG are abundant in thylakoid membrane playing a significant role in photosynthesis [118]. SQDGs from *Sargassum vulgare* brown alga showed antiviral activity against HSV1 and V2 (Herpes Simplex Virus 1 and 2) viruses [119].

17.1.1.5.7 Iminosugar

These are natural aza or imino monosaccharides in which nitrogen replaces oxygen in ring structure. Nojirimycin, a 5-amino-5-deoxyglucose antibiotic, was first to be isolated and characterized in 1960. Later, more than 25 analogues of nojirimycin were studied in plant and microbes [120].

Iminosugars show nematicidal [121], antiviral [122], and insecticidal [123] activities because of their glycosidase potency, interfering with processing of glycoprotein. 1-Deoxynojirimycin iminosugar with Glc inhibits synthesis of infective viruses such as dengue (DENV), hepatitis B, hepatitis C, HIV, and influenza A viruses because of virus release inhibition due to inhibition of endoplasmic reticulum α -glycosidases [124]. Batzellasides A, B, and C are extracted from *Batzella* sp. sea sponge, consisting of an iminosugar nucleus with a long chain of alkyl substituent. Batzellasides differ in the lengths of alkyl chains. Batzellasides A, B, and C show inhibition of *Staphylococcus epidermidis* [120].

17.1.1.6 Fatty acids

Marine fatty acids in marine organisms possess biological properties such as antiviral and antimicrobial potencies.

Paragantia cf. waguensis, a calcareous sponge, possesses acetylenic fatty acid [125], exhibiting antimicrobial activity against *E. coli* and *S. aureus*. Brominated unsaturated fatty acids from marine sponge showed antimicrobial fatty acids [126]. Motualevic acids A, B, C, D, E, and F from marine sponge *Siliquariaspongia* sp. have shown inhibitory potency toward *S. aureus* and MRSA [127]. Marine alga diatom *Phaeodactylum tricorutum* has shown antibacterial activity, which was due to unique (6Z, 9Z, 12Z)-hexadecatrienoic acid, a polyunsaturated fatty acid, and (9Z)-hexadecenoic acid, a monounsaturated fatty acid [128], both of which are inhibitory toward Gram-positive bacteria and marine pathogen Gram-negative *Listonella anguillarum* (9Z)-hexadecenoic acid kills bacteria at great speed, showing potent activity against multidrug-resistant strains of *S. aureus*. *P. tricorutum* produces eicosapentaenoic acid, an antibacterial fatty acid inhibitory toward a range of Gram-positive and Gram-negative bacteria, as well as multidrug-resistant *S. aureus* [129]. Asperamides A and B, a sphingolipid and their corresponding glycosphingolipid possessing a 9-methyl-C20-sphingosine moiety, from *A. niger EN-13*, an endophytic fungus from marine brown alga *Colpomenia sinuosa* [130], showed inhibitory action against *C. albicans*. Marine fungi are of great importance as potential sources of agricultural pesticide leads such as unsaturated fatty acid glycerol esters, asperxanthone and asperbiphenyl, extracted from marine fungus *Aspergillus* sp. *MF-93* [131], active against tobacco mosaic virus.

17.1.1.7 Polyketides

Polyketides can be defined as natural secondary metabolites used in human therapy as antibiotics and antifungal agents. Classical examples are nystatin, amphotericin, and rapamycin antibiotics. Polyketides such as polycyclic ether macrolides and open-chain polyketides are produced and stored by marine sponges and show strong antiviral and antimicrobial activities.

Marine sponges of the *Xestospongia* species show the presence of various polyketides of halenaquinone type, such as orholquinone 8 and xestosaprol C methylacetal 7 [132]. Orholquinone 8 exhibited inhibition of enzymes farnesyl transferase from yeast, human and *P. falciparum*. Marine macrolide, neopeltolide, from a deepwater sponge species of *Neopeltidae* [133] showed antifungal activity for *C. albicans*. Marine 7-O-methylkoninginin D and trichodermaketones A, B, C, D are antifungal polyketides from fungus *Trichoderma koningii*, exhibiting synergistic antifungal potency against *C. albicans* [134]. Curvularin and α,β -dehydrocurvularin are marine polyketides from fungus *Eupeenicillium* sp. in association with sponge *Axinella* sp. [135]. Marine macrolides, (+) brefeldin A, (+) brefeldin C, and 7-oxobrefeldin A from *Penicillium* sp. PSU-F44 [136] exhibited antimicrobial potency for *Microsporum gypseum* and MRSA.

Marine fungal *Nigrospora* sp. PSV-F18 and PSU-F5 showed the presence of nigrosporapyrones A, B, C, and D and nigrospoxydons A, B, and C, which are antimicrobial macrolides [137].

17.1.1.8 Polysaccharides

Polysaccharides are structurally very diverse biological macromolecules because of presence of various sugars and their derivatives such as uronic acid. In nature, each sugar is linked covalently to another sugar at different sites in the sugar ring. Marine plants, animals, organisms, bacteria, and fungi are a source of a large diverse variety of polysaccharides [138], some of which exhibit antiviral and antimicrobial actions.

Edible *Nostoc flagelliforme*, a species of blue-green alga, shows nostoflan, an acidic polysaccharide which shows antiviral activity (anti-HSV-1) [139], inhibiting virus binding. Lectin is a marine polysaccharide from *Oscillatoria agardhii* NIES-204, a filamentous cyanobacterium inhibiting HIV replication in MT-4 cells [140]. Chitinase is a marine antifungal polysaccharide from marine South China sea sponge inhibiting *Streptomyces* sp. DA11. *Craniella australiensis* exhibited antifungal defense activity for *C. albicans* and *A. niger* [141], which may be because of its microbial symbiont exhibiting chitinase activity bringing about chitin degradation.

17.1.1.9 Phenolic compounds

The vastest group of secondary metabolites in plants is the group of phenols. It is naturally spread wide and present in natural compounds with aromatic moieties. They have a wide range of structures from simple one aromatic ring structure to extremely complex polymeric compounds. Commonly, in marine regions, phenolic compounds with halogens as moieties occur in high frequency. Marine sponges exhibit phenolic compounds, which are studied commonly for antimicrobial activity.

Sponge *Dysidea granulosa* showed presence of 2-(2',4'-dibromophenoxy)-4,6-dibromophenol exhibiting wide spectrum and strong antibacterial activity potency especially toward MRSA and sensitive *S. aureus*, vancomycin-resistant and -sensitive *Bacillus* and *Enterococci* species [142].

Presence of bromines and phenolic hydroxyl groups at C-2 and C-5 is essential for antimicrobial activity. Bromophenol compounds are present in marine red algae and bacteria show antimicrobial activity. Crude extracts from marine algae *Odonthalia corymbifera* exhibited antimicrobial activity [143]. Natural bromophenol compound 2, 2', 3, 3'-tetrabromo-4, 4', 5, 5'-tetrahydroxydiphenylmethane was most active against *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Aspergillus fumigates*, and *C. albicans*. Marine *Pseudoalteromonas* extract of CMMED 290 species, 4, 4', 6-tribromo-2, 2'-biphenol exhibited significant antimicrobial action against MRSA [144]. Marine bacterium *Pseudoalteromonas phenolica* O-BC30T produces 2, 2', 3-tribromobiphenyl-4, 4'-dicarboxylic acid [145], exhibits anti-MRSA, *Bacillus subtilis*, *Enterococcus serolicida*, but not for Gram-positive bacteria or fungi. Other antimicrobial bromophenyl compounds have also been isolated from the marine bacterium *Pseudoalteromonas haloplanktis* INH strain [146].

Anthraquinones, coumarins, and flavonoids from marine extracts show antimicrobial action. *Aspergillus versicolor* derived from *Petrosia* species marine sponge shows five bioactive anthraquinones which exhibited antimicrobial activity for Gram-positive bacteria [147]. Marine-derived 05F16 *Aspergillus* sp. possesses hexahydroanthrones, tetrahydrobostrycin, and 1-deoxytetrahydrobostrycin [148] showing antibacterial potency for *E. coli* and *S. aureus*. Anthraquinone monodictyoquinone A (1,8-dihydroxy-2-methoxy-6-methylanthraquinone) is antimicrobial found in sea urchin fungus *Monodictys* sp. [149]. Anthraquinone monodictyoquinone A was found in marine ALAA 2000 *Nocardia* sp., from marine

red alga *Laurencia spectabilis* and exhibited antimicrobial action toward Gram-positive, Gram-negative bacteria, and fungi. 7-Methylcoumarin and flavonoids, rhamnazin, and cirsimaritin are antimicrobial phenolic compounds from marine *Streptomyces* [150]. Derivatives of chroman-ammonificins A and B, from marine bacterium *Thermovibrio ammonificans* present in hydrothermal vent are found to be antimicrobial [151].

Edible seaweed *Ecklonia cava* shows antimicrobial phlorotannins [152]. Marine fungus *Zygosporium* sp. *KNC52* showed the presence of sulfoalkyl resorcinol with multidrug-resistant bacteria antimicrobial potency [153].

17.1.1.10 Steroids

Steroids are natural products which are glycosides in nature and marine or terrestrial in origin. Many glycosides exhibit various biological activities including antimicrobial.

Marine steroidal glycosides show their presence in microalgae and invertebrates such as echinoderms, soft corals, and sponges [154]. *Euryspongia*, a marine sponge from Palau, showed two new steroidal sulfates Eurysterols A and B [155] with antifungal potency activity against wild-type and amphotericin B-resistant *C. albicans* strains. Geodisterol-3-O-sulfite and 29-demethylgeodisterol-3-O-sulfite, two novel sulfated sterols, exhibited reversal of fluconazole resistance [156]. Marine endophytic fungus *Colletotrichum* sp. containing ring B aromatic steroids exhibited showed antimicrobial activity against the fungus *Microbotryum violaceum*, *E. coli*, and *Bacillus megaterium* [157].

17.1.2 Antimicrobial drugs of marine origin under clinical trials

There are various marine originating chemical antimicrobial lead compounds which can be further explored for human health issues. There are currently over 3000 new substances identified from marine organisms in the past three decades, giving researchers a large pool of novel molecules from which to find new compounds to develop [158].

They have to be clinically tried out before being implemented for general prescriptions. This requires ample amounts of compounds under trial to be isolated and extracted in pure forms from the source. Obtaining them from invertebrates in sufficient amounts can prove difficult. There are various such compounds that are presently under clinical trials. Aqua culture is an alternative but may not be viable in all cases. Microorganisms may be used as sustainable sources for production of required compounds for production of intermediates in the first step of semisynthesis which can later produce final compound of interest.

17.1.2.1 Antibacterial compounds under clinical trials

In the era of rapid emergence of antibiotic-resistant bacteria, marine sponge extracts have shown the best antimicrobial potency against terrestrial bacteria [159]. When 101 arctic sponges were antimicrobially screened against opportunistic infections causing bacteria, approximately 10% of them showed significant results, values of IC₅₀ ranging from 0.2 µg/mL to 5 µg/mL [160]. About 800 compounds with antibiotic properties have been isolated and identified from marine sponges [161]. Of 31 sponges checked, 18 showed strong antimicrobial potency against Gram-positive and Gram-negative bacteria and are being screened for a range of therapeutically significant substances [162]. Presently, various such antibacterial compounds are under trials, at various stages.

Examples of antibacterial compounds under clinical trials include the following:

- Cribrostatin 6 is an alkaloid from *Cribrorhynchus* sp. being tried out against antibiotic-resistant strain of *Streptococcus pneumoniae* [163].
- Isojaspic acid, cacospongins D, and jaspaginol are meroditerpenes from *Cacospongia* sp. tried out against *S. epidermidis* showing an MIC of 20 µg/mL [164].
- Isoaaptamine is an alkaloid from *A. aaptos* inhibitory for *S. aureus* exhibiting an MIC of 3.7 µg/mL [39].
- Microcionin-1 is a terpenoid from *Fasciospongia* sp. inhibitory toward *Micrococcus luteus* showing an MIC of 6 µg/mL [165].
- Pseudopterosins from soft corals are diterpene glycoside with eicosanoid metabolism under Phase II trial for wound healing.

17.1.2.2 Antiviral compounds under clinical trials

No cure has yet been available for adenovirus serotype 5 (AdV-5) associated with respiratory infections [166] or rotaviruses associated with severe gastroenteritis of animals and humans or diarrhea in immunocompromised patients, which may prove fatal [167]. About 40 antiviral substances from marine species have been reported, half of which have

shown prospects in treatment of HIV infection. On this background, marine sponges, sources of novel antivirals, may prove to be good therapeutic agents [168]. Avarol inhibits HIV infection progression and increases humoral immune response. Avarol in 0.3, 0.9 μM concentration inhibited 50%, 80% of viruses, respectively, released by infected cells [169]. Avarol derivatives, 6'-hydroxyavarol and 3'-hydroxyavarone, strongly inhibit HIV reverse transcriptase in HIV. Avarol converts viral genomic RNA to proviral DNA and integrates it in host chromosomal DNA [170]. Various antiviral marine metabolites are currently under clinical trial.

Examples of antiviral compounds under clinical trials are the following:

- 4-Methylaaptamine is an alkaloid from *A. aaptos inhibitory toward* HSV-1 [38].
- Papuamides A–D are cyclic depsipeptides from *Theonella* sp. acting against HIV-1 [171].
- Ara-A is a nucleoside from *Cryptotethya crypta* inhibitory toward HSV-1, HSV-2, and VZV [172].
- Avarol is a sesquiterpene hydroquinone from *Dysidea avara* acting against HIV-1, UAG suppressor glutamine tRNA inhibitor [169].
- Haplosamates A and B are sulfated steroids from *Xestospongia* sp. alias Haplosclerida, antiviral (inhibitor of enzyme HIV-1 integrase) in action [173].
- Dragmacidin F is an alkaloid from *Halicortex* sp. acting against HIV-1 [174].
- Hamigeran B, a phenolic macrolide from *Hamigera tarangaensis* has antiviral–antiherpes and antipolio virus potency [175].
- Mycalamides A–B are nucleosides from *Mycale* sp. with anti-A59 coronavirus (HSV-1) action [176].
- Mirabamides A, C, and D are peptides from *S. mirabilis* with antiviral (HIV-1) potency [48].
- FDA-approved vidarabine (Ara-A), Vira-A®, is a nucleoside Ara-A from marine sponge *C. crypta* and is an arabinosyl nucleoside, inhibiting synthesis of viral DNA [177].
- Azidothymidine (zidovudine), Ara-A, acyclovir, Ara-C—modified semisynthetic arabinosyl nucleosides in use against viruses [178].

17.1.2.3 Antifungal compounds under clinical trials

Invasive mycoses, an increasing resistant fungal infection in patients of AIDS, on immunodepressants, with blood cancers, undergoing transplants [179], have proved fatal. *Candida*, *Aspergillus*, *Cryptococcus*, and other opportunistic fungi are common culprits. Sponges belonging to *Jaspis* sp. have given Jaspamide cyclodepsipeptide, a 19-unit macrocyclic depsipeptide, exhibiting in vitro antifungal potency against *C. albicans* [180].

Examples of antifungal compounds under clinical trials are the following:

- Jaspamide, a macrocyclic depsipeptide from *Jaspis* sp., has shown an MIC against *C. albicans* of 25 $\mu\text{g}/\text{mL}$ [180].
- Eurysterols A–B are sterols from *Euryspongia* sp. inhibiting *Amphotericin B-resistant C. albicans*, with an MIC of 62.5 $\mu\text{g}/\text{mL}$ and 15.6 $\mu\text{g}/\text{mL}$ [155].
- Naamine D, an imidazole alkaloid, from *Leucetta cf. chagosensis*, bioactive against *C. neoformans*, with an MIC of 6.25 $\mu\text{g}/\text{mL}$ [181].
- Mirabilin B is a tricyclic guanidine alkaloid, from *M. unguifera*, acting against *C. neoformans*, with an MIC of 7.0 $\mu\text{g}/\text{mL}$ [36].
- Hamacanthin A is an indole alkaloid, from *Spongisorities* sp., active against *C. albicans*, with an MIC of 6.25 $\mu\text{g}/\text{mL}$ [182].
- Macanthins A–B are indole alkaloids, from *Spongisorities* sp., active against *C. albicans* and *C. neoformans*, with MIC of 1.6 $\mu\text{g}/\text{mL}$ and 6.2 $\mu\text{g}/\text{mL}$, respectively [182].
- Agelasines and agelasimines are purine derivatives, from *Agelas* sp., bioactive against *C. krusei*, and MIC of 15.6 $\mu\text{g}/\text{mL}$ [183].

17.1.2.4 Antimalarial compounds under clinical trials

Plasmodium vivax, the predominant malarial parasite, has caused havoc by spreading malaria in vast areas of Asia and America, while showing accelerating antibiotic resistance. A need for new antimalarial compounds led to antimicrobial agents from marine sponges. *Cymbastela hooperi* has exhibited antimalarial potency against *P. falciparum* through isonitriles, terpenoid isocyanates, and isothiocyanates [184]. *Diacarnus megaspinorhabdosa*, a marine sponge exhibited antimalarial potency toward chloroquine-resistant and -sensitive *P. falciparum* through epidioxy-substituted norsesterterpenes and norditerpene endoperoxides [185].

Examples of antimalarial compounds under clinical trials are the following:

- Monamphilectine A, an antimalarial β -lactam obtained from *Hymeniacion* sp., acting against *chloroquine-resistant P. falciparum* W2, with an MIC of 0.6 μ M [186].
- Manzamine A is an alkaloid obtained from *Haliclona* sp./*Haplosclerida* and *C. hooperi*/*Halichondrida*, *Diacarnus levii*/*Poecilosclerida*, *Toxoplasma gondii*, *Plasmodium berghei*, *P. falciparum*, acting against *chloroquine-resistant P. falciparum* W2 with an MIC of 4.5 ng/mL [185]).
- Kalihinol A, an isonitrile-containing kalihinane diterpenoid, from *Acanthella* sp./*Halichondrida*, with an MIC of 0.0005 μ g/mL, against *P. falciparum* D6 clone [187].
- Diisocyanoadociane, a tetracyclic diterpene, from *C. hooperi*, acting against *P. falciparum*, with an MIC of 0.005 μ g/mL for D6 clone [188].
- Halichondramide is a macrolide, from *P. falciparum*, with an MIC of 0.002 μ g/mL, against *P. falciparum* D6 clone [184].
- Sigmosceptrellin B is a norsesiterpene acid, from *Diacarnus erythraeanus*, *T. gondii*, active against *P. falciparum* D10, with an MIC of 1200 ng/mL [184].
- (E)-Oroidin is an alkaloid, from *Agelas oroides*, bioactive against *P. falciparum*, with an MIC of 0.30 μ g/mL for D6 clone [189].
- Plakortin and dihydroplakortin are cycloperoxidases, from *Plakortis simplex*, acting against *P. falciparum*, D10 at 1263-1117 nM [190].

Manzamines are efficient antimalarials from a variety of sponges [191] and have exhibited inhibitory activity against *P. falciparum* (D6 clone), MIC 0.0045 μ g/mL [191], by increasing host immunity [187].

17.1.3 Future outlook and conclusion

Natural products have always played a significant role in drug discovery for treating human diseases. Drugs developed from marine sources have ignited a hope to offer novel mechanisms to fight some of the most debilitating diseases such as HIV, osteoporosis, Alzheimer's, and cancer. Although costs required for developing drugs from marine sources have been exorbitant, development of new technology and better understanding of marine species and associated ecosystem has helped us in developing research in the area of drug development. Bright future awaits pharmaceutical industry for developing new drugs from antimicrobial lead compounds obtained from marine sources. The progress is slow, but surely drug manufacturing units have started showing interest in implementing natural marine sources for drug developing. A future trend is developing in research today, positively toward use of marine natural resources. There are ample of marine lead compounds, more than imagined [192].

Metabolites derived from marine species such as sponges span wide with respect to their chemical components such as alkaloids, peptides, terpenoids, polyketides, and others, with a variety of antimicrobial and other properties [187]. When these compounds are prepared for the market, they need to have a known chemistry, enhanced bioavailability, and minimized side effects. Manzamines are metabolites from marine sponges that can be potentially used as drugs against tuberculosis [193], HIV [169], malaria [184], and others. Ara-A, ara-C, and acyclovir are a few products originating from marine sponges in clinical use [169].

It has been observed that medicines derived from various metabolites and derivatives from marine species such as sponges possess their efficiencies as medicines, based on their doses, qualitative, and quantitative effects of inhibition and their other effects. Besides, they are present in the marine species in very low quantities, which presents difficulties in their being reproduced in ample amounts in the market. Avarol, obtained from sponge *D. avara* sponge, is an efficient drug for treatment of HIV [169], which could not be available for studies further than preclinical ones because of its low availability for assessment [194]. Another advantage of marine species metabolites is that their carbon skeletons can be used as carriers or vehicles for generating efficient derivatives. Mankind now faces a challenge of preparing the miracle drugs in large quantities, transforming bioactive metabolites to medicines by selecting proper marine species, isolating the correct metabolite, with its precise action and its target point toward a disease.

Although marine environment has umpteen numbers of species which are natural resources for antimicrobial compounds, very few of these secondary metabolites have reached the stage of being approved as drugs, while some metabolites and their derivatives are still under clinical trials or preclinical trials at various stages.

These trials require a large amount of these metabolites, which has lead to novel ideas like chemically modifying marine natural products or MNPs to transform them into "druglike" products, farming organisms in natural environment, and culturing organisms artificially [195]. Preclinical trials need very systematic, detailed pharmacokinetic investigation to

tailor MNPs, a challenging task. Antimicrobial efficiency of marine metabolites has shown a promising future for development as human therapeutic agents. A revolution has been set up because of the technique of genome mining for natural product discovery. Technology is being targeted optimally for drug research, its approvals and its launches, for the betterment of human life. This chapter has attempted to give a sketch of antimicrobial lead compounds from marine species, a step forward toward the development of medicinal and biological agents from marine natural sources. This may be an endeavor toward exploring an untrodden path in drug discovery, from marine environment, for the global health benefits of mankind.

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