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·Review·

Antimicrobial metabolites from marine microorganisms

Prasanna Habbu[1*], Vijayanand Warad[2], Rajesh Shastri[1], Smita Madagundi[1], Venkatrao H. Kulkarni[3]

[1] *Postgraduate Department of Pharmacognosy & Phytochemistry, SET's College of Pharmacy, Dharwad 580002, Karnataka, India;*

[2] *Department of Pharmacognosy and Phytochemistry, Sridevi College of Pharmacy, Mangalore 575006, Karnataka, India;*

[3] *Postgraduate Department of Pharmacology, SET's College of Pharmacy, Dharwad 580002, Karnataka, India*

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[ABSTRACT] Marine ecological niches have recently been described as "particularly promising" sources for search of new antimicrobials to combat antibiotic-resistant strains of pathogenic microorganisms. Marine organisms are excellent sources for many industrial products, but they are partly explored. Over 30 000 compounds have been isolated from marine sources. Bacteria, fungi, and cyanobacteria obtained from various marine sources secret several industrially useful bioactive compounds, possessing antibacterial, antifungal, and antimycobacterial activities. Sustainable cultivation methods for promising marine organisms and biotechnological processes for selected compounds can be developed, along with the establishment of biosensors for monitoring the target compounds. The semisynthetic modifications of marine-based bioactive compounds produce their new derivatives, structural analogs and mimetics that could serve as novel lead compounds against resistant pathogens. The present review focuses on promising antimicrobial compounds isolated from marine microbes from 1991−2013.

[KEY WORDS] Antibacterial metabolites; Antifungal metabolites; Marine microbes

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Introduction

Emerging resistance to antibiotics has raised serious questions regarding the next source of new chemical entities that can meet the challenge of continually emerging drug resistance [1]. Although considerable progress is being made within the fields of chemical synthesis and engineered biosynthesis of antimicrobial compounds, nature still remains the richest and the most versatile source for new antibiotics [2-4]. The marine environment, which represents approximately half of the global biodiversity, contains a rich source of structurally diverse and biologically active metabolites [5-6]. Over the past ten years, marine natural products researchers have expanded the scope of their studies from macro-organisms, such as algae, sponges, ascidians, and soft corals to marine microorganisms [7-8]. Marine microorganisms have recently gained attention as important sources of biologically active secondary metabolites for the development of new pharmaceutical agents [5]. Products from marine organisms have shown many interesting activities, such as anti-microbial, cytotoxic, anticancer, anti-diabetic, anti-fungal, anti-coagulant, anti-inflam-matory, and other pharmacological activities [9-10]. In relation to anti-microbial properties, the marine environment is believed to be able to provide novel leads against pathogenic microbes that are evolving and developing resistance to existing pharmaceuticals [11-13]. Thus, novel anti-biotics are urgently needed to counteract and reverse the spread of anti-biotic resistant pathogens [14-15]. Hence, this review focuses on the anti-microbial metabolites derived from marine microbes and their potential medical application as novel functional ingredients in anti-microbial therapy.

Anti-microbial metabolites from marine microorganisms

Contributing to the global search for new antimicrobials

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[*Corresponding author] Tel: 91836-2448540, Fax: 91836-2467190, E-mail: prasherbs@yahoo.com.

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to combat anti-biotic resistant strains of pathogenic bacteria, marine ecological niches have been described recently as "particularly promising" [16]. Several studies have reported novel anti-microbial marine secondary metabolites isolated from marine bacteria, fungi, algae, sponges, worms, fish, etc. [17].

Sediment/water derived microbes and their metabolites

Any solid fragment of inorganic or organic material may be termed sediment. Familiar ocean sediments include those found along the coast, *viz.*, rocks and cobbles at the beach, fragments of seashells, or sand and mud at the bottom of the sea. Marine sediments originate from a variety of sources, including continental and oceanic crust, volcanoes, microbes, plants and animals, chemical processes, and outer space. Sediments are broadly categorized in to two types. First type is granular sediments resulting from the fragmentation of inorganic or organic parent materials (mud, silt and sand). Second type is chemical sediment forming directly from dissolved compounds in sea water (fragments of lime stone and lime-stone like rocks). Although microorganisms have been isolated from a variety of marine sources, sediments continue to receive the greatest attention, perhaps because of their similarity to terrestrial soils and because they have been shown to be a good source of therapeutically useful metabolites [18].

24-Membered macrolactins are generally produced by *Bacillus* sp. and exhibit anti-bacterial, anti-cancer, and anti-viral activities [19]. Ethyl acetate fraction of a marine sediment derived *Bacillus sp*. 091D194 has led to the isolation of macrolactins A (**1**), Q (**2**) and new glycosylated macrolide, Macrolactin W (**3**). Compound **3** exhibited potent anti-bacterial activity against Gram-positive and Gram-negative pathogenic bacteria [20]. In previous reports, Gustafson and co-workers have reported that, compound **1** isolated from unclassified marine bacterium inhibited *Staphyllococcus aureus* (SA) and *Bacillus subtilis* (BS) at a concentration of 5 and 20 μg/disc, respectively [21]. Macrolactins F (**4**) and K show weak antibacterial activity. Macrolactins G−M inhibit SA [22]. Macrolactins O (**5**) to R inhibit SA in a dose-dependent manner with IC_{50} values being 53.5, 57.7, 12.1, and 61.5 μmol·L^{-1}, respectively [23]. Macrolactin S (**6**) isolated from a marine BS, show significant anti-microbial activity against *Escherechia coli* (EC) but weak activity against pathogenic BS and SA [24]. Macrolactin T (**7**) and V exhibit anti-fungal and significant anti-bacterial activity, respectively [25-26]. Fijimycins A−C (**8**−**10**) and Etamycin A (**11**) isolated from a marine sediment derived *Streptomyces sp*. possess significant anti-bacterial activity against three methicillin resistant *Stephyllococcus aureus* (MRSA) strains. The MIC_{100} values for these compounds are found to be between 4−6 μg·mL^{-1} [27]. Two rare neosidomycin metabolites Kahakamides A and B (**12** and **13**) are isolated from marine shallow water sediment associated actinomycete *Nocardiopsis dassonvillei*. These are previously represented by neosidomycin [28] and SF-2140 [29]. Compound **12** exhibit anti-bacterial activity against BS in the disk diffusion assay [30]. Marine sediment derived *Streptomyces sp.* (MB-M-0392) yields heronamycin A (**14**) (A benzothazine ansamycin). Compound **14** show moderate anti-microbial activity against two different strains of BS with IC_{50} values being 18 and 14 μmol·L^{-1} respectively [31].

Marine microorganisms are the biggest reservoir providing a wide variety of structurally unique, biologically significant nonribosomal peptides, especially cyclopeptides derivatives [32-33]. In an effort towards finding novel anti-fungal metabolites from *Halobacillus lotoralis* YS3106, Yang *et al.* have isolated Halolitoralin A (**15**) (a cyclic hexapeptide), Halolitoralin B (**16**), and Halolitoralin C (**17**) (two cyclic tetrapeptides). Compound **15** show good anti-fungal activity against *Candida albicans* (CA) (20 μg·mL^{-1}) and *Tricophyton rubrum* (TR) (25 μg·mL^{-1}) as compared to other two [34]. Sea water associated marine bacterium *Pseudomonas* UJ-6 is known to contain 1-Acetyl-beta-corboline (**18**). The compound exhibits anti-bacterial activity against MRSA with MIC being 32−128 μg·mL^{-1} [35]. Mervat *et al.* have isolated a novel triazolo pyrimidine anti-biotic, Essramycin (**19**) from marine sediment derived *Streptomyces sp.* Merv8102. Anti-microbial activity of Essramycin is determined by serial dilution technique against EC*, Pseudomonas aeruginosa* (PA) SA. and *Micrococcus luteus* (ML). Compound **19** shows potent anti-bacterial activities with MIC ranging between 1.0−8.0 μg·mL^{-1} against the organisms studied [36]. Chlorinated bisindole pyrroles, lynamicins A−E (**20**−**24**), are isolated from a marine sediment associated actinomycete, NPS12745 with the proposed genus *Marinispora.* These compounds are found to be active against drug-resistant pathogens such as MRSA and vancomycin resistant *Enterococcus faecium* (VREF). MIC values of linamycins are depicted in Table 1 [37]. The bisindole pyrroles represent a much smaller series of metabolites, including chromopyrrolic acid, produced by *Chromobacterium* V*iolaceum,* and three bisindole pyrroles, lycogarubins A−C, produced by the myxomycete *Lycogala epidendrum*. Hashimoto *et al.* have reported anti-viral activity of bisindole pyrroles against HSV (IC_{50} 17.2 μg·mL^{-1}) *in vitro* [38-40]. Rabelomycin (**25**) and Phenanthroviridone (**26**) are isolated from marine derived *Micromonospora rosaria.* Both compounds exhibit good anti-microbial activities against SA with MIC values being 1.0 and 0.25 μg·mL^{-1}, respectively [41]. A marine actinomycete *Marinispora*, strain NPS008920, produce a series of novel 2-alkylidene-5-alkyl-4-oxazolidinones, Lipoxazolidinone A (**27**), B (**28**), and C (**29**). Compound **27** shows a broad spectrum of activity with MIC values ranging from 0.5 to 5 μg·mL^{-1} against Gram-positive bacteria and 12 μg·mL^{-1} against two strains of *Haemophilus influenzae* (HI). In contrast, hydrolysis product shows only weak activity against methicillin sensitive *Staphyllococcus aureus* (MSSA), indicating the importance of an intact oxazolidinone ring system to offer anti-biotic activity [42]. A marine sediment derived fungus *Aspergillus protuberus* SP1 is identified from different coastal locations of Kanyakumari district of south India.

Table 1 Anti-microbial secondary metabolites from marine derived microorganisms

Marine source	Type of organism	Organism(s) isolated	Secondary metabolite(s)	Antimicrobial assay against	MIC/IC_{50}*	Ref.
Sediment/ water						
	Bacteria	*Streptomyces* sp.	Fijimycins A−C and etamycin A	MRSA	4−16 μg·mL^{-1}	[27]
	Actinomycete	*Nocardiopsis dassonvillei*	Kahakamides A and B	BS	Slight inhibition by disk diffusion assay	[30]
	Bacteria	*Streptomyces* Sp. (MB-M-0392)	Heronamycin A	Two different strains of *BS*	18 and 14 mol·L^{-1} respectively*	[31]
	Bacteria	*Halobacillus lotoralis* YS3106	Halolitoralin A (a cyclic hexapeptide), B and C (two cyclic tetrapeptides),	CA *TR*	20, 30 and 30 μg·mL^{-1} respectively. 25, 35 and 40 μg·mL^{-1} respectively	[34]
	Bacteria	*Pseudomonas* UJ-6	Contain 1-acetyl-beta-carboline	MRSA	32−128 μg·mL^{-1}	[35]
	Bacteria	*Streptomyces* sp. Merv8102	Essramycin	EC, PA, SA and ML	1.0−8.0 μg·mL^{-1}	[36]
	Actinomycete	*Marinispora* NPS12745	Lynamicins A−E	MRSA, MSSA, MDRSE, Pen-S , Pen-R and VREF	Range of MIC's against the tested organisms Lynamicin A 1.8−24 μg·mL^{-1} ; Lynamicins B 0.8−8 μg·mL^{-1} ; Lynamicins C 1−20 μg·mL^{-1} ; Lynamicins D 3−32 μg·mL^{-1} ; Lynamicins D 12−32 μg·mL^{-1}	[37]
	Actinomycete	*Micromonospora Rosaria* SCSIO N160	Rabelomycin and Phenanthroviridone	SA	1.0 and 0.25 μg·mL^{-1} , respectively	[41]
	Actinomycete	*Marinispora*, strain NPS008920	Lipoxazolidinone A	MSSA MRSA SE (Pen-S) Pen-R VSE VRE Two strains of HI	MIC ranging from 0.5 to 5 μg·mL^{-1} against Gram positive bacteria 12 μg·mL^{-1}	[42]
	Fungus	*Aspergillus protuberus* SP1	*n*-Butanol fraction	PM EC, KP and BS	Inhibition zones around the spot was observed	[43]
	Bacteria	*Bacillus* sp. 091D194	Macrolactin W	BS, SA, EC and PA	64 μg·mL^{-1} respectively	[20]
	Fungus	*Zopfiella latipes* CBS 611.97	Zopfiellamides A and B	AC, BB, BS, BL, CI, ML, MP, Ss and AC	2 and 10 mg·mL^{-1} (for zopfiellamide-A)	[44]
Algae						
Gracilaria Sp. SGR-01	Fungus	*Daldinia eschscholzii*	Helicascolisides A, B and C	EC, PA, BS, SA and CM	No antibacterial activity was observed	[52]
Diginea sp.	Bacteria	*Pseudomonas* sp	Cyclic tetrapeptides	BS and VA	No activity	[61]
Sargassum sp.	Fungus	ZZF36	6-Oxo-de-methyllasiodiplodin, (*E*)-9-Etheno-lasiodiplodin, Lasiodiplodin, de-*O*-Methyllasiodipodin, 5-Hydroxy-de-*O*-methylasiodiplodin	SA, BS, EC, SE, CA, FO	6.25−100 μg·mL^{-1} against specific organisms	[62]
Enteromorpha prolifera	Fungus	*Eurotium herbariorum* HT-2	Cristatumin E	EA and EC	44.0 μmol·L^{-1} respectively	[63]
Laurencia sps.	Fungus	*Penicillium chrysogenum* QEN-24S,	Penicisteroid A	AN and AB	Inhibition zones around the spot was observed	[66]
Sponge						
Clidamia hirta	Fungus	*Cryptopsoriopsis* sps.	1-(2,6-Dihydroxyphenyl)pentan-1-one# and (*Z*)-1-(20,2-butyryl-3-hydroxyphenoxy)-6-hydroxyphenyl)-3-hydroxybut-2-en-1-one*	bacterial pathogens# and PF*	8 to 30 μg·mL^{-1}#, and 6 μg·mL^{-1}*	[72]
Suberites domuncula	Fungus	*Eurotium cristatum* KUFC7356	Eurocristatine	SA , EC, PA, CA, AF, TR	No antibacterial and antifungal activity	[73]
Aplysina aerophoba and Aplysina cavernicola	*α*-proteobacteria *γ*-proteobacteria	*Micrococcus* sps., *Vibrio* sps., *α-Pseudoalteromomnas and Bacillus* sps.	_	Gram positive and gram negative microbes, MRSA and SE strains	Inhibition zones were determined against each microbe	[74]

Continued

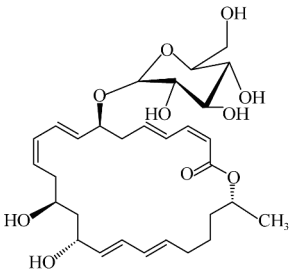
Marine source	Type of organism	Organism(s) isolated	Secondary metabolite(s)	Antimicrobial assay against	MIC/IC_{50}*	Ref.
Petrosia ficiformis.	Bacteria	*Rhodococcus Erythropolis* and *Pseudomonas* sps.	−	SA and other Gram positive rods	Inhibition zones around the spot was observed	[75]
Dysidea granulose	Bacteria	*Enterobacter* sp. TTAG	Crude extracts	SA, EC, ST and KP	Lowest MIC was 5 mg·mL^{-1}	[76]
Haliclona sp.	γ-Proteobacteria	*Pseudomonas fluorescens* H40, H41 and *P. aeruginosa* H51	Crude extracts	VREF and MDRKP	Inhibition zones around the spot was observed	[77]
Unidentified sponge	Fungus	*Aspergillus ochraceus* MP2	α-Campholene aldehyde and Lucenin-2	KP, SA and PA	Zone of inhibition at varying concentrations was observed	[78]
Corals						
Cladiella sp.	Fungus	*Aspergillus versicolor* LCJ-5-4	Versicoloritides and tetraorcinol	SA, EC, EA, BS, PA and CA	MIC > 150 μmol·L^{-1}	[88]
Montipora aequitubercu lata	Bacteria	*Pseudoalteromonas flavipulchra*		Against 21 clinical isolates including 15 strains of MRSA, two strains of EF, one strain of SP..	Mean zone of inhibition was observed	[85]
Hard coral	Fungus	*Zygosporium* SP. KNC52	Sulfoalkylresorcinol	MT, MB, MA PA and MRSA strain	166 μg·mL^{-1} respectively 50 and 12.5 μg·mL^{-1} respectively	[87]
Bryozoan						
Unidentified	Bacteria sps.	*Flavobacteria, α-* and *γ-Proteobacteria* and *actinobacteria*	−	EC, BS, SL and CG	Inhibition zones was examined up to three days	[92]
Miscellaneous						
	Fungus	*Aspergillus carneus* KMM 4638	Carneamides A−C, Carnequinazolines A−C and carnemycin A, B	SA, BC, EC, PA and CA	No activity	[93]
	Bacteria	*Pseudoalteromonas Phenolica* O-BC30	2, 2', 3-Tribromophenyl-4, 4'-dicarboxylic acid	Clinical isolates of MRSA	1−4 μg·mL^{-1}	[94]
	Bacteria	*Streptomycetes* sp. BCC 45596	Urdamycinone E, urdamycinone G and dehydroxyaquayamycin	MT	3.13−12.50 μg·mL^{-1}	[95]
	Bacteria	*Brevibacillus laterosporus* PNG276	Tauramamide as its methyl and ethyl esters	Ecs	0.1 μg·mL^{-1}	[96]
	Actinomycete	*Nocardiopsis dassonvillei* HR10-5	Nocapyrones E–G	BS	26, 14, and 12 μmol·L^{-1}, respectively	[97]
	Cyanobacterium	*Fischerella* sp.	Ambiguine H isonitrile, and Ambiguine I isonitrile	EC SAlb BS SC CA	10 and 2.5 μg·mL^{-1} respectively 0.625 and 0.078 μg·mL^{-1} respectively 1.25 and 0.312 μg·mL^{-1} respectively 5 and 0.312 μg·mL^{-1} respectively 6.25 and 0.39 μg·mL^{-1}	[99]
	Cyanobacterium	*Fischerella ambigua*	Ambiguine K and M isonitriles	MT	6.6 and 7.5 μmol·L^{-1}, respectively	[103]
	Fungus	*Aspergillus carbonarius* WZ-4-11	Two dimeric naphtho-γ-pyrones,	MT	43 and 21.5 μmol·L^{-1}, respectively	[104]
	Bacteria	*Streptomyces* strain	Marinopyrroles A and B	MRSA strains	0.61 and 1.1 μmol·L^{-1} respectively (MIC_{90})	[105]
	Bacteria	*Rapidithrix* sp.	Ariakemicins A and B	Brb SA BS Cm Pv EC PA CA	83 μg·mL^{-1} 0.46 μg·mL^{-1} 83 μg·mL^{-1} > 700 μg·mL^{-1} > 700 μg·mL^{-1} > 700 μg·mL^{-1} > 700 μg·mL^{-1} > 700 μg·mL^{-1}	[106]

Different polar and non-polar fractions of the fungi have been tested for anti-microbial activity. *n*-Butanol fraction shows maximum anti-microbial activity against Gram-positive and negative pathogens [43]. A culture of the facultative marine ascomycete *Zopfiella latipes*, originally isolated from Indian Ocean soil, is the source of Zopfiellamides A (**30**) and B (**31**) which are moderately active against *Arthrobacter citreus* (AC), *Bacillus brevis* (BB), BS, *Bacillus licheniformis* (BL), *Corynebacterium insidiosum* (CI), ML, *Mycobacterium phlei* (MP), *Streptomyces* sp. (Ss), and *Acinetobacter calcoaceticus* (AC). The MICs are found to be between 2 and 10 mg·mL^{-1} for **30** [44]. Halorosellins A and B (**32** and **33**) along with 3-acetyl-7-hydroxy-5-methoxy-3, 4-dimethyl-3*H*-isobenzofuran-1-one have been isolated from the culture broth of the marine fungus *Halorosellinia oceanica* of Thai origin. The isobenzofuran-1-one derivative exhibits moderate anti-mycobacterial activity with MIC being 200 μg·mL^{-1} [45]. The filamentous marine fungus *Keissleriella* sp. isolated from a yellow sea sediment source gives 3, 6, 8-trihydroxy-3-[3, 5-dimethyl-2-oxo-3(*E*)-heptenyl]-2, 3-dihydr-onaphthalen-1(4*H*)-one, which is anti-fungal *in vitro* against CA, TR and *Aspergillus niger* (AN) [46]. An anti-fungal cyclododecapeptide, Lobocyclamide B has been isolated from a benthic mat of *L. confervoides* from the Bahamas. Lobocyclamide B displays anti-fungal activity against fluconazole-resistant *Candida albicans* (FRCA) [47]. Structures of the before mentioned secondary metabolites are depicted in Fig. 1.

Algal derived microbes and their metabolites

Marine algae are relatively simple, chlorophyllous plants which usually grow either under or partly under water. They are not differentiated into root, stem and leaf, and are reproduced by spores instead of seeds. The large marine algae are often given the common name of seaweeds and designated as green, red and brown algae, according to color. Chlorophyl gives the characteristic green color to the green algae [48]. Marine macroalgae or seaweeds are plants adapted to the marine environment, generally in coastal areas. There are a very large number of species around the world, belonging to several phylogenic groups. Broadly, three types of seaweeds are defined according to their pigments, brown seaweeds (e.g., *Laminaria*, *Fucus*, *Sargassum*), red seaweeds (e.g., *Gelidium*, *Palmaria*, *Porphyra*), and green seaweeds (e.g., *Ulva*, *Codium*). Macroalgae differ from other marine plants such as seagrasses and mangroves in that macroalgae lack roots, leafy shoots, flowers, and vascular tissues. They are distinguished from microalgae (e.g., diatoms, phytoplankton, and the zooxanthellae that live in coral tissue), which require a microscope to be observed [49]. With the exception of green seaweeds, terrestrial and marine plants have little in common. This partly explains the unique chemical compositions observed in seaweeds [50]. The marine environment also induces the production of unique chemicals to resist the environmental stresses the plants are subjected to. In one way, seaweeds can be considered as extremophile organisms, especially those located in places with long daily periods of dryness. The vast majority of seaweeds are collected for human consumption and for hydro-colloid production. The Food and Agriculture Organization Guide of United Nations to the Seaweed Industry provides an excellent overview of the seaweed resource and markets worldwide [51].

In their work on red algae (*Gracilaria Sp.* SGR 01) associated endophytic fungus *Daldinia eschscholzii,* a new lactone, Kustiariyah *et al.* have isolated Helicascolide C (**34**), which exhibits fungistatic activity against phytopathogenic fungus *Cladusporium cucumerinum* [52]. Previous reports on marine fungus *Helicascus kanaloanus* have suggested isolation of helicascolide A and B [53]. Various fungal species like *Cladosporium spp.* [54-55], *Nigrospora sacchari* [56], *Bombardioidea anartia* [57], *Xylaria multiplex* [58], *Paraphaeosphaeria sp.* [59], and *Curvularia sp.* [60] are known to produce lactone derivatives such as Cladospolides A–C, Phomalactone, Bombardolides A–D, Multiplolides A–B, Modiolides A–B and ten-membered lactones, which have diverse properties like herbicidal, anti-bacterial, anti-fungal and cytotoxic activities. Cyclic tetrapeptides are isolated from marine bacteria (*Pseudomonas sp.* and *Pseudoalteromonas sp.*) associated with seaweed *Diginea sp.* and the sponge *Halisarca ectofibrosa.* Crude extracts of *Pseudoalteromonas sp.* show anti-bacterial activity against BS and *Vibrio anguillarum* (VA), whereas none of the isolated peptides shows anti-biotic activity [61]. A brown alga (*Sargassum sp.*) associated endophytic fungus ZZF36 extract leads to the isolation of 6-Oxo-de-methyllasiodiplodin (**35**), (*E*)-9-Etheno-lasiodiplo-din (**36**), Lasiodiplodin (**37**), de-O-methyllasiodiplodin (**38**), and 5-Hydroxy-de-O-methylasiodiplodin (**39**). The anti-microbial activities of these compounds have been tested [62]. Ye *et al.* have reported a diketopiperazine dimer, Cristatumin E (**40**), from a fungus *Eurotium* herbariorum HT-2 associated with algae *Enteromorpha prolifera*. Compound **40** shows anti-bacterial activity against *Enterobacter aerogenes* (EA) and EC with the same MIC values being 44.0 μmol·L^{-1}, respectively [63]. Polyoxygenated steroids are well known secondary metabolites from marine macroorganisms, such as corals, sponges, and starfish [64-65]. However, polyoxygenated steroids, especially those containing five or more oxygenated carbons are also reported from marine-derived fungi. In view of this, Gao *et al.* have isolated Penicisteroid A (**41**) from an endophytic fungus *Penicillium chrysogenum* QEN-24S associated with red algae of the genus *Laurencia.* Compound **41** displays potent inhibitory activity against the pathogenic fungus AS with a clear inhibition zone of 18 mm in diameter at the concentration of 20 μg/disk and also mild inhibitory activity against *Alternaria brassicae* (AB) with inhibition zone of 8 mm[66]. Fig. 2 shows the structures of potential metabolites from algal derived microbes.



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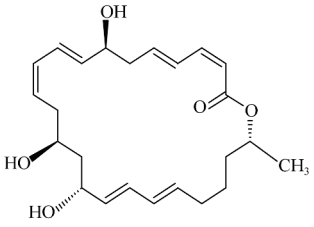

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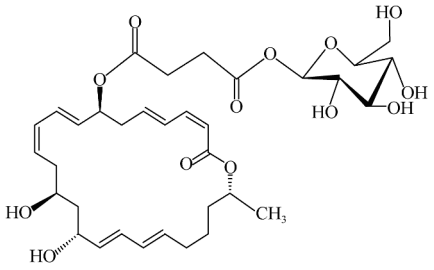

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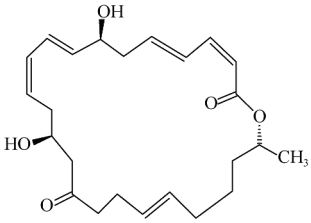

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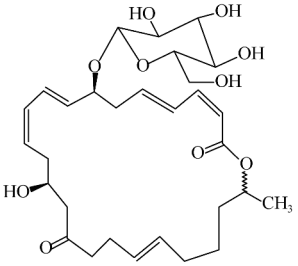

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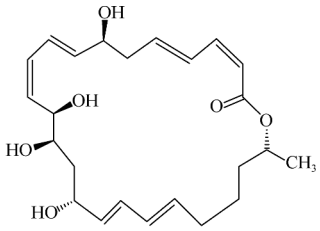

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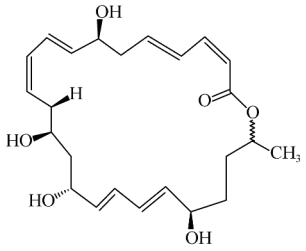

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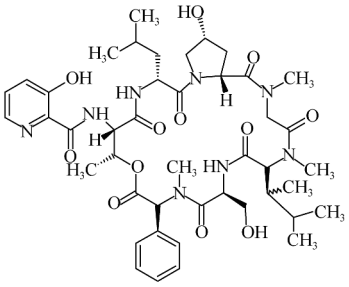

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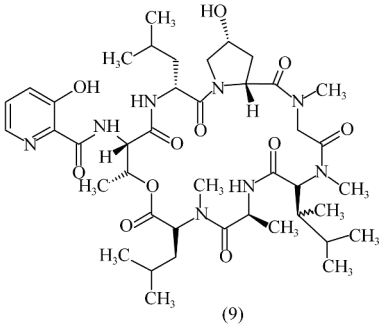

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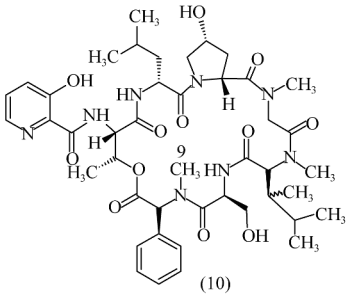

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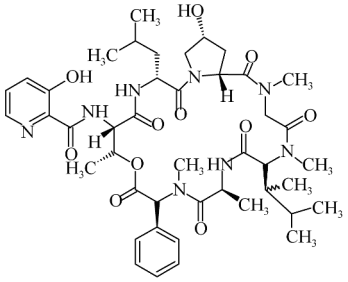

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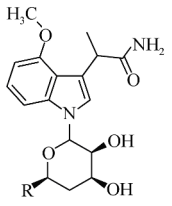
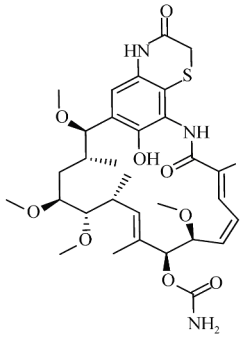


(12, 13)

Kahakamides A R = $COCH_3$

Kahakamides B R = $CONH_2$



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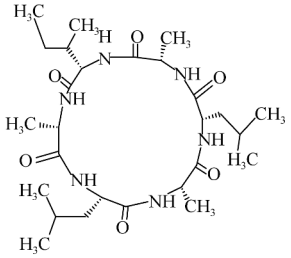

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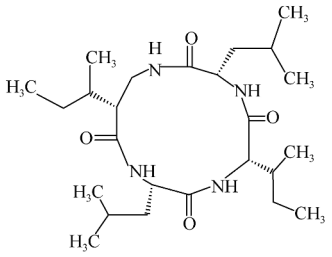

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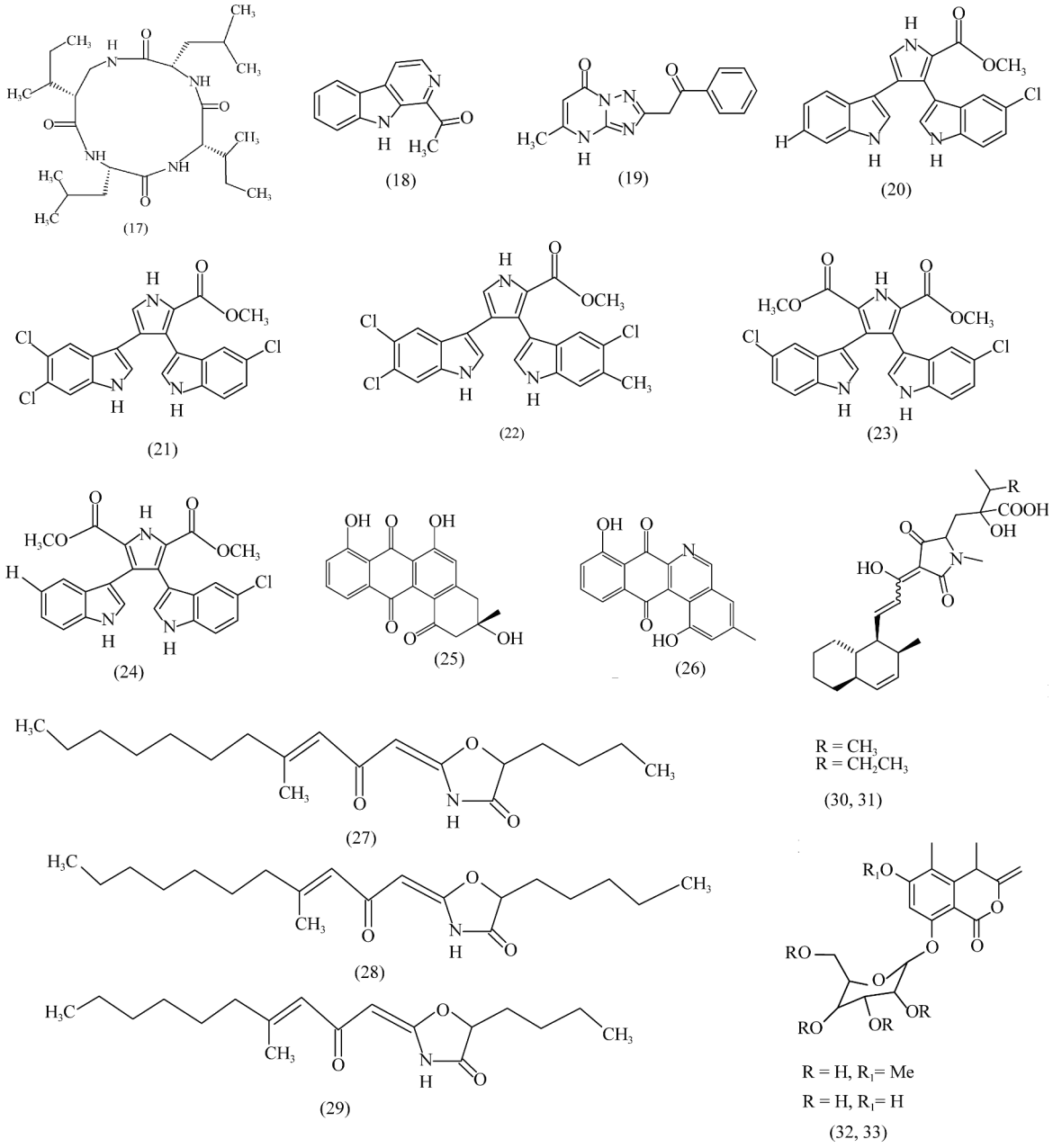

Fig. 1 Anti-microbial compounds from sediment derived microbes

Sponge derived microbes and their metabolites

Numerous natural products from marine invertebrates show striking structural similarities to metabolites of microbial origin, suggesting that microorganisms are the true source of these metabolites or are intricately involved in their biosynthesis [67]. Marine invertebrates like sponges are a rich source of structurally unique natural compounds, several of which have shown a wide variety of biological activities [68]. Sponges harbor a rich diversity of microorganisms in their tissues and in some case constitute up to 40% of the biomass [69]. Many sponges are symbiotic organisms and the content of microbial endosymbionts in them can be very significant and comparable in the mass and volume to the cells of the host. Secondary metabolites of the 18 000 marine natural products described, over 30% of them are from sponges and of the anti-tumor natural product patent registrations in recent years over 75% are from sponges, which may explain at least partly the vast variety of secondary metabolites in sponges [70].

Emericellopsis minima, an endophytic fungi of marine sponge *Hyrtois erecta* secrets a bicyclic sesquiterpene designated as (5*E*)-2-methyl-5-[(1′*R*, 5′*R*)-2-methylidene-7-oxobicyclo-3, 2, 1-oct-6-ylidene]-4-oxopentanoic acid. No anti-bacterial and anti-fungal activity has been observed for tested

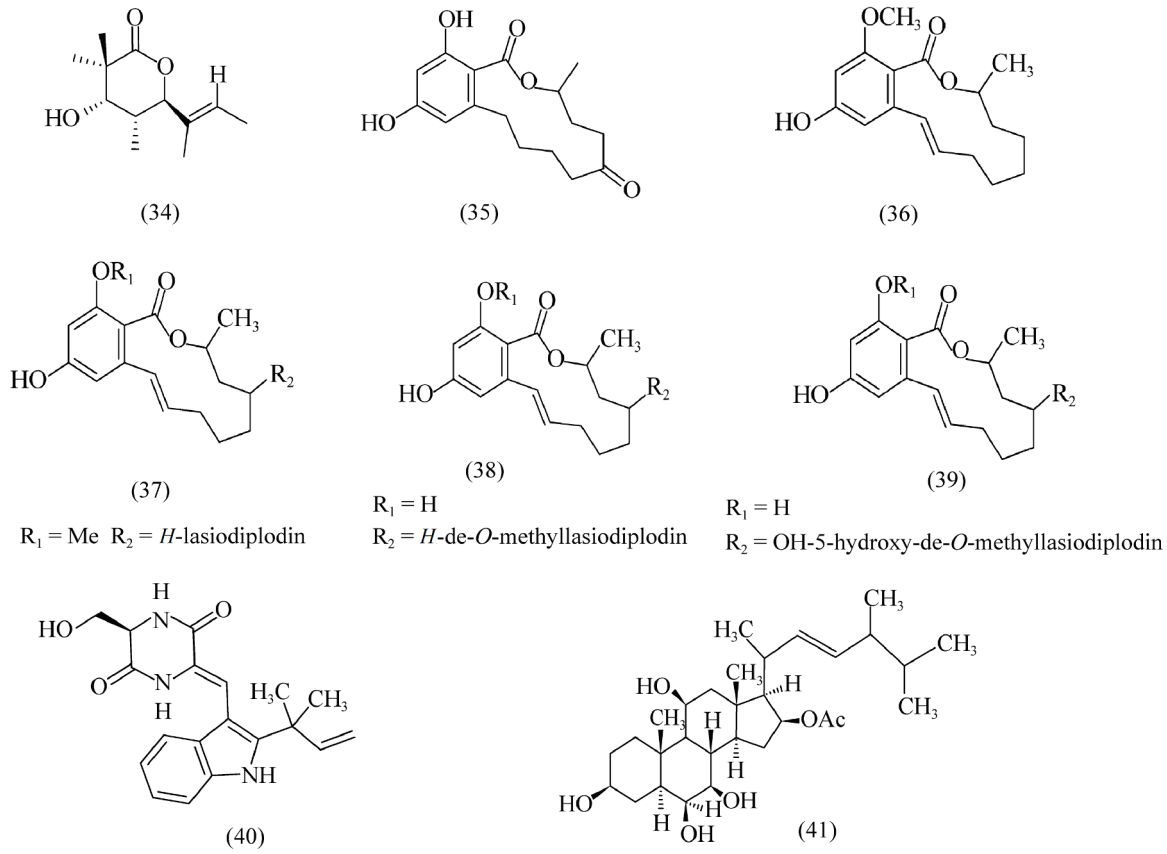

Fig. 2 Anti-microbial compounds from algal derived microbes

organisms [71]. Bioactive anti-microbial metabolites 1-(2, 6-dihydroxyphenyl) pentan-1-one (**42**) and (*Z*)-1-20-(2-butyryl-3-hydroxyphenoxy)-6-hydroxyphenyl)-3-hydroxybut-2-en-1-one (**43**) are isolated from *Cryptopsoriopsis* sps., an endophyte of *Clidamia hirta*. Compound **42** is found to be active against bacterial pathogens with IC_{50} values ranging from 18 to 30 μg·mL^{-1}, whereas compound **43** is active against *Pseudomonas fluoroscens* (PF) with IC_{50} being 6 μg·mL^{-1} [72]. A novel diketo piperzine dimer, Eurocristatine (**44**), has been isolated from sponge associated endophytic fungus *Eurotium cristatum* KUFC7356. Compound **44** does not exhibit anti- bacterial or anti-fungal activity [73]. Endophytic bacterial sps. *Arthobacter, Micrococcus* sp., an unknown *α*-proteobacteria, *γ*-proteobacteria (*Vibrio, α-Pseudoalteromomnas*) and a novel *Bacillus* sps. are isolated from two sponge species *Aplysina aerophoba* and *Aplysina cavernicola*. The sponge isolates show anti-microbial activities against Gram-positive and Gram- negative bacteria and MRSA and *Staphylococcus epidermis* (SE) strains [74]. Two epibiotic bacterial strains, *Rhodococcus* sps. and *Pseudomonas* sps., have been isolated from marine sponge *Petrosia ficiformis*. Both isolates exhibit antimicrobial activity [75]. An endosymboint bacterium, *Enterobacter* sp. TTAG, is isolated from marine sponge *Dysidea granulose*. Crude extracts of bacteria LB3 show significant anti-bacterial activity against clinical pathogens *SA*, *EC, Salmonalla typhi* (ST), *Klebiesella pneumonia* (KP) with lowest MIC being 5 mg·mL^{-1} [76]. Marine sponge associated furmicutes (*Bacillus & Virgibacillus* sps.), *α*-proteobacteria (*Pseudovibrio* sps.), and *γ*-proteobacteria (*Pseudomonas & Stenostophomonas*) have been isolated. The bacterial strains *Pseudomonas fluorescens* H_{40} and H_{41} and *P. aeruginosa* H_{51} exhibited anti-microbial activity against Gram-positive and Gram-negative bacteria, including Vancomycin resistant *Enterococcus faecium* (VREF) and multidrug resistant *Klebsiella pneumoniae* (MDRKP) [77]. *α*-Campholene aldehyde (**45**) and Lucenin-2 (**46**) have been obtained from *Aspergillus ochraceus* MP2, fungi of a marine sponge. Both 45 and 46 show significant anti-microbial activity against potential human pathogens [78]. The fungus *Curvularia lunata*, isolated from the marine sponge *Niphates olemda*, is the source of 1, 3, 8-Trihydroxy-6-methoxy anthraquinone, Lunatin (**47**) and amodified bis anthraquinone, Cytoskyrin-A (**48**). Both **47** and **48** have been found to be active against SA, EC, and BS but inactive against CA [79]. A culture of the fungus *Emericella variecolor* isolated from a sponge collected in the Caribbean Sea off Venezuela has yielded an anti-microbial metabolite, Varixanthone (**49**) which displays anti-

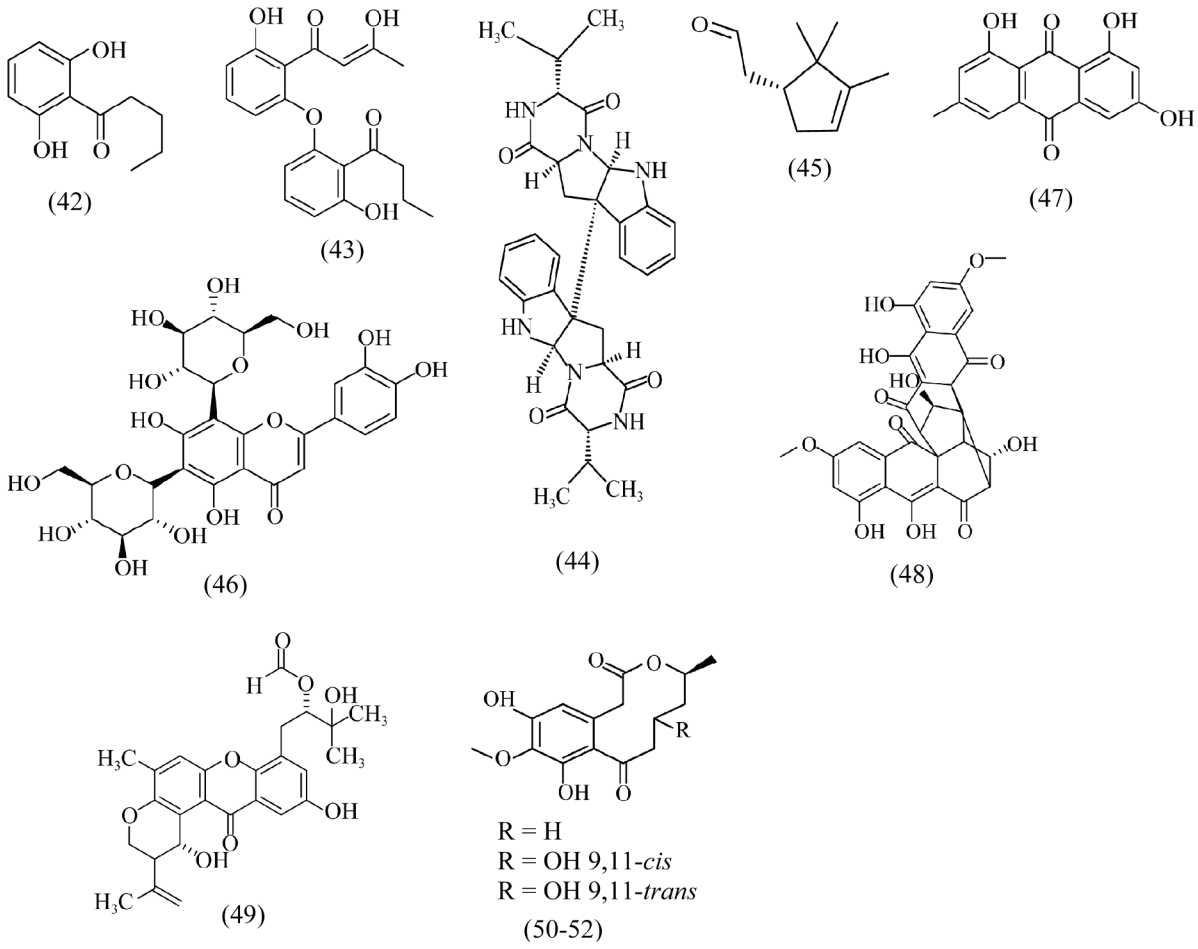

Fig. 3 Anti-microbial compounds from sponge derived microbes

microbial activity against a range of bacteria [80]. The marine sponge *Xestospongia exigua* collected from the Bali Sea, Indonesia, is the source of fungal isolates of *Penicillium cf. montanense*. Cultures of these isolates give the Xestodecalactones A−C (**50**−**52**). Xestodecalactones have been found to be active against CA [81]. The structures of some metabolites from sponge derived microbes are shown in Figure 3.

Coral derived microbes and their metabolites

Almost all corals are colonial organisms; they are composed of hundreds to hundreds of thousands of individual animals, called polyps [82-83]. Coral reefs are the most diverse of all marine ecosystems, although most of this diversity remains uncharacterized [84]. Coral reefs support more species per unit area than any other marine environment, including about 4 000 species of fish, 800 species of hard corals, and hundreds of other species. This biodiversity is considered a key to finding new medicines for the 21st century. Many drugs are now being developed from coral reef animals and plants as possible cures for cancer, arthritis, human bacterial infections, viruses, and other diseases.

Wen *et al.* have isolated a yellow pigmented endophytic bacterial strain *Pseudoalteromonas flavipulchra* from marine coral *Montipora aequituberculata*. Anti-biogram assay of the strain shows potent anti-bacterial activity against MRSA which is mediated by generation of hydrogen peroxide through its activity of L-amino acid oxidase [85]. Alkylresor**cin**ols are found in many living organisms such as lower and higher plants, algae, sponge, and microbes and are important in many aspects of cell biochemistry and physiology [86]. A new alkylresorcinol containing sulfoalkyl side chain, Sulfoalkylresorcinol (**53**), has been reported by Kanoe *et al.*, from a coral derived fungus *Zygosporium* sp. KNC52. This compound exhibits mild anti-microbial activity against *Mycobacterium tuberculosis* (MT), *Mycobacterium bovis* (MB) and *Mycobacterium avium* (MA) with the same MIC being 166 μg·mL^{-1}, respectively. It also inhibit the growth of PA and MRSA strains with the same MIC_{50} being 12.5 μg·mL^{-1}, respectively. It is also mentioned that, anti-bacterial mechanism is due to the inhibition of the *in vitro* polymerization of FtsZ. a protein which is a structural homolog of eukaryotic tubulin and that participates in bacterial cell division [87]. Cyclopentapeptides, Versicoloritides A−C (**54**−**56**), a new orcinol tetramer, Tetraorcinol A (**57**) and two new lactones, Versicolactones A and B have been isolated

from a coral associated fungus *Aspergillus versicolor* LCJ-5-4. All the compounds show good anti-microbial activity against bacterial and fungal pathogens as shown in Table 1 [88]. Fig. 4 depicts the anti-microbial compounds from coral associated microbes.

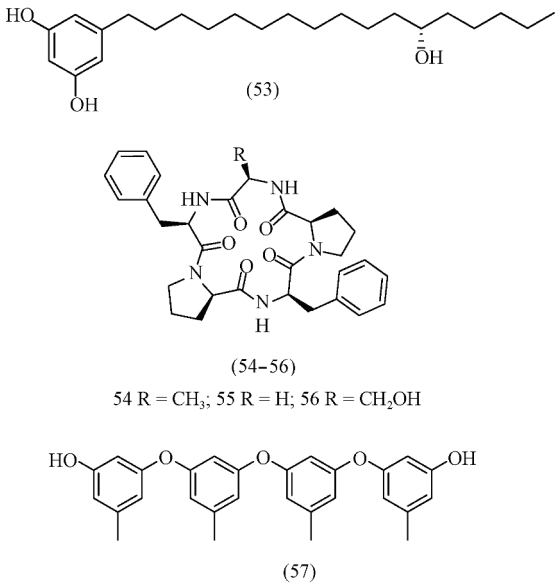

Fig. 4 Anti-microbial compounds from coral associated microbes

Bryozon derived microbes and their metabolites

Bryozoans are one of the most abundant types of marine animal fossils, and they are also common inhabitants of marine and fresh water today. Bryozoans are almost entirely colonial [89] andareunique among animals in that many of them have "disposable bodies". The body of the animal, called the "polypide", is only a part of the whole organism, as the body lives in a structure called the "cystid" [90]. The ma rine bryozoans are represented in all seas by individuals from two classes, *Stenolaemata* and the *Gymnolaemata* [91]. Three Gram-negative bacteria, flavobacteria, α- and γ-proteobacteria and a Gram-positive acti-nobacteria have been isolated from marine *Bryozoan* sps. Approximately 30% of the 340 bacteria isolated from the bryozoan samples show anti-bacterial activities against at least one indicator strain as shown in Table 1. BS is inhibited by 84%, *Staphylococus lentus* by 67% and EC by 4% of all active isolates. A total of 50% of the strains are active against Gram-positive indicator bacteria. No inhibitory activity against *Candida glabrata* (CG) is observed [92].

Miscellaneous marine microbes and their metabolites

Figure 5 depicts the structures of potential anti-microbial metabolites from miscellaneous marine derived microorganisms. Carneamides A−C (**58**−**60**), Carnequinazolines A−C (**61**−**63**), Carnemycin A (**64**), B (**65**) and a drimane sesqueterpenoid have been isolated from marine derived fungus *Aspergillus carneus* KMM 4638. These compounds exhibit anti-microbial activity against the tested organisms [93]. A novel anti-biotic compound 2, 2', 3-tribromophenyl-4, 4'-dicarboxylic acid has been isolated from a marine *Pseudoalteromonas phenolica* O-BC30. This compound exhibits anti-MRSA activity againstten clinical isolates of MRSA with MIC's ranging from 1− 4 μg·mL^{-1}. A high activity is also found against BS & *E nterococcus serolicida* (ES) [94]. Novel *C*-glycosylated benz [α] anthraquinone derivatives Urdamycinone-E (**66**), Urdamycinone-G (**67**), and dehydroxyaquayamycin (**68**) have been isolated from the marine derived *Streptomycetes* sps. BCC45596. These compounds exhibit potent anti-tubercular activity with MICs ranging from 3.13−12.50 μg·mL^{-1} [95]. A novel lipopeptide anti-biotic, Tauramamide (**69**), as its methyl and ethyl esters, has been isolated from marine bacterial isolate *Brevibacillus laterosporus* PNG276. Compound **69** and its ethyl ester show potent and relatively selective inhibition of pathogenic *Enterococcus* sp. (Ecs) with MIC being 0.1 μg·mL^{-1} [96]. *Nocardiopsis dassonvillei* HR10-5, a marine-derived actinomycete, produce three new α-pyrones, Nocapyrones E−G (**70**−**72**). These pyrones show anti-microbial activity against BS with MIC values being 26, 14, and 12 μmol·L^{-1}, respectively [97]. Branched filamentous cynanobacteria belonging to stigonamataceae are known to secrete isonitrile-containing indole alkaloids. To date, four classes of tetracyclic and pentacyclic indole alkaloids Viz. Hapalindoles [98], Ambiguines [99], Fischerindoles [100] and Welwitindolinones [101] have been identified. Anti-microbial 12-*epi*-Hapalindole-H, Ambiguine-A isonitrile (**73**), Ambiguine-B isonitrile (**74**), Ambiguine-D isonitrile (**75**), Ambiguine-E isonitrile (**76**), and Ambiguine-F isonitrile (**77**), have been previously isolated from *Fischerella ambigua* [99]. Following this, Avi Raveh *et al.* have isolated Ambiguine-H isonitrile (**78**), Ambiguine-I isonitrile (**79**) from marine *Fischerella* sp.. These compounds possess anti-bacterial and anti-mycotic activities. The MIC values of **78** and **79** are shown in Table 1 [102]. Bioassay-guided fractionation of marine cyanobacterium *Fischerella ambigua* (UTEX 1903) has yielded Ambiguine K−O isonitriles. Ambiguine-K and M isonitriles show the most potent activity against MT, with MIC values being 6.6 and 7.5 μmol·L^{-1}, respectively [103]. A marine fungal strain WZ-4-11 of *Aspergillus carbonarius* produces dimeric naphtho-γ-pyrones namely 8′-O-Demethylnigerone (**80**), and 8′-O-Demethy-lisonigerone (**81**). Both compounds show weak antimyco-bacterial activities against MT, with MIC values being 43.0 and 21.5 μmol·L^{-1}, respectively [104]. Two prominent metabolites, Marinopyrroles A and B (**82** and **83**), have been isolated from a fraction of obligate marine *Streptomyces* strain. Both compounds display anti-microbial activity against MRSA strains with MIC_{90} values being 0.61 and 1.1 μmol·L^{-1} respectively [105]. A marine gliding bacterium *Rapidithrix* sp. produces polyketide non-ribosomal peptide anti-biotics, Ariakemicins A and B (**84** and **85**). The antibiotics selectively inhibit the growth of Gram-positive bacteria as shown in Table 1 [106].

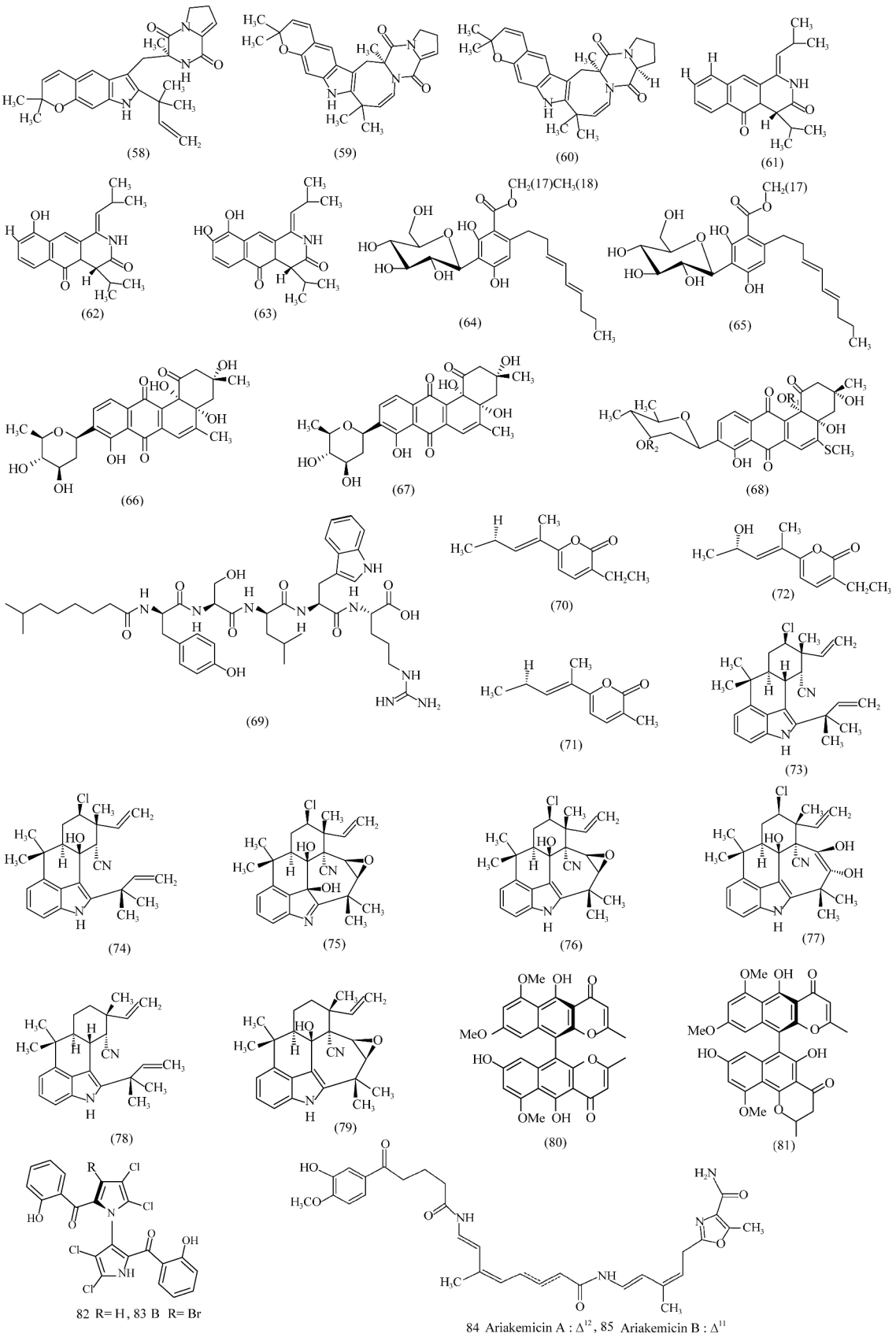

Fig. 5 Miscellaneous marine microbes and their metabolites

Conclusion

Contemporary trends in drug discovery from natural sources emphasize investigation of the marine environment to yield numerous, often highly complex chemical compounds [107]. Marine natural product research continues to be an important cornerstone for anti-microbial drug discovery. With modern advances in selective organic synthesis, ribosome crystallography, chemical biology tools for target elucidation, and novel methods for uncovering new natural products, this area can continue to provide new medicines towards unmet medical needs [108].

Many studies have proven that marine microorganisms produce novel secondary metabolites as a resistance mechanism to overcome pathogenic invasion [109]. So far, a great number of anti-microbial compounds have been found in a handful of the one million different microbial species [110]; it is believed that searching for natural products synthesized by microorganisms could be a promising way to solve the problem of microbial resistance to some commonly used drugs [111] and meet the emergency demand of discovering highly effective, low toxicity, and no environmentally impacted anti-biotics to fight against resistant microbial species. Although plenty of anti-microbial compounds have been isolated from marine sources, non-specific toxicities in humans, partly known biosynthetic pathways, and poor yield of anti-microbial compounds, limit the research in this area. However, optimization of fermentation conditions that has been found to show bioactivity in order to enhance the yield of active substances synthesized by microbes and to search for the regulatory gene in biosynthesis pathway of anti-microbial compounds and use genetic engineering technology to increase the production of anti-infective substances should be intensively studied in the future. The urgent need for new pharmaceuticals for the treatment of cancer, HIV, and other infectious diseases, and other diseases, demands a vigorous exploration of all approaches to exploiting the fungal and bacterial metabolites from marine sources.

Acknowledgements

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Abbreviations:

BS	*Bacillus substilis*
SA	*Staphylococcus aureus*
MRSA	Methicillin-resistant *Stephyllococcus aureus*
CA	*Candida albicans*
TR	*Tricophyton rubrum*
EC	Escherichia coli
PA	*Pseudomonas aeruginosa*
ML	*Micrococcus luteus*
MSSA	Methicillin sensitive *Stephyllococcus aureus*
SE	*Staphylococcus epidermidis*
MDRSE	Multiple drug resistant *Staphylococcus epidermidis*
Pen-S	Penicillin sensitive *Streptococcus pneumonia*
Pen-R	Penicillin resistant *Streptococcus pneumonia*
VREF	Vancomycin-resistant *Enterococcus faecium*
HI	*Haemophilus influenza*
PM	*Pneumococcus mirabilis*
KP	*Klebiesella pneumonia*
CM	*Candida maltose*
VA	*Vibrio anguillarum*
SE	*Salmonella enteritidis*
FO	*Fusarium oxysporum*
BL	*Bacillus licheniformis*
MP	*Mycobacterium phlei*
AC	*Acinetobacter calcoaceticus*
EA	Enterobacter aerogenes
AN	*Aspergillus niger*
AB	*Alternaria brassicae*
PF	*Pseudomonas fluoroscens*
ST	*Salmonalla typhi*
MDRKP	Multidrug resistant *Klebsiella pneumoniae*
SP	*Salmonella pneumonia*
MT	*Mycobacterium tuberculosis*
MB	*Mycobacterium bovis*
MA	*Mycobacterium avium*
SL	*Staphylococcus lentus*
CG	*Candida glabrata*
BC	*Bacillus cereus*
Ecs	*Enterococcus* sp.
SAlb	*Staphyloccocus albus*
SC	*Saccharomyces cerevisia*
Brb	*Brevibacterium* sp.
Cm	*Cytophaga marinoflava*
Pv	*Pseudovibrio* sp.
AC	*Arthrobacter citreus*
BB	*Bacillus brevis*
CI	*Corynebacterium insidiosum*
Ss	*Streptomyces sp*.

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