Abstract

Marine floras are highly diverse and productive. Few marine ecosystems are expected to show higher biological diversity than in tropical rain forests. They are chemically different from terrestrial flora and can withstand adverse marine conditions. The production of unique chemicals has diversified further due to the continuous evolution of marine flora with the change of environmental conditions since billions of years ago. They demonstrate a worthy resource for novel potent drugs that might prove to be economical, safer, and useful medicine for dreadful human diseases. They are rich sources of bioactive compounds such as polyphenols and sulfated polysaccharides that have antimicrobial, antioxidant, antitumor, and disease-healing properties. Plant products are widely used since old times as natural medicines and after the exploration of marine floras discovery of marine medicines has also increased. Here, in this chapter, we present the latest developments on drugs originated from marine natural products and their usages.
9.1 Introduction

Drugs are a boon to ensure the continual of the human race generation after generations. Drug discovery from natural sources is perceived to be much more sustainable and diverse as compared to artificial means. This is because the natural sources undergo continuous change and coevolve in response to the dynamic external environment; as a result, they are the answers to the most complex, resistant, and incurable diseases. Multiple drug resistance in the treatment of cancer and infectious diseases like tuberculosis is progressing at a frightening rate. A number of drugs developed in past years are failing to live up to the dynamic status of the microbes causing these diseases. Thus, with the increasing complexity of the world the diseases get more and more complex and resistant to cures. An exploration for new drugs is the need of the hour. Thus, under these circumstances, discovering the biomedical potential of natural products can serve the purpose. Natural products have provided an endless source of medicine since prehistoric times. A vast array of phytochemicals with potential biological activity have been identified that confer therapeutic and pharmacological effects. In spite of the huge diversification of drug discovery technology, natural products from plants and other biological sources remain an undiminished source of new pharmaceuticals. Amongst plants, marine flora has been an excellent source of a wide range of bioactive compounds with exceptional biological activities (Wratten et al. 1977; Faulkner 2002). The hidden reserves of the marine environment, the ocean provides society with an essential biomedical resource through the rich diversity of marine organisms. Many marine organisms have contributed to biomedicine (novel antibiotics, anti-inflammatory agents, and anti-neoplastic drugs) through the unique molecules they produce (Blunt et al. 2016).

Marine plants have evolved and adapted to life in a largely stable but extremely harsh environment, which has led to the development of many unique chemical features that are not found in terrestrial plants. The marine environment is characterized by high concentrations of halogens, mainly in the form of chloride and bromide salts. Other chemical entities, such as sulfate, are also found in high concentrations. Marine plants use these elements in biosynthetic pathways to produce phytochemicals such as halogenated terpenes, acetogenins, and alkaloids which are unique to the marine environment. Adaptation to wave shock and ocean currents peculiar to the marine environment has resulted in the synthesis of complex polysaccharides (complex sugars) which play a vital role to reduce the surface tension of seawater (Kathiresan et al. 2008). As these constituents are generated and accumulated in response to a set of very unique and distinct environmental conditions and genetic compositions, they emphasize the insurmountable potential
of marine plants. In addition, many of the marine organisms are largely dependent on chemical defense due to lack of protective shield and locomotor organs; they synthesize diverse chemical compounds to discourage predators and competitors and also to paralyze their prey. Moreover, the ocean comprises nearly 72% of the earth’s surface and is immensely rich in biodiversity with marine flora comprising cyanobacteria, fungi, microalgae, seaweeds, mangroves, and other halophytes. Together all of them form a great reserve that has a profound potential to be explored in the field of drug discovery. With the advent of the modern chemical and molecular genetics technologies, these reserves can be investigated to procure a number of resources, including medicinal products, cosmetics, foods, industrial chemicals, and other environment-friendly products (Sithranga et al. 2010).

During the late 1960s, pioneering initiatives to extract drugs from the sea began. In earlier times strange episodes of memory loss reported by a fisherman were attributed to a bloom of a dinoflagellate, *Pfiesteria*. Gradually, over a period of time it has all culminated into the announcement of a new cancer-fighting drug isolated from a marine organism, this reemphasizes the potential of the ocean to benefit human health (Javed et al. 2011). Thousands of medicinally important compounds have been obtained from organisms dwelling in the sea with hundreds of novel natural products being added up to the list every single year. The use of marine floras for pharmaceuticals can be traced back to ancient times in many of the Asian countries like India, China. Since the seaweeds especially brown seaweeds are the good reservoir of iodine and hence consuming them as food source assures least incidence of goiter and glandular diseases. Moreover, maritime countries have been utilizing seaweeds as antiheminthic, anesthetics and ointment and also for the curing of cough, wounds, gout, goiter, etc., since ancient times. Many societies, particularly those in the Indo-Pacific region and Asia, have developed important uses for marine algae. As man has become more aware of the unique chemical composition of marine algae, numerous additional products have been developed. Numerous species of marine algae are used in many countries such as China as herbal medicines to treat many maladies, ranging from intestinal problems to sunstroke. During the recent past, many marine natural products have been identified that are in the preclinical or early clinical stage and some are already in the market. Marine flora have recently received attention for exploration because of their diversity and are being appreciated as a rich source of natural chemical compounds for the unearthing of more efficient drugs against complex and incurable diseases (Sithranga et al. 2010). In this chapter, we discuss about the promising use of natural products coming from marine flora as a natural medicine against human diseases but also about their potential to limit infections.
9.2 Natural Products from Marine Algae That Can Be Used as Drugs

Marine algae are a heterogenous group of organisms varying greatly in size from unicellular (3–10 μm) to massive multicellular entities of up to 70 m long. Based on their size, two major types of marine algae have been recognized – microalgae and macroalgae (seaweeds). The class microalgae include mainly blue green algae or cyanobacteria whereas macroalgae comprise brown algae, red algae, and green algae. Organisms belonging to each of this class are great sources of marine natural products that can be utilized as potent leads for new drug discovery.

9.2.1 Potent Natural Drugs from Microalgae (Blue Green Algae/ Cyanobacteria)

Cyanobacteria from the marine environment belong to one of the most primitive and simplest prokaryotic organisms on earth. They can execute photosynthesis and are also adapted to extreme habitats on earth. They are an important component of biogeochemical cycles and represent one of the most crucial components of food chains and food webs in various oceanic ecosystems. Marine cyanobacteria have been explored up to an extent and it has been found to be excellent deliverers of bioactive natural products that can be further explored for its medicinal use for irrepressible diseases such as cancer and AIDS. They are of great interest for the extraction of novel compounds for their application in pharmaceuticals because of their immense biodiversity and their relatively simple growth needs. The use of natural products as an alternative to synthetic chemicals is a renewable, eco-friendly, and much better option, since microbial resistance against conventional antibiotics is growing. However, the use of cyanobacterial compounds as medicine is still under infancy, therefore, further research is recommended in this direction.

There are many cytotoxic compounds obtained from marine cyanobacteria, that are mainly peptides chemically and show inhibitory effect on various cancerous cell lines such as lipopeptides extracted from *Lyngbya* sp. (obynamide, palauimide, lyngbyabellin, ulongamides A, ulongapeptin, apratoxins) (Liu and Rein 2010) and *Symplaca hydnoides* (guamamide, micromide, and tasiamide); and deacetyl- hectochlorin from *Bursatella leachii*. Other bioactive compounds extracted from *Lyngbya* spp. (jamaicamides A-C, lyngbyabellins E, dolabellin, aurilides, wewakpeptins, macrolides) were found to restrict the growth of lung cell line of human (Liu 2009; Liu and Rein 2010). Many other lipopeptides of medicinal value have also been isolated and identified from *Anabena torulosa* (laxophycins) and *Hyalidium* (cyclic depsipeptides) in the recent past. An acyl amide, columbamides from *Moorea bouillinii* has also been identified that has a moderate affinity for cannabinoid receptors. *M. producens* produces bioactive compounds such as hectoramide, hectochlorin, and jamaicamides.

In addition to lipopeptides, terpene alkaloids such as bartolosides from *Nodosilinea* species and *Synechocystis salina* have also been extracted. *Nodularia*
**spumigena** yielded pseudoaeruginosins NS1 and NS2 that are potent trypsin inhibitors. **Okeania** yielded polyhydroxy macrolide, macrolactone, and lipopeptide kurahyne that are antimalarial. Recently, janadolide was identified from **Okeania** sp., which shows activity against **Trypanosoma brucei**. Another cyanobactin, wewakazole, was isolated from **Moorea producens** and it exhibits cytotoxic activity toward human cancer cell lines. In addition, odoamide, a more potent cytotoxic compound, was obtained from a Japanese **Okeania** species, which is active against human cervical cancer cells. Two more cyanobacterial products, coibamide and apratoxin, were also reported which can suppress vascular endothelial growth factor (VEGF and its receptor VEGFR2) expression and show anticancer activity. Anti-fungal compounds, lobocyclamides, were also isolated from marine blue green algae, **Lyngbya confervoides**. Antimalarial agents such as carmabin, dragomabin, and dragonamide were extracted from **Lyngbya majuscula**. Sulfolipid, an anti-HIV compound from **Phormidium tenue**, was also identified. Hectochlorin, microginin-FR1, largamides, and Microcystin-LR were also identified from cyanobacteria and these could be potent remedies against deadly diseases. Marine blue green algae are also valuable for chromophore phycocyanobilin (PCB) and C-phycocyanin (C-PC) with anti-inflammatory activity. These microorganisms are rich source of vitamins, minerals, and amino acids, and many species are used as a dietary nutritional supplement such as **Aphanizomenon flosaquae**, **Coccopedia**, **Cyanidium caldarium**, **Spirulina platensis**, and **Synechococcus elongates**. Hopefully, these bioactive metabolites will serve as good candidates to be utilized in medicinal chemistry and future drug discovery. Moreover, these organisms can further be explored at genome and proteome levels using advanced molecular biology tools and techniques, to figure out genes or gene clusters that are involved in the biosynthesis of these natural products.

### 9.2.2 Potent Natural Drugs from Macroalgae

Macroalgae/seaweeds include members of Rhodophyta (red), Phaeophyta (brown), and Chlorophyta (green) of marine origin. All the species belonging to this class are macroscopic and multicellular. They protect the organisms that are used as food and offer habitat for many marine organisms and also perform photosynthesis and release up to 90% of earth’s oxygen. In addition, they are diverse resources for biologically active natural products such as proteins and polysaccharides that can further be utilized for pharmaceuticals.

### 9.3 Brown Algae (Phaeophyta)

The brown algae comprising the class Phaeophyceae are a large group of multicellular algae, including many seaweeds located in colder waters within the Northern Hemisphere. Most brown algae live in marine environments, where they play an important role both as a source of food and shelter. Most brown algae contain the
pigment fucoxanthin in abundance, giving them characteristic greenish-brown color by masking the effect of other pigments, chlorophyll a and c, b-carotenes and xanthophylls (Bold et al. 1985) and are responsible for the distinctive that gives them their name. Phaeophyceae members are the most complex algae and there are no unicellular or colonial forms in this class. Large brown algae are used as a shelter for some bottom-dwelling animals. They also serve as a substrate for other algae that grow as epiphytes, or plants that grow on other plants. Few macroalgae, Macrocystis and Nereocystis form a canopy called Kelp forests and another one, Sargassum forms floating mats of the Sargasso Sea that provide shelter for many organisms in the sea and allow a high level of diverse organisms to survive. More than 2000 species of brown algae are reported. Some species are important for commercial use because of their medicinal use. Many natural products of medicinal value have been extracted from them (Table 9.1).

### 9.3.1 Cytotoxic Compounds from Brown Algae

Several cytotoxic compounds with potential anti-cancer activities were isolated and identified from the brown algae during past years such as bifurcadiol from Bifurcaria bifurcata (Guardia et al. 1999), Sargol from Sargassum tortile (Numata et al. 1991), Leptosins from the fungus Leptsphaeria species that shelter in association with the Sargassum tortile (Takahashi et al. 1994). Terpenoid C was isolated from Stylopopodium zonale and its methyl ester shows cytotoxic activity (Dorta et al. 2002). Recently, it was reported that Stoechospermum marginatum yields spartane diterpenes, which can induce apoptosis in melanoma cells. Many other cytotoxic compounds have also been isolated from brown algae in the recent past, which are stated in Table 9.1. All these cytotoxic natural products are candidate drugs for cancer treatment.

### 9.3.2 Antimicrobial Compounds from Brown Algae

A meroditerpenoid, methoxybifurcarenone, was isolated and identified from Cystoseira tamariscifolia, which shows a fungicidal effect on three pathogenic fungi of tomato and bactericidal effect on Agrobacterium tumefaciens and Escherichia coli (Bennamara et al. 1999). Another antifungal compound, deoxy lapachol, was also isolated from Landsburgia quercifolia and this compound was cytotoxic to leukemic cells (Perry et al. 1991). Zonarol 140 from Dictyopteris zonaroides was reported to be an antifungal compound (Fenical et al. 1973). Extracts from Dictyota dichotoma displayed antifungal activity against Trichophyton mentagrophytes, Candida albicans, and Fusarium oxysporum. Extracts from seven more species (Dictyopteris delicatula, Dictyota bartayresiana, D. dichotoma, Padina gymnospora, Sargassum plagiophyllum, Spatoglossum asperum, Stoechospermum marginatum) also exhibited antifungal activity. Lobophorolide from Lobophora variegate exhibits antifungal activity against
| Name (Blue-green algae) | Drug/active compound | Source organism | Disease/activity |
|------------------------|----------------------|----------------|-----------------|
| Cyanobacteria          | Obynamide, Palau’imide, Lyngbyabellin, Ulongamides A, Ulongapeptin, Apratoxins | Lyngbya sp | Cytotoxic (cancer cell lines) |
|                        | Jamaicamides, Lyngbyabellins, Dolabellin, Auirilides, Wewakpeptins, Macrolides | Lyngbya sp | Lung cancer |
|                        | Laxophycins, Hyalidium | Anabena torulosa | Antimicrobial, antifungal |
|                        | Guamamide, Micromide, and Tasiamide | Symploca hydnoides | Anticancerous |
|                        | Cyclic Depsipeptides | Hyalidium | Cancer therapeutics |
|                        | Columbamides | Moorea bouillini | Nervous system-related disorder |
|                        | Hectoramide, Hectorchlorins and Jamaicamides, Cyanobactin Wewakazole | M. producens | Anticancerous |
|                        | Bartolosides | Nodosilinea species | No strong biological activities |
|                        | Microcystin | Synechocystis salina | Antibacterial |
|                        | Pseudoaer-Uginosins NS1 and NS2 | Nodularia spumigena | Trypsin inhibitor |
|                        | Poly-Hydroxy Macrolide, Macrolactone and Lipopeptide Kurahyne | Okeania | Antimalarial |
|                        | Odoamide | Okeania | Cytotoxin |
|                        | Depsipeptides Coibamide | Leptolyngbya sp | Tumor growth in a nude mouse |
|                        | Coibamide A and Apratoxin | Lyngbya majuscula | Anticancer |
|                        | Lobocyclamides | Lyngbya confervoides | Antifungal |
|                        | Carmabin, Dragomabin and Dragonamide | Lyngbya majuscule | Antimalarial |
|                        | Sulfolipid | Phormidium tenue | Anti-HIV compound |
|                        | Phycocyanobilin (PCB) and C-Phycocyanin (C-PC) | Spirulina platensis | Anti-inflammatory |
|                        | Yoshi None | Leptolyngbya sp., | Anti-obesity |
|                        | Brown algae | | |
|                        | Meroditerpenoids, Cystodiones G–L and Cystones | Cystoseira usneoides; | Inflammatory inhibitor |
|                        | Cadinane sesquiterpene cadinane-4(15)-ene-1b, 5a-diol | Dictyopteris divaricata; | Anticancer |
|                        | Sesquiterpene | Taonia atomaria | Anticancer |
|                        | Mozukulin A and B | Cladosiphon okamuranus | |

(continued)
| Name                | Drug/active compound                          | Source organism                  | Disease/activity                                      |
|---------------------|-----------------------------------------------|-----------------------------------|------------------------------------------------------|
| Disulfides          | Disopyperis membranacea                       |                                   | Antibacterial, anti-inflammatory activity             |
| Sulfoquinovosyldiacylglycerol (SQDG) | Lobophora species                          |                                   | Antiprotozoal                                         |
| Lobophorenols A–C  | L. rosacea                                   |                                   | Bleaching and necrosis                                |
| Dolastane diterpenes | Canistrocarpus cervicornis                   |                                   | Inhibited HIV-1 (anti-HIV)                            |
| Spartane diterpenes | Stoechospermum marginatum                    |                                   | Induced apoptosis in melanoma cells (cytotoxic)       |
| Red algae           | C15-acetogenins                               | Laurencia marilzae                | Antibacterial, insecticidal, antifungal and antiviral activity |
| Eudesmane           | L. obtusa                                    |                                   | Antimicrobial                                         |
| Brominated eudesmanes (selinanes), brominated cycloeudesmane | L. Pinnata |                                   | Antibacterial, insecticidal                           |
| Brominated indole-related alkaloids | Laurencia similis                          |                                   | Antibacterial                                         |
| Obtusol             | Laurencia dendroidea                          |                                   | Larvicidal (insecticidal)                            |
| 12-epoxyobtusallene IV, obtusallene X, and marilzabicycloallenes C and D | Laurencia marilzae |                                   | Antibacterial                                         |
| Bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (BDDE) | Odonthalia corymbifera |                                   | Antidiabetic agent                                    |
| Mycosporine-like amino acids shinorine and porphyra-334 | Porphyra sp. |                                   | Immunomodulatory effect                               |
| Galaxamide          | Galaxaura filamentosa                        |                                   | Antitumor agents                                      |
| Polyhalogenated monoterpenes, (-)-anverene  | Plocamium cartilagineum                    |                                   | Antibacterial                                         |
| Bromophenol         | Odonthalia corymbifera                       |                                   | Antimicrobial                                         |
| Palytoxin           | Chondria armata                               |                                   | Insecticidal                                          |
| Meroterpenoids      | Hypnea musciformis                            |                                   | Anti-oxidative                                        |
| Polyhalogenated indoles Halogenated indoles | Rhodophyllis membranacea |                                   | Antitumor, antimicrobial, antioxidative, and antioxidant |
| Green algae         | Sesquiterpene chlorellatin A and ergosterol derivatives chlorellatin B | Chlorella sorokiniana | Antibacterial and Antifeedant (continued) |

(continued)
Dendrophylla salina, Lindra thalassiae, and C. albicans (Kubanek et al. 2003). Few sesquiterpenes were isolated from Dictyopteris divericata and Taonia atomaria, which were capable of inhibiting bacterial adhesion and barnacle settlement. Extracts of Dictyopteris delicatula, Padina gymnospora, Sargassum tenerrimum, Turbinaria conoides, and Zonaria crenata of the Phaeophyceae exhibited broad-spectrum activity.

A very important compound, diacetoxy–8-hydroxy2,6-dollabeladiene, which is a dollabelladiene derivative was isolated from Dictyota pfaffi (Barbosa et al. 2004) and it exhibited potent anti-(herpes simplex virus) HSV-1 activity and slight inhibition of HIV-1 reverse transcriptase. Similarly, a diterpene from D. menstrualis (Pereira et al. 2002) displayed antiretroviral activity. Dolastane diterpenes obtained from Canistrocarpus cervicornis was found to be active against HIV-1 (Bunt et al. 2016). Additionally, many of the antimicrobial compounds have been reported recently (Table 9.1) that can be utilized for new drug discovery against pathogenic strains of viruses, bacteria as well as fungi.

9.3.3 Other Compounds with Medicinal Value from Brown Algae

Dictyopteris membranacea produces a series of six disulfides and two known disulfides that displayed anti-inflammatory activity. Several prenyl toluquinones from Cystoseira crinite exhibited potent radical-scavenging effects (Fisch et al. 2003) and a phlorotannin, eckstolonol from Ecklonia stolonifera had antioxidant property (Kang et al. 2003). Recently, it was reported that Cystoseira usneoides yields meroditerpenoids, cystodiones, and cystones along with eight known meroditerpenes with antioxidant and anti-inflammatory activity. Phlorotannins, phlorofucofuroecko, from Ecklonia stolonifera isolated the brown alga Ecklonia stolonifera shows antihypertensive activity. Meroterpenes extracted from brown algae possess anti-adipogenic and pro-osteoblastogenic activities and have been found to be active against Leishmania amazonensis. Fucosterol from Pelvetia siliquosa demonstrated antidiabetic activity. Phloroglucinol and its derivatives isolated from Ecklonia stolonifera were reported to be as hepatoprotective agents.

Table 9.1 (continued)

| Name                  | Drug/active compound                      | Source organism       | Disease/activity         |
|-----------------------|------------------------------------------|-----------------------|--------------------------|
| 4-Hydroxy-2,3-dimethyl-2-nonen-4-olide | Ulva. pertusa                          | Anti-inflammatory     |
| Fatty acid esters and carotenoid metabolites | U. intestinalis and U. prolifera          | Antimicrobial         |
| Dimethylsulfoniopropionate and acrylate | Ulva sp.                                | Antifeedant and Antipredatory |
| Astaxanthin and sulfolipids      |                                         |                       |
| Palytoxin               | Chondria armata                           | Insecticidal          |
| Kahalalide F            | Bryopsis sp.                              | Anticancer (phase II) |

*Dendrophylla salina, Lindra thalassiae, and C. albicans* (Kubanek et al. 2003). Few sesquiterpenes were isolated from *Dictyopteris divericata* and *Taonia atomaria*, which were capable of inhibiting bacterial adhesion and barnacle settlement. Extracts of *Dictyopteris delicatula, Padina gymnospora, Sargassum tenerrimum, Turbinaria conoides*, and *Zonaria crenata* of the Phaeophyceae exhibited broad-spectrum activity.

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In the recent past also, many important natural compounds have been obtained from brown algae and all these compounds can prove to be a good lead compounds for new drug discovery (Fig. 9.1).

**9.4 Red Algae**

The red algae are one of the largest and oldest classes of algae, comprising over 8000 species. The majority of species are multicellular and mostly live in intertidal and in subtidal zone of the marine environment. The red color of Rhodophyceae members is because of the presence of two pigments phycoerythrin and phycocyanin in abundance, in addition to chlorophyll a (no chlorophyll b), ß-carotene, and a number of unique xanthophylls (Bold et al. 1985). Red algae are considered to be the most important source of biologically active natural metabolites in comparison to other classes of algae.
9.4.1 Cytotoxic Compounds from Marine Red Algae

A cytotoxic and unique anti-tumor agent, halmon, which is a polyhalogenated monoterpene, was isolated from *Portieria hornemaniii* and this compound is at the clinical stage of drug discovery (Fuller et al. 1992, 1994). Laurinterol from *Laurencia okamurai* induced apoptosis and could cause restricted growth of melanoma cells. Triterpenes, 2-acetoxy-15-bromo-6,17-dihydroxy-3-palmitoyl-neoparguera-4(19), 9 (11)-dienen, teurilene and thyrsiferyl 23-acetate isolated from *Laurencia obtusa* had cytotoxic properties (Suzuki et al. 1985, 1987). Several cytotoxic cyclic monoterpenes were also isolated from *Desmio hornemanni* (Higa 1985) and they show cytotoxic activity against carcinomas. Furoplocamioid C, perfuroplocamioid, pirene and tetrachlorinated cyclohexane extracted from *Plocumium cartilagineum* were active against human tumor cell lines (de Ines et al. 2004). Sulfur-containing polybromoindoles from *Laurenda brongniartii* were cytotoxic to melanoma cell line (Sun et al. 2006). Few monoterpene aldehydes and sesquiterpenes from *Plocumium corallorhiz* and *Laurencia tristicha* were reported to inhibit the growth of esophageal cell line and HeLa cell line respectively. Thyresenol, a polyether squalene-derived product, was isolated from *Laurencia viridis* that shows potent cytotoxic activity and anticancer property. Dehydrothyrsifero from *Laurencia pinnaatifida* induced apoptosis in breast cancer cells.

9.4.2 Antimicrobial Compounds from Marine Red Algae

Sulquinosyl diacyl glycerol from *Gigartina tenella* shows inhibitory activity against HIV-l reverse transcriptase (Ohata et al. 1998). 2,3,6-Tribromo 4,5-dihydroxybenzyl isolated from *Symphyocladia latiuscula* was shown to be active against HSV. Sulfoquinovosyl diacyl glycerol was isolated from *Caulerpa racemose* and *Ishige okamurai*, which exhibited an inhibitory effect on HSV-2 (Wang et al. 2007). Venustatriol, thyrsiferol, and thyrsiferyl 23-acetate were obtained from *Laurencia venusta* and these bioactive compounds showed antiviral activity on vesicular stomatitis virus (VSV) and herpes simplex virus type 1 (HSV-l) (Sakemi et al. 1986). Sesquiterpene hydroquinone, peyssonol A from *Peyssonnelia* species, was found to possess anti-HIV reverse transcriptase activities (Talpir et al. 1994).

Polybrominated indoles from *Laurencia brongniarti* show growth inhibitory activity against *Bacillus subtilis* and *Saccharomyces cerevisiae*. Bromobeckerelide and chlorobeckerelide from *Beckerella subcostatum* and P-hydroxybenzaldehyde, dichloro-acetamide, and 3,5-dinitriguaiacol from *Marginisporum aberrans* showed antimicrobial activity against *Bacillus subtilis* (Blunt et al. 2016). *L. elata* yielded elatol that displayed growth inhibitory activity against pathogenic bacteria *Staphylococcus* epidermis, *Klebsiella pneumonia*, *K. pneumonia*, and *Salmonella* sp. Laurinterol, isolaurninterol, allo-laurinterol, cupalaurenol 3, and 2,3,5,6-tetrbromindol from *Laurencia* species displayed a wide spectrum of antibacterial activity against many pathogenic as well as antibiotic-resistant bacteria.
10-hydroxykahukuene and laurenmariallene from *Laurencia mariannensis* also showed antimicrobial activity. Lanosol enol ether from *Fucus vesiculosus* showed antibacterial and antifungal activity (Barreto and Meyer 2006). Diterpenebenzoic acids, callophycoic acids, and callophycols from *Callophycus serratus* showed adequate levels of antimicrobial, antimalarial, and anticancerous activity (Lane et al. 2007). Cyclic ethers from *Laurencia glandulifera* showed antistaphylococcal activity. Ptilodene, an eicosanoid from *Ptilota filicina* sp., exhibited antimicrobial activity against pathogenic bacteria. Extracts of *Centroceras clavulatum*, *Champia parvula*, *Gelidiella acerosa*, *Gracilaria corticata*, *Hypnea musciformis*, *H. valentiae*, *Laurencia obtusa*, and *Polysiphonia* sp. showed promising broad-spectrum activity (Debbab et al. 2013).

Among all, red algae (examples: *Centroceras clavulatum*, *Gelidiella acerosa*, *Gracilaria corticata*, *Hyalomenia floresia*, *Hypnea musciformis* *Hyalomenia floresia*, *Gelidiella acerosa* *Gracilaria foliifera*, *Hypnea musciformis*, *Hypnea valentiae*, *Gracilaria acerosa*, and *Hyalomenia floresia*) were reported to show the highest antifungal activity. They displayed antifungal activity against pathogenic fungi *Candida albicans*, *Trichophyton mentagrophytes* to a greater extent. (Padmakumar and Ayyakkannu 1997) (Fig. 9.2).

### 9.4.3 Other Compounds with Medicinal Value from Red Algae

Snyderol, a sesquiterpene from *Laurencia obtuse*, was reported to be active against malarial parasite *Plasmodium falciparum*. Chondriamide and its derivatives were extracted from *Chondria atropurpurea* that showed antihelminthic activity. Parguerene and isoparguerene from *Jania rubens* also exhibited antihelminthic activity (Awad 2004). Ceratospongamide, a cyclic heptapeptide from symbiotic *Ceratodictyon spongiosum* with *Sigmadocia symbiotica*, displayed anti-inflammation activity. Vidalols from *Vidalia obtusaloba* were reported to be anti-inflammatory. In addition, tribromo dihydroxy benzyl cyclohexanone from *Symphyocladia latiussula* possesses antioxidant activity. Bromophenols, isolated from *Polysiphonia urceolata* and *Odonthalia corymbifera*, were potent reactive oxygen species scavengers (Li et al. 2007; Duan et al. 2007). Three meroterpenoids from *Hypnea musciformis* with variable anti-oxidative activities were isolated. Palytoxin with insecticidal activity was isolated from *Chondria armata*. Red algae, *Laurencia dendroidea* produce obtusol, which harbors larvicidal activity against the dengue fever mosquito *Aedes aegypti*. *Odonthalia corymbifera* yielded dibromo dihydroxybenzyl ether which can serve as an anti-diabetic agent. Shinorine and porphyra-334 isolated from *Porphyra sp.* possess immunomodulatory effects.

Natural products generated by *Laurencia dendroidea* were studied in detail to investigate sterol biosynthesis pathway and cloning and functional characterization of a cycloartenol cyclase was figured out. Additionally, biological activities of natural products coming from *Gracilaria* spp. were investigated. Synthetic analogues of galaxamide initially isolated from *Galaxaura filamentosa* were
designed and proven as potential antitumor agents. Other synthetic studies such as polyhalogenated monoterpenes, anverene, epoxyobtusallene IV, obtusallene X, and marilzabicycloallenes were also performed (Blunt et al. 2017). Many other natural products with antimicrobial, cytotoxicity against cancerous cells, and other compounds with medicinal value have also been isolated from red algae in the recent past and they are presented in Table 9.1. They have great potential for being utilized in pharmaceuticals.
9.5 Green Algae

Green algae are not only found in freshwater but also in the intertidal zone and in shallow waters of sea, where there are plenty of nutrients and sunlight. Green algae have characteristic green color due to an equal proportion of chlorophyll a and b (Bold et al. 1985). This class of algae is supposed to be more closely related to terrestrial higher plants as compared to any other class. There are many bioactive natural products reported from marine green algae that have potential usage in pharmaceuticals.

9.5.1 Cytotoxic Compounds from Marine Green Algae

A unique brominated diphenyl methane derivative, Isorawsonol, was isolated from Arrainvillia rawsonii, which has antumorigenic and immunosuppressive effects. Communesins, penostatins, cytochalasans, and penochalasins isolated from Enteromorpha intestinals showed cytotoxic activity against lymphocytic leukemia cell. Halimedatrial and other diterpenoid metabolites isolated from Halmida lamouroux have anticancerous and antimicrobial activities. Depsipeptide kahalalide isolated from Bryopsis sp. (Hamann and Scheuer 1993) was found to be active against prostate cancer and HL-60 cell lines and this bioactive compound has been selected for Phase I clinical trials (Dmitrenok et al. 2006).

9.5.2 Antimicrobial Compounds Isolated from Marine Green Algae

A unique diterpene aldehyde halitunal obtained from Halimeda tuna exhibited antiviral activity against murine coronavirus (Koehn et al. 1991). Sphingosine isolated from Indian green alga Ulva fasciata exhibited antiviral activity against semeliki forest virus (SFV) (Garg et al. 1992). Triterpene sulfate esters, Capisterones, extracted from Panicillus capitatus showed antifungal activity against a pathogenic fungus, Lindra thallasiae (Puglisi et al. 2004). The extract of Cladophora fascicularis yielded dibromophenoxy dibromoanisol, a diphenyl ether that shows antimicrobial activity against Escherichia coli, Bacillus subtilis, and Staphylococcus aureus (Kuniyoshi et al. 1985). The extracts from green algae, Caulerpa cupressoides, C. peltata, C taxifolia, Codium arabicum, Enteromorpha intestinalis, Ulva fasciata, and U. lactuca demonstrated activity against pathogenic bacteria Staphylococcus aureus and all the Vibrio species. Bioactive compounds extracted from Caulerpa cupressoides, C. racemosa, Ulva fasciata, and U. lactuca showed broad-spectrum activity.
9.5.3 Other Compounds with Medicinal Value from Green Algae

Cymobarbatol and its derivatives were isolated from the \textit{Cymopolia barbat}, which possess antimutagenic activity (Wall et al. 1989). Ascosalipyrrolidinones isolated from \textit{Ulva} species and its endophytic fungus \textit{Ascochyta salicorniae} was showed antiplasmodial activity. Glucopyranosyl-istigmasta diene isolated from \textit{Ulva lactuca} was found to be anti-inflammatory (Awad in 2000). Caulerpals isolated from \textit{Caulerpa taxifolia} was discovered as an inhibitor of tyrosine phosphatase (Mao et al. 2006). \textit{U. pertusa} yielded 4-hydroxy-2,3-dimethyl-2-nonen-4-olide, which can inhibit cytokine production in dendritic cells. From \textit{Chlorella sorokiniana}, few new marine natural products such as, sesquiterpene chlorellatin, ergosterol-derivative (chlorellatin), and lutein were identified. Dimethyl sulfoxypropionate and acrylate were obtained from an unidentified \textit{Ulva} species, which is used as defensive compounds. The carotenoid astaxanthin and sulfolipids isolated from green algae are also tested for biological activities.

9.6 Potent Natural Drugs from Marine Fungi

Marine fungi are the species of fungi that sustain their life in the marine and estuarine environments. They can be either facultative or obligatory. Facultative marine fungi spent most of their life under terrestrial or freshwater conditions and they are capable of living under marine habitats. Thousands of marine fungi belonging to Basidiomycetes, Ascomycetes, and other classes have been reported from the sea and a large number of species are yet to be discovered. Marine fungi can be saprophytic on dead plants and animals or parasitic on mangroves, algae, or other marine plants. Marine fungi are a recognized source of distinct natural products. There are different techniques or substrate for isolation of marine fungi. It is recommended that chemists should collaborate with marine mycologists in order to procure marine fungi from recognized culture collections.

A number of new bioactive compounds have been reported from marine fungi. Several phenolic compounds like aspergilols were obtained from \textit{Aspergillus versicolor}, which can be used as laxatives, antimalarial as well as antineoplastics. Disulfide-bridged dipeptide, diterpene, norditerpene, decalin derivatives, and long-chain peptaibols, trichoderin were extracted from \textit{Trichoderma}. Trichoderin is an anti-tuberculosis aminolipopeptide. \textit{Penicillium} has yielded a wide range of new metabolites, including meroterpenoids, chrysamides, alkaloids, polyketides, and cerebrosides that can serve as a lead compound for new drug discovery. Sponge-derived \textit{Penicillium sp.} led to the production of some macrocyclic polyketides. Several natural compounds such as monoterpensoids, diterpenoids, sesquiterpenes cyclic dipeptides, phenolics, asteltoxins, alkaloids, pseurotin, and chromone were isolated from \textit{Aspergillus sp}. New metabolites isopyrrolonaphthoquinone and sansalvamide A amide were also obtained from the genera \textit{Biscogniauxia}. A number of new metabolites like diterpene glycosides, steroid, cyclopentanone, chlorogriseofulvin, hexaketide and (-)-orthosporin, polyketide-derived linear and
macrocyclic polyesters, coumarins have also been obtained from different marine fungi that are highly beneficial for pharmaceutical industries.

9.7 Bioactive Compounds from Mangroves and Associated Fungi

The term “mangrove” describes trees or shrubs growing in saline coastal habitats, together they form a “mangrove forest” or “mangrove swamp”. Plants growing in such an environment usually belong to Rhizophoraceae, Combretaceae, Lythraceae, and Avicenniaceae families. Most of them are facultative halophytes that live in the intertidal zone. Mangroves are well adapted to the conditions that present in marine conditions such as change in humidity, high salt, tides, and biotic stresses like the presence of a huge number of microorganisms and herbivores, etc. Having pneumatophores or prop roots is a very critical adaptation possessed by them, which allow them to do a gaseous exchange and they are capable of excreting and storing in salt glands or hairs.

Because of the constant evolutionary force, mangroves are highly diverse both biologically as well as chemically (Strobel et al. 2004). This chemical biodiversity can be highly useful for the isolation of bioactive natural products that can serve as a lead compound for drug discovery. Moreover, they harbor diverse endophytic fungi as symbionts (Anada and Sridhar 2002) that can also be an important reservoir of diverse chemical compounds (Li et al. 2009; Pang et al. 2008). Mangrove, Aegiceras corniculatum has been a rich source of antiplasmodial embelin analogue. Ceriops tagal yielded bioactive compound, dolabranes tagalsin. From the seeds of Xylocarpus moluccensis, tirucallane and tetranortriterpenes were extracted. Additionally, tetranortriterpenoids and limonoids were extracted from Xylocarpus granatum and X. moluccensis respectively.

Endophytic fungi also yield diverse potential bioactive compounds that can be suitable for medical and agrochemical applications such as cyclic depsipeptide isolated from Kandelia candel-associated fungus showed cytotoxic activity against human breast cancer MCF-7 cells when tested in the MTT assay (Huang et al. 2007). Similarly polyketides isolated from a Penicillium sp., a symbiont of Aegiceras corniculatum exhibited cytotoxic activities (Lin et al. 2008). Dichlororesorcinol derivatives extracted from Cosmospora vilior and endophytic Eurotium rubrum exhibited potent antioxidant activity. Endophytic fungus, Lasiodiplodia produced polyketides, preussomerin analogues that can be utilized for medicinal uses. Further, Mucor irregularis was explored for the presence of secondary metabolites, and rhizovarins were isolated. Nectriacids and epicitreoisocoumarinol are two polyketides isolated from Nectria species that showed potent inhibition of α-glucosidase. Neosartoryadins from Neosartorya udagawae exhibited activity against the H1N1 influenza virus. Endophytic Penicillium also generated varieties of metabolites such as diketopiperazines spirobrocazine, brocazine, etc., that are crucial compounds for drug discovery. Brocazine displayed cytotoxic activity against tumorigenic cells and strong pathogenic strain of S. aureus. Other important
metabolites like pestalotiopsis, macrolides, phomopsis, cytochalasins, pseudolagarobasidiu, stemphylium, talaromyces, rhytidhysteron, and chamigrane sesquiterpenes were also extracted from other mangrove-associated fungi (Fig. 9.3).

9.8 Conclusion

Finding natural “eco-friendly” plant products to prevent or treat human diseases will be a better alternative management process in pharmacy. The wealthy and exceptional chemical diversity of natural products has long been a significant reservoir of remedies. Chemical diversity has been associated with biological diversity and the marine environment possesses diverse biota which can provide varieties of chemical compounds that have the potential to be used as medicines. This probability has been an inspiration for the isolation of interesting different chemical compounds, which are unique and extraordinary in nature as compared to the ones that come from terrestrial sources. Marine organisms are subjected to extreme environmental conditions including high salinity, insufficient aeration, hydrostatic pressure,
infection, and predation by other organisms. The adaptations to the harsh conditions can be either physical by conferring motility or chemical. Plants being sessile hugely rely on the chemical defense mechanisms and have evolved phytotoxins and deterrents to enhance their survival to cope up with freely moving predators. Therefore, the potency of the metabolites coming from marine flora is more. Thus, a vast multitude of potential drugs has been isolated from the marine flora with better efficiency and specificity for the treatment of deadly and incurable human diseases. The use of natural products as antibiotics is highly needed as the microbial resistance to these drugs is increasing in humans and animals. Using natural and renewable marine floral compounds is still in its infancy, but considering its importance in the present scenario, further investigation in this direction will surely deliver an effective and sustainable means of disease treatment.

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