

# **Handbook of Marine Macroalgae**

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## **Biotechnology and Applied Phycology**

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# Preface

Marine environment becoming the most explored habitat because of its chemical and biological diversity. Recently, marine floral and faunal exploration and exploitation becoming a great deal of interest which is the key to combat various diseases. Among the marine sources, algae or seaweeds are the more valuable sources of structurally diverse bioactive compounds. Even though, seaweed salads have been supplied as a regular diet, much information is not available whether the algal food has any significance on human health. For example, the beneficial effects of seaweeds and their bioactive substances like phlorotannins, sulphated polysaccharides, peptides and carotenoid pigments extend their applications from eco-biotechnological to the industrial standpoint. Hence, the utilization of marine macroalgal substances as potential biological and industrial products should be well established worldwide to gain various health and medical benefits. Although Asians consume seaweeds because of the known importance in their daily lives, many of the westerners might not think of the 'seaweed' as a nutritional or a daily supplement in their food. It is because of the term 'weed', which generally represents the unwanted plants in any ecosystem. Hence, I would like to introduce a more appropriate term "sea-vegetables" in this book, which could bring a positive notion in human beings to think 'algae' or 'seaweed' as consumable vegetables from sea.

The present book "*Handbook of Marine Macroalgae: Biotechnology and Applied Phycology*", describes the characteristic feature of marine macroalgal substances, source species, types, production and applications (biological, biotechnological, industrial). There are four discriminating parts present in the present book: **Part-I** deals with an overview of introduction and prospects of marine macroalgal introduction, their eco-physiological and biochemical importance along with various aspects of macroalgal biodiversity; **Part-II** provides a general and complex aspects of

isolation, extraction and physicochemical properties of various marine macroalgal compounds; **Part-III** discusses various biological and biomedical applications; **Part-IV** deals an over view on the *in vitro* cultivation other biotechnological prospects of marine macroalgae; and **Part-V** provides the information on the industrial utilization of marine macroalgae with their resource management strategies. Each part is a collection of comprehensive information on the past and present research of marine macroalgae, compiled of proficient scientists worldwide. Although significant activities and applications of marine macroalgal derived substances have been shared by various chapters, specific and unique biological, biomedical and industrial applications have been covered individually. Functional foods I personally intended to mention that the present findings and the recent information in this book will be helpful to the upcoming researchers to establish a phenomenal research from wide range of research areas.

I express my sincere thanks to all the authors, who have contributed in this book and their relentless effort was the result of scientific attitude and immense perseverance descended from their present and past experiences. I am grateful to the experts, who have provided state-of-the-art contributions that are included in this book. I also thank the personnel of Wiley-Blackwell publishers for their continual support, which is essential for the successful completion of the present task.

I hope that the fundamental as well as applied contributions in this book might serve as a potential research and development leads for the benefit of humankind. Altogether, algal biotechnology will be the hottest field in future towards the enrichment of targeted algal species, which further establishes a sustainable oceanic environment. The present book would be a reference book for the emerging students in the academic and industrial research.

Se-Kwon Kim

# Editor

**Se-Kwon Kim**, PhD, is currently working as a professor of marine biochemistry in the Department of Chemistry, Pukyong National University (PKNU), Busan, South Korea.

Dr. Kim received his MSc and PhD degrees from PKNU and joined as a faculty member in the same university. He conducted his postdoctoral research at the Bioprocess laboratory, Department of Food Science and Technology, University of Illinois, Urbana-Champaign, Illinois USA (1988–1989). He became a visiting scientist at the Memorial University of Newfoundland in Canada (1999–2000).

In the year 2004, Dr. Kim became the Director for 'Marine Bioprocess Research Center (MBPRC)' at Pukyong National University. He served as president for the 'Korean Society of Chitin and Chitosan' (1986–1990), and the 'Korean Society of Marine Biotechnology' (2006–2007). Dr. Kim was also the Chairman for 7<sup>th</sup> Asia-Pacific Chitin and Chitosan Symposium, which was held in South Korea in 2006. He is one of the board members of 'International Society of Marine Biotechnology (IMB)' and 'International Society for Nutraceuticals and Functional Foods (ISNFF)'.

He was the editor-in-chief of the Korean Journal of Life Sciences (1995–1997), the Korean Journal of Fisheries Science and Technology (2006–2007) and the Korean Journal of Marine Bioscience and Biotechnology (2006-till date). To the credit for his research, he won the best paper awards from the American Oil Chemists' Society (AOCS) and the Korean Society of Fisheries Science and Technology (KS-FST) in 2002.

His major research interests are investigation and development of bioactive substances derived from marine organisms and their application in oriental medicine, cosmetics and nutraceuticals via marine bioprocessing and mass-production technologies. Furthermore, he expanded his research fields especially in the field of dietary supplements from sea vegetables for the development of anti-diabetic, anti-arthritic, anti-hypertensive, anti-cancer, anti-aging substances towards the health promotion of senior citizens.

To date, he has authored over 450 research papers and holds 72 patents. In addition, he has written or edited more than 30 books.

# **PART I**

## **Introduction to Algae and Their Importance**

# 1

## Biological Importance of Marine Algae

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### 1.1 Introduction

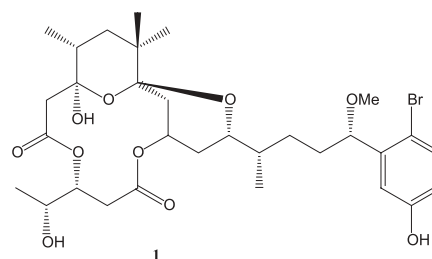
Marine organisms are potentially productive sources of highly bioactive secondary metabolites that might represent useful leads in the development of new pharmaceutical agents (Iwamoto *et al.* 1998, 1999, 2001). During the last four decades, numerous novel compounds have been isolated from marine organisms and many of these substances have been demonstrated to possess interesting biological activities (Faulkner, 1984a,b, 1986, 1987, 1988, 1990, 1991, 1992, 1993, 1994, 1995, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002).

Algae are very simple, chlorophyll-containing organisms (Bold and Wynne, 1985) composed of one cell or grouped together in colonies or as organisms with many cells, sometimes collaborating together as simple tissues. They vary greatly in size – unicellular of 3–10 µm to giant kelps up to 70 m long and growing at up to 50 cm per day (Hillison, 1977). Algae are found everywhere on Earth: in the sea, rivers and lakes, on soil and walls, in animal and plants (as symbionts-partners collaborating together); in fact just about everywhere where there is a light to carry out photosynthesis.

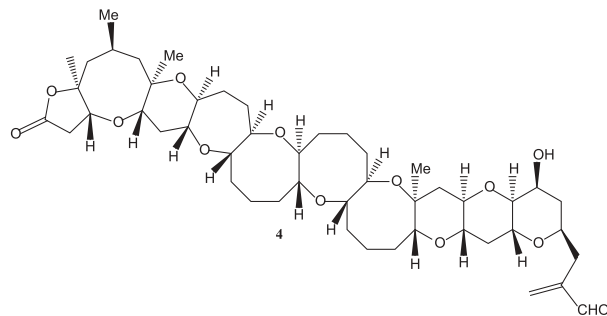
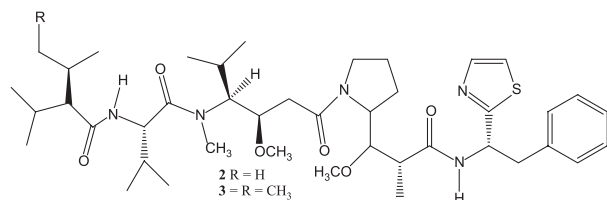
Algae are a heterogeneous group of plants with a long fossil history. Two major types of algae can be identified: the macroalgae (seaweeds) occupy the littoral zone, which included green algae, brown algae, and red algae, and the microalgae are found in both benthic and littoral habitats and also throughout the ocean waters as phytoplankton (Garson, 1989). Phytoplankton comprise organisms

such as diatoms (Bacillariophyta), dinoflagellates (Dinophyta), green and yellow-brown flagellates (Chlorophyta; Prasinophyta; Prymnesiophyta, Cryptophyta, Chrysophyta and Rhaphidophyta) and blue-green algae (Cyanophyta). As photosynthetic organisms, this group plays a key role in the productivity of oceans and constitutes the basis of the marine food chain (Bold and Wynne, 1985; Hillison, 1977).

The true origins of compounds found in marine invertebrates have been a subject of discussion. They may vary from compound to another, but there are strong hints that dietary or symbiotic algae are one of the participants in the production of these metabolites. For example, as early as 1977, the blue-green algae, *Lyngbya majuscula* was recognized as the source of aplysiatoxin 1 found in the sea hares *Aplysia* that feed on this alga (Mynderse *et al.*, 1997). Similarly, a series of highly active antitumor compounds, dolastatin 2 and 3, isolated from sea slugs are considered to be of blue-green algal origin (Shimizu, 2000). Also, eukaryotic algae and various dinoflagellate metabolites are found in shellfish and other invertebrates as toxins (Shimizu, 2000). Brevetoxins 4, ciguatoxins 5, and dinophysistoxins-1&2 and 6 and 7 are well known examples of paralytic shellfish toxins (Hall and Strichartz, 1990).



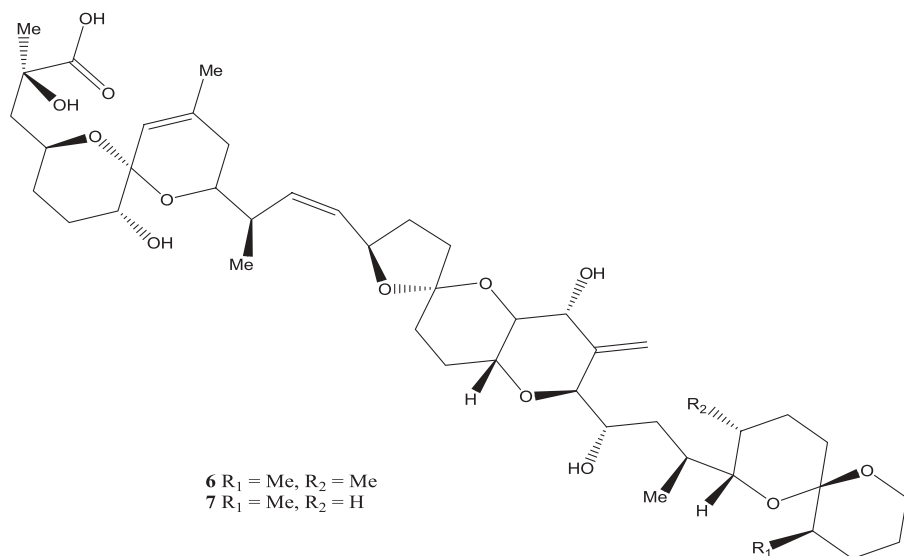
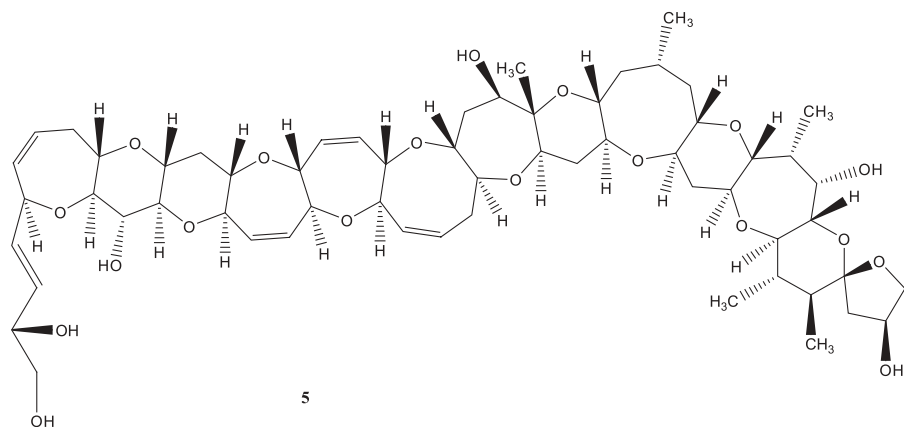
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## 1.2 Interesting natural products and their biological activities from macroalgae (seaweeds)

Marine macroalgae or seaweeds have been used as foods especially in China and Japan and crude drugs for treatment of many diseases such as iodine deficiency (goiter, Basedow's disease and hyperthyroidism). Some seaweeds have also been used as a source of additional vitamins, treatment of various intestinal disorders, as vermifuges, and as hypocholesterolemic and hypoglycemic agents. Seaweeds have been employed as dressings, ointments and in gynecology (Trease and Evans, 1996).

Macroalgae can be classified into three classes: green algae (Chlorophyta), brown algae (Phaeophyta) and red algae (Rhodophyta) (Garson, 1989).



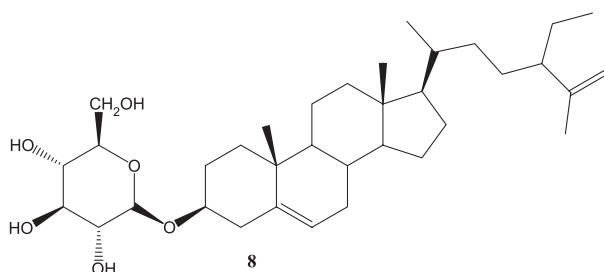


### 1.2.1 Chlorophyta (green algae)

The characteristic green color of green algae is mainly due to the presence of chlorophyll *a* and *b* in the same proportion like higher plants (Bold and Wynne, 1985). There are few reports of novel secondary metabolites among the Chlorophyta than the other algal division; the following are the most important biologically active natural products isolated from these algae.

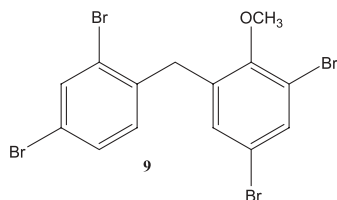
#### Anti-inflammatory substances

An anti-inflammatory, 3- $\beta$ -D-glucopyranosylstigmasta-5,25-diene **8** have been isolated by Awad in 2000 (Awad, 2000) from the green alga *Ulva lactuca*.



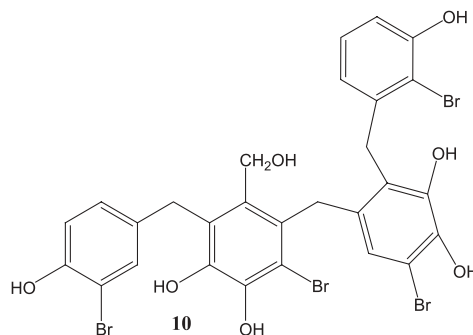
Habu is a deadly snake found in Okinawa where 200–300 people are bitten by the snake every year. A patient must be given immediate medical treatment with the serum prepared from a horse-developed antibody by injection of snake toxin. However, about 20% of the patients are allergic to the serum.

In order to develop an alternative drug, Okinawa Prefectural Institute of Public Health has been conducting screening strategies to find a compound with anti-inflammatory activity, which can be measured by the suppression of inflammation caused by the injection of toxin into a mouse limb. A diphenyl ether **9** isolated from an alga was found to be effective in this assay (Higa, 1989). The extract of the green alga *Cladophora fascicularis* was separated by different chromatographic methods to produce 2-(2',4'-dibromophenoxy)-4,6-dibromoanisole (Kuniyoshi, Yamada and Higa, 1985), the first example of diphenyl ether from green algae. It was also active in inhibiting the growth of *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* (Kuniyoshi, Yamada and Higa, 1985).

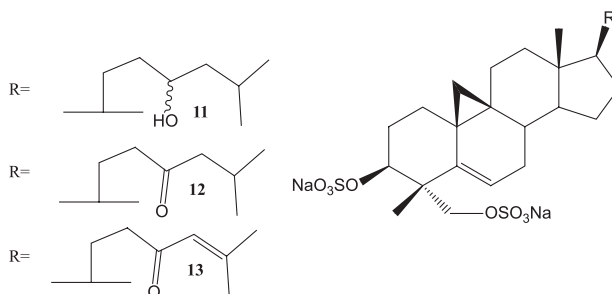


#### Cytotoxic and immunosuppressive activities

Bioassay-guided fractionation utilizing inhibitory activity against inosine 5'-monophosphate dehydrogenase inhibitor (IMPDH) leads to the isolation of a new brominated diphenylmethane derivative. Isorawsonol **10** was isolated from the tropical green alga *Arrainvillia rawsonii* by Chen and colleagues in 1994 (Chen *et al.*, 1994). The activity of IMPDH has been linked with cellular proliferation and inhibition of that enzyme has been demonstrated to have anticancer and immunosuppressive effects (Chen *et al.*, 1994).



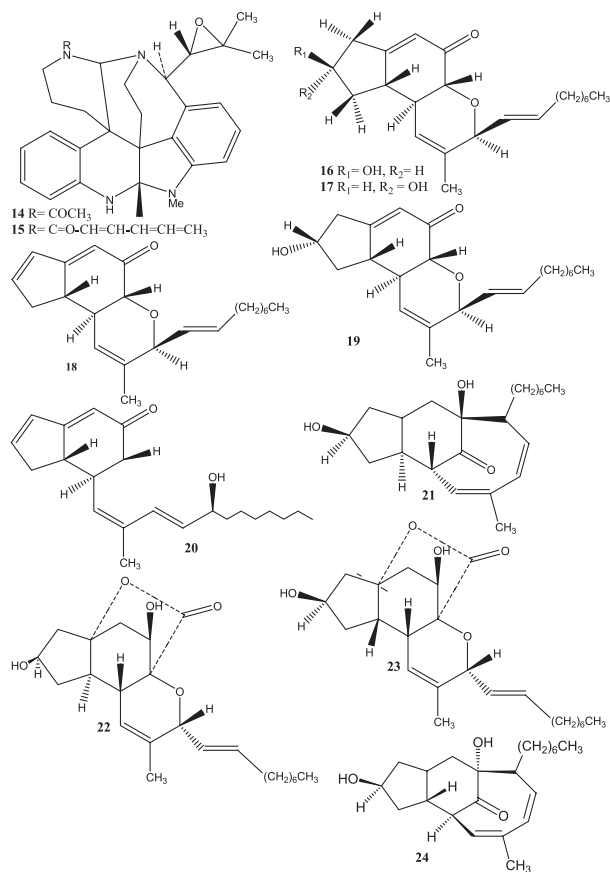
Bioactivity-directed fractionation of the extract of the green alga *Tydemania expeditionis* using the protein tyrosine kinase pp60<sup>V-stc</sup> led to the isolation of three new cycloartenol disulfates **11–13**; they showed modest inhibition of this enzyme (Govindan *et al.*, 1994).



Communesins A **14** and B **15**, exhibiting cytotoxic activity against cultured P-388 lymphocytic leukemia cells, were isolated from the mycelium of a strain of *Penicillium* species stuck on the marine alga *Enteromorpha intestinalis* (Numata *et al.*, 1993).

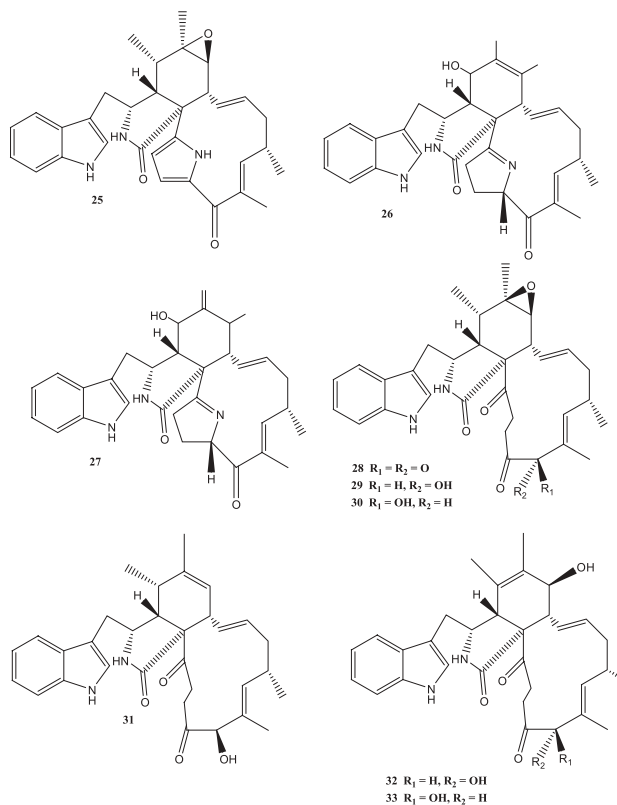
Penostatins A **16**, B **17**, C **18**, D **19** (Takahashi *et al.*, 1996) and E **20** (Iwamoto *et al.*, 1999) have been isolated from a strain of *Penicillium* species originally separated from the marine alga *Enteromorpha intestinalis* (L.) Link (Ulvaaceae). The compounds A–C and E exhibited significant cytotoxicity against the cultured P388 cell line (Iwamoto *et al.*, 1999; Takahashi *et al.*, 1996). Penostatins F, G, H **21–23** and I **24**

were isolated from a strain of *Penicillium* originally separated from the marine alga *Enteromorpha intestinalis* (L.) Link (Ulvaaceae). All the compounds exhibit significant cytotoxicity against cultured P388 cells (Iwamoto *et al.*, 1998).



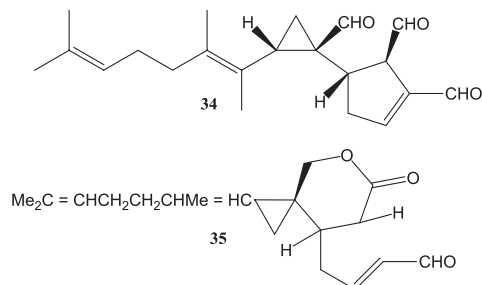
towards reef fishes, and significantly reduces feeding in herbivorous fishes (Paul and Fenical, 1983).

The cyclic depsipeptide kahalalide F **36** was originally isolated from both the mollusc *Elysia rufescens* and from the dietary source, the green alga *Bryopsis* sp. (Hamann and Scheuer, 1993) was introduced into Phase I trials by Pharma Mar as a lead compound against prostate cancer.

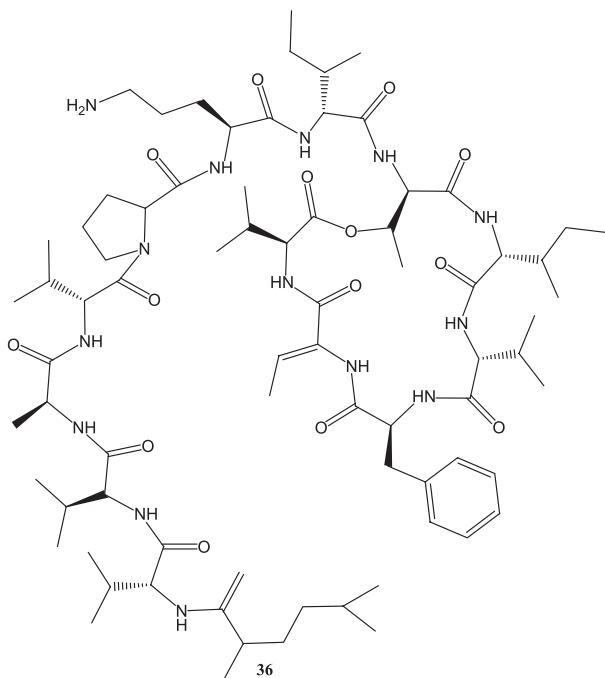


The novel compounds cytochalasins, penochalasins A–C **25–27** (Numata *et al.*, 1996), D–H **28–32**, and chaetoglobosin O **33** (Iwamoto *et al.*, 2001) were isolated from a strain of *Penicillium* species originally separated from the marine alga *Enteromorpha intestinalis*. All these compounds exhibited potent cytotoxic activity against cultured P388 cells.

Four new diterpenoid metabolites were isolated from several species of the green algae *Halimeda* (Udoteaceae). These new compounds show potent antimicrobial and cytotoxic properties in bioassays. Among these four compounds were halimediatrial **34** and halimedalactone **35** (Paul and Fenical, 1983). Halimediatrial **34** is a diterpene trialdehyde that was extracted from *Halmida lamouroux* (Chlorophyta, Udoteaceae) species. This compound was found to be toxic



The green alga *Bryopsis* sp. was the source of the cyclic depsipeptides kahalalide P **37** and Q **38**, with moderate inhibition of the HL-60 cell lines (Dmitrenok *et al.*, 2006).

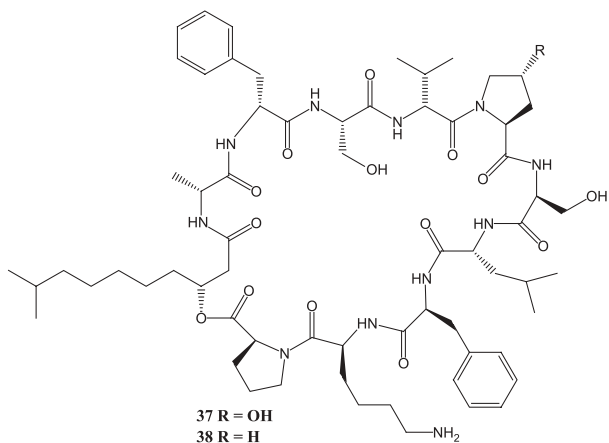


### Antibacterial activity

Cycloedesmol **39** is an antibiotic cyclopropane containing sesquiterpene; it was isolated from the marine alga *Chondria oppositoclada* Dawson (Fenical and Sims, 1974). Cycloedesmol was found to be a potent antibiotic against *Staphylococcus aureus* and *Candida albicans*.

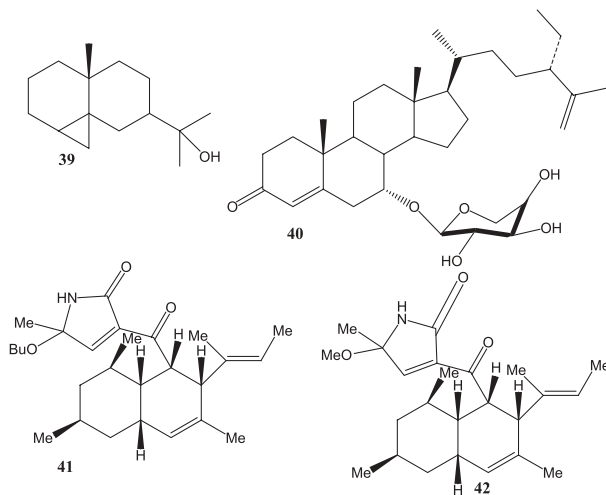
Lyengaroside A **40** was isolated from the green alga *Codium iyengarii* and displayed a moderate antibacterial activity (Ali *et al.*, 2002).

Green algae extract of *Caulerpa prolifera* exhibited moderate to significant activity against unidentified strains of marine bacteria (Smyrniotopoulos *et al.*, 2003).



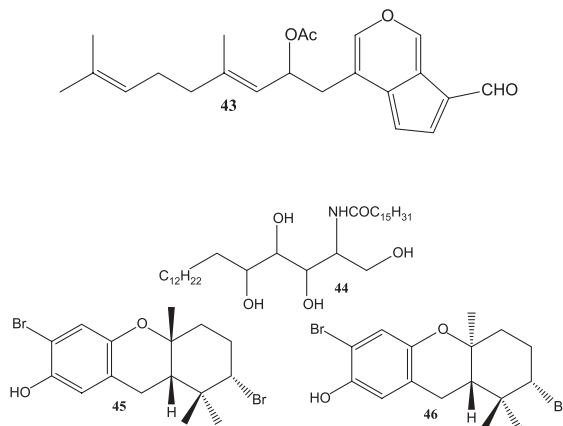
### Antiplasmodial activity

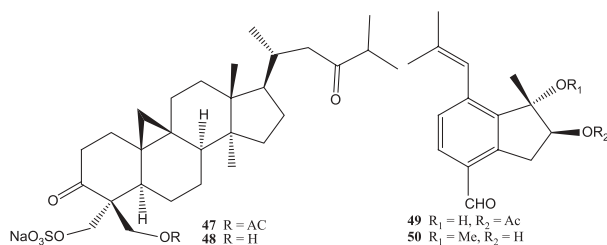
The endophytic and obligate marine fungus *Ascochyta salicorniae* was isolated from the green alga *Ulva* spp.. *Ascochyta salicorniae* was found to produce the unprecedented and structurally unusual tetrameric acid contiguous metabolites ascosalipyrrolidinones A **41** and B **42**. Ascosalipyrrolidinone A **41** has antiplasmodial activity toward *Plasmodium falciparum* strains Kl and NF-54, as well as showing antimicrobial activity and inhibiting tyrosine kinase p56lck (Osterhage *et al.*, 2000).



### Antiviral activity

Halitunal **43** is a novel diterpene aldehyde possessing a unique cyclopentadieno [c] pyran ring system; it has been isolated from the marine alga *Halimeda tuna*. Halitunal shows antiviral against murine coronavirus A59 *in vitro* (Koehn *et al.*, 1991).





In 1992 Garg and coworkers (Garg *et al.*, 1992) isolated the antiviral derivative, sphingosine, *N*-palmitoyl-2-amino 1,3,4,5-tetrahydroxyoctadecane **44**, which demonstrated antiviral activity and *in vivo* protection against Semliki forest virus (SFV). This compound was isolated from the Indian green alga *Ulva fasciata*.

#### Antimutagenic activity

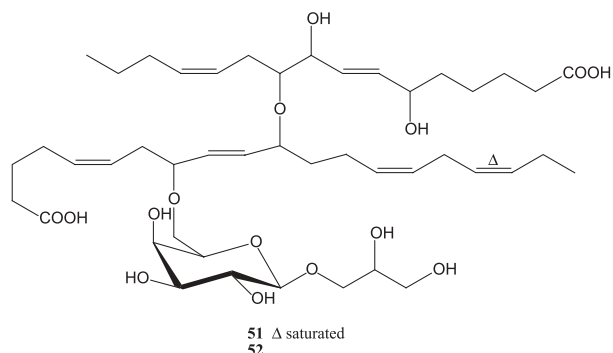
Two new compounds, cymobarbatol **45** and 4-isocymobarbatol **46** were isolated from the marine green alga *Cymopolia barbat*. Both compounds were found to be non-toxic over a broad concentration range against *Salmonella typhimurium* strains T-98 and T-100. Both compounds exhibited strong inhibition of the mutagenicity of 2-aminoanthracene and ethylmethanesulfonate towards, respectively, the T-98 strains plus a metabolic activator and T-100 (Wall *et al.*, 1989).

#### Antifungal activity

Capisterones A **47** and B **48** are triterpene sulfate esters isolated from the green alga *Penicillus capitatus*. Both compounds exhibited potent antifungal activity against the marine algal pathogen *Lindra thallasiae* (Puglisi *et al.*, 2004).

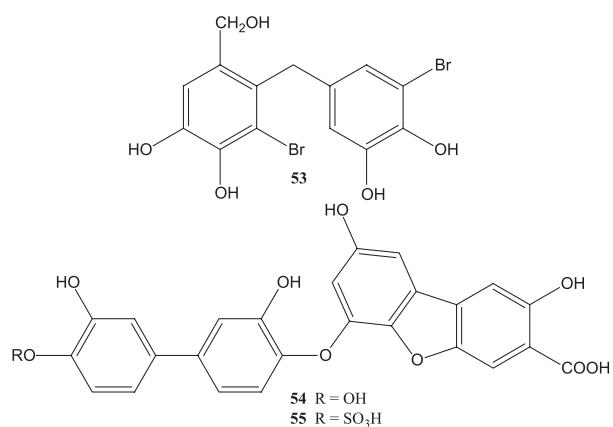
Two sesquiterpenes, caulerpals A **49** and B **50** were isolated from green alga *Caulerpa taxifolia* in addition to the known caulerpin (Aguilar-Santos, 1970); they were shown to be potent inhibitors of human protein tyrosine phosphatase 1 B (hPTP I B) (Mao, Guo and Shen, 2006). Capisterones A **47** and B **48**, originally isolated from *Penicillus capitatus* (Garg *et al.*, 1992), were re-isolated and absolute stereochemistry assigned using electronic CD. In addition, the capisterones have been shown to significantly enhance fluconazole activity in *Saccharomyces cerevisiae* (Li *et al.*, 2006).

A new class of ether-linked glycolipids, nigricanosides A **51** and B **52** were isolated as methyl esters from the green alga *Avrainvillea nigrans*. Nigricanoside A dimethyl ester was found to be a potent antimetabolic agent, acting by stimulating the polymerization of tubulin and inhibiting the proliferation of both MCF-7 and HCT-116 cells (Williams *et al.*, 2007).



#### Protein tyrosine phosphatase 1B inhibitors (PTP1B)

Hydroxyisoavrainvilleol **53** was originally isolated from the tropical green alga *Avrainvillea nigrans* (Colon *et al.*, 1987) but has now been isolated from red alga *Polysiphonia urceolata* as a protein tyrosine phosphatase 1B inhibitor (PTP1B) (Liu *et al.*, 2008). A vanillic acid biphenyl derivative **54** and the sulfate adduct **55** were isolated from the Australian green alga *Cladophora socialis* as a protein tyrosine phosphatase 1B (PTPa1B) inhibitor (Feng *et al.*, 2007).



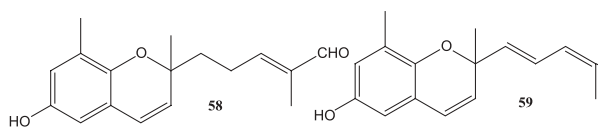
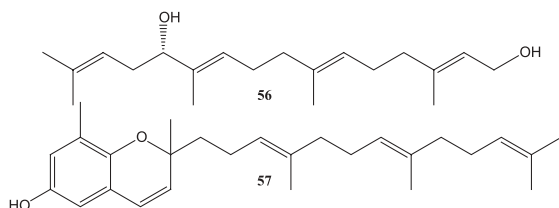
### 1.2.2 Phaeophyta (brown algae)

The brown color of these algae results from the dominance of the xanthophyll pigments and fucoxanthin; this masks the other pigments, chlorophyll *a* and *c*,  $\beta$  carotenes, and other xanthophylls (Bold and Wynne, 1985). Food reserves of brown algae are typically complex polysaccharides and higher alcohols. The principal carbohydrate reserve is laminaran. The cell walls are made of cellulose and alginic acid. Many bioactive metabolites have been isolated from brown algae with different pharmacological activities as shown below:

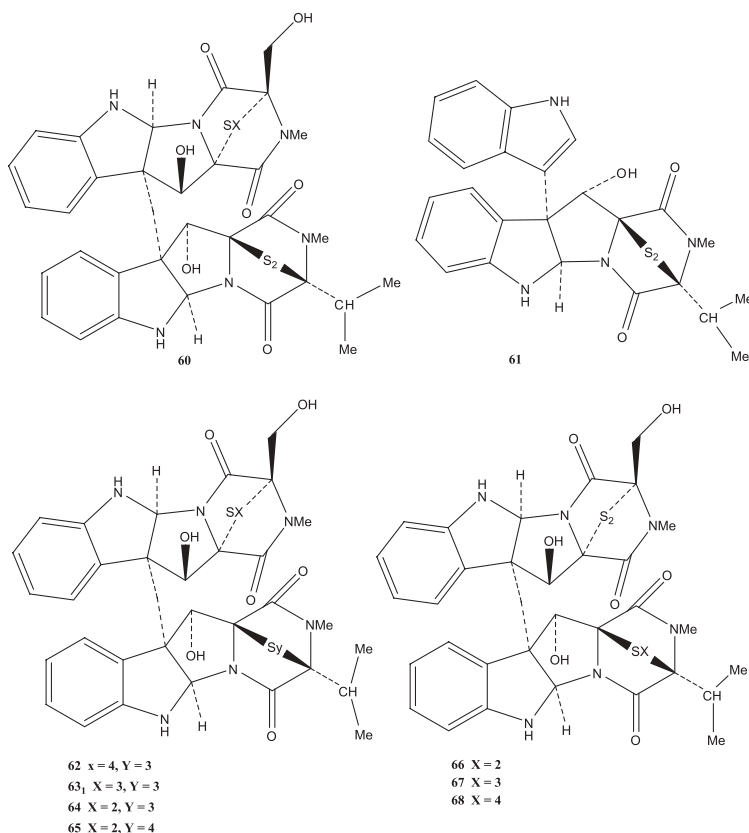
### Cytotoxic and antitumor activity

A linear cytotoxic diterpene bifurcadiol **56** was isolated from the brown alga *Bifurcaria bifurcata* by Guardia and colleagues in 1999 (Guardia *et al.*, 1999), which exhibits cytotoxicity against cultured human tumor cell lines (A549, SK-OV-3, SKL-2, XF 498, and HCT).

Meroterpenoids, sargol, sargol-I and sargol-II **57–59** were isolated from the brown alga *Sargassum tortile* and showed cytotoxic activity (Numata *et al.*, 1991).



Leptosins A, B, C (I, X = 4,3,2 **60**), D, E and F (II, X = 2,3,4 **61**), belonging to a series of epipolythiodioxopiperazine derivatives, have been isolated from the mycelia of a strain of *Leptosphaeria* species attached to marine alga *Sargassum tortile*. All these compounds showed potent cytotoxicity against cultured P388 cells, except leptosins A and C, which exhibited significant antitumor activity against sarcoma 180 ascites (Takahashi *et al.*, 1994). Further investigation of the secondary metabolites of this fungus has led to the isolation of four additional cytotoxic compounds, named leptosins G, G1, G2 **62–64** and H **65** (Takahashi *et al.*, 1995a). Leptosins K, K1 **66–67** and K<sub>2</sub> **68** were also isolated and showed a potent cytotoxic activity against P388 cell line (Takahashi *et al.*, 1995b).



Leptosins I **69** and J **70** have been also isolated from the mycelia of a strain of *Leptosphaeria* species OUPS-4 attached to the marine alga *Sargassum tortile*. These compounds exhibited significant cytotoxic activity against cultured P388 cells (Takahashi *et al.*, 1994a,b).

Leptosins M, MI, N and N1 **71–74** that have been isolated from a strain of *Leptosphaeria* species were originally separated from the marine alga *Sargassum tortile*. All these compounds exhibited significant cytotoxicity against cultured P388 cells. In addition, leptosin M proved to exhibit significant cytotoxicity against human cancer cell lines, and to

inhibit specifically two protein kinases, PTK and CaMKIII, and human topoisomerase II (Yamada *et al.*, 2002).

Three cytotoxic diterpenes dictyotins A, B and C **75–77** were isolated from the brown alga *Dictyota dichotoma* by Wu and coworkers in 1990 (Wu, Li and Li, 1990).

Dolabellane, a type of diterpene **78**, has been isolated from unidentified species of *Dictyota* and exhibits significant cytotoxicity. (Tringali, Prattellia and Nicols, 1984).

A cytotoxic compound named as turbinaric acid **79** was isolated from *Turbinaria ornate* (Asari, Kusumi and Kaki-sawa, 1989).

