

Review

## Medicinal and pharmaceutical uses of seaweed natural products: A review

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### Abstract

In the last three decades the discovery of metabolites with biological activities from macroalgae has increased significantly. However, despite the intense research effort by academic and corporate institutions, very few products with real potential have been identified or developed. Based on Silverplatter MEDLINE and Aquatic Biology, Aquaculture & Fisheries Resources databases, the literature was searched for natural products from marine macroalgae in the Rhodophyta, Phaeophyta and Chlorophyta with biological and pharmacological activity. Substances that currently receive most attention from pharmaceutical companies for use in drug development, or from researchers in the field of medicine-related research include: sulphated polysaccharides as antiviral substances, halogenated furanones from *Delisea pulchra* as antifouling compounds, and kahalalide F from a species of *Bryopsis* as a possible treatment of lung cancer, tumours and AIDS. Other substances such as macroalgal lectins, fucoidans, kainoids and aplysiatoxins are routinely used in biomedical research and a multitude of other substances have known biological activities. The potential pharmaceutical, medicinal and research applications of these compounds are discussed.

### Introduction

Global utilisation of macroalgae is a multi-billion dollar industry. Much of this is based on farming of edible species or on the production of agar, carrageenan and alginate. Of all seaweed products, hydrocolloids have had the biggest influence on modern western societies. They have attained commercial significance through their use in various industries which exploit their physical properties such as gelling, water-retention and their ability to emulsify (Renn, 1997). Little commercial exploitation of products extracted from seaweeds occurs outside the hydrocolloid industry. However, in recent years pharmaceutical firms have started looking towards marine organisms, including seaweeds, in their search for new drugs from natural products. These products are also increasingly being used in medical and biochemical research. Prior to the 1950s, the medicinal properties of seaweeds were restricted to traditional and folk medicines (Lincoln et al., 1991). During the 1980s and 90s, compounds with biological

activities or pharmacological properties (bioactivities) were discovered in marine bacteria, invertebrates and algae (Mayer & Lehmann, 2000). According to Ireland et al. (1993), algae have been the source of about 35% of the newly discovered chemicals between 1977–1987, followed by sponges (29%) and cnidarians (22%). The discovery of new products from seaweeds has decreased since 1995 and attention has now shifted to marine micro-organisms (Kelecom, 2002).

Modern screening programmes are motivated by the chemical ecology of marine organisms. The selection of samples for assays of biological activities useable in drug development is often based on ecological observations and includes specimens with unique (usually chemical) mechanisms for coping with environmental pressures (Haefner, 2003). Another avenue for discovery of novel compounds is through assaying for marine toxins. Toxins in macroalgae are scarcer than in microalgae and cyanophytes, and only a handful of such toxins have been described. Research into the active ingredients of seaweeds used in folk

remedies underlies another area of drug discovery. Since pharmaceutical companies have access to extensive libraries of natural products, and many compounds are of marine origin, high-throughput automated systems can be used for rapid screening in the search for new drugs (Cordell, 2000).

This review focuses on important bioactive chemicals identified in macroalgae in the Rhodophyta, Phaeophyta and Chlorophyta over the last three decades and describes the range of biological activities for which they are responsible. Focus is placed on the main classes of compounds that could be of medicinal and pharmaceutical value. The use of macroalgal constituents as research tools in medical research is also covered. Emphasis is placed on active substances that elicit biochemical responses in animals and plants, rather than those that are used for their physical properties such as mycosporine-like amino acids as UV sunscreens, phycobiliproteins as fluorescent tags, or alginates and carrageenans in tissue engineering. The health benefits of constituents of edible seaweeds and their role in nutrition and disease prevention is also excluded from the review, as much research remains to be done before science-based dietary recommendations can be made (Kris-Etherton et al., 2002).

## Methods

The largest part of the peer-reviewed publications was obtained from literature searches of two online databases. Silverplatter MEDLINE was used to find records of present and potential medicinal, bio-medical and pharmaceutical uses of macroalgal-derived products. MEDLINE covers the period from 1966 to present, and includes more than 11 800 000 records in 3 800 journals from about 70 countries (<http://www.ovid.com>). The research journals Aquatic Biology, and Aquaculture & Fisheries Resources accessible via Biblioline (<http://www.nisc.com>) were also used. This database contains more than 1 100 000 records and extends back to 1971. English records were extracted using the list of search terms:

(seaweed\* or macroalg\*) and ((biol\* and activ\*) or (secondary and metabolite\*) or anti\* or cytotox\* or carrageenan\* or agar\* or algin\* or inhibit\*).

The wildcard '\*' is used to expand the abbreviated term in the search; for example, anti\* searches for any term in which 'anti' occurs as a prefix, such as antiviral, antibacterial or antitumour. A series of review articles on marine natural products was also located,

and this gave additional information that might have been missed by the electronic searches.

Much of the work on biological activities has been done using crude aqueous extracts and fractions of these extracts and these are usually not reported here. The review was limited only to activities that have been associated with a particular known compound or at the very least a broad group of compounds such as sulphated polysaccharides.

## Antiviral activity

Some sulphated polysaccharides from red algae show antiviral activities towards viruses responsible for human infectious diseases. Most notable are *Aghardhiella tenera* and *Nothogenia fastigiata*. Witvrouw et al. (1994) tested a galactan sulphate from *Aghardhiella tenera*, and Damonte et al. (1994) and Kolender et al., (1995) a xylomannan sulphate from *Nothogenia fastigiata* against human immunodeficiency virus (HIV), Herpes simplex virus (HSV) types 1 and 2 and respiratory syncytial virus (RSV). These polysaccharides are active during the first stage of the RNA virus replication when the virus adsorbs onto the surface of the cell (De Clercq, 1996, 2000). An important requirement of an antiviral polysaccharide is that it must have very low cytotoxic activities towards mammalian cells, and most of the algal polysaccharides, particularly those of *Aghardhiella tenera* and *Nothogenia fastigiata*, have this characteristic (De Clercq, 1996).

Carrageenans (Figure 1) demonstrate potential *in vitro* antiviral activity. Carlucci et al. (1997, 1999a, 1999b) noted that  $\lambda$ -carrageenan and partially cyclized  $\mu/\iota$ -carrageenan from *Gigartina skottsbergii* have potent antiviral effects against different strains of HSV types 1 and 2 during the virus adsorption stage. Carrageenans from cystocarpic and tetrasporophytic stages of *Stenogramme interrupta* show similar antiherpetic activity (Cáceres et al., 2000). Zeitlin et al. (1997) tested a range of antiviral substances for their possible effectiveness as vaginal microbicide against genital herpes in mice, and found that carrageenan and fucoidan, or fucoidin, are good candidates for further development. None of these studies have shown that carrageenans exhibit significant levels of cytotoxicity or anticoagulant activity. A carrageenan-based vaginal microbicide called Carraguard has been shown to block HIV and other sexually transmitted diseases *in vitro*. Carraguard entered phase III clinical trials involving 6000 non-pregnant, HIV-negative women in South Africa and Botswana in 2003 (Spieler, 2002).

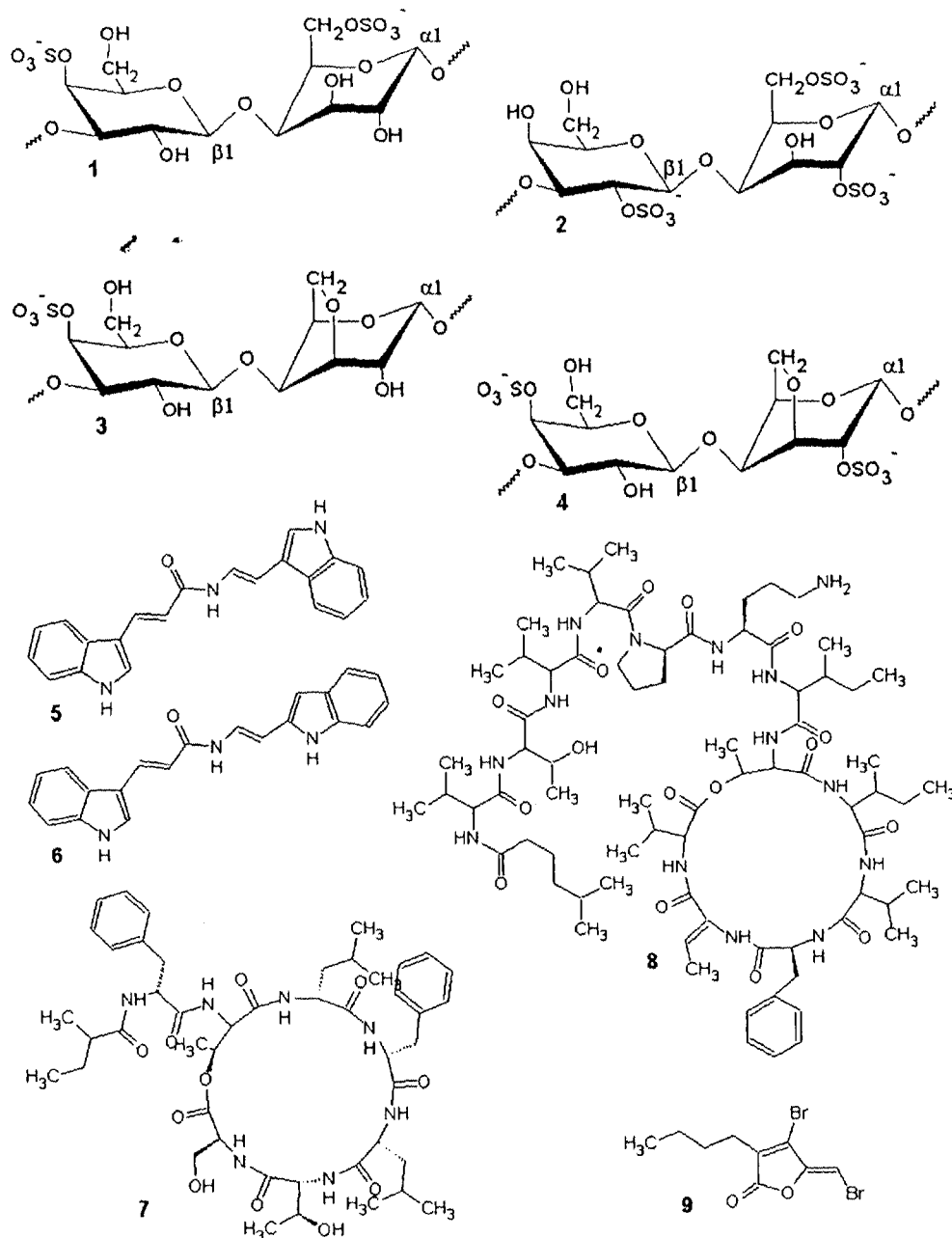


Figure 1. Idealised structures of  $\mu$ -carrageenan (1),  $\lambda$ -carrageenan (2),  $\kappa$ -carrageenan (3) and  $\iota$ -carrageenan (4). Some carrageenans have potent antiviral activities against several strains of HSV types 1 and 2. A carrageenan-based microbicide, Carraguard, is currently undergoing phase III clinical trials; it is used to block HIV and other sexually transmitted diseases *in vitro*. Chondriamide A (5) from *Chondria atropurpurea* shows antiviral activity against HSV type II and cytotoxicity against human nasopharyngeal and colorectal cancer cells. Chondriamide C (6), also from *Chondria atropurpurea*, displays cytotoxic and *in vitro* anthelmintic properties. The cyclic depsipeptides kahalalide A (7) and F (8) are produced by a species of *Bryopsis*. Both show *in vitro* activity against *Mycobacterium tuberculosis*. Kahalalide F has anti-HIV qualities which are being further studied in clinical trials and its effectiveness as treatment of lung cancers and tumours are also being studied. (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone (9) is a halogenated compound from *Delisea pulchra* which displays strong antifouling properties.

A sulphated polysaccharide from *Schizymenia pacifica* inhibits HIV reverse transcriptase *in vitro* (Nakashima et al., 1987a, 1987b), a later stage in HIV replication. It has minimal effect on human DNA and RNA polymerase activity. Some agaroids such as high molecular weight galactan sulphate from *Gracilaria corticata* have antiviral properties against HSV types 1 and 2, and this action is likely due to an inhibition of the initial virus attachment to the host cell (Mazumder et al., 2002).

Fucoidan has potent antiviral properties towards viruses such as RSV (Malhotra et al., 2003), HIV, (Sugawara et al., 1989), HSV types 1 and 2 and human cytomegalovirus (Feldman et al., 1999; Majczak et al., 2003; Ponce et al., 2003). The antiviral properties of fucoidan seem to stem from inhibiting binding of the viral particle to the host cell (Baba et al., 1988). It has the additional benefit of inhibiting binding of sperm to the zona pellucida in humans (Oeninger et al., 1991), thus allowing for the compound to be developed into a possible vaginal microbicide with contraceptive properties. Uncharacterised polysaccharide fractions obtained from *Caulerpa* sp., *Corallina* sp., *Hypnea charoides*, *Padina arborescens* and *Sargassum patens* also have high antiviral activity against HSV types 1 and 2 while maintaining low levels of cytotoxicity (Zhu et al., 2003).

The antiviral activities discussed thus far are for algal polysaccharides, but other compounds exhibit similar properties. Chondriamide A (Figure 1) from *Chondria atropurpurea* shows antiviral activity against HSV type II (Palermo et al., 1992). Kahalalide F (Figure 1) produced by a species of *Bryopsis* has also been noted for its effectiveness in some AIDS study cases, and its antiHIV qualities are being further studied in clinical trials (Hamann et al., 1996; Haefner, 2003).

### Antibiotic activity

Chemicals responsible for antibiotic activities are widespread in macroalgae. Interesting substances in particular are the halogenated compounds such as haloforms, halogenated alkanes and alkenes, alcohols, aldehydes, hydroquinones and ketones (Lincoln et al., 1991). The list of terpenoids with antibiotic qualities is especially long, and many of these are also halogenated. Compounds such as sterols and heterocyclic and phenolic compounds sometimes have antibiotic properties. Many of these could be developed into antiseptics and cleansing agents, but their antibiotic activity *in vivo* is

often only achieved at toxic concentrations (Lincoln et al., 1991).

The depsipeptides kahalalide A (Figure 1) and F from *Bryopsis* sp. were noted for their *in vitro* activity against *Mycobacterium tuberculosis* (el Sayed et al., 2000), but the future of these peptides seems to lie with the development of kahalalide F for treatment of lung cancer, tumours and AIDS.

A promising antibacterial agent is a halogenated furanone, or fimbrolide, that belong to a class of lactones (Figure 1) from *Delisea pulchra*. It has been examined for its effectiveness as an active ingredient in bacterial antifouling agents (Kjelleberg & Steinberg, 2001), and as a possible treatment for chronic *Pseudomonas aeruginosa* infection. *Pseudomonas aeruginosa* infection is characterised by the production of mucoid alginate and formation of a 'biofilm' in the lungs of cystic fibrosis sufferers (Høiby, 2002). Inhibition of bacterial colonisation is achieved by the inhibiting effect of furanone on the quorum sensing mechanism of cells by functioning as an intercellular signal antagonist. The result is a disruption of intra- and inter-species cell-cell communication (Rasmussen et al., 2000). The effect has been observed in a wide range of Gram-negative bacteria. Effects are seen on the swarming of *Serratia liquefaciens* (Rasmussen et al., 2000) and the bioluminescence and virulence in several pathogenic *Vibrio* species (Manefield et al., 2000; Kjelleberg & Steinberg, 2001). It also inhibits carbapenem antibiotic synthesis and exoenzyme virulence factor production in the phytopathogen *Erwinia carotovora* (Manefield et al., 2001).

### Agglutination, coagulation and the stimulation of cell migration

Macromolecule recognition processes are common in cells and their specificity is their most important characteristic. Many research programs exploit recognition events and these have become focus areas of research in biology, chemistry, medicine and pharmacology. Biological reactions that involve recognition events include processes such as cell agglutination and coagulation, the stimulation of cell migration and fertilisation.

Lectins, sometimes referred to as haemagglutinins or agglutinins, are glycoproteins with an ability to agglutinate red blood cells (Boyd & Reguera, 1949). Various polysaccharides are present on cell surfaces, and as a result many cells including microbes and yeasts (e.g. Patchett et al., 1991; Bird et al., 1992; Cisar et al., 1995),

tumour cells (Hori et al., 1986) and erythrocytes are selectively agglutinated by lectins (Chen et al., 1995). Lectins are inhibited by sugars of the same type as those on the surface of the cells being agglutinated (Sharma & Sahni, 1993). They are useful in exploring properties of biological structures and processes, and have found applications in biology, cytology, biochemistry, medicine and food science and technology. Lectins from *Codium* spp. have been developed into commercially available reagents and are routinely used in biochemical studies.

Lectins with haemagglutinating properties occur in a variety of red, green and brown algae (e.g. Rogers & Hori, 1993; Benevides et al., 1998; Shanmugan et al., 2002). They react with a wide array of erythrocytes, including human blood group types. Agglutination reactions with human blood groups have led to their use in assays for blood typing. Lectins are also used to characterise cell-surface polysaccharides or to examine cell binding patterns in lectinosorbent assays (Llovo et al., 1993; Wu et al., 1996; Wu et al., 1998). Lectins from *Codium fragile* subsp. *tomentosoides* have been developed into a histochemical reagent by coupling them to colloidal gold, forming a lectin-gold conjugate. This conjugate is useful for studies of the surface topography of cells of animal tissues (Griffin et al., 1995).

Other common examples of lectins from macroalgae are hypnins A—D in *Hypnea japonica* (Hori et al., 1986), a sulphated polysaccharide in *Gracilaria verrucosa* (Kakita et al., 1997) and a haemagglutinin in an ammonium sulphate fraction of a buffer extract of *Gracilaria chorda* (Kakita & Kitamura, 2003). Anticoagulant effects are often related to the sulphate and sugar content of the components (Jurd et al., 1995; Shanmugan et al., 2002). Cell migration is also stimulated by lectins. For example, the lectin amansin from *Amansia multifida*, induces neutrophil migration *in vitro* and *in vivo* in the peritoneal cavity or dorsal air pouch of mice (Neves et al., 2001). Lastly, lectins from *Gracilaria verrucosa* induce morphological changes and growth suppression in the dinoflagellate *Chatonella antiqua* (Tanabe et al., 1993).

### Activities related to cellular growth

#### Mitogenic activity

Mitogenic activities, the stimulation of mitosis in previously non-dividing cells, have been demonstrated in mouse lymphocytes using lectins from *Eucheuma serra* (Kawakubo et al., 1997). Amansin isolated from *Amansia multifida* has been found to stimulate periph-

eral blood mononuclear cells and causes a gradual reduction in mitogenic capacity with progressive increase in the lectin concentration (Lima et al., 1998). Fucoidan enhances new blood vessel formation by modulating the expression of surface proteins (Matou et al., 2002), and lipogenic activity has been demonstrated for lectins from *Codium fragile* in isolated rat and hamster adipocytes (Ng et al., 1989).

#### Effects on fertilisation and larval development

Various seaweed-derived compounds affect fertilisation and larval or embryonic development in both invertebrates and vertebrates. Fucoidan inhibits the initial binding of sperm and subsequent recognition events necessary for penetration of the human zona pellucida (Oehninger et al., 1991; Patankar et al., 1993). This property of fucoidan, together with its antiviral activity, makes it a potential candidate for development into vaginal microbicide with contraceptive properties (Baba et al., 1988; Zeitlin et al., 1997). Premakumara et al. (1996) identified a sphingosine derivative from *Gelidiella acerosa* as a post-coital contraceptives agent in studies on pregnant rats. The action of the orally administered substance is via an antiprogesterone mechanism with no maternal toxicity (Premakumara et al., 1995). The lectin diabolin isolated from *Laminaria diabolica* causes the development of a fertilisation envelope around unfertilised eggs of the sea urchin *Hemicentrotus pulcherrimus*, thus preventing cleavage (Nakamura & Moriya, 1999; Nomura et al., 2000). Terpenoids are also known for their effects on fertilisation and subsequent development of embryos. For example, caulerpenyne, a sesquiterpene from *Caulerpa taxifolia*, affects embryogenesis, larval development and metamorphosis of the sea urchin *Paracentrotus lividus* (Pesando et al., 1996, 1998). It also interferes with microtubule-dependent events during the first mitotic cycle of sea urchin eggs (Pedrotti & Lemee 1996), and affects regulation of intracellular pH in sea urchin eggs and sea bream hepatocytes (Galgani et al., 1996).

#### Cytotoxicity, antimitogenic, anticancer and antitumour properties

Kahalalide F which is produced by *Bryopsis* sp. and subsequently assimilated by the grazer *Elysia rufescens* has anticancer and antitumour properties (Hamann & Scheuer, 1993; Hamann et al., 1996). It is effective in controlling tumours that cause lung, colon and

prostate cancer (Horgen et al., 2000; Nuijen et al., 2000; Sparidans et al., 2001), and has been patented for use as a possible active substance in therapeutics for the treatment of human lung carcinoma (Scheuer et al., 2000). It has entered phase II clinical studies for liver carcinoma treatment. Kahalalide F functions by acting on the lysosomal membrane (Stokvis et al., 2002), a mechanism that distinguishes it from all other known antitumour agents. It also induces cell necrosis *in vivo* and selectively targets tumour cells *in vitro*. The cytotoxic activity of Kahalalide F is not mediated by mRNA and protein synthesis *de novo*, nor caspase activation. Kahalalides O and G, also from *Bryopsis* sp. (and *Elysia ornata*) do not show significant cytotoxicity towards the cancer lines tested (Hamann et al., 1996; Goetz et al., 1997; Horgen et al., 2000; el Sayed et al., 2000).

Several sulphated macroalgal polysaccharides have cytotoxic properties. Fucoidans are known to have antitumour, anticancer, antimetastatic and fibrinolytic properties in mice (Coombe et al., 1987; Maruyama et al., 1987), and they also reduce cell proliferation (Religa et al., 2000). Translam, the 1 → 3:1 → 6-β-D-glucans produced by enzymatic action on laminaran (laminarin), has antitumour properties (Saito et al., 1992). Kaeffer et al. (1999) noted that ulvan has cytotoxicity or cytostaticity targeted to normal or cancerous colonic epithelial cells.

Chondriamide A (Figure 1) isolated from *Chondria atropurpurea* shows cytotoxicity against human nasopharyngeal and colorectal cancer cells (Palermo et al., 1992). Terpenes are exceptionally wide in their range of cytotoxic and antitumour activities. Examples include (*S*)-12-hydroxygeranylgeraniol and (*S*)-13-hydroxygeranylgeraniol derivatives from *Bifurcaria bifurcata* which are toxic towards fertilised sea urchin eggs (Valls et al., 1995; Culioli et al., 2001); caulerpenyne from *Caulerpa taxifolia* which is cytotoxic towards several human cell lines and as such has anticancer, antitumour and antiproliferative properties (Fischel et al., 1995; Parent-Massin et al., 1996; Barbier et al., 2001); the hydroquinone diterpene, mediterraneol, from *Cystoseira mediterranea* which is an inhibitor of mitotic cell division (Francisco et al., 1985); and the meroterpenes, usneoidone E and Z, from *Cystophora usneoides* which have antitumour properties (Urones et al., 1992).

#### Antithrombic and anticoagulant activities

Fucoidans have *in vivo* and *in vitro* heparin-like antithrombic and anticoagulant activities that are medi-

ated by blood coagulation inhibitors such as heparin cofactor II or antithrombin III (Church et al., 1989; Collicet et al., 1991; Matou et al., 2002). The anticoagulation activity is the result of direct fucan-thrombin interaction (Graufel et al., 1989), and it usually increases with the amount of sulphation (Nishino & Nagumo, 1991, 1992). Sulphated fucans from *Fucus vesiculosus* and *Ascophyllum nodosum* have been patented as anticoagulant substances. The work was motivated by the need to find a potential replacement for cattle-derived heparin and the fear of the transmission of bovine spongiform encephalitis (BSE) through the use of bovine-derived products (Trento et al., 2001). Sulphated fucoidan has several advantages over heparin. It shows concentration-dependent inhibition of thrombin generation from platelets; it exhibits concentration-dependent inhibition of thrombin-induced platelet aggregation; it lacks the hypotensive effect found in thrombin; it reduces the sticking of polymorphonucleated leukocytes to rabbit aorta; and it shows a dose-dependent inhibition of thrombin-induced thrombosis (Trento et al., 2001). Some older literature reports laminaran as having anticoagulant properties (Hoppe & Schmid, 1962, cited by Chapman, 1970), but it is possible that this activity comes from fucoidan which is often present in the same extracted fraction as laminaran.

#### Toxins—vermifuges, insecticides, ichthyotoxins, neurotoxins and others

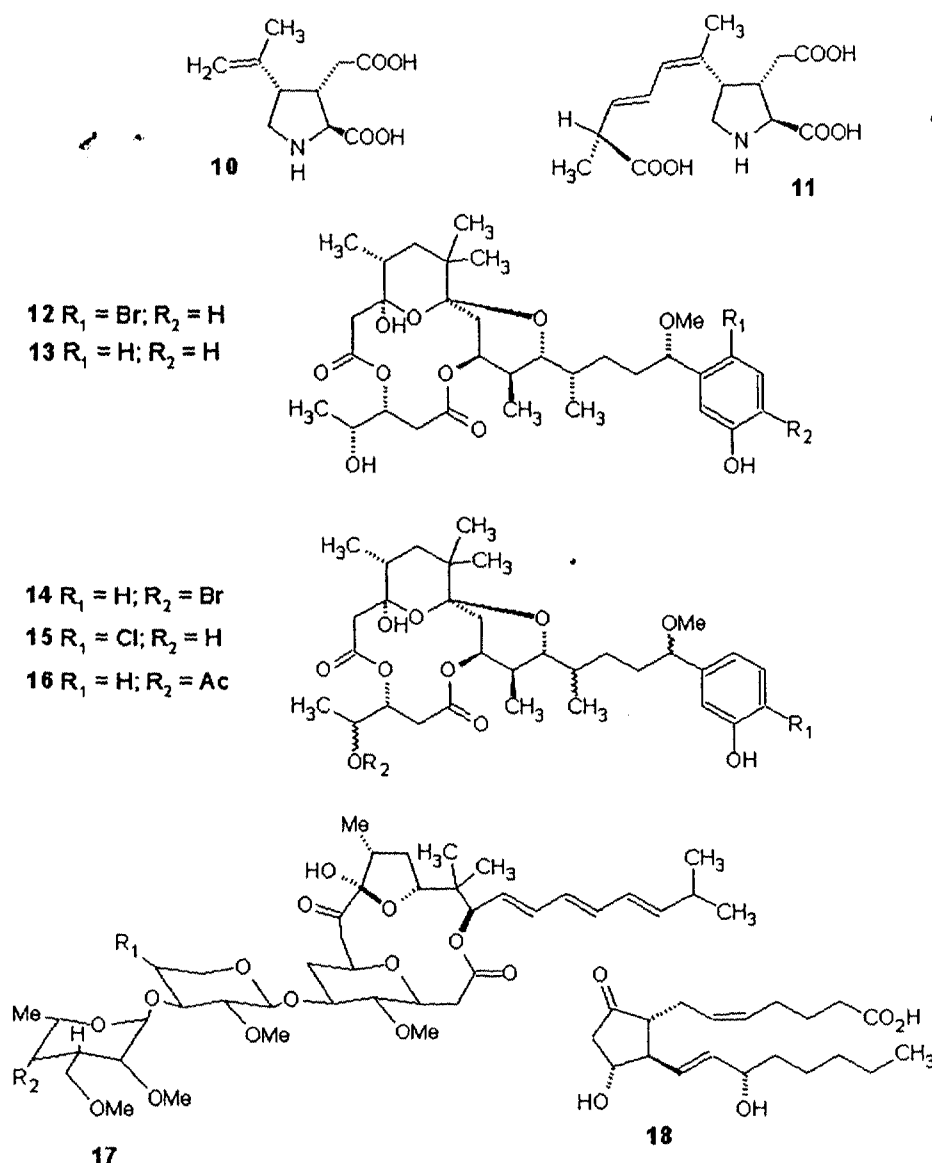
Toxins are better known from microalgae and cyanophytes, but some are also known from macroalgae. Bioactivities of these compounds vary from being neurologically active in humans and other mammals, to algicidal, anthelmintic, insecticidal and ichthyotoxic activities. In some cases they show acute toxicity and may cause death in humans at naturally occurring concentrations. The most important compounds are kainoids, aplysiatoxin and polycavernosides. Prostaglandin E<sub>2</sub> is also sometimes noted for its acute toxicity, and is discussed in a later section.

##### Amino acid toxins

Kainoids are pyrrolidine dicarboxylates with excitatory and excitotoxic activities (Carcache et al., 2003). They are unusual amino acids structurally related to, and having similar functions as, glutamic and aspartic acids, both well-known neuronal excitants (agonists) or neurotransmitters (Laycock et al., 1989). Kainoids are im-

portant tools in research (Higa & Kuniyoshi, 2000) into neurophysiological disorders such as Alzheimer's and Parkinson's disease and epilepsy (Ben-Ari & Cossart, 2000; Hopkins et al., 2000; Carcache et al., 2003).

Pennate marine diatoms in the genera *Nitzschia*, *Pseudo-nitzschia* and *Amphora* are the best known sources of domoic acid (Figure 2), the compound responsible for amnesic shellfish poisoning (Bates,



**Figure 2.**  $\alpha$ -Kainic (**10**) and domoic acids (**11**) are pyrrolidine dicarboxylates with excitatory and excitotoxic activities. Kainoids occur in some pennate diatoms where they cause amnesic shellfish poisoning, but they are also produced by some members of the Ceramiales. They are used as tools in research into neurophysiological disorders such as Alzheimer's and Parkinson's disease, and epilepsy. Domoic acid-containing extracts of *Digenea simplex* and *Chondria armata* have been used by the Japanese as anthelmintic agent, and it also has insecticidal properties. Aplysiatoxin (**12**) and debromoaplysiatoxin (**13**) are potent tumour promoters used in medical research, and are responsible for non-fatal poisonings associated with eating *Gracilaria coronopifolia*. The related manaualealide A (**14**), manaualealide B (**15**) and manaualealide C (**16**) which also occur in *Gracilaria coronopifolia* were shown to induce diarrhoea in mice. Polycavernoside A (**17**) has been isolated from the red alga *Polycavernosa tsudae*. Polycavernosides are complex glycosidic toxins belonging to a class of macrocyclic lactones and are the causative agents for the fatal human poisonings following consumption of *Polycavernosa tsudae*. Prostaglandin  $E_2$  (**18**) is a product of PUFA metabolism in some species of *Gracilaria* and is the causative agent responsible for the fatal 'ogonori' poisoning resulting from the consumption of species of *Gracilaria*.

1998, 2000). Domoic acid and another kainoid, kainic acid (Figure 2), have also been isolated from the macroalgae *Digenea simplex*, *Chondria armata*, *Chondria baileyana*, *Alsidium corallium*, *Amansia glomerata*, *Vidalia obtusiloba*, *Laurencia papillosa* and *Centroceras clavulatum* (Ceramiales) (Takemoto & Daigo, 1958; Impellizzeri et al., 1975; Laycock et al., 1989; Smith & Kitts, 1994; Sato et al., 1996). A related compound, N-methyl-D,L-aspartic acid, occurs in *Bryopsis plumosa*, *Gloiopeltis furcata*, *Coelothrix charoides*, *Ahnfeltia paradoxa*, *Gymnogongrus flabelliformis*, *Chondrus elatus* and *Amansia glomerata* (Sato et al., 1996). Zaman et al. (1997) reported the isolation of isodomoic acids A, B, E, F, G and H from *Chondria armata*. Curiously, kainic acid was also detected in two spontaneous dwarf mutants of *Palmaria palmata* (Palmariales) (Laycock et al., 1989; Ramsey et al., 1994). Other neuronal agonists such as L-cysteic acid in *Caulerpa racemosa* and D-homocysteic acid in *Palmaria palmata* are known (Laycock et al., 1989), but domoic and kainic acids are the most potent. The complex molecular structure of these receptor-specific neuronal agonists makes them difficult to synthesise and they are usually extracted from algal material, mainly *Digenea simplex*, as required. Kainoids are high-value products, and their production through biotechnology might be a viable option for the future development of algal cultivation for specialised chemicals.

Domoic acid-containing extracts of *Digenea simplex* and *Chondria armata* have been used by the Japanese as an anthelmintic agent for centuries (Higa & Kuniyoshi, 2000). In addition to their toxicity to roundworms, kainoids have insecticidal activities against houseflies and cockroaches (Maeda et al., 1984, 1986, 1987) and are effective when applied both intraperitoneally and topically. Despite much research into the toxicity of domoic and kainic acids, particularly on diatoms in the light of amnesic shellfish poisoning, and also the studies of Maeda et al. (1984, 1986, 1987) on domoic acid in *Chondria armata*, the physiological or ecological roles of the kainoids remain unknown.

#### Aplysiatoxins

Aplysiatoxins were first isolated from the digestive gland of the sea hare *Stylocheilus longicauda* (Kato & Scheuer, 1974) and later from the blue-green alga, *Lyngbya majuscula* (Serdula et al., 1982). Several cases of non-fatal poisonings were attributed to aplysiatoxin (Figure 2) and debromoaplysiatoxin (Figure 2) in *Gracilaria coronopifolia* (Nagai et al.,

1996, 1997). The characteristic clinical symptoms of the first aplysiatoxin poisonings of people eating *Gracilaria coronopifolia* in Hawaii in 1994 were vomiting, diarrhoea and a burning sensation of the mouth and throat (Nagai et al., 1996). The burning sensation appears to distinguish the aplysiatoxin poisonings from 'ogonori' poisonings associated with a prostaglandin (Ito & Nagai, 2000). In subsequent experiments on mice, aplysiatoxin poisoning resulted in death caused by haemorrhagic shock resulting from bleeding of the small intestine (Ito & Nagai, 1998, 2000). The related manauelalides A, B and C (Figure 2) were also isolated from *Gracilaria coronopifolia* and they were shown to induce diarrhoea in mice (Nagai et al., 1997). Also extracted from *Gracilaria coronopifolia* were malyngamides M and N (Kan et al., 1998).

Although a few isolated cases of *Gracilaria* poisonings were known before the incidents in Hawaii, these were the first reported cases of aplysiatoxin poisoning following consumption of *Gracilaria coronopifolia*. There is some confusion as to whether aplysiatoxin is produced by *Gracilaria coronopifolia* or by its epiphytic cyanophytes. Aplysiatoxin is found in *Lyngbya majuscula*, together with lyngbyatoxin A (Osborne et al., 2001) and other cyanophytes such as *Schizothrix calcicola* and *Oscillatoria nigroviridis* (Mynderse & Moore, 1978; Serdula et al., 1982; Entzeroth et al., 1985). *Lyngbya majuscula* is responsible for swimmer's itch, a severe form of contact dermatitis (Moore et al., 1982). Nagai et al. (1996) observed epiphytic blue-green algae on the thallus surface of *Gracilaria coronopifolia* and isolated aplysiatoxin from a particulate residue washed off the macroalgal samples, and suggest that these epiphytes might be the true source of the toxins that caused the non-fatal poisonings in Hawaii. Aplysiatoxin from *Lyngbya* was shown to increase malignant transformation, stimulate DNA synthesis and inhibit the binding of phorbol-12,13-dibutyrate and epidermal growth factor to cell receptors. Debromoaplysiatoxin from *Lyngbya* inhibits the binding of these two substances as strongly as aplysiatoxin, but does not increase malignant transformation or stimulate DNA synthesis.

Aplysiatoxin and debromoaplysiatoxin have received much attention in the medical literature, because of their potent tumour-promoting properties (Ito & Nagai, 2000). They are placed in the same class as the commonly used tumour-promoters 12-O-tetradecanoylphorbol-13-acetate (TPA) derived from species of *Euphorbia*, and teleocidin (Fujiki & Suganuma, 1996; Levine, 1998). Examples of their



use in cancer and pharmacological research include the studies by Mullin et al. (1990), Fujiki et al. (1991), Hennings et al. (1992), Ueyama et al. (1995) and Levine (1998). Although progress has been made in the chemical synthesis of aplysiatoxin (Okamura et al., 1991, 1993), the toxin still appears to be extracted as required. Nothing is known about the biological function of the aplysiatoxins.

#### *Polycavernosides*

Polycavernoside A (Figure 2) and its analogues polycavernosides A<sub>2</sub>, A<sub>3</sub>, B and B<sub>2</sub> have been isolated from the red alga *Polycavernosa tsudae* (Yotsu-Yamashita et al., 1995) and subsequently several other analogues have been synthesised and reported by Barriault et al. (1999). It should be noted that the literature associates *Polycavernosa tsudae* with *Gracilaria edulis*, which it calls a synonym (Yotsu-Yamashita et al., 1993, 1995), and with *Gracilaria tsudae* (Nagai et al., 1996; Ito & Nagai, 2000).

Polycavernosides are complex glycosidic toxins belonging to a class of macrocyclic lactones (Barriault et al., 1999). Polycavernoside A is the causative agent for the fatal human poisonings in Guam in 1991, following consumption of *Polycavernosa tsudae* (Yotsu-Yamashita et al., 1993). Due to the association between *Polycavernosa tsudae* and *Gracilaria edulis* in the literature, it is sometimes seen as a third form of *Gracilaria* poisoning together with aplysiatoxins and prostaglandins (Higa & Kuniyoshi, 2000). The toxicity of polycavernoside A in mouse bioassays was established at 0.2–0.4 mg kg<sup>-1</sup>, and symptoms include progressive onset of severe scratching of the face and body, spasms, paralysis, acute eye damage and death (Barriault et al., 1999). In humans, the symptoms are more severe than those reported for aplysiatoxin poisoning: diarrhoea, vomiting, abdominal pain, low blood pressure, and in some cases paresthesia, convulsions or loss of consciousness. In extreme cases it results in death (Ito & Nagai, 2000). Polycavernoside A is very rarely produced as a natural marine toxin and chemical synthesis is the only source of this compound (White et al., 2001). Nothing is known about the biological role in the producing organism.

#### *Algicides, fungicides, vermifuges, insecticides and ichthyotoxic compounds*

The anthelmintic and insecticidal properties of kainoids have been discussed earlier. Other substances

toxic to insects, worms and fishes are present in macroalgae. The bis-indolic amides chondriamides A, B and C have been isolated from *Chondria atropurpurea* (Palermo et al., 1992; Davyt et al., 1998). Chondriamides A and C, 3-indoleacrylamide and the O, N<sup>1</sup>, N<sup>1'</sup>-trimethyl derivative of chondriamide B, also from *Chondria atropurpurea*, display cytotoxic and *in vitro* anthelmintic properties against *Nippostrongylus brasiliensis*, a gastrointestinal nematode parasite in rats (Davyt et al., 1998). Terpenoids are very diverse in their algicidal, fungicidal and insecticidal activities, and they also include ichthyotoxic compounds. Often these compounds function as antifeedants in the producer seaweeds, but relevant bioactivities towards test organisms are produced when applied *in vitro* or *in vivo*. Some compounds may prove to be useful in household, industrial or aquaculture applications if they could be developed into suitable products. One example is crenulacetal C, a diterpene from *Dictyota dichotoma* which inhibits *Polydora websterii*, a harmful lugworm damaging pearl cultivation (Takikawa et al., 1998). A second example includes a variety of sesquiterpenes isolated from *Laurencia scorparia* that show anthelmintic activity *in vitro* against the parasitic stage of *Nippostrongylus brasiliensis* (Davyt et al., 2001). A third example is the polyhalogenated monoterpenes, aplysiaterpenoid A and telfairine isolated from *Plocamium telfairiae*, that show insecticidal activity against mosquito larvae (*Culex pipiens pallens* and *Anopheles gambiae*) and German cockroaches (*Blattella germanica*) (Watanabe et al., 1989, 1990).

#### **Anti-inflammatory activity and effects on the immune response**

Macroalgae, especially red algae, are rich in 20-carbon atom polyunsaturated fatty acids (PUFAs), chiefly eicosapentaenoic and docosahexanoic acids (Stefanov et al., 1988; Gerwick & Bernart, 1993). Seaweeds are capable of metabolising various C20-PUFAs via oxidative pathways (Gerwick et al., 1993) and in the Gracilariales, prostaglandins are one of the products. Two alternative pathways for the production of prostaglandin have been proposed. The first involves fatty acid cyclooxygenase acting on arachidonic acid, as in mammalian systems (Noguchi et al., 1994). The other mechanism uses lipoxygenase, also acting on arachidonic acid (Gregson et al., 1979). In many red algae, the metabolised products of PUFAs, called oxylipins, resemble eicosanoid hormones in higher

plants and humans which fulfil a range of physiologically important functions (Gerwick et al., 1993; Imbs et al., 2001). The anomalous production of these compounds underlies a number of diseases related to inflammation (Gerwick & Bernart, 1993), and so eicosanoids and their derivatives have received much research attention in the search for development of new classes of antiinflammatory drugs (Jacobs et al., 1993). Gerwick and Bernart (1993) list studies on macroalgal eicosanoids with antiviral, antimicrobial and antihypertensive properties and showing various enzyme-inhibiting activities.

The eicosanoid prostaglandin  $E_2$  ( $PGE_2$ ) (Figure 2) is the likely agent responsible for 'ogonori' poisoning resulting from the human consumption of a species of *Gracilaria* (Fusetani & Hashimoto, 1984; Noguchi et al., 1994). The cases of ogonori poisoning appear to have been brought about by soaking the seaweed in freshwater, thus causing the production of  $PGE_2$ .  $PGE_2$  production was further enhanced interacting with a diet rich in seafood, leading to the high availability of arachidonic acid, the precursors of  $PGE_2$ . More  $PGE_2$  was produced via the action of fatty acid cyclooxygenase, causing haemorrhaging of the victim's stomach. Symptoms included nausea, vomiting and hypotension and death resulted from hypotensive shock (Noguchi et al., 1994). Symptoms are similar to those of misoprostol overdose. Misoprostol is a  $PGE_1$  analogue used for the prevention of nonsteroidal antiinflammatory drug-induced gastropathy (Graber & Meier, 1991). Poisonings involving prostaglandins are rare but have been mentioned in medical literature (Al Hassan et al., 1987; Graber & Meier, 1991; Bond & van Zee, 1994).

$PGE_2$  and  $PGF_2$  were detected in *Gracilaria lichenoides* (Gregson et al., 1979).  $PGE_2$  and 15-keto- $PGE_2$  were found in *G. asiatica* (Sajiki, 1997; Sajiki & Kakimi, 1998) and *G. verrucosa* was found to contain  $PGA_2$ ,  $PGE_2$ ,  $PGF_2$ , and 15-keto- $PGE_2$  (Fusetani & Hashimoto, 1984; Imbs et al., 2001).

Eicosanoids such as leukotrienes and hydroxyeicosatetraenoic acid have physiologically active characteristics such as chemoattraction of neutrophils or smooth muscle cells, the contraction of muscles, and have connections with various kinds of diseases in mammals (Gurr & Harwood, 1991; Sajiki & Kakimi, 1998). The combined effect of prostaglandins and expansion of *Laminaria stipes* is also well-known in obstetrics and gynaecology where it is used as a cervical dilator (Blumenthal, 1988; el Refaey & Templeton, 1995; Lee et al., 1998).

Translam,  $1 \rightarrow 3:1 \rightarrow 6\text{-}\beta\text{-D-glucans}$  produced from laminaran, has immunostimulating activities in animals and plants and it has been suggested that they might serve as radioprotective substances in patients with radiation illness (Kuznetsova et al., 1994; Zaporozhets et al., 1995; Chertkov et al., 1999). Preparations containing  $1 \rightarrow 3:1 \rightarrow 6\text{-}\beta\text{-D-glucans}$ , laminaran, and fucoidan are manufactured by the health industry and marketed for their beneficial properties on the immune system. The producers of these tablets cite numerous papers discussing the biological activities of the  $1 \rightarrow 3:1 \rightarrow 6\text{-}\beta\text{-D-glucans}$ . Laminarans themselves generally have very low levels of bioactivity, but their immunomodulatory effect on anterior kidney leukocytes of the salmon *Salmo salar* has been noted (Dalmo & Seljelid, 1995; Dalmo et al., 1996). Porphyrans likely contributes to macrophage stimulating activity in mice (Yoshizawa et al., 1995). The compound 6-n-tridecylsalicylic acid was isolated from *Caulocystis cephalornithos* and shown to be active after oral administration in both acute and chronic animal models of inflammation such that it has similar antiinflammatory activity but less ulcerogenic activity on a molar basis than salicylic acid (Buckle et al., 1980; Kazlauskas et al., 1980). Lastly, carnosadine identified in *Grateloupia carnosa* has been patented as an antiinflammatory agent with positive carcinostatic and immunological effects (Wakamiya et al., 1984).

#### Antilipemic, hypocholesterolaemic, hypoglycemic, hypotensive and related activities

High plasma cholesterol levels and high blood pressure are causes of cardiovascular disease. Some macroalgal polysaccharides and fibres such as alginate, carrageenan, funoran, fucoidan, laminaran, porphyran and ulvan have been noted to produce hypocholesterolemic and hypolipidemic responses due to reduced cholesterol absorption in the gut (Kiriya et al., 1968; Lamela et al., 1989; Panlasigui et al., 2003). This is often coupled with an increase in the faecal cholesterol content and a hypoglycaemic response (Ito & Tsuchida, 1972; Nishide et al., 1993; Dumelod et al., 1999). Others have reported lowering of systolic blood pressure (antihypertensive responses) (Renn et al., 1994a, 1994b) and lower levels of total cholesterol, free cholesterol, triglyceride and phospholipid in the liver (Nishide & Uchida, 2003). Evidence suggests that ulvan as a dietary fibre plays a protective role in the rat such that it modulates the stimulatory ef-

fect of mucin secretion by goblet cells into the colon (Barcelo et al., 2000). A crude methanolic extract from *Pelvetia babingtonii* showed potent  $\alpha$ -glucosidase inhibitory activity which could make it effective in suppressing postprandial hyperglycemia (Ohta et al., 2002). Hypolipidemic activities have been identified in ethanolic extracts of *Solieria robusta*, *Iyengaria stellata*, *Colpomenia sinuosa*, *Spatoglossum asperum* and *Caulerpa racemosa*, as shown by decreases in the serum total cholesterol, triglyceride and low density lipoprotein cholesterol levels in rats (Ara et al., 2002). PGE<sub>2</sub> from *Gracilaria lichenoides* has antihypertensive properties when administered intravenously to hypertensive rats (Gregson et al., 1979). Some of these substances, most notably the fibres, are likely to be exploited by 'nutraceutical' companies that market them as health products.

### Carcinogens and ulcer-causing compounds

Carrageenan is used in experimental research in animals where it induces pleurisy and ulceration of the colon (Noa et al., 2000). The carrageenan-induced rat paw edema assay and carrageenan air pouch models are widely used as test systems for the evaluation of non-steroidal antiinflammatory drugs and cyclooxygenase activity (Wallace, 1999; Dannhardt & Kiefer, 2001). Despite its role in inducing ulceration in animals, carrageenan is an important ingredient in many types of processed food. The role of carrageenans, particularly low molecular weight degraded carrageenans, in promoting colorectal ulcers, tumours and cancers in humans is controversial and much debated and is the subject of other reviews (eg. Tobacman, 2001). The molecular weight of carrageenan seems to be at the centre of the safety debate. The International Agency for Research on Cancer classified degraded carrageenan as a possible human carcinogen, but native carrageenan remains unclassifiable with respect to causing human cancers (Carthew, 2002) and it is generally regarded as safe (Tobacman, 2001).

### Enzyme inhibitors and stimulants

In humans, secreted phospholipase A<sub>2</sub> (PLA<sub>2</sub>) is involved in the development of a variety of inflammatory diseases via the production of arachidonic acid, the precursor of prostaglandins and leukotrienes (Flower & Blackwell, 1976). Secreted phospholipase A<sub>2</sub> could therefore act as target for a class of antiinflammatory

drugs and a substantial research effort has been focused on this group of enzymes. Several macroalgae show potent bee venom-derived PLA<sub>2</sub> activity. Compounds active against PLA<sub>2</sub> include rhiphocephalin, a linear sesquiterpene from *Rhiphocephalus phoenix*; caulerpenyne, a sesquiterpene from *Caulerpa prolifera*; cymopol and cyclocymopol, prenylated bromohydroquinones from *Cymopolia barbata*; an acetylene containing fatty acid derivative from *Liagora farinosa*; a macrocyclic enol-ether from *Phacelocarpus labillardieri*; and stypoldione, an orthoquinone from *Stypodium zonale* (Mayer et al., 1993). Fucoidan also inhibits cytotoxic and myotoxic activities of several PLA<sub>2</sub> myotoxins from crotaline snake venoms that result in muscle necrosis caused by snake bites (Angulo & Lomonte, 2003).

An inhibitor of pancreatic lipase has been purified from an extract of *Caulerpa taxifolia* (Bitou et al., 1999). The substance, caulerpenyne, competitively inhibits lipase activities, and *in vivo* oral administration to rats demonstrated a reduced and delayed peak plasma triacylglycerol concentration. Phlorofucofuroeckol A is an antiplasmin inhibitor found in *Ecklonia kurome* (Fukuyama et al., 1989, 1990). The compound 5'-deoxy-5-iodotubercidin isolated from *Hypnea valentiae* strongly inhibits the action of adenosine uptake into rat and guinea-pig brain slices, and inhibits adenosine kinase obtained from guinea-pig brain and rat brain and liver Davies et al., 1984). Its also causes muscle relaxation and hypothermia when injected into mice (Davies et al., 1984). Inosine-5'-monophosphate dehydrogenase is inhibited by the brominated diphenylmethane derivative, isorawsonol, which has been isolated from *Avrainvillea rawsonii* (Chen et al., 1994). The linear diterpenes eleganolone and elegandiol, isolated from *Cystoseira brachycarpa* var. *balearica*, inhibit contractile activities of acetylcholine and histamine on ileum musculature of guinea pigs (Della Pietra et al., 1993, 1995). Patier et al. (1993) noted the effect of laminaran in enhancing D-glycanase activities in suspended cell cultures of *Rubus fruticosus*. A fucoidan isolated from *Cladosiphon okamuranus* has shown antipeptic activity and this characteristic has been suggested to protect the gastric mucosa from ulceration (Shibata et al., 2000).

### Conclusions

Writing this review involved a thorough search of medical literature not usually read by phycologists. Phycologists may be surprised to discover how frequently sea-

weed natural products are discussed in medicine. Many bioactive substances must have evolved due to ecological pressures acting on seaweeds. Examples are competition for space and the maintenance of clean thallus surfaces, grazing pressures by herbivores, tolerance to dangerous levels of sunlight or UV-B radiation, desiccation during exposure at low tide or highly saline waters and conditions resulting from thallus breakage and wound formation. The chemical means that are employed by algae to overcome these problems can be potentially useful to humans and may result in new technologies such as natural antifoulants and novel UV-screens. Investigations of natural models can provide a more efficient way of discovering novel chemicals with unique pharmacological properties or biomedical uses.

The list of compounds in this review are by no means exhaustive, but they do cover the most important classes of active substances in seaweeds and much of the breadth of biological activities exhibited by seaweed natural products. Some have great potential as a source of environmentally-friendly pesticides, agrochemical compounds and drugs and tools for use in biochemical, pharmaceutical and medical research. An understanding of the chemical constituents of macroalgae is important, not only for the discovery of new therapeutic substances, but because such information may be of value to those interested in the scientific basis that underlies folklore remedies.

The ecological function of the toxins and bioactive substances isolated from macroalgae is generally unknown. One exception includes terpenoids which usually function as feeding deterrents and antifoulants. Some compounds such as the polysaccharides are thought to simply be storage carbohydrates, but do they exhibit similar bioactivities (especially antiviral and antibiotic properties) in the producer organism as shown in *in vitro* and *in vivo* assays in a range of animal and plant systems? The ecological role of the macroalgal kainoids, aplysiatoxins and polycavernosides is almost completely unknown. Perhaps this review will also spark renewed interest in secondary metabolites and toxins in seaweeds, and prompt researchers to discover the ecological significance of many of the products for which *in vivo* and *in vitro* bioactivities are known, but whose ecological importance remains a mystery.

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