Journal of Applied Phycology **16:** 245–262, 2004.

Review

Medicinal and pharmaceutical uses of seaweed natural products: A review

Albertus J. Smit
Department of Botany, University of Cape Town, Rondebosch, 7700, South Africa; Current address: School of Biology, Faculty of Science, University of KwaZulu-Natal, Westville Campus, Private Bag X54001, Durban, 4000, South Africa
**Author for correspondence (e-mail: ajsmit@science.uct.ac.za)*

Received 15 August 2003; revised and accepted 21 April 2004

Key words: biological activity, macroalga, medicine, pharmaceuticals, pharmacology, seaweeds

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 λ-carrageenan and partially cyclized μ/ί-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).

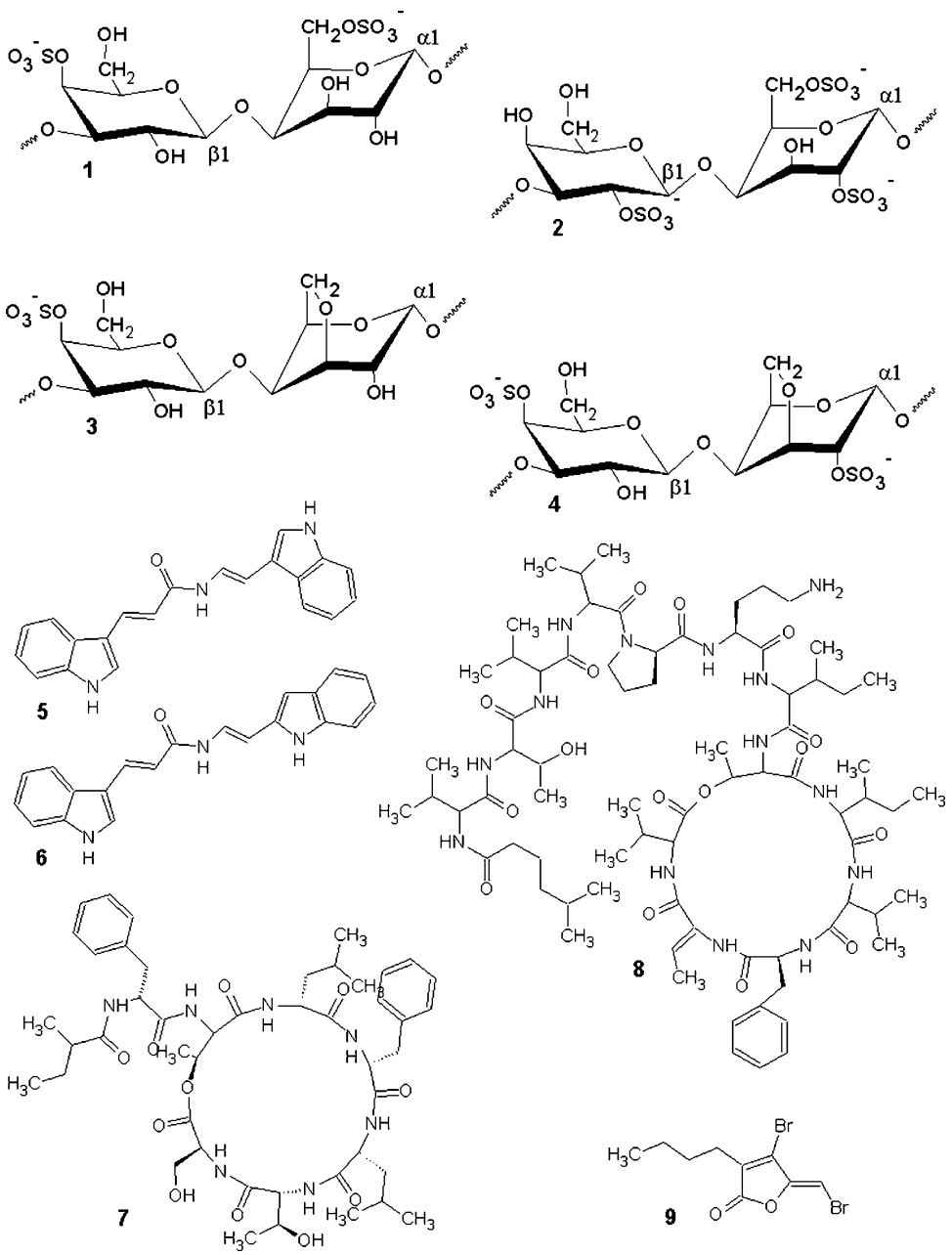

Figure 1. Idealised structures of μ-carrageenan (**1**), λ-carrageenan (**2**), κ-carrageenan (**3**) and ι-carrageenan (**4**). Some carrageenans have potent antiviral activities against several strains of HSV types 1 and 2. A carrageenan-based microbicide, Carraguard, is currently undergoing phase 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. (5*Z*)-4-bromo-5-(bromomethylene)-3-butyl- 2(5*H*)-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; Shanmugam 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 peripheral 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 contragestative 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 $1 \rightarrow 3{:}1 \rightarrow 6$-$\beta$-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 mediated by blood coagulation inhibitors such as heparin cofactor II or antithrombin III (Church et al., 1989; Colliec 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 know 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_2 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,

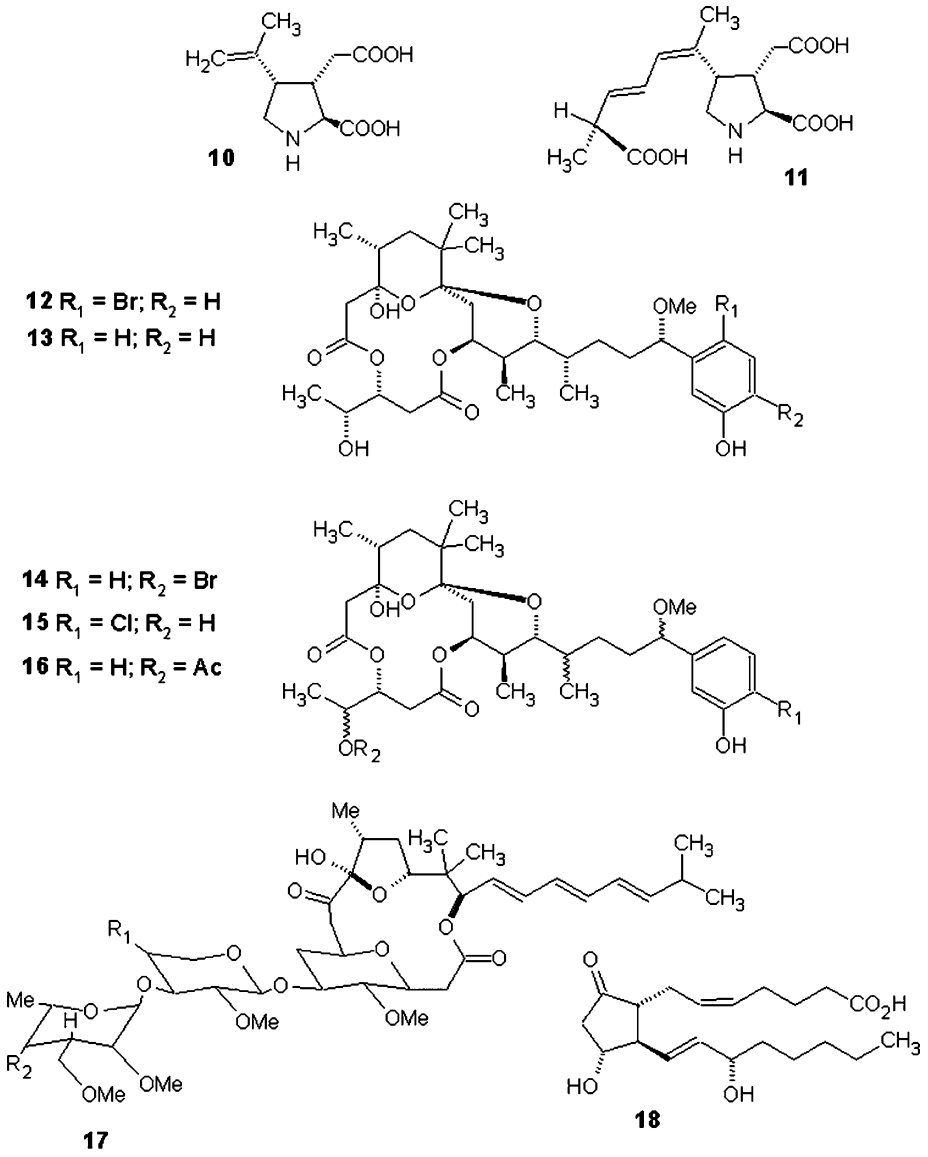

Figure 2. α-Kainic (**10**) and domoic acids (**11**) are pyrrolidine dicarboxylates with excitatory and excitotoxic activities. Kainoids occur in some pennate diatoms where they cause amnesic shellfish poisoning, but they are also produced by some members of the Ceramiales. They are used as tools in 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 manauealide A (**14**), manauealide B (**15**) and manauealide 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 manauealides 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_2, A_3, B and B_2 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 *Polycarvernosa tsudae* (Yotsu-Yamashita et al., 1993). Due to the association between *Polycarvernosa 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^{-1}, 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^1, N1′-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 (*Blatella 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 hydroxyeicotetraenoic 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, $1\rightarrow3{:}1\rightarrow6$-$\beta$-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 $1\rightarrow3{:}1\rightarrow6$-$\beta$-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 $1\rightarrow3{:}1\rightarrow6$-$\beta$-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). Porphyran 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 antiinflamatory 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 (Kiriyama 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 α-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_2 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_2 (PLA_2) 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_2 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_2 activity. Compounds active against PLA_2 include rhiphocephalin, a linear sesquiterpene from *Rhipocephalus 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 *Stypopodium zonale* (Mayer et al., 1993). Fucoidan also inhibits cytotoxic and myotoxic activities of several PLA_2 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 Pieta 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-sunscreens. 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.

Acknowledgements

The author would like to thank Rob Anderson, John Bolton and two anonymous reviewers for valuable comments regarding the structure and content of the manuscript. The search for the literature upon which the review is based was made possible by the *SeaweedAfrica* project (http://www.seaweedafrica.org/), which is funded under the INCO-DEV section of the fifth framework programme. Lastly, I wish to acknowledge the critical advice and comments of Prof. Brian Whitton during the review stages of the manuscript.

References

Abe S, Kaneda T (1975) Studies on the effects of marine products on cholesterol metabolism in rats. XI. isolation of a new betaine, ulvaline, from a green laver *Monostroma nitidum* and its depressing effect on plasma cholesterol levels. Bull. Japan Soc. Fish. 41: 567–571.

Al Hassan JM, Ali M, Thomson M, Fatima T, Gubler CJ, Criddle RS (1987) Prostaglandin associated mortality following intravenous injection of catfish epidermal secretions in rabbits. Prosta. Leukotr. Med. 28: 95–102.

Angulo Y, Lomonte B (2003) Inhibitory effect of fucoidan on the activities of crotaline snake venom myotoxic phospholipases A(2). Biochem Pharmacol. 66: 1993–2000.

Ara J, Sultana V, Qasim Rahmad VU (2002) Hypolipidaemic activity of seaweed from Karachi coast. Phytother. Res. 16: 479–483.

Baba M, Snoeck R, Pauwels R, De Clercq E (1988) Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stromatitis virus, and human immunodeficiency virus. Antimicrob. Agents Chemother. 32: 1742–1745.

Barbier P, Guise S, Huitorel P, Amade P, Pesando D, Briand C, Peyrot V (2001) Caulerpenyne from *Caulerpa taxifolia* has an antiproliferative activity on tumor cell line SK-N-SH and modifies the microtubule network. Life Sci. 70: 415–429.

Barcelo A, Claustre J, Moro F, Chayvaille JA, Cuber JC, Plaisancie P (2000) Mucin secretion is modulated by luminal factors in the isolated vascularly perfused rat colon. Gut 46: 218–224.

Barriault L, Boulet SL, Fujiwara K, Murai A, Paquette LA (1999) Synthesis and biological evaluation of analogs of the marine toxin polycavernoside A. Bioorg. Med. Chem. Lett. 9: 2069–2072.

Bates S (1998) Ecophysiology and metabolism of ASP toxin production. In Anderson DM, Cembella AD, Hallegraeff GM (eds), Physiological Ecolology of Harmful Algal Blooms, Springer-Verlag, Heidelberg, pp. 405–426.

Bates S (2000) Domoic-acid-producing diatoms: another genus added! J. Phycol. 36: 978–985.

Ben-Ari Y, Cossart R (2000) Kainate, a double agent that generates seizures: two decades of progress. Trends Neurosci. 23: 580–587.

Benevides NMB, Holanda ML, Melo FR, Freitas ALP, Sampaio AH (1998) Purification and partial characterisation of the lectin from the marine red alga *Enantiocladia duperreyi* (C. Agardh) Falkenberg. Bot. Mar. 41: 521–525.

Bird KT, Chiles TC, Longley RE, Kendrick AF, Kinkema MD (1992) Agglutinins from marine macroalgae of the southeastern United States. J. Appl. Phycol. 5: 213–218.

Bitou N, Ninomiya M, Tsujita T, Okuda H (1999) Screening of lipase inhibitors from marine algae. Lipids 34: 441–445.

Blumenthal PD (1988) Prospect comparison of Dilapan and *Laminaria* for pretreatment of the cervix in second trimester induction of abortion. Obstet. Gynecol. 72: 243–246.

Bond GR, van Zee A (1994) Overdosage of misoprostol in pregnancy. Am. J. Obstet. Gynecol. 171: 561–562.

Boyd WC, Reguera RM (1949) Hemagglutinating substances in various plants. J. Immunol. 62: 333–339.

Buckle PJ, Baldo BA, Taylor KM (1980) The anti-inflammatory activity of marine natural products–6-n-tridecylsalicylic acid, flexibilide and dendalone 3-hydroxybutyrate. Agents and Actions. 10: 361–367.

Cáceres PJ, Carlucci MJ, Damonte EB, Matsuhiro B, Zúñiga EA (2000) Carrageenans from Chilean samples of *Stenogramme interrupta* (Phyllophoraceae): Structural analysis and biological activity. Phytochemistry 53: 81–86.

Carcache LM, Rodriguez J, Rein KS (2003) The structural basis for kainoid selectivity at AMPA receptors revealed by low-mode docking calculations. Bioorg. Med. Chem. 11: 551–559.

Carlucci MJ, Ciancia M, Matulewicz MC, Cerezo AS, Damonte EB (1999a) Antiherpetic activity and mode of action of natural carrageenans of diverse structural types. Antivir. Res. 43: 93–102.

Carlucci MJ, Pujol CA, Ciancia M, Noseda MD, Matulewicz MC, Damonte EB, Cerezo AS (1997) Antiherpetic and anticoagulant properties of carrageenans from the red seaweed *Gigartina skottsbergii* and their cyclized derivatives: correlation between structure and biological activity. Int. J. Biol. Macromol 20: 97–105.

Carlucci MJ, Scolaro LA, Damonte EB (1999b) Inhibitory action of natural carrageenans on *Herpes simplex* virus infection of mouse astrocytes. Chemotheraphy 45: 429–436.

Carthew P (2002) Safety of carrageenan in foods. Env. Health Perspect. 110: A176.

Chapman VJ (1970) Seaweeds and Their Uses, 2nd edn, The Camelot Press Ltd., London, 304 pp.

Chen H, Sun P, Song Q (1995) Lectins, a powerful defensive weapon of aquatic animals. J. Oceanogr. Huanghai Bohai Seas 13: 61–71.

Chen J, Gerwick WH, Shatzman R, Laney M (1994) Isorawsonol and related IMP dehydrogenase inhibitors from the tropical green alga *Avrainvillea rawsonii*. J. Nat. Prod. 57: 947–952.

Chertkov KS, Davydova SA, Nesterova TA, Zviagintseva TN, Eliakova LA (1999) Efficiency of polysaccharide translam for early treatment of acute radiation illness. Radiats Biol Radioecol. 39: 572–577.

Church FC, Meade JB, Treanor RE, Whinna HC (1989) Antithrombin activity of fucoidan. J. biol. Chem. 264: 3618–3623.

Cisar JO, Sandberg AL, Abeygunawardana C, Reddy GP, Bush CA (1995) Lectin recognition of host-like saccharide motifs in streptococcal cell wall polysaccharides. Glycobiol. 5: 655–662.

Colliec S, Fischer AM, Tapon-Bretaudiere, J, Boisson C, Durand P, Jozefonvicz J (1991) Anticoaggulant properties of a fucoidan fraction. Thromb. Res. 64: 143–154.

Coombe DR, Parish CR, Ramshaw IE, Snowden JM (1987) Analysis of the inhibition of tumour metastasis by sulphated polysaccharides. Int. J. Cancer 39: 82–88.

Cordell GA (2000) Biodiversity and drug discovery—a symbiotic relationship. Phytochemistry 55: 463–480.

Culioli G, Daoudi M, Ortalo-Magne A, Valls R, Piovetti L (2001) (S)-12-hydroxygeranylgeraniol-derived diterpenes from the brown alga *Bifurcaria bifurcata*. Phytochemistry 57: 529–535.

Dalmo RA, Bogwald J, Ingebrigtsen K, Seljelid R (1996) The immunomodulatory effect of laminaran [β-(1,3)-D-glucan] on Atlantic salmon, *Salmo salar* L., anterior kidney leucocytes after intraperitoneal, peroral and peranal administration. J. Fish Dis. 19: 449–457.

Dalmo RA, Seljelid R (1995) The immunomodulatory effect of LPS, laminaran and sulphated laminaran [β-(1,3)-D-glucan] on Atlantic salmon, *Salmo salar* L., macrophages *in vitro*. J. Fish Dis. 18: 175–185.

Damonte EB, Neyts J, Pujol CA, Snoeck R, Andrei G, Ikeda S, Witvrouw M, Reymen D, Haines H, Matulewicz MC, Cerezo A, Coto CE, De Clercq E (1994) Antiviral activity of a sulfated polysaccharide from the red seaweed *Nothogenia fastigiata*. Biochem. Pharmacol. 47: 2187–2192.

Dannhardt G, Kiefer W (2001) Cyclooxygenase inhibitors—current status and future prospects. Eur. J. Med. Chem. 36: 109–126.

Davies LP, Jamieson DD, Baird-Lambert JA, Kazlauskas R (1984) Halogenated pyrrolopyrimidine analogues of adenosine from marine organisms: pharmacological activities and potent inhibition of adenosine kinase. Biochem. Pharmacol. 33: 347–355.

Davyt D, Entz W, Fernandez R, Mariezcurrena R, Mombru AW, Saldana J, Dominguez L, Coll J, Manta E (1998) A new indole derivative from the red alga *Chondria atropurpurea*. Isolation, structure determination, and anthelmintic activity. J. Nat. Prod. 61: 1560–1563.

Davyt D, Fernandez R, Suescun L, Mombru AW, Saldana J, Dominguez L, Coll J, Fujii MT, Manta E (2001) New sesquiterpene derivatives from the red alga *Laurencia scoparia*. Isolation, structure determination, and anthelmintic activity. J. Nat. Prod. 64: 1552–1555.

De Clercq E (1996) Chemotheraphy of human immunodeficiency virus (HIV) infection: anti-HIV agents targeted at early stages in the virus replicative cycle. Biomed. Pharmacother. 50: 207–215.

De Clercq E (2000) Current lead natural products for the Chemotheraphy of human immunodeficiency virus (HIV) infection. Med. Res. Rev. 20: 323–349.

Della Pieta F, Bilia AR, Breschi MC, Cinelli F, Morelli I, Scatizzi R (1993) Crude extracts and two linear diterpenes from *Cystoseira balearica* and their activity. Planta Med. 59: 135–138.

Della Pieta F, Breschi MC, Scatizzi R, Cinelli F (1995) Relaxing activity of two linear diterpenes from *Cystoseira brachycarpa* var. *balearica* on the contractions of intestinal preparations. Planta Med. 61: 493–496.

Dumelod BD, Ramirez RP, Tiangson CL, Barrios EB, Panlasigui LN (1999) Carbohydrate availability of arroz caldo with λ-carrageenan. Int. J. Food Sci. Nutr. 50: 283–289.

el Refaey H, Templeton A (1995) Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: a randomized comparison between two misoprostol regimen. Hum. Reprod. 10: 475–478.

el Sayed KA, Bartyzel P, Shen X, Perry TL, Zjawiony JK, Hamann MT (2000) Marine natural products as antituberculosis agents. Tetrahedron 56: 949–953.

Entzeroth M, Blackman AJ, Mynderse JS, Moore RE (1985) Structures and stereochemistries of oscillatoxin B, 31-noroscillatoxin B, oscillatoxin D, and 30-methyloscillatoxin D. J. Org. Chem. 50: 1255–1259.

Featonby-Smith BC, van Staden J (1984) Identification and seasonal variation of endogenous cytokinins in *Ecklonia maxima* (Osbeck) Papenf. Bot. Mar. 27:527–531.

Feldman SC, Reynaldi S, Stortz CA, Cerezo AS, Damont EB (1999) Antiviral properties of fucoidan fractions from *Leathesia difformis*. Phytomed. 6: 335–340.

Fischel JL, Lemée R, Formento P, Caldani C, Moll JL, Pesando D, Meinesz A, Grelier P, Pietra F, Guerriero A, Milano G (1995) Cell growth inhibitory effects of caulerpenyne, a sesquiterpenoid from the marine alga *Caulerpa taxifolia*. Anticancer Res. 15: 2155–2160.

Flower RJ, Blackwell GJ (1976) The importance of phospholipase A_2 in prostaglandin biosynthesis. Biochem. Pharmacol. 25: 285–291.

Francisco C, Banaigs B, Valls R, Codomier L (1985) Mediterraneol a, a novel rearranged diterpenoid-hydroquinone from the marine alga *Cystoseira mediterranea.* Tetrahedron Lett. 26: 2629–2632.

Fujiki H, Suganuma M (1996) Naturally-derived tumor promoters and inhibitors of carcinogenesis. J. Toxicol. 15: 129–156.

Fujiki H, Suganuma M, Yoshizawa S, Nishiwaki S, Winyar B, Sugimura T (1991) Mechanisms of action of okadaic acid class tumor promoters on mouse skin. Env. Health Persp. 93: 211–214.

Fukuyama Y, Kodama M, Miura I, Kinzyo Z, Kido M, Mori H, Nakayama Y, Takahashi M (1989) Structure of an anti-plasmin inhibitor, eckol, isolated from the brown alga *Ecklonia kurome* Okamura and inhibitory activities of its derivatives on plasma plasmin inhibitors. Chem. Pharm. Bull. 37: 349–353.

Fukuyama Y, Kodama M, Miura I, Kinzyo Z, Mori H, Nakayama Y, Takahashi M (1990) Anti-plasmin inhibitor. VI. Structure of phlorofucofuroeckol A, a novel phlorotannin with both dibenzo-1,4-dioxin and dibenzofuran elements, from *Ecklonia kurome* Okamura. Chem. Pharm. Bull. 38: 133–135.

Fusetani N, Hashimoto K (1984) Prostaglandin E_2: a candidate for causative agent of 'ogonori' poisoning. Bull. Jpn. Soc. Sci. Fish. 50: 463–469.

Galgani I, Pesando D, Porthe-Nibelle J, Fossat B, Girard JP (1996) Effect of caulerpenyne, a toxin extracted from *Caulerpa taxifolia* on mechanisms regulating intracellular pH in sea urchin eggs and sea bream hepatocytes. J. Giochem. Toxicol. 11: 243–250.

Gerwick WH, Bernart MW (1993) Eicosanoids and related compounds from marine algae. In Attaway DH, Zaborsky OR (eds), Marine Biotechnology, Vol.1, Pharmaceutical and Bioactive Natural Products, Plenum Press, NY, pp. 101–152.

Gerwick WH, Proteau PJ, Nagle DG, Wise ML, Jiang ZD, Bernart MW, Hamberg M (1993) Biologically active oxylipins from seaweeds. Hydrobiol. Ogia 260/261: 653–665.

Goetz G, Nakao Y, Scheur PJ (1997) Two acyclic kahalalides from the sacoglossan mollusk *Elysia rufescens*. J. Nat. Prod. 60: 562–567.

Graber DJ, Meier KH (1991) Acute misoprostol toxicity. Ann. Emerg. Med. 20: 549–551.

Graufel V, Kloareg B, Mabeau S, Durand P, Jozefonvicz J (1989) New natural polysaccharides with potent antithrombic activity: fucans from brown algae. Biomaterials 10: 363–368.

Gregson RP, Marwood JF, Quinn RJ (1979) The occurrence of prostaglandins PGE_2 and $PGF_{2\alpha}$ in a plant—the red alga *Gracilaria lichenoides*. Tetrahedron Lett. 46: 4505–4506.

Griffin RL, Rogers DJ, Spencer-Phillips PT, Swain L (1995) Lectin from *Codium fragile* ssp. *tomentosoides* conjugated to colloidal gold: a new histochemical reagent. Br. J. Biomed. Sci. 52: 225–227.

Gurr MI, Harwood JL (1991) Lipid biochemistry, an introduction. 4th ed., Chapman and Hall, London, p.406.

Haefner B (2003) Drugs from the deep: marine natural products as drug candidates. Drug Discov. Today 8: 536–544.

Hamann MT, Scheuer PJ (1993) Kahalalide F: A bioactive depsipeptide from the sacoglossan mollusk, *Elysia rufescens* and the Green Alga *Bryopsis* sp. J. Am. Chem. Soc. 115: 5825–5826.

Hamann MT, Otto CS, Scheuer PJ, Dunbar DC (1996) Kahalalides: Bioactive peptides from a marine mollusk *Elysia rufescens* and its algal diet *Bryopsis* sp. J. Org. Chem. 61: 6594–6600.

Hennings H, Lowry DT, Robinson VA, Morgan DL, Fujiki H, Yuspa SH (1992) Activity of diverse tumor promoters in a keratinocyte co-culture model of initiated epidermis. Carcinogenesis 13: 2145–2151.

Higa T, Kuniyoshi M (2000) Toxins associated with medicinal and edible seaweeds. J. Toxicol. Tox. Rev. 19: 119–137.

Høiby N (2002) Understanding bacterial biofilms in patients with cystic fibrosis: current and innovative approaches to potential therapies. J. Cystic Fibrosis 1: 249–254.

Hopkins KJ, Wang G-J, Schmued LC (2000) Temporal progression of kainic acid induced neuronal and myelin degeneration in the rat forebrain. Brain Res. 864: 69–80.

Horgen FD, delos Santos DB, Goetz G, Sakamoto B, Kan Y, Nagai H, Scheuer PJ (2000) A new depsipeptide from the sacoglossan mollusk *Elysia ornata* and the green alga *Bryopsis* species. J. Nat. Prod. 63: 152–154.

Hori K, Miyazawa K, Fusetani N, Hashimoto K, Ito K (1986) Hypnins, low-molecular weight peptidic agglutinins isolated from a marine red alga, *Hypnea japonica*. Biochim. Biophys. Acta. 873: 228–236.

Imbs AB, Vologodskaya AV, Nevshupova NV, Khotimchenko SV, Titlyanov EA (2001) Response of prostaglandin content in the red alga *Gracilaria verrucosa* to season and solar irradiance. Phytochemistry 58: 1067–1072.

Impellizzeri G, Mangiafico S, Oriente G, Piatelli M, Sciuto S, Fattorusso E, Magno S, Santacroce C, Sica D (1975) Amino acids and low molecular weight carbohydrates of some marine red algae. Phytochemistry 14: 1549–1557.

Ireland CM, Copp BR, Foster MP, McDonald LA, Radisky DC, Swersey JC (1993) Biomedical potential of marine natural products. In Attaway DH, Zaborsky OR (eds), Marine Biotechnology, Vol. 1, Pharmaceutical and Bioactive Natural Products, Plenum Press, NY, pp. 1–43.

Ito E, Nagai H (1998) Morphological observations of diarrhea in mice caused by aplysiatoxin; the causative agent of the red alga *Gracilaria coronopifolia* poisoning in Hawaii. Toxicon 36: 1913–1920.

Ito E, Nagai H (2000) Bleeding from the small intestine caused by aplysiatoxin, the causative agent of the red alga *Gracilaria coronopifolia* poisoning. Toxicon 38: 123–132.

Ito K, Tsuchida Y (1972) The effect of algal polysaccharides on depressing of plasma cholesterol level in rats. Proc. Int. Seaweed Symp. 7: 451–455.

Jacobs RS, Bober MA, Pinto I, Williams AB, Jacobson PB, de Carvalho MS (1993) In Attaway DH, Zaborsky OR (eds), Marine Biotechnology, Vol. 1, Pharmaceutical and Bioactive Natural Products, Plenum Press, NY, pp. 77–99.

Jurd KM, Rogers DJ, Blunden G, McLellan DS (1995) Anticoagulant properties of sulphated polysaccharides and a proteoglycan from *Codium fragile* ssp. *atlanticum*. J. Appl. Phycol. 7: 339–345.

Kaeffer B, Benard C, Lahaye M, Blottiere HM, Cherbut C (1999) Biological properties of ulvan, a new source of green seaweed

sulfated polysaccharides, on cultured normal and cancerous colonic epithelial cells. Planta Med. 65: 527–531.

Kakita H, Fukuoka S, Obika H, Li ZF, Kamishima H (1997) Purification and properties of a high molecular weight hemagglutinin from the red alga, *Gracilaria verrucosa*. Bot. mar. 40: 241–247.

Kakita H, Kitamura T (2003) Hemagglutinating activity in the cultivated red alga *Gracilaria chorda* Holmes, from Japan. In Chapman ARO, Anderson RJ, Vreeland VJ, Davison IR (eds), Proceedings of the 17th International Seaweed Symposium, Oxford University Press, Oxford, pp. 175–182.

Kan Y, Fujita T, Nagai H, Sakamoto B, Hokama Y (1998) Malyngamides M and N from the Hawaiian red alga *Gracilaria coronopifolia*. J. Nat. Prod. 61: 152–155.

Kato Y, Scheuer PJ (1974) Aplysiatoxin and debromoaplysiatoxin, constituents of the marine mollusk *Stylocheilus longicauda* (Quoy and Gaimard, 1824). J. Am. Chem. Soc. 96: 2245–2246.

Kawakubo A, Makino H, Ohnishi J-I, Hirohara H, Hori K (1997) The marine red alga *Eucheuma serra* J. Agardh, a high yielding source of two isolectins. J. Appl. Phycol. 9: 331–338.

Kazlauskas R, Mulder J, Murphy PT, Wells RJ (1980) New metabolites from the brown alga *Caulacystis caphalornithos*. Aust. J. Chem. 33: 2097–2101.

Kjelleberg S, Steinberg P (2001) Surface warfare in the sea. Microbiology Today 28: 134–135.

Kelecom A (2002) Secondary metabolites from marine microorganisms. An. Acad. Bras. Cienc. 74: 151–170.

Kiriyama S, Okazaki Y, Yoshida A (1968) Hypocholesterolemic effect of polysaccharides and polysaccharide foodstuffs in cholesterol fed rats. J. Nutr. 97: 382–388.

Kolender AA, Matulewicz MC, Cerezo AS (1995) Structural analysis of antiviral sulfated α-D -(1 3)-linked mannans. Carbohyd. Res. 273: 179–185.

Kris-Etherton PM, Hecker KD, Bonanome A, Coval SM, Binkoski AE, Hilpert KF, Griel AE, Etherton TD (2002) Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. Am. J. Med. 113: 71S-88S.

Kuznetsova TA, Krylova NV, Besednova NN, Vasil'eva VN, Zviagintseva TN, Krashevskii SV, Eliakova LA (1994) The effect of translam on the natural resistance indices of the irradiated organism. Radiats Biol Radioecol. 34: 236–239.

Lamela M, Anca J, Villar R, Otero J, Calleja JM (1989) Hypoglycemic activity of several seaweed extracts. J. Ethnopharmacol. 27: 35–43.

Laycock MV, de Freitas ASW, Wright JLC (1989) Glutamate agonists from marine algae. J. Appl. Phycol. 1: 113–122.

Lee C-N, Cheng W-F, Lai H-L, Shyu M-K, Chen T-M, Wu R-T, Shih J-C, Hsieh F-J (1998) Comparison between intravenous prostaglandin E_2 and extraamniotic prostaglandin $F_{2\alpha}$ instillation for termination in second-trimester pregnancy. J. Matern-Fetal Invest. 8:134–138.

Levine L (1998) Proteolysis negatively regulates agonist-stimulated arachidonic acid metabolism. Cell. Signal. 10: 653–659.

Lima HC, Costa FHF, Sampaio AH, Neves SA, Benevides NMB, Teixeira DIA, Rogers DJ, Freitas ALP (1998) Induction and inhibition of human lymphocyte transformation by the lectin from the red marine alga *Amansia multifida*. J. Appl. Phycol. 10: 153–162.

Lincoln RA, Strupinski K, Walker JM (1991) Bioactive compounds from algae. Life Chem. Rep. 8: 97–183.

Llovo J, Lopez A, Fabregas J, Munoz A (1993) Interaction of lectins with *Cryptosporidium parvum*. J. Infect. Dis. 167: 1477–1480.

Maeda M, Kodama T, Saito M, Tanaka T, Yoshizumi H, Nomoto K, Fujita T (1987) Neuromuscular action of insecticidal domoic acid on the American cockroach. Pest. Biochem. Biophysiol. 28: 85–92.

Maeda M, Kodama T, Tanaka T, Ohfune Y, Nomoto K, Nishimura K, Fujita T (1984) Insecticidal and neuromuscular activities of domoic acid and its related compounds. J. Pest. Sci. 9: 27–32.

Maeda M, Kodama T, Tanaka T, Yoshizumi H, Takemoto T, Nomoto K, Fujita T (1986) Structures of isodomoic acids A, B and C, novel insecticidal amino acids from the red alga *Chondria armata*. Chem. Pharmaceut. Bull. 34: 4892–4895.

Majczak GAH, Richartz RRTB, Duarte MER, Noseda MD (2003) Antiherpetic activity of heterofucans isolated from *Sargassum stenophyllum* (Fucales, Phaeophyta). In Chapman ARO, Anderson RJ, Vreeland VJ, Davison IR (eds), Proceedings of the 17th International Seaweed Symposium, Oxford University Press, Oxford, pp. 169–174.

Malhotra R, Ward M, Bright H, Priest R, Foster MR, Hurle M, Blair E, Bird M (2003) Isolation and characterisation of potential respiratory syncytial virus receptor(s) on epithelial cells. Microbes Infect. 5: 123–133.

Manefield M, Harris L, Rice SA, De Nys R, Kjelleberg S (2000) Inhibition of luminescence and virulence in the black tiger prawn (*Penaeus monodon*) pathogen *Vibrio harveyi* by intercellular signal antagonists. Appl. Environ. Microbiol. 66: 2079–2084.

Manefield M, Welch M, Givskov M, Salmond GPC, Kjelleberg S (2001) Halogenated furanones from the red alga, *Delisea pulchra*, inhibit carbapenem antibiotic synthesis and exoenzyme virulence factor production in the phytopathogen *Erwinia carotovora*. FEMS Microbiol. Lett. 205: 131–138.

Maruyama H, Nakajima J, Yamamoto I (1987) A study on the anticoagulant and fibrinolytic activities of a crude fucoidan from the edible brown seaweed *Laminaria religiosa*, with special reference to its inhibitory effect on the growth of sarcoma-180 ascites cells subcutaneously implanted into mice. Kitasato Arch. Exp. Med. 60: 105–121.

Matou S, Helley D, Chabut D, Bros A, Fischer A-M (2002) Effect of fucoidan on fibroblast growth factor-2-induced angiogenesis *in vitro*. Thromb. Res. 106: 213–221.

Matsubara K, Matsuura Y, Hori K, Miyazawa K (2000) An anticoagulant proteoglycan from the marine green alga, *Codium pugniformis*. J. Appl. Phycol. 12: 9–14.

Mayer AMS, Lehmann VKB (2000) Marine pharmacology in 1998: Marine compounds with antibacterial, anticoagulant, antifungal, antiinflammatory, anthelmintic, antiplatelet, antiprotozoal, and antiviral activities; with actions on the cardiovascular, endocrine, immune, and nervous systems; and other miscellaneous mechanisms of action. Pharmacologist 42: 62–69.

Mayer AMS, Paul VJ, Fenical W, Norris JM, de Carvalho MS, Jacobs RS (1993) Phospholipase A_2 inhibitors from marine algae. Hydrobiologia 260/261: 521–529.

Mazumder S, Ghosal PK, Pujol CA, Carlucci MJ, Damonte EB, Ray B (2002) Isolation, chemical investigation and antiviral activity of polysaccharides from *Gracilaria corticata* (Gracilariaceae, Rhodophyta). Int. J. biol. Macromol. 31: 87–95.

Moore RE (1982) Toxins, anticancer agents, and tumor promoters from marine prokaryotes. Pure and Appl. Chem. 54: 1919–1934.

Mullin JM, McGinn MT, Snock KV, Imaizumi S (1990) The effects of teleocidin and aplysiatoxin tumor promoters on epithelial tight

junctions and transepithelial permeability: comparison to phorbol esters. Carcinogen. 11: 377–385.

Mynderse JS, Moore RE (1978) Toxins from blue-green algae: Structures of oscillatoxin A and three related bromine-containing toxins. J. Org. Chem. 43: 2301–2303.

Nagai H, Yasumoto T, Hokama Y (1996) Aplysiatoxin and debromoaplysiatoxin as the causative agents of a red alga *Gracilaria coronopifolia* poisoning in Hawaii. Toxicon 34: 753–761.

Nagai H, Yasumoto T, Hokama Y (1997) Manauealides, some of the causative agents of a red alga *Gracilaria coronopifolia* poisoning in Hawaii. J. Nat. Prod. 60: 925–928.

Nakamura H, Moriya M (1999) Purification and partial characterization of a lectin-like protein from the sea algae *Laminaria diabolica* that induces fertilization envelope formation in sea urchin eggs. Zool. Sci. 16: 247–253.

Nakashima H, Kido Y, Kobayashi N, Motoki Y, Neushul M, Yamamoto N (1987a) Antiretroviral activity in a marine red alga; reverse transcriptase inhibition by an aqueous extract of *Schizymenia pacifica*. J. Cancer Res. Clin. Onc. 113: 413–416.

Nakashima H, Kido Y, Kobayashi N, Motoki Y, Neushul M, Yamamoto N (1987b) Purification and characterization of an avian myeloblastosis and human immunodeficiency virus reverse transcriptase inhibitor, sulfated polysaccharides extracted from sea algae. Antimicrob. Agents Chemotheraphy 31: 1524–1528.

Neves SA, Dias-Baruff M, Freitas AL, Roque-Barreira MC (2001) Neutrophil migration induced *in vivo* and *in vitro* by marine algal lectins. Inflam. Res. 50: 486–490.

Ng TB, Li WW, Yeung HW (1989) Effects of lectins with various carbohydrate binding specificities on lipid metabolism in isolated rat and hamster adipocytes. Int. J. Biochem. 21: 149–155.

Nishide E, Anzai H, Uchida H (1993) Effects of alginates on the ingestion and excretion of cholesterol in the rat. J. Appl. Phycol. 5: 207–211.

Nishide E, Uchida H (2003) Effects of *Ulva* powder on the ingestion and excretion of cholesterol in rats. In Chapman ARO, Anderson RJ, Vreeland VJ, Davison IR (eds), Proceedings of the 17th International Seaweed Symposium, Oxford University Press, Oxford, pp. 165–168.

Nishino T, Nagumo T (1991) The sulfate-content dependence of the anticoagulant activity of a fucan sulfate from the brown seaweed *Ecklonia kurome*. Carbohyd. Res. 214: 193–197.

Nishino T, Nagumo T (1992) Anticoagulant and antithrombin activities of oversulfated fucans. Carbohyd. Res. 229: 355–362.

Noa M, Más R, Carbajal D, Valdés S (2000) Effect of D-002 on acetic acid-induced colitis in rats at single and repeated doses. Pharmacol. Res. 41: 391–395.

Noguchi T, Matsui T, Miyazawa K, Asakawa M, Iijima N, Shida, Fuse M, Hosaka Y, Kirigaya C, Watabe K, Usui S, Kukagawa A (1994) Poisoning by the red alga 'ogonori' (*Gracilaria verrucosa*) on the Nojima Coast, Yokohama, Kanagawa Prefecture, Japan. Toxicon 32: 1533–1538.

Nomura K, Nakamura H, Suzuki N (2000) False fertilization in sea urchin eggs induced by diabolin, a 120K kelp protein. Biochem. Biophys. Res. Comm. 273: 691–693.

Nuijen B, Bouma M, Talsma H, Manada C, Jimeno JM, Lopez-Lazaro L, Bult A, Beijnen JH (2000) Development of a lyophilized parenteral pharmaceutical formulation of the investigational polypeptide marine anticancer agent kahalalide F. Drug Dev. Ind. Pharm. 27: 767–780.

Oehninger S, Clark GF, Acosta AA, Hodgen GD (1991) Nature of the inhibitory effect of complex saccharide moieties on the tight binding of human spermatozoa to the human zona pellucida. Fertil. Steril. 55: 165–169.

Ohta T, Sasaki S, Oohori T, Yoshikawa S, Kurihara H (2002) β-Glucosidase inhibitory activity of a 70% methanol extract from ezoishige (*Pelvetia babingtonii* de Toni) and its effect on the elevation of blood glucose level in rats. Biosci. Biotechnol. Biochem. 66: 1552–1554.

Okamura H, Kuroda S, Ikegami S, Tomita K, Sugimoto Y, Sakaguchi S, Ito Y, Katsuki T, Yamaguchi M (1993) A formal synthesis of aplysiatoxin: enantioselective synthesis of Kishi's aldehyde. Tetrahedron 49: 10531–10554.

Okamura H, Kuroda S, Tomita K, Ikegami S, Sugimoto Y, Sakaguchi S, Katsuki T, Yamaguchi M (1991) Synthesis of aplysiatoxin: stereoselective synthesis of key fragments. Tetrahedrom Lett. 32: 5137–5140.

Osborne NJT, Webb PM, Shaw GR (2001) The toxins of *Lyngbya majuscula* and their human and ecological health effects. Env. Int. 27: 381–392.

Panlasigui LN, Baello OQ, Dimatangal JM, Dumelod BD (2003) Blood cholesterol and lipid-lowering effects of carrageenan on human volunteers. Asia-Pac. J. Clin. Nutr. 12: 209–214.

Palermo JA, Flower BP, Seldes AM (1992) Chondriamides A and B, new indolic metabolites from the red alga *Chondria* sp. Tetrahedron Lett. 33: 3097–3100.

Parent-Massin D, Fournier V, Amade P, Lemee R, Durand-Clement M, Delescluse C, Pesando D (1996) Evaluation of the toxicological risk to humans of caulerpenyne using human hematopoietic progenitors, melanocytes, and keratinocytes in culture. J. Toxicol. Env. Health 47: 47–59.

Patankar MS, Oehninger S, Barnett T, Williams RL, Clark GF (1993) A revised structure for fucoidan may explain some of its biological activities. J. Biol. Chem. 268: 21770–21776.

Patchett RA, Kelly AF, Kroll RG (1991) The adsorption of bacteria to immobilized lectins. J. Appl. Bacteriol. 71: 277–284.

Patier P, Yvin J, Kloareg B, Liénart Y, Rochas C (1993) Seaweed liquid fertilizer from *Ascophyllum nodosum* contains elicitors of plant D-glycanases. J. Appl. Phycol. 5: 343–349.

Pedrotti ML, Lemee R (1996) Effect of microalgae treated with natural toxins on the nutrition and development of filter-feeding sea-urchin larvae. Mar. Env. Res. 48: 177–192.

Pesando D, Huitorel P, Dolcini V, Amade P, Girard JP (1998) Caulerpenyne interferes with microtubule-dependent events during the first mitotic cycle of sea urchin eggs. Eur. J. Cell Biol. 77: 19–26.

Pesando D, Lemée R, Ferrua C, Amade P, Girard J-P (1996) Effects of caulerpenyne, the major toxin from *Caulerpa taxifolia* on mechanisms related to sea urchin egg cleavage. Aquat. Toxicol. 35: 139-155.

Ponce NMA, Pujol CA, Damonte EB, Flores ML, Stortz CA (2003) Fucoidans from the brown seaweed *Adenocystis utricularis*: extraction methods, antiviral activity and structural studies. Carbohyd. Res. 338: 153–165.

Premakumara GAS, Ratnasooriya WD, Tillekeratne LMV (1995) Studies on the post-coital contraceptive mechanisms of crude extract of Sri Lankan marine red alga, *Gelidiella acerosa*. Contraception 52: 203–207.

Premakumara GAS, Ratnasooriya WD, Tillekeratne LMV (1996) Isolation of a non-steroidal contragestative agent from Sri Lankan marine red alga, *Gelidiella acerosa*. Contraception 54: 379–383.

Ramsey UP, Bird CJ, Shacklock PF, Laycock MV, Wright JL (1994) Kainic acid and 1'-hydroxykainic acid from Palmariales. Nat. Toxins 2: 286–292.

Rasmussen TB, Manefield M, Andersen JB, Eberl L, Anthoni U, Christophersen C, Steinberg P, Kjelleberg S, Givskov M (2000) How *Delisea pulchra* furanones affect quorum sensing and swarming motility in *Serratia liquefaciens* MG1. Microbiology 146: 3237–3244.

Religa P, Kazi M, Thyberg J, Gaciong Z, Swedenborg J, Hedin U (2000) Fucoidan inhibits smooth muscle cell proliferation and reduces mitogen-activated protein kinase activity. Eur. J. Vasc. Endovasc. Surg. 20: 419–426.

Renn DW (1997) Biotechnology and the red seaweed polysaccharide industry: status, needs and prospects. Tibtech 15: 9–14.

Renn DW, Noda H, Amano H, Nishino T, Nishizana K (1994a) Antihypertensive and antihyperlipidemic effects of funoran. Fisheries Sci. 60: 423–427.

Renn DW, Noda H, Amano H, Nishino T, Nishizana K (1994b) Study on hypertensive and antihyperlipidemic effect of marine algae. Fisheries Sci. 60: 83–88.

Rogers DJ, Hori K (1993) Marine algal lectins: New developments. Hydrobiologia 260/261: 589–261.

Saito K, Nishijima M, Ohno N (1992) Structure and antitumor activity of the less-branched derivatives of an alkali-soluble glucan isolated from *Omphalia lapidescens*. Chem. Pharmaceut. Bull. 40: 261–263.

Sajiki J (1997) Effects of acetic acid treatment on the concentrations of arachidonic acid and prostaglandin E_2 in the red algae, *Gracilaria asiatica* and *G. rhodocaudata*. Fisheries Sci. 63: 128–131.

Sajiki J, Kakimi H (1998) Identification of eicosanoids in the red alga, *Gracilaria asiatica*, using high-performance liquid chromatography and electrospray ionization mass spectrometry. J. Chromatogr. 795: 227–237.

Sato M, Nakano T, Takeuchi M, Kanno N, Nagahisa E, Sato Y (1996) Distribution of neuroexitatory amino acids in marine algae. Phytochemistry 42: 1595–1597.

Schaeffer DJ, Krylov VS (2000) Anti-HIV activity of extracts and compounds from algae and cyanobacteria. Ecotox. Env. Safe. 45: 208–227.

Scheuer PJ, Haman MT, Gravalos DG (2000) Cytotoxic and antiviral compound. US Patent Number 6011010.

Serdula M, Bartolini G, Moore RE, Gooch J, Wiebenga N (1982) Seaweed itch on windward Oahu, Hawaii. Med. J. 41: 200–201.

Shanmugam M, Mody KH, Ramavat BK, Murthy ASK, Siddhanta AK (2002) Screening of Codiacean algae (Chlorophyta) of the Indian coasts for blood anticoagulant activity. Indian Ind. J. mar. Sci. 31: 33–38.

Sharma GM, Sahni MK (1993) Marine proteins and clinical chemistry. In Attaway DH, Zaborsky OR (eds), Marine Biotechnology, Vol. 1. Pharmaceutical and Bioactive Natural Products. Plenum Press, NY, pp. 153–180.

Shibata H, Kimura-Takagi I, Nagaoka M, Hashimoto S, Aiyama R, Iha M, Ueyama S, Yokokura T (2000) Properties of fucoidan from *Cladosiphon okamuranus* tokida in gastric mucosal protection. Biofactors 11: 235–245.

Smith DS, Kitts DD (1994) A competitive enzyme-linked immunoassay for domoic acid determination in human body fluids. Food Chem. Toxicol. 32: 1147–1154.

Sparidans RW, Stokvis E, Jimeno JM, Lopez-Lazaro L, Schellens JH, Beijnen JH (2001) Chemical and enzymatic stability of a cyclic depsipeptide, the novel, marine-derived, anti-cancer agent kahalalide F. Anticancer Drugs 12: 575–582.

Spieler R (2002) Seaweed compound's anti-HIV efficacy will be tested in southern Africa. Lancet 359: 1675.

Stefanov K, Konaklieva M, Brechany EY, Christie WW (1988) Fatty acid composition of some algae from the Black Sea. Phytochemistry 27: 3495–3497.

Stokvis E, Rosing H, López-Lázaro L, Rodriguez I, Jimeno JM, Supko JG, Schellens JHM, Beijnen JH (2002) Quantitative analysis of the novel depsipeptide anticancer drug Kahalalide F in human plasma by high-performance liquid chromatography under basic conditions coupled to electrospray ionization tandem mass spectrometry. J. mass Spectrom. 37: 992–1000.

Sugawara I, Itoh W, Kimura S, Mori S, Shimada K (1989) Further characterization of sulfated homopolysaccharides as anti-HIV agents. Experientia 45: 996–998.

Takemoto T, Daigo K (1958) Constituents of *Chondria armata* and their pharmacological effects. Chem. Pharmaceut. Bull. 6: 578–580.

Takikawa M, Uno K, Ooi T, Kusumi T, Akera S, Muramatsu M, Mega H, Horita C (1998) Crenulacetal C, a marine diterpene, and its synthetic mimics inhibiting *Polydora websterii*, a harmful lugworm damaging pearl cultivation. Chem. Pharmaceut. Bull. 46: 462–466.

Tanabe H, Kamishima H, Kobayashi Y (1993) Inhibitory effect of red alga lectin and skipjack fat on the growth of the red tide plankton *Chattonella antiqua*. J. Ferment. Bioeng. 75: 387–388.

Tobacman JK (2001) review of harmful gastrointestinal effects of carrageenan in animal experiments. Env. Health Perspect. 109: 983–994.

Trento F, Cattaneo F, Pescador R, Porta R, Ferro R (2001) Antithrombin activity of an algal polysaccharide. Thromb. Res. 102: 457–465.

Ueyama H, Sasaki I, Shimomura K, Suganuma M (1995) Specific protein interacting with a tumor promoter, debromoaplysiatoxin, in bovine serum is α-1-acid glycoprotein. J. Cancer Res. Clin. Onc. 121: 211–218.

Urones JG, Basabe P, Marcos IS, Pineda J, Lithgow AM, Moro RF, Brito Palma FMS, Araujo MEM, Gravalos MDG (1992) Meroterpenes from *Cystoseira usneoides*. Phytochemistry 31: 179–182.

Valls R, Piovetti L, Banaigs B, Archavlis A, Pellegrini M (1995) (S)-13-hydroxygeranylgeraniol-derived furanoditerpenes from *Bifurcaria bifurcata*. Phytochemistry 39: 145–149.

Wakamiya T, Nakamoto H, Shibata T (1984) Structural determination of Carnosadine, a new cyclopropyl amino acid, from the alga *Grateloupia carnosa*. Tetrahedron Lett. 25: 4411–4412.

Wallace JL (1999) Distribution and expression of cyclooxygenase (COX) isoenzymes, their physiological roles, and the categorization of nonsteroidal anti-inflammatory drugs (NSAIDs). Am. J. Med. 107: 11S-17S.

Watanabe K, Miyakado M, Ohno N, Okada A, Yanagi K, Moriguchi K (1989) A polyhalogenated insecticidal monoterpene from the red alga, *Plocamium telfairiae*. Phytochemistry 28: 77–78.

Watanabe K, Umeda K, Kurita Y, Takayama C, Miyakado M (1990) Two insecticidal monoterpenes, telfairine and aplysiaterpenoid A, from the red alga *Plocamium telfairiae*: structure elucidation, biological activity, and molecular topographical consideration by a semiempirical molecular orbital study. Pest. Biochem. Physiol. 37: 275–286.

White JD, Blakemore PR, Browder CC, Hong EJ, Robarge LA (2001) Total synthesis of the marine toxin polycavernoside A

via selective macrolactonization of a trihydroxy carboxylic acid. J. Am. Chem. Soc. 123: 8593–8595.

Witvrouw M, Este JA, Mateu MQ, Reymen D, Andrei G, Snoeck R, Ikeda S, Pauwels R, Bianchini NV, Desmyter J, de Clercq E (1994) Activity of a sulfated polysaccharide extracted from the red seaweed *Aghardhiella tenera* against human immunodeficiency virus and other enveloped viruses. Antiviral Chem. Chemotheraphy 5: 297–303.

Wu AM, Wu JH, Watkins WM, Chen CP, Song SC, Chen YY (1998) Differential binding of human blood group Sd(a+) and Sd(a-) Tamm-Horsfall glycoproteins with *Dolichos biflorus* and *Vicia villosa*-B4 agglutinins. FEBS Lett. 429: 323–326.

Wu AM, Wu JH, Watkins WM, Chen CP, Tsai MC (1996) Binding properties of a blood group Le(a+) active sialoglycoprotein, purified from human ovarian cyst, with applied lectins. Biochim. Biophys. Acta—Mol. Basis Dis. 1316: 139–144.

Yoshizawa Y, Ametani A, Tsunehiro J, Nomura K, Itoh M, Fukui F, Kaminogawa S (1995) Macrophage stimulation activity of the polysaccharide fraction from a marine alga (*Porphyra yezoensis*): structure-function relationships and improved solubility. Biosci. Biotech. Biochem. 59: 1933–1937.

Yotsu-Yamashita M, Haddock RL, Yasumoto T (1993) Polycavernoside A: a novel glycosidic macrolide from the red alga *Polycavernosa tsudai* (*Gracilaria edulis*). J. Am. Chem. Soc. 115: 1147–1148.

Yotsu-Yamashita M, Seki T, Paul VJ, Naoki H, Yasumoto T (1995) Four new analogs for polycavernoside A. Tetrahedron Lett. 36: 5563–5566.

Zaman L, Arakawa O, Shimosu A, Onoue Y, Nishio S, Shida Y, Noguchi T (1997) Two new isomers of domoic acid from a red alga, *Chondria armata*. Toxicon 35: 205–212.

Zaporozhets TA, Zvyagintseva TN, Besednova NN, Elyakova LA (1995) Influence of translam for the immune response irradiated mice. Radiobiol. 35: 260–263.

Zeitlin L, Whaley KJ, Hegarty TA, Moench TR, Cone RA (1997) Tests of vaginal microbicides in the mouse genital herpes model. Contraception 56: 329–335.

Zhu W, Ooi VEC, Chan PKS, Ang Jr PO (2003) Inhibitory effect of extracts of marine algae from Hong Kong against Herpes simplex viruses. In Chapman ARO, Anderson RJ, Vreeland VJ, Davison IR (eds), Proceedings of the 17th International Seaweed Symposium, Oxford University Press, Oxford, pp. 159–164.