J Appl Phycol (2014) 26:2211–2264
DOI 10.1007/s10811-014-0245-2

The potential of seaweed as a source of drugs for use in cancer chemotherapy

Catherine Murphy · Sarah Hotchkiss · Jenny Worthington · Stephanie R. McKeown

Received: 19 September 2013 / Revised and accepted: 21 January 2014 / Published online: 20 February 2014

Abstract This review discusses studies on marine macroalgae that have been investigated for their potential as sources of novel anti-cancer drugs. The review highlights the very large number of studies of crude, partially purified and purified seaweed extracts, collected from many locations, which have shown potential as sources of potent anti-cancer drugs when tested in vitro and/or in vivo. The activity of polysaccharides, polyphenols, proteinaceous molecules, carotenoids, alkaloids, terpenes and others is described here. In some reports, mechanistic studies have identified specific inhibitory activity on a number of key cellular processes including apoptosis pathways, telomerase and tumour angiogenesis. However, despite the potential shown by these studies, translation to clinically useful preparations is almost non-existent. It is hoped this review will serve as a source document and guide for those carrying out research into the potential use of macroalgae as a source of novel anti-cancer agents.

Keywords Macroalgae · Tumour · Sulphated polysaccharide · Carbohydrate · Polyphenol · Carotenoid

C. Murphy (✉) · S. Hotchkiss
Cybercolloids Ltd, Unit 4A, Site 13, Carrigaline Industrial Estate, Carrigaline, County Cork, Ireland
e-mail: catherine@cybercolloids.net

S. Hotchkiss
e-mail: sarah@cybercolloids.net

J. Worthington
Axis Bioservices Ltd, Coleraine, Northern Ireland, UK
e-mail: jenny@axisbio.co.uk

S. R. McKeown
School of Biomedical Sciences, University of Ulster, Coleraine, Northern Ireland, UK
e-mail: sr.mckeown@ulster.ac.uk

Introduction

This review provides an overview of the evidence that macroalgae-derived natural products provide a potential source for novel anti-cancer drugs. To contextualize their use, a short initial discussion of the issues relating to cancer treatment is provided.

Approaches to cancer treatment

The initial presentation of a tumour is the result of genetic changes which occur in critical genes within a cell that control its normal growth and development. This leads to unregulated proliferation of the cell and its progeny which results, except in the case of most haematological malignancies, in the development of a solid tumour. The increase in tumour size depends on a large number of interacting factors including a reduction in cell death (particularly through the apoptosis pathway), an increase in proliferation and the generation of new blood vessels to provide oxygen and nutrients to support the growing mass (King and Robins 2006). Tumours are classified in relation to their tissue of origin to include squamous cell carcinomas, adenocarcinomas, sarcomas, lymphomas and neuroectodermal cancers; however, even within each group, there is much heterogeneity (Weinberg 2007). Six main characteristics of tumours have been proposed: the ability to proliferate without reliance on external growth signals, insensitivity to anti-growth signals, resistance to apoptosis, limitless replicative potential, the ability to encourage angiogenesis and the ability to metastasise (Hanahan and Weinberg 2011). In many instances, this final characteristic is the one that results in death of the individual since there are very few effective treatments of metastatic cancer. As tumours grow, the genome becomes increasingly unstable with the acquisition of further deleterious mutations that promote malignant progression.

The complexity of tumour pathology makes treatment very challenging. When a patient presents with a single solid tumour, it may be possible to remove it through surgical excision or by sterilization with external beam radiotherapy; however, in many cases, this is not possible. Even when surgery or radiotherapy is used as a first-line treatment, in many patients this approach is not curative. This can be for a number of reasons, e.g. lack of accessibility for complete excision, limitations in the dose of radiation used due to the risk of damage to critical normal structures in the radiation field etc. When surgery or radiotherapy is not possible or limited, then cytotoxic chemotherapy (CCT) is a main treatment option. CCT can be used as a first-line treatment or as an adjunct to other therapeutic approaches. The aim of CCT is to destroy all cancer cells within the body, including those that have spread to distant tissues, i.e. metastasized (Kintzios 2004). Conventional CCT drugs are primarily designed to act on rapidly proliferating cells (King and Robins 2006). Unfortunately, many healthy cells in the body with high rates of proliferation can also be affected, e.g. cells in the bone marrow, intestinal villi and hair follicles. Side effects are consequently moderate to severe and include nausea, anaemia, weakening of the immune system, hair loss, diarrhoea and vomiting. Due to the heterogeneous nature of tumours and their inherent genetic instability, tumours may develop resistance to CCT through selection for resistant subclones. The majority of the most common cancers are therefore not curable with a single CCT drug, and treatment approaches frequently include surgery and/or radiotherapy, where practical, and/or a combination of several drugs (Kintzios 2004).

More recently, research into CCT has focussed on improving the specificity of cytotoxic agents by targeting specific features of the tumour micro-environment including the poorly formed vasculature (Wu and Staton 2012), hypoxic tumour cell sub-populations (McKeown et al. 2007) and infiltrating inflammatory cells (Joyce 2005). In addition, considerable efforts are being made to identify molecular targets specific to tumour cells (Kaufman et al. 2008). However, to date, there have only been a few successes with this approach, and most novel agents still require combination with more conventional cytotoxic drugs and/or surgery/radiotherapy. One approach to identify new CCT agents is to mine the natural environment. This review now focusses on the potential of marine-derived macroalgae as a source of new CCT agents.

Marine natural products as a source of pharmaceuticals

Natural products in medicine

Humans have made use of natural resources as a source of medicinal compounds for thousands of years. In many Asian and African countries, traditional therapies are still widely used as a primary treatment. In addition, many people in developed countries (70 to 80 %) have used some form of alternative or complementary medicine (http://www.who.int/mediacentre/factsheets/2003/fs134/en/). Bioactivity is an inherent characteristic of natural products as they are derived from living materials that use chemicals to interact with other tissues and foreign organisms through binding with specific receptors (Maschek and Baker 2008). This bioactivity can be defined as a physiological response elicited by a molecule binding to a specific ligand; the response may be beneficial or deleterious (Colegate and Molyneux 2008). The most commonly identified bioactive natural products have been shown to elicit anti-oxidant (Jiménez-Escrig et al. 2001), antimicrobial (Hornsey and Hide 1974; Reichelt and Borowitzka 1984; Kubanek et al. 2003), anti-viral (Ponce et al. 2003) or anti-tumour (Usui et al. 1980; this review) activity.

A bioactive substance may be used as a crude extract or as a pure/semi-pure isolate. There are advantages and disadvantages to both approaches. Clearly crude extracts are easier and cheaper to produce; however, they are likely to suffer from seasonal, spatial and morphological variation which will affect the quality of the final product (Colegate and Molyneux 2008). Other compounds will be present in crude extracts, and the effects of these impurities, either synergistic or antagonistic, are rarely known. Isolation of a pure bioactive molecule allows for the dose to be reproducible and structural determination to be carried out which enables elucidation of the mechanism of action (Colegate and Molyneux 2008). A problem with natural product isolation is that yields tend to be low.

It has been reported that over 50 % of prescribed drugs are either natural products or synthetic chemicals that derive from natural products (Newman et al. 2000). This increases to 63 % of drugs used for CCT (Cragg and Newman 2009). Pharmaceuticals from natural products can be derived from many different plant and animal species. A small number of marine-derived compounds have entered clinical trials (Table 1), although only one is derived from seaweed (kahalalide F; see "Protein and peptides"). This is somewhat surprising given the extensive evidence of the potential of marine macroalgae as a source of anti-cancer drugs. This evidence is summarised and discussed below.

Seaweed as a source of pharmaceutical agents

Macroalgae, commonly known as seaweeds, have been consumed in Asia and parts of Europe for centuries. The biggest consumers of seaweed today are China, Japan, Korea, Indonesia, Philippines and Hawaii and to a lesser extent, France, Ireland, Iceland, Norway, Wales and coastal areas of the USA and Canada (Yuan 2008). The benefits of eating seaweed were first identified through epidemiological studies that showed the low prevalence of diseases such as coronary

Table 1 Anti-cancer agents from marine sources which are currently in clinical development

Chemical name and synonyms	Class of molecule	Isolated from		Stage of study
		Species	Class	
Aplidine Dehydrodidemnin B Plitidepsin	Depsipeptide	*Aplidium albicans*	Ascidian	Phase II clinical trial
Bryostatin-1	Macrocyclic lactone	*Bugula neritina*	Bryozoa	Phase II clinical trials
Cryptophycins	Depsipeptide	*Nostoc* sp. *Dysidea arenaria*	Cyanobacteria sponge	Phase II clinical trials on cryptophycin 52 discontinued in 2002, phase II trials of analogues in progress
Didemnin B	Cyclic depsipeptide	Didemnidae	Ascidian	Phase II clinical trials
Dolastatins	Peptide	*Dolabella auricularia*	Mollusk	Phase II clinical trials
Trabectedin and Yondelis	Isoquinoline alkaloid	*Ecteinascidia turbinata*	Ascidian	Approved for sarcoma and ovarian cancer, other clinical trials ongoing (Phase II/III)
Halichondrin B	Polyether macrolide derivative	Found in a variety of marine sponges	Sponge	Phase II clinical trials
Kahalalide F	Depsipeptide	*Elysia rufescens*	Mollusk	Phase I/phase II clinical trials

Data summarised from Mayer and Gustafson (2008) and updated by searching PubMed and http://www.marinebiotech.org/dfsindex.html

heart disease and diet-related cancers in countries with high seaweed consumption (Kono et al. 2004; Yang et al. 2010b; Teas et al. 2011).

Seaweed is an excellent source of bioactive chemicals. In addition to the primary metabolites required for normal growth, seaweeds produce many secondary metabolites in response to a wide range of fluctuating environmental pressures. These include seasonal changes which influence salinity, temperature and light (Abdala-Díaz et al. 2006), UV radiation exposure (Pavia and Brock 2000) and herbivory (Van Alstyne 1988). Terpenes and polyketides, which are oligomers of the primary metabolites isoprene and acetate, account for most secondary metabolites (Maschek and Baker 2008). It should be noted that there is great diversity in seaweed composition, with many compounds being unique to a group. For example, the pigment fucoxanthin is only present in brown seaweeds, and the carbohydrate ulvan is only present in green seaweeds. There is also natural variability which can occur in the same species of seaweed and even within different parts of the same thallus. Thus, if a potential source of drug is identified, in order to confirm and extend the observations, it is important that all of the above factors are recorded and controlled for, in so far as it is possible. However, this variability is only occasionally referred to in publications although it is of the utmost importance (Stengel et al. 2011).

Over a 22-year period (1960–1982), a large number (16,000) of marine organism-derived samples were screened for anti-tumour activity at the National Cancer Institute (NCI; in the USA). The programme was discontinued as few new chemical leads were discovered. In 1985, a new in vitro 60-cell panel was introduced which allowed easier screening of natural products (Roussis et al. 2004). Despite the diversity of marine-derived products identified currently, just four are approved for use as drugs in Europe (see Table 2). They are also approved in the USA except for trabectedin which is currently in phase III clinical trial (Mayer et al. 2010). It should be noted that synthetic or semi-synthetic routes to these drugs are now known.

Seaweed as a source of anti-cancer agents

Anti-cancer agents can be viewed in two ways. When seaweeds are ingested as a nutrient source, epidemiological studies have indicated that they may provide some protection from the development of cancers. This is probably linked to the anti-oxidant properties of their constituent molecules. However, when prepared as a concentrated extract, there is

Table 2 Drugs in current use originally derived from marine sources

Chemical name	Brand name	Chemical class	Use	Isolated from	Class
Cytarabine	Cytosar-U® Depocyt®	Nucleoside	Anti-cancer	*Cryptotheca crypta*	Sponge
Vidarabine	Vira-A®	Nucleoside	Anti-viral	*Tethya crypta*	Sponge
Trabectedin	Yondelis®	Isoquinoline	Anti-cancer	*Ecteinascidia turbinata*	Sea squirt
Ziconotide	Prialt®	Peptide	Pain reliever	*Conus magus*	Snail

considerable evidence that seaweeds also contain molecules that have cytotoxic properties. This review focusses primarily on the latter. The presence of cytotoxins in macroalgae is not surprising since these molecules will protect against herbivory and encroachment of other seaweeds into their habitat. Recent evidence for this is summarised in Tables 4, 6, 7, 8, 9, 10 and 11. It should be noted that most of these papers have only investigated the effects of crude extracts or semi-pure extracts on cells in vitro. Although this is an essential first step, there are very many issues to be addressed if any of these potential sources is to be translated into a modern pharmaceutical product.

Identification and development of seaweed-derived cytotoxic compounds

The potential of seaweeds as a source of anti-cancer drugs has primarily been investigated using partially purified fractions or crude extracts. In some reports, the exact source of the fractions is unclear. In so far as is possible, these studies have been summarised in Tables 4, 6, 7, 8, 9, 10 and 11 under the type of fraction investigated. Many of the early studies used mouse models to investigate the anti-tumour effects of seaweeds administered either raw or as a crude extract (see Tables 10 and 11). Since the 1980s, research on seaweed extracts has focussed more on isolated fractions, particularly of polysaccharides and also small molecule extracts including terpenes, sterols, macrolides, alkaloids, halogenated phenols and carotenoids (almost exclusively fucoxanthin). Extracted peptides/proteins have also been studied, but to a more limited extent than other chemical groups. More recently, there has been increased interest in the bioactivity of polyphenols.

Polysaccharides

Structure, occurrence and isolation

Polysaccharides are the most widely studied cytotoxic agents derived from macroalgae, and the most common source of these polysaccharides is from brown seaweeds. The sulphated polysaccharide variants such as fucoidans or ascophyllans are based on L-fucose sugars (Berteau and Mulloy 2003). Typical percentages of sulphated polysaccharides found in macroalgae are given in Table 3. In addition, some reports have investigated the unsulphated polysaccharide, alginate. Laminarin has also been studied as a chemically sulphated derivative. Extraction of polysaccharides is normally in aqueous, alkali or acidic medium; for more detailed information, see McHugh (1987), Lahaye and Robic (2007) and Rioux et al. (2007).

One of the main groups of polysaccharides present in green seaweeds is the sulphated heteropolysaccharides known as ulvans. They are composed mainly of sulphate, rhamnose, xylose and glucuronic acid (Lahaye and Robic 2007). In red seaweeds, the major polysaccharide groups present are sulphated galactans called agar and carrageenans; the latter are more highly sulphated than agars. Porphyran is another type of sulphated polysaccharide found in red seaweeds.

Cytotoxicity

Brown seaweed polysaccharides are the most widely investigated extracts. The majority of these investigations focus on fucoidan whilst other extracts that have been studied include alginate, laminarin or unclassified crude polysaccharide extracts. Most of the extracts classified as 'brown unidentified and miscellaneous' (Table 4) are likely to be fucoidan; however, the fractions were not sufficiently characterised or purified for the authors to name the specific polysaccharide. A review focussed on fucoidan has been published recently (Senthilkumar et al. 2013). It should be acknowledged that this lack of clarity on the identification of polysaccharides may in part be due to the difficulty in characterising these complex molecules. Strategies to address this include hydrolysis and high-performance liquid chromatography (HPLC) to discover monosaccharide composition, followed by mass spectrometry (MS) and/or nuclear magnetic resonance

Table 3 Typical percentages (on a dry weight basis) of polysaccharides found in macroalgae

Species	Type of polysaccharide	Typical percentages	Reference
Ulva and *Enteromorpha* spp.	Ulvan	8–29	Lahaye and Robic (2007)
Gracilaria spp.	Agar	19–36	Marinho-Soriano and Bourret (2003)
Eucheuma isiforme	Carrageenan	32–45	Freile-Pelegrín et al. (2006)
Sargassum sp. *Fucus* sp.	Fucoidan	Up to 8 12	Ale et al. (2012)
Laminaria gurjanovae	Laminarin	22	Bocanegra et al. (2009)
Ascophyllum, *Lessonia*, *Laminaria* and *Durvillaea* spp.	Alginate	14–24	McHugh (1987)

Table 4 Polysaccharides from seaweeds with anti-cancer properties

Seaweed	Component	Study model	Notes	Reference
Fucoidan				
Undaria pinnatifida (B)	Fucoidan	Tumour cells: PC-3 Normal cells In vivo	Inhibited growth in dose-dependent manner and induced apoptosis. Results suggested effect through inactivation of PI3K/Akt and the p38 MAPK pathways and activation of ERK1/2 MAPK pathway. G_0/G_1 phase arrest. Down-regulation of Wnt/β-catenin pathway	Boo et al. (2013)
Sargassum mcclurei (B)	Fucoidan	Tumour cells: DLD-1 Normal cells In vivo	No cytotoxicity at doses of 1 to 200 μg mL^{-1}. Inhibited colony formation at 100 μg mL^{-1}, no link to sulphation	Thinh et al. (2013)
Undaria pinnatifida (B)	Fucoidan	Tumour cells: SMMC-7721 Normal cells In vivo		Yang et al. (2013)
Cladosiphon novaecaledoniae (B)	Low mol weight fucoidan (<500 Da)	Tumour cells: MDA-MB-231, MCF-7 Normal cells In vivo	Synergistic, dose-dependent reduction in cytotoxicity towards both cell lines in combination treatment with cisplatin, tamoxifen or paclitaxel. Induction of apoptosis, reduced expression of Bcl-xL and Mcl-1 (both cell lines), increased expression of Bax (MCF-7 only). Modulation of ERK and Akt phosphorylation in certain combinations. Enhanced ROS and reduced GSH	Zhang et al. (2013)
Sargassum (B)	Fucoidan	Tumour cells: HepG2 Normal cells In vivo: female nu/nu nude mice injected SC with Bel-7402 cells. Treated with fucoidan 20, 200 mg/kg injected IP	In vitro: no effect on bFGF, VEGF, IL-8 and heparanase observed in HepG2. In vivo: no effect on bFGF and VEGF. Reduction in tumour volume and weight. Reduction in PCNA, no apoptosis found	Zhu et al. (2013)
Fucus vesiculosus (B)	Fucoidan	Tumour cells Normal cells: DC In vivo	DC cells were exposed to 5-FU. Fucoidan improved cytoprotection—increased cell viability and size compared to cells treated only with 5-FU; it affected apoptosis-related proteins (cIAP-1, cIAP-2, Bcl-xL and Bax) and also increased immune-related surface markers of DC cells	Jeong et al. (2012)
Undaria pinnatifida (B)	Fucoidan	Tumour cells: Normal cells: HUVECs In vivo: ex vivo rat aortic ring from female SD rats	Inhibited proliferation, migration and tube formation in HUVECs. Suppressed rat aortic ring angiogenesis. Reduced VEGF in HUVECs	Liu et al. (2012a)
Unknown	Fucoidan	Tumour cells: MCF-7 Normal cells In vivo	Fucoidan was found to bind to β1-integrin and induced caspase 8 activation, causing apoptosis in MCF-7 cells	Yamasaki et al. (2012)
Unknown (purchased)	Fucoidan	Tumour cells: 4T1 Normal cells In vivo: 4T1 cells injected into the mammary fat pad of Balb/c mice	In vitro: inhibited growth, decreased Bcl-2 and survivin. Induced caspase 3 activation and apoptosis. In vivo: induced apoptosis and decreased VEGF expression and angiogenesis. Reduced tumour weight. Reduced lung metastasis of 4T1 cells.	Xue et al. (2012)
Sargassum sp. (B) and *Fucus vesiculosus* (B)	Fucoidan	Tumour cells: LLC, B16 Normal cells	In vitro: both fucoidans reduced the viability of LLC and B16 cells by inducing apoptosis. In vivo: fucoidan enhanced NK cell activity (no tumour cells implanted).	Ale et al. (2011a)

Table 4 (continued)

Seaweed	Component	Study model	Notes	Reference
		In vivo: male C57BL/6J mice injected IP with fucoidan (50 mg/kg)		
Sargassum henslowianum (B), *F. vesiculosus* (B)	Fucoidan	Tumour cells: B16 Normal cells In vivo	Dose-dependent inhibition (0.1–1 mg mL^{-1}); induction of apoptosis and increased caspase-3 activity	Ale et al. (2011b)
Undaria pinnatifida (B)	Fucoidan	Tumour cells: AGS Normal cells In vivo	Connection shown between increasing cytotoxicity and increasing molecular weight or sulphate content. Dose-dependent cytotoxicity found at 0.2–0.8 mg mL^{-1}	Cho et al. (2011)
Sargassum filipendula (B)	Fucoidan	Tumour cells: HeLa, PC3, HepG2 Normal cells In vivo	All fractions tested showed some cytotoxic action at doses of 0.1–2 mg mL^{-1}	Costa et al. (2011a)
Sargassum filipendula (B)	Fucoidan	Tumour cells: HeLa Normal cells In vivo	Inhibited proliferation and caused apoptosis (0.1 to 2.0 mg mL^{-1}); the greatest effect was seen after 72 h. AIF was released into cytosol with a decrease in Bcl-2 and increase in Bax; no effects were found on caspases or levels of ERK, p38, p53, pAKT and NF-κB	Costa et al. (2011b)
Saccharina latissima (*Laminaria saccharina*) (B)	Fucoidan fractions: (1) unfractionated, (2) mostly sulphated fucoidans and (3) *O*-sulphated manno-glucuronofucans	Tumour cells: MDA-MB-231, B16-F10 Normal cells: HUVEC In vivo: C57BL/6 (B6) mice were injected SC with B16-F10 cells plus PBS or a fucoidan (100 μg); fucoidan also given every 3 days (50 mg kg^{-1}). Angiogenesis was examined after 7 and 21 days	In vitro: 100 μg mL^{-1} of (1) and (2), not (3) reduced HUVEC tubulogenesis, PAI-1 and bFGF-induced pathways. All fractions inhibited adhesion between MDA-MB-231 cells and human platelets; no effects on B16-F10 proliferation. In vivo: reduced vascularisation in 7 day study (haemoglobin content and CD34+ cells). Reduced tumour angiogenesis, microvessel density and tumour weight was observed in 21-day study with (1) or (2), not (3)	Croci et al. (2011)
Ecklonia cava, *Sargassum horneri*, *Costaria costata* (all B)	Fucoidan	Tumour cells: SK-MEL-28, DLD-1 Normal cells In vivo	No cytotoxicity at 1–200 μg mL^{-1}. However most fractions inhibited colony formation in both cell lines (8–55 % depending on fraction and cells)	Ermakova et al. (2011)
Dictyopteris delicatula (B)	7 characterised fucoidan fractions	Tumour cells: HeLa Normal cells In vivo	Screened for bioactivity. Proliferation assay: best fractions (2 mg mL^{-1}) inhibited tumour cell growth by 60–90 %	Magalhaes et al. (2011)
Dictyopteris polypodioides (B) and *Sargassum* sp. (B)	Fucoidan Normal cells In vivo	Tumour cells: RPMI-7951	Fucoidan did not inhibit cell growth a little cell death observed (up to 200 μg mL^{-1}). Growth of colonies in soft agar was 44 and 28 % for fucoidan from *Sargassum* sp. and *D. polypodioides*, respectively	Sokolova et al. (2011)
Fucus vesiculosus (B)	Fucoidan Normal cells: FHC In vivo	Tumour cells: HT-29, HCT116	Dose-dependent inhibition of tumour cell growth; no effect on normal cells (doses 0–20 μg mL^{-1}). Induced apoptosis via the death receptor and mitochondrial pathways	Kim et al. (2010a)
Undaria pinnatifida (B)	Fucoidan isolated from sporophyll	Tumour cells: PC-3, HeLa, A549, HepG2 Normal cells: Vero In vivo	Dose-dependent cytotoxicity to cancer cell lines; not cytotoxic to normal cell line (0–1 mg mL^{-1})	Synytsya et al. (2010)

Table 4 (continued)

Seaweed	Component	Study model	Notes	Reference
Fucus vesiculosus (B)	Fucoidan	Tumour cells: HCT-15 Normal cells In vivo	Inhibited growth (0–100 μg mL^{-1}) with increased DNA fragmentation, apoptosis, Bax and caspases 3 and 9 expression; Bcl-2 and Akt were decreased	Hyun et al. (2009)
Laminaria cichorioides (B)	Fucoidan Normal cells: JB6 Cl41 In vivo	Tumour cells	No cytotoxicity towards JB6 Cl41 cells up to 200 μg mL^{-1}. Decreased the phosphorylation of EGFR in JB6 Cl41 cells (but not EGFR levels). Fucoidan suppressed EGF-induced phosphorylation of MEK, ERK1/2, p90RSK, JNKs and c-Jun	Lee et al. (2008)
Undaria pinnatifida (B)	Hydrolysed fucoidans Normal cells In vivo	Tumour cells: A549	Microwave hydrolysis of fucoidan was not as effective as boiling acid hydrolysis in improving cytotoxicity; suggested partial removal of sulphate groups by microwaving decreased fucoidan bioactivity (0–1 mg mL^{-1} tested)	Yang et al. (2008)
Fucus evanescens (B)	Fucoidan	Tumour cells Normal cells In vivo: LLC cells implanted in thigh of C57Bl/6 mice	At 10 mg/kg, there was moderate anti-tumour and anti-metastatic effects; also enhanced anti-metastatic, but not anti-tumour effect, of cyclophosphamide. 10 mg kg^{-1} was well tolerated, but 25 mg kg^{-1} fucoidan, both alone and with cyclophosphamide, was toxic causing some deaths	Alekseyenko et al. (2007)
L. saccharina, *L. digitata*, *F. vesiculosus*, *F. spiralis*, *A. nodosum*, *F. evanescens*, *F. serratus*, *F. distichus*, *C. okamuranus* (all B)	Fucoidan Normal cells: HUVECs In vivo	Tumour cells: MDA-MB-231	Study using adhesion assays (MDA-MB-231) and angiogenesis assays (HUVECs). Caused decrease of PAI-1 release from HUVECs. In general, fucoidans inhibited inflammation, angiogenesis and heterotypic tumour cell adhesion (results varied depending on source of fucoidan)	Cumashi et al. (2007)
Fucus evanescens (B)	Fucoidan Normal cells: Namalwa In vivo	Tumour cells: MT-4	Fucoidan (500 μg mL^{-1}) was not cytotoxic in MT-4 or Namalwa cells. Pretreatment of MT-4 (but not Namalwa) cells with fucoidan followed by exposure to etoposide led to ~2-fold increase in apoptosis compared with etoposide alone. Apoptosis not related to caspase-3 activation	Philchenkov et al. (2007)
Cladosiphon okamuranus (B)	Fucoidan and over-sulphated-fucoidan Normal cells In vivo	Tumour cells: U937	Results showed mechanism of apoptosis induced by over-sulphated-fucoidan may be via a caspase-3- and caspase-7-dependent pathway; native fucoidan activity was weak (concentration range, 0–100 μg mL^{-1})	Teruya et al. (2007)
Cladosiphon okamuranus (B)	Fucoidan	Tumour cells: MKN-45 Normal cells: Hs 677.st In vivo	Fucoidan (1 mg mL^{-1}) inhibited cell growth in cancerous but not normal cells. Also inhibited effect of 5-FU in normal cells, with only slight effect in cancer cells	Kawamoto et al. (2006)
Undaria pinnatifida (B)	Fucoidan	Tumour cells Normal cells In vivo: A20 leukaemia cells injected SC into DO-11-10-Tg mice	Fucoidan was fed before and after tumour implantation; it inhibited tumour growth possibly through Th1 and NK cell responses	Maruyama et al. (2006)
Fucus vesiculosus (B)	Fucoidan	Tumour cells: HS-Sultan Normal cells In vivo	Activation of caspase 3, down-regulation of ERK pathways	Aisa et al. (2005)

Table 4 (continued)

Seaweed	Component	Study model	Notes	Reference
Sargassum stenophyllum (B)	Sarg A, a sulphated polysaccharide	Tumour cells: B16F10 Normal cells: In vivo: angiogenesis assays: CAM and gelfoam plug implanted SC in mice flank. Tumour growth delay: B16F10 melanoma cells injected SC into back of Male Swiss-Tecpar mice	Anti-angiogenic effect shown in both assays. Growth delay: Sarg A dosed for 3 days once tumour reached a minimum size; caused inhibition of tumour growth with no systemic toxicity. In vitro: Sarg A reduced cell viability and migration of B16F10 cells	Dias et al. (2005)
Fucus vesiculosus (B)	Fucoidan and over sulphated fucoidan	Tumour cells: Normal cells: HUVECs In vivo: anti-angiogenic activity: S-180 packed in a membrane and implanted into the dorsal air sac of mice; tumour growth: LLC and B16 implanted in right hind foot pads in mice	In vitro: both fucoidan and over-sulphated derivative suppressed the action of $VEGF_{165}$. In vivo: treatment started day 1 or days 3–5 for anti-angiogenic and anti-tumour assays, respectively. Both angiogenesis and tumour growth was reduced by over-sulphated fucoidan	Koyanagi et al. (2003)
Sporophyll from *Undaria pinnatifida* (B)	Fucoidan (Mekabu)	Tumour cells Normal cells In vivo: mice inoculated with P-388 tumour cells	Survival was prolonged when fucoidan was administered for 4 days prior to tumour cell inoculation. In normal mice, fucoidan caused a significant increase in NK cells activity and T cell production of IFN-gamma; anti-tumour effect appeared to be mediated by IFN-gamma-activated NK cells	Maruyama et al. (2003)
Bostrychia montagnei (R), *Porphyra columbina* (R), *Laminaria brasiliensis* (B), *Sargassum stenophyllum* (B)	Sulphated galactans, alginic acid, fucoidan	Tumour cells: HeLa Normal cells: In vivo	Fucoidan most cytotoxic of the polysaccharides tested (doses 2.5–40 $\mu g\ mL^{-1}$)	Stevan et al. (2001)
Ascophyllum nodosum (B)	Fucoidan	Tumour cells: NSCLC-N6 Normal cells: In vivo: NSCLC-N6 in nude mice	In vitro: reduced proliferation, blocked in G_1 phase of the cell cycle. In vivo: anti-tumour activity with no observed toxicity at the effective dose	Riou et al. (1996)
Sargassum thunbergii (B)	Fucoidan	Tumour cells Normal cells In vivo: LLC tumour implanted in mice; lung metastases induction measured after removal of primary tumour	Fucoidan, given IP after primary tumour excision, reduced lung metastases; this was further reduced in combination with 5-FU. Also increased Thy1.2, L3T4 and asialo-GM1-positive cells, activated complement C3 and macrophages, decreased activity of hepatic microsomal drug-metabolising system	Itoh et al. (1995)
Sargassum thunbergii (B)	31 fractions tested, fucoidans found to be effective	Tumour cells Normal cells In vivo: Ehrlich carcinoma implanted IP in ICR/Slc mice	24 h after implantation of tumour 20 mg kg^{-1} day^{-1} was injected IP for 10 days. 2 fucoidan fractions were found to increase mice survival compared to control	Zhuang et al. (1995)
Ascophyllum nodosum (B)	Low molecular weight and crude fucans	Tumour cells: Colo 320 DM Normal cells: CCL39 In vivo	Fucoidan fractions inhibited growth of both cell lines, more inhibition to Colo 320 DM cell line. No significant difference between crude and LMW fractions	Ellouali et al. (1993)
Sargassum thunbergii (B)	Fucoidan	Tumour cells Normal cells In vivo: Ehrlich carcinoma implanted IP in mice	Inhibited tumour growth (20 mg kg^{-1} day^{-1}) with no sign of systemic toxicity. Results suggested that anti-tumour activity of fucoidan is related to enhancement of immune responses	Itoh et al. (1993)

Table 4 (continued)

Seaweed	Component	Study model	Notes	Reference
Laminaria religiosa (B)	Fucoidan	Tumour cells: L-1210 Normal cells In vivo: L-1210 inoculated IP in CDF1 mice	In vitro: no significant effect. In vivo: preincubation of cells (2 h) with extract had a small effect. Multiple dosing of tumour bearing mice (daily for 6 days) increased time to cancer associated death by 33 % at all concentrations tested	Maruyama and Yamamoto (1984)
Sargassum kjellmanianum (B)	Fucoidan and over-sulphated fucoidan	Tumour cells Normal cells In vivo: L-1210 implanted in mice	Over-sulphated, but not native fucoidan, had anti-tumour activity towards leukaemic cells	Yamamoto et al. (1984a)
Laminaria angustata var. *longissima*, *L. japonica*, *L. japonica* var. *ochotensis*, *Ecklonia cava*, *Eisenia bicyclis* (B)	Fucoidan	Tumour cells: L-1210	Effect of crude fucoidan fractions prepared from edible brown seaweeds against L-1210 leukaemia	Yamamoto et al. (1984b)
Eisenia bicyclis (B)	Fucoidan	Tumour cells Normal cells In vivo: S-180 implanted in ICR/JCL mice; 50 mg kg^{-1} day^{-1} of purified extract	Pilot study: 50 mg kg^{-1} day^{-1} led to tumour growth inhibition of 30 % and complete tumour regression in 2 of 5 mice	Usui et al. (1980)
Laminarin				
Laminaria digitata (B)	Laminarin	Tumour cells: HT-29 Normal cells In vivo	Bcl-2, cytochrome c expression decreased, Bad, Bax increased. Induced apoptosis with accumulation of cells in sub-G_1 and G_2–M phase. Inhibited phosphorylation of ErbB2	Park et al. (2013)
Unknown	Laminarin sulphate	Tumour cells: PC-3 Normal cells In vivo	Inhibited proliferation, increased apoptosis, cell cycle blocked in S phase, expression of PTEN and P27kip1 was increased	Zou et al. (2010)
Unknown	Laminarin sulphate	Tumour cells: B16-BL6, 13762 MAT Normal cells In vivo: B16-BL6 cells injected IV in female C57/BL6 mice; 13762 MAT cells injected IV in female Fisher 344 rats	In vitro: studied anti-heparanase (HEP) activity of laminarin (HEP is proportional to metastatic activity). HEP was inhibited by chemically sulphated laminarin sulphate (LS) but not sodium laminarin in B16-BL6 and 13762 MAT cells. In vivo: lung colonies reduced by 80–90 % by LS; there was a small effect on primary tumours	Miao et al. (1999)
Unknown	Sulphated laminarin, mol weight 12.5 kDa	Tumour cells: RIF-1 Normal cells: FBHE, HMEC-1 In vivo: CAM assay and RIF-1 tumour cells implanted SC on flank of male C3H/Km mice	In vitro: 3–30 mg mL^{-1} chemically sulphated laminarin prevented tubule formation in matrigel for both endothelial cell types. IC50: RIF-1 30 μg mL^{-1}, FBHE 1 μg mL^{-1}. In vivo: 10–50 μg $pellet^{-1}$ of PS decreased angiogenesis in CAM assay and caused chick embryo death. In mice IP administration caused haemorrhagic deaths; 13 mg kg^{-1} IV was tolerated and reduced tumour growth	Hoffman et al. (1996)
Laminaria cloustoni (B)	Sulphated degraded laminarin	Tumour cells Normal cells In vivo: S180 cells implanted in the suprascapular region of male T.1 white mice	Groups of mice received 10–40 mg kg^{-1} into the tumour transplant site, or 10 mg kg^{-1} directly into the tumour once it was visible. An inhibition in tumour growth was seen for all groups	Jolles et al. (1963)

Table 4 (continued)

Seaweed	Component	Study model	Notes	Reference
Alginate				
Sargassum vulgare (B)	Alginate	Tumour cells Normal cells In vivo: Swiss mice with S-180 implanted SC into the right hind groin	Inhibition in tumour growth, ranged from 27 to 88 % depending on route of administration, dose (50 and 100 mg m^{-2} day^{-1}) and sample viscosity. Some liver and kidney toxicity; interstitial tissue in kidneys was preserved, suggests potential for regeneration	De Sousa et al. (2007)
Sargassum fusiforme (B)	Probably alginate	Tumour cells Normal cells In vivo: S-180 implanted into the abdominal cavity of Kunming mice	Mice received 75 mg kg^{-1} day^{-1} for 10 days from the day after inoculation. Life was prolonged by 63 % in the treatment group	Gu et al. (1998)
Sargassum fulvellum (B)	Sodium alginate, mol weight 33,400 and M/G ratio of 2.78	Tumour cells Normal cells In vivo: S-180 implanted SC in mice	Inhibited growth of S-180 in mice	Fujihara et al. (1984)
Brown unidentified polysaccharides and miscellaneous				
Sargassum coreanum (B)	Crude polysaccharide fraction, containing a high percentage of fucose	Tumour cells: HL-60, CT-26, B-16, HeLa Normal cells In vivo	Several size fractions tested; crude polysaccharide extracts of >30 kDa inhibited cell growth best. Apoptosis observed linked to increased Bax, caspase 3 and PARP cleavage	Ko et al. (2012)
Ascophyllum nodosum (B)	Ascophyllan and fucoidan	Tumour cells: HeLa, XC Normal cells: MDCK, Vero, PtK1, CHO In vivo	Both were cytotoxic to Vero and XC cells in a colony formation assay; other cell lines were unaffected (concentration 0–1,000 μg mL^{-1}). Ascophyllan significantly promoted the growth of MDCK cells at 1,000 μg mL^{-1}	Jiang et al. (2010)
Hydroclathrus clathratus (B)	Sulphated polysaccharide fraction	Tumour cells: HL-60, MCF-7, HEp-2, HepG-2 Normal cells: Vero, L929 In vivo: S-180 inoculated SC in the right back in BALB/c mice	In vitro: inhibited growth of HL-60, MCF-7 and HepG-2 cancer cells; no cytotoxicity to Vero and HEp-2 cells (up to 2000 mg mL^{-1}). Caused G_1 phase arrest and increased NO in cultured macrophages. In vivo: suppressed tumour growth and prolonged life, with no observed side effects; increased TNF-α in mouse macrophages (20–50 mg kg^{-1} day^{-1})	Wang et al. (2010)
Ecklonia cava (B)	Sulphated polysaccharide	Tumour cells: CT-26, U937, HL-60, B-16 Normal cells In vivo	Most effective in U-937 cells (12.5–100 μg mL^{-1}); caused apoptosis and sub-G_1 phase arrests. Dose-dependent enhancement of DNA fragmentation. Regulation of caspases 7 and 8, PARP, Bax and Bcl-xL were affected	Athukorala et al. (2009)
Sargassum latifolium (B)	Unidentified water-soluble fractions	Tumour cells: 1301, HepG2, HCT-116 Normal cells: RAW264.7 In vivo	Inhibited cytochrome P450 1A and glutathione-*S*-transferases. 1 extract reduced 1301 cell viability (IC_{50} 17 μg mL^{-1}) and induced apoptosis; others had IC_{50}s>40 μg mL^{-1}. Arrested cells in S phase and inhibited NO, COX-2 and TNF-α	Gamal-Eldeen et al. (2009)
Ascophyllum nodosum (B)	Ascophyllan, alginate, fucoidan	Tumour cells: U937 Normal cells: RAW264.7 In vivo	Ascophyllan inhibited the growth of U937 cells, more than alginate and fucoidan (0–1,000 μg mL^{-1}). Caused apoptosis and DNA fragmentation. Fucoidan also cytotoxic, alginate had little effect. Ascophyllan induced the secretion of TNF-α and G-CSF in RAW264.7 cells (0–1,000 μg mL^{-1})	Nakayasu et al. (2009)

Table 4 (continued)

Seaweed	Component	Study model	Notes	Reference
Sargassum stenophyllum (B)	Carbohydrate fraction	Tumour cells Normal cells: chick embryo culture In vivo: chick embryo culture	Anti-vascular effect with or without hydrocortisone. Basic FGF-stimulated vasculogenesis was partially reversed. Also decreased % cephalic length (in vitro and in vivo). The polyanionic characteristics of the carbohydrate were similar to the heparin: suggest polysaccharides interfere with heparan sulphate proteoglycans during microvessel formation	Dias et al. (2008)
Sargassum pallidium (B)	Carbohydrate fractions	Tumour cells: HepG2, A549, MGC-803 Normal cells In vivo	Cytotoxic to all cell lines studied; doses tested 0–1 mg mL^{-1}. Low molecular weight and more highly sulphated polysaccharides were most effective	Ye et al. (2008)
Ecklonia cava (B)	Carbohydrate fractions	Tumour cells: CT-26, THP 1, B-16, U937 Normal cells: V79-4 In vivo	Toxic against all cancer cell lines tested. Not as toxic as polyphenol fraction. Low cytotoxicity against V79-4. Also looked at polyphenol-rich fractions (see polyphenol table)	Athukorala et al. (2006)
Sargassum confusum (B)	Brown algal polysaccharide	Tumour cells Normal cells In vivo: S-180 in mice	IP doses of 50, 100 and 200 mg kg^{-1} inhibited tumour growth. Thymocyte and splenocyte function were enhanced	Liu and Meng (2005)
Sargassum confusum (B)	Brown algal polysaccharide	Tumour cells Normal cells In vivo: S-180 tumour in mice	Inhibited the growth of the tumour in vivo. SOD and GSH-PX activity were increased and MDA content decreased, indicating improved immune function and anti-oxidant status	Liu and Meng (2004)
Sargassum fulvellum (B)	Polysaccharide fraction (almost pure, probably sulphated)	Tumour cells Normal cells In vivo: S-180 implanted SC in mice	Inhibited tumour growth	Yamamoto et al. (1977)
Red seaweed polysaccharides				
Not known, commercial product	Native and degraded (40 kDa) ι-carrageenan	Tumour cells: HOS Normal cells In vivo: NOD SCID mice injected SC with HOS cells into the axilla	In vitro: degraded carrageenan reduced proliferation, induced apoptosis, native had no effect. In vivo: received 100 μL intratumoural injection of 1.4 μg μL^{-1} native or degraded carrageenan 3 times daily, every 2 days for 28 days. Degraded carrageenan reduced tumour weight, reduced blood vessel formation in tumour, improved survival. Suppressed LRP6 expression	Jin et al. (2013)
Gracilaria lemaneiformis (R)	Sulphated polysaccharide	Tumour cells Normal cells In vivo: H22 cells implanted in the right thigh of the lower limb in female ICR mice	Treatment: 200 or 600 mg kg^{-1} for 14 days before implantation; continued for 4 weeks. Inhibited growth of tumours; also increased IL-8, splenocyte proliferation, macrophage phagocytosis and CD8+ T cells in the blood. May have an immune modulating effect	Fan et al. (2012)
Laurencia majuscula (R)	Arabino-pyranoside	Tumour cells: LOVO, Bel-7402 Normal cells In vivo	Hexadecyl-1-*O*-α-l-arabinopyranoside is the active molecule. IC_{50} values: Bel-7402 (11.5 μM) and LOVO (15.82 μM). Expression of CDK1 and cyclin A decreased markedly, with slight changes in cyclin B1; arrested cell cycle in G_2/M	Du et al. (2010)

Table 4 (continued)

Seaweed	Component	Study model	Notes	Reference
Champia feldmannii (Diaz-Pifferer) (R)	Sulphated polysaccharide	Tumour cells: HL-60, MDA-MB-435, SF-295, HCT-8 Normal cells In vivo: S-180 implanted SC into the left hind groin in female Swiss mice	In vitro: IC_{50} values were >25 μg mL^{-1}. In vivo: reduced tumour weight and increased spleen weight. Authors suggest immune function enhancement. Some, potentially reversible, toxicity was observed; liver function remained normal	Lins et al. (2009)
Not known, commercial product	Porphyran	Tumour cells: AGS Normal cells: IEC-6, Fhs 74 Int In vivo	No effect on normal cells; proliferation reduced in dose-dependent manner in AGS cells	Kwon and Nam (2006)
Chondrus ocellatus (R)	λ-Carrageenan	Tumour cells Normal cells In vivo: H-22 cells implanted SC into the right hind groin of ICR mice	Degraded λ-carrageenan enhanced the anti-tumour effect 5-FU and improved immunocompetence damaged by 5-FU. Lymphocyte proliferation and TNF-α levels were improved in mice receiving carrageenan	Zhou et al. (2006)
Chondrus ocellatus (R)	Low molecular weight λ-carrageenan	Tumour cells Normal cells In vivo: S-180 implanted SC into right hind groin of ICR mice	Anti-tumour activity, spleen weight, lymphocyte proliferation and TNF-alpha were studied. Enhanced anti-tumour activity of 5-FU and improved immunocompetence which is damaged by 5-FU	Zhou et al. (2005)
Chondrus ocellatus (R)	λ-Carrageenan of different molecular weights	Tumour cells Normal cells In vivo: S-180 and H22 cells implanted SC in ICR mice	Tumours in the treated mice weighed less than untreated. Lower MW fractions were most effective. Enhanced NK cell activity and lymphocyte proliferation	Zhou et al. (2004)
Schizymenia dubyi (R)	Sulphated heteropolysaccharide rich in uronic acids	Tumour cells: NSCLC-N6 Normal cells In vivo	Cell growth irreversibly inhibited in G_1 phase of cell cycle	Bourgougnon et al. (1994)
Gracilaria dominguensis (R)	Highly sulphated agar like polysaccharide	Tumour cells Normal cells In vivo: Ehrlich carcinoma implanted IP in mice	Agar like polysaccharide composed of alternating (1→3)-linked β-*d*-galactopyranosyl 6-sulphate and (1→4)-linked 3,6-anhydro-α-*l*-galactopyranosyl residues. Inhibited the transplantation of Ehrlich ascites carcinoma in mice	Fernández et al. (1989)
Green seaweed polysaccharides				
Monostroma nitidium (G)	Water-soluble sulphated polysaccharides	Tumour cells: AGS, HeLa Normal cells: RAW264.7 In vivo	Marked cytotoxicity against AGS and HeLa cells (125-500 μg mL^{-1}). Did not affect proliferation of RAW 264.7 cells (6.25–50 μg mL^{-1}). NO and PGE_2 production from Raw 264.7 cells, suggests they may act as strong immunomodulators	Karnjanapratum and You (2011)
Enteromorpha intestinalis (G)	Sulphated polysaccharide	Tumour cells: S-180 Normal cells In vivo: S-180 implanted into the right armpits in male ICR mice	Low toxicity in vitro (at 800 μg mL^{-1}) indicating that anti-tumour activity is probably immune function related. Reduced tumour mass, increased thymus and spleen mass. Increased TNF-α, NO and ROS which inhibit tumour growth	Jiao et al. (2009)
Capsosiphon fulvescens (G)	Polysaccharide (hot water-soluble fraction)	Tumour cells: AGS Normal cells In vivo	Inhibited cell proliferation and induced apoptosis by inhibiting IGF-IR signalling and PI3K/Akt pathway. Increased caspase-3 activation; decreased Bcl-2 expression and phosphorylation of IGF-IR	Kwon and Nam (2007)

Table 4 (continued)

Seaweed	Component	Study model	Notes	Reference
Miscellaneous				
11 species of tropical algae (R, G and B)	Sulphated polysaccharides	Tumour cells: HeLa Normal cells In vivo	Dose-dependent inhibition of HeLa cell growth (0.01–2 mg mL^{-1})	Costa et al. (2010)
Unknown, commercial product	Viva-Natural (V-N) commercial supplement	Tumour cells Normal cells In vivo: LLC implanted IP in mice	Adriamycin, cisplatin, 5-fluorouracil and vincristine at low doses were not effective when given alone, but had anti-tumour activity when combined with V-N; this was not found with BCNU, methotrexate and 6-thioguanine. Activation of peritoneal macrophages in mice was induced by single dose of the polysaccharide fraction of V-N; the combination of low dose drugs plus V-N was no more effective than V-N alone. Therefore, the mechanism of action or beneficial combination is not clear yet	Furusawa and Furusawa (1990)
Various species including *Undaria pinnatifida* and *Sargassum ringgoldianum*	15 kinds of polysaccharide extracts	Tumour cells Normal cells In vivo: BALB/c mice (1) Ehrlich carcinoma (solid) SC implant. Oral dose: 14 before and 13 days after implant. (2) Meth A carcinoma IC implant. Oral dose, 7–19 days post-implant	Ehrlich carcinoma: ~50 % growth inhibition by green-algal sulphated polysaccharides, sodium alginate, *U. pinnatifida*, both kappa- and lambda-carrageenan and porphyran. Meth A fibrosarcoma: growth inhibited by fucoidan from *U. pinnatifida* and *S. ringgoldianum* (most active), 3 kinds of carrageenans and porphyran	Noda et al. (1990)
Unknown, commercial product	Viva-Natural, commercial supplement	Tumour cells Normal cells In vivo: mice implanted IP with LLC and leukaemia in AKR mice	Viva-Natural had a similar or better action to some of the immunomodulators and could ameliorate the activity of some of the immunosuppressive agents (measured by anti-LLC activity). It could also reverse potentiation by cyclosporine of leukaemia in AKR mice at the preleukaemic stage	Furusawa and Furusawa (1989)
17 kinds of polysaccharide extracts from 10 species of seaweeds (R, G and G)	Includes fucoidan, laminarin, porphyran and carrageenan	Tumour cells Normal cells In vivo: Male ddY and BALB/c mice; 2 groups. (1) Implanted with Erlich carcinoma SC on the back, treated with stomach sonde 14 days before and 13 days after implantation, (2) implanted with Meth A fibrosarcoma IC on the side, treated IP after 7–19 days	Green algal sulphated polysaccharides (ulvans), fucoidan, porphyran and Na alginate inhibited Ehrlich carcinoma. Fucoidan, porphyran and iota, kappa and lambda were effective against meth A fibrosarcoma. However, toxic deaths were seen for kappa and lambda. Also examined effects of lipid extracts (see Table 8)	Noda et al. (1989)

(NMR) spectroscopy to further identify substitutions and linkages. The identification of seaweed polysaccharides is further hampered by the structural diversity in polysaccharide type. The polysaccharides in question may have repeating sugar residues in their backbone, but may vary in sugar substitutions, sulphation and molecular weight. Take as an example the review mentioned above, which found that fucoidan extracted from five different seaweed species had fucose contents ranging from 13 to 36 % and degrees of sulphation which varied from 8 to 25 % (Senthilkumar et al. 2013).

In the published literature, the analytical identification of macroalgal-derived polysaccharides shown to have activity as CCT agents varies widely. In a few studies, a thorough analysis has been carried out. For example, Thinh et al. (2013) used ion exchange HPLC to study monosaccharide composition and a combination of NMR and MS to elucidate linkage type and sulphation in fucoidan. In others, a general carbohydrate extraction technique and more qualitative analysis has been carried out. In these cases, it is likely that the polysaccharide extract contains impurities and unknown polysaccharide fractions; see, for example, Zhou et al. (2004) who characterised a carrageenan extract by viscosity, total sugars, FTIR and qualitative UV and HPLC. Many other studies report little or no characterisation at all, yet if they are to be progressed it will be essential that further characterisation is done. A review by Jiao et al. (2011) describes several strategies for analysis of polysaccharides from seaweeds. However, considerable time and resources are required to analyse these complex molecules effectively.

Importance of sulphation

Fucoidan is a sulphated polysaccharide. The importance of fucoidan sulphation to cytotoxic activity has been well established. Several studies, both in vitro and in vivo, have compared the activity of native fucoidan with that of fractions which have either been artificially over-sulphated or contain more sulphate by means of the fractionation technique used (Yamamoto et al. 1984a; Koyanagi et al. 2003; Teruya et al. 2007; Croci et al. 2011). For example, an over-sulphated fucoidan fraction, but not a native fraction, had an anti-tumour effect against L-1210 leukaemic cells in mice (Yamamoto et al. 1984a). This differential effect was also reported in studies by Koyanagi et al. (2003) who observed an in vivo enhancement of anti-angiogenic activity in S180 tumours grown in imprinting control region (ICR) mice in a dorsal air sac and anti-tumour effects in LLC and B16 cells implanted in the foot pad of ICR mice. The inhibitory effects were greater for over-sulphated fucoidan, although native fucoidan did have some efficacy. In a study of three fucoidan fractions isolated from *Laminaria saccharina* (now *Saccharina latissima*), it was shown that human umbilical vein endothelial cell (HUVEC) tubulogenesis in vitro and matrigel plug vascularisation in vivo was correlated with the level of sulphation, with the greatest inhibition found in the fraction with the highest sulphation (Croci et al. 2011). However, no significant differences were found regarding the degree of sulphation in several fucoidan extracts in a colony formation assay of DLD-1 cells (Thinh et al. 2013).

The importance of sulphation has been shown for other polysaccharides besides fucoidan. Chemically sulphated laminarin, but not sodium laminarin, had anti-heparanase activity in vitro and reduced metastasis in vivo, with a small effect on tumour proliferation and growth (Miao et al. 1999). This anti-heparanase effect is important as it could provide a novel compound with activity against tumour metastasis, a feature of tumours which currently is inhibited by very few drugs. In crude carbohydrate fractions from *Sargassum pallidum*, more highly sulphated polysaccharides were found to be more cytotoxic to cancer cell lines (Ye et al. 2008). Virtually all the polysaccharides studied in green and red seaweeds are sulphated (see Table 4). When compared to other sulphated polysaccharides, the action of alginate (unsulphated) has been found to be inferior to both fucoidan and ascophyllan (sulphated) (Nakayasu et al. 2009).

Effect on tumour angiogenesis

Tumours require a constant supply of both nutrients and oxygen which can only be achieved if new blood vessels form within the growing mass. Since the vasculature in normal tissues is largely quiescent, targeting angiogenesis in tumours provides a specific target which can inhibit the ability of tumours to grow. This has led to considerable efforts to find compounds (both synthetic and natural) which target tumour vasculature. Several studies have shown that angiogenesis can be inhibited by the sulphated polysaccharides fucoidan and laminarin (see Table 4). No substantial evidence has yet been found to suggest that the unsulphated polysaccharide alginate or the sulphated red and green algal polysaccharides affect angiogenesis.

Although some information can be obtained using tube formation assays in vitro, angiogenesis is a three-dimensional process, and it is mostly studied using in vivo models, primarily involving either chick eggs or various experimental techniques in mice. The chicken embryo chorioallantoic membrane (CAM) assay is commonly used where the substance of interest is implanted in a chick egg membrane and its effect on angiogenesis quantified (Dias et al. 2005). In a study of fucoidan isolated from *Sargassum stenophyllum*, both the CAM assay and a gelfoam plug assay in mice revealed the fucoidan to have anti-angiogenic activity. As discussed

above, Koyanagi et al. (2003) found fucoidans reduced angiogenesis as well as eliciting anti-tumour effects in mouse models. Fucoidan has also been reported to reduce the pro-angiogenic cytokine and vascular endothelial growth factor (VEGF), and this was associated with a significant reduction in angiogenesis and tumour size in 4T1 tumours in vivo (Xue et al. 2012). In a recent report, it has been shown that production of VEGF-A and tube formation is significantly reduced in HUVECs exposed to fucoidan isolated from *Undaria pinnatifida* (Liu et al. 2012a).

Plasminogen activator inhibitor-1 (PAI-1) is a protein present at elevated concentrations in cancer patients that is produced in endothelial cells and is proposed as a good target for cancer drug development (Andreasen 2007). In a survey of the bioactivity of nine different fucoidans from brown seaweeds, it was reported that some of the fucoidans caused a decrease in PAI-1 release from HUVECs in vitro providing a rationale for their use in developing a targeted anti-cancer drug (Cumashi et al. 2007). As discussed above, decreased HUVEC tubulogenesis was observed on exposure to fucoidans especially those with higher sulphation levels which was also correlated with lower levels of PAI-1 secretion; they also found in vivo effects on angiogenesis (Croci et al. 2011).

A study has shown that a sulphated laminarin (LAM S5) can inhibit angiogenesis in the CAM assay; however, there were issues with toxicity (chick embryo deaths). When they tested LAM S5 against RIF-1 tumours grown in C3H/Km mice, toxicity was also found, with haemorrhagic deaths occurring at higher doses. A synergistic anti-tumour effect was found when mice were treated with LAM S5 in combination with a corticosteroid or a cytotoxic agent (melphalan) (Hoffman et al. 1996). The CAM assay was also used to show that vasculogenesis stimulated by basic fibroblast growth factor (bFGF) could be reduced by a polysaccharide extracted from *S. stenophyllum* (Dias et al 2008). A recent in vivo study found no differences in the levels of the pro-angiogenic molecules bFGF and VEGF in mice treated with fucoidan, but did find a reduction in tumour weight and volume (hepatocellular carcinoma, Bel-7402). The authors suggested a mechanism unrelated to tumour angiogenesis was responsible for the observed anti-proliferative activity (Zhu et al. 2013).

The effect of molecular weight on polysaccharide bioactivity

In a study of fucoidan extracted from the brown seaweed *U. pinnatifida*, cytotoxicity was observed against AGS stomach cancer cells; this was significantly greater in the lower molecular weight fucoidan fraction, i.e. <30 kDa compared to >30 kDa fraction (Cho et al. 2011). There is also evidence showing that the red seaweed polysaccharide, carrageenan, has better anti-tumour activity in low molecular weight forms. When S180 or H22 tumours were exposed to extracts of varying molecular weight, the tumours grew more slowly when mice were treated with lower molecular weight or degraded carrageenan (Zhou et al. 2004, 2005, 2006); this was accompanied by immunomodulatory effects. It should be noted that in various studies, degraded carrageenan (also called poligeenan) has been found to induce colitis and ulceration in animal studies (Watt and Marcus 1971; Benard et al. 2010). Concerns have been mostly limited to poligeenan (carrageenan is a high molecular weight polysaccharide). However, there is an ongoing debate regarding the safety of carrageenan (Tobacman 2001, 2002; Carthew 2002; Burges Watson 2008).

Enhancement of immune response

Many studies have shown that polysaccharides can prolong survival in tumour bearing mice; this is often shown to be caused by a reduction in tumour size that is associated with an improvement in the animals' immune defences. For example, it was reported that fucoidan inhibited the growth of Ehrlich carcinoma cells in mice through an enhancement of the host's immune function (Itoh et al. 1993). Fucoidan from the sporophyll of *U. pinnatifida* was found to prolong survival in P-388 tumour-bearing mice. This was associated with a significant enhancement of the activity of natural killer (NK) lymphocytes and increased production of interferon gamma (IFN γ) by T cells (Maruyama et al. 2003). Fucoidan was also found to modulate Th1 and NK cell responses in mice inoculated with leukaemic cells (Maruyama et al 2006). Ale et al. (2011a) also reported that fucoidan enhanced NK cell activity in non-cancerous mice.

The action of an unidentified polysaccharide from *Sargassum confusum* was examined in S-180 tumours grown in mice. It was found to improve immune function as measured by increased superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) activity and thymocyte and splenocyte production, as well as decreased malondialdehyde (MDA) (Liu and Meng 2004, 2005).

Ascophyllan was found to induce cytokine release (tumour necrosis factor (TNF) and granulocyte colony-stimulating factor) from macrophage-derived RAW264.7 cells (Nakayasu et al. 2009), and a sulphated polysaccharide derived from the brown seaweed *Hydroclathrus clathratus* was reported to increase TNF-α in mouse serum (Wang et al. 2010).

An in vivo study on λ-carrageenan of various molecular weights found that, in general, NK and lymphocyte cell proliferation in animals implanted with S180 and H22 tumours was higher in animals treated with carrageenan than the negative control (Zhou et al. 2004). The same group also showed that recovery from damage caused by 5-fluorouracil (5-FU) was linked to an improvement in immunocompetence, as measured by an increase in spleen weight and lymphocyte proliferation; this suggested that these extracts may have a role

in ameliorating damage caused by standard chemotherapeutic agents such as 5-FU (Zhou et al. 2005, 2006).

Jiao et al. (2009) characterised a sulphated polysaccharide from the green seaweed, *Ulva* (formerly *Enteromorpha intestinalis*), with an average molecular weight of 46.8 kDa and a high rhamnose content. Very little in vitro activity was found against S-180 sarcoma cells; however, when the cells were implanted in vivo, there was a reduction in tumour mass, an increase in thymus and spleen mass and an increase in TNF-α production and lymphocyte proliferation. The authors suggested immuno-enhancement rather than direct anti-tumour cytotoxicity as the mechanism of action. Increased levels of the immunomodulators nitric oxide (NO) and prostaglandin E_2 (PGE_2) were observed when mouse leukaemic cells (RAW 264.7) were treated with a sulphated polysaccharide extracted from *Monostroma nitidium*; this effect was independent of a direct cytotoxic effect seen against AGS tumour cells (Karnjanapratum and You 2011).

Cell death by apoptosis

Polysaccharides are known to cause cell death primarily via an apoptosis pathway, with the apoptosis-controlling proteins caspases, Bax and Bcl-2 frequently involved. For example, caspase 3 was found to be activated in HS-Sultan (malignant lymphoma) cells treated with fucoidan (Aisa et al. 2005). However, Philchenkov et al. (2007) found that no cytotoxicity occurred in MT-4 and Namalwa lymphoblastoid cells on treatment with 500 μg mL^{-1} of fucoidan, although pre-treatment with fucoidan prior to etoposide exposure doubled the level of apoptosis in MT-4 cells but not in Namalwa cells. Unlike the previous study (Aisa et al. 2005), they found that apoptosis was not related to caspase-3 activation (Philchenkov et al. 2007). Further evidence of caspase involvement has come from a study of U937 cells; this showed that over-sulphated fucoidan induced apoptosis through a caspase-3 and caspase-7 activation-dependent pathway, whilst the activity of native fucoidan was weak (Teruya et al. 2007). Fucoidan was also found to up-regulate caspases 3 and 9 and Bax (pro-apoptotic proteins) in HCT-15 cells, whilst Bcl-2 and Akt (anti-apoptotic proteins) were reduced (Hyun et al. 2009). In a study of the effects of fucoidan on HT-29 and HCT116 human colon cancer cells, fucoidan was found to cause apoptosis in a dose-dependent manner, whilst having no effect on normal FHC colonocytes. Molecular analysis of the HT29 cells showed that fucoidan increased levels of a number of pro-apoptotic proteins involved in the mitochondrial-mediated pathway of apoptosis; these included cleaved caspases 3, 7, 8 and 9; cleaved poly(ADP-ribose) polymerase (PARP); Bak and truncated Bid. A number of anti-apoptotic effectors were reduced including the X-linked inhibitor of apoptosis protein (XIAP), survivin and Mcl-1. An enhancement of mitochondrial membrane permeability, as well as release of cytochrome c and Smac/Diablo from the mitochondria, was also observed. Further molecular changes, including increased levels of Fas-L, TNF-related apoptosis-inducing ligand (TRAIL) and DR5, implicated the activation of the death receptor-mediated apoptotic pathway (Kim et al. 2010a).

In contrast, no changes in caspases, ERK, p38, p53 or pAKT levels were found to accompany the apoptosis induced by fucoidan in HeLa cells; however, apoptosis inducing factor (AIF) was found in the cytosol, as well as up-regulation of Bax and down-regulation of Bcl-2 (Costa et al. 2011b). In U937 cells, apoptosis was induced by a sulphated polysaccharide from *Ecklonia cava*; this was associated with an up-regulation of Bax and PARP, activation of caspases 7 and 8 and down-regulation of Bcl-2 (Athukorala et al. 2009).

The sulphated polysaccharide porphyran, isolated from an unidentified red seaweed, was found to induce apoptosis in AGS cancer cells but not in three normal cell lines. This was accompanied by enhanced cleavage of PARP and caspases 3 and 9 and reduced phosphorylation of insulin-like growth factor-1 receptor (IGF-1R) which correlated with Akt down-regulation (Kwon and Nam 2006). In a study of AGS cells exposed to a crude polysaccharide extracted from the green alga *Capsosiphon fulvescens*, similar results were found; cell proliferation was inhibited and apoptosis induced. This was associated with inhibition of IGF-1R signalling and the PI3K/Akt pathway (Kwon and Nam 2007).

Several other studies have shown that apoptotic tumour cell death is caused by exposure to polysaccharides (Gamal-Eldeen et al. 2009; Nakayasu et al. 2009; Zou et al 2010; Ale et al. 2011a, b; see Table 4). Clearly, although apoptosis is frequently involved in the cytotoxic effect of polysaccharides, there may be different aspects of the apoptotic response involved depending on the experimental cells and the extract composition.

Many studies have clearly shown that polysaccharides, from a wide range of macroalgal sources, have an effect on tumour cell growth both in vitro and in vivo. These compounds act in a variety of ways including direct inhibition of proliferation and activation of apoptosis mediated through a number of different molecular pathways. In addition, they can act indirectly by targeting the blood vessels growing in the tumour and/or via immunomodulation mechanisms that boost the bodies' natural mechanisms for eradication of tumour cells.

Conclusions

Polysaccharides, and sulphated polysaccharides in particular, have been the most studied groups of macroalgal-based anti-cancer agents. They have shown good potential, and there is much evidence regarding their in vitro and in vivo potential.

However, none has entered clinical trials, which may be related to the difficulties encountered when purifying and unambiguously identifying their structure. Since polysaccharides are complex molecules with varied levels of sulphation and sugar moieties, it is likely that even the most pure fractions will contain polysaccharide molecules with a range of structures. In addition, identification of a suitable administration route and the formulating of these relatively large molecular structures will be difficult. With all of the positive evidence for their potential utility, it is perhaps time for these problems to be addressed.

Polyphenols

Structure and occurrence

Polyphenols are secondary metabolites of seaweeds. Their presence and concentrations can be linked to environmental factors (Maschek and Baker 2008). Oxidative stress is toxic in vivo, and the presence of reactive oxygen species (ROS) is normally balanced by anti-oxidant defences. However, when ROS are in excess, they can cause a rise in intracellular Ca^{2+} and iron, which may damage DNA and is implicated in many age-related degenerative conditions including cancer (Alfadda and Sallam 2012). Polyphenols act as anti-oxidants by preventing the formation of free radicals, binding metal ions and/or improving the body's own anti-oxidant system (Cox et al. 2010). It should be noted that polyphenols can also have pro-oxidant effects under certain conditions (Perron et al. 2011).

Phlorotannins are oligomers and polymers of phloroglucinol that are found exclusively in brown algae. Phlorotannins bind to metals and proteins, and they have an astringent taste which often makes brown algae unpalatable to humans (Ragan and Glombitza 1986). There is a wide molecular weight range of phlorotannins isolated from *Ascophyllum nodosum* (0.32–400 kDa), with the majority being about 10 kDa (Ragan and Glombitza 1986). Environmental factors which may affect polyphenol levels in macroalgae include UV radiation exposure (Pavia and Brock 2000), herbivory (Van Alstyne 1988), season (Abdala-Díaz et al. 2006) and geographical location (Tanniou et al 2013). There are fewer studies of polyphenol extracts from green and red as compared to brown seaweeds. Polyphenol levels are lower in the red and green seaweeds and are predominantly a mixture of catechins, gallate catechins and gallic acid (Yoshie et al. 2000; Rodríguez-Bernaldo de Quirós et al. 2010). Environmental factors and the method of isolation have a major effect on the levels of polyphenols extracted; Table 5 summarises the information available.

Polyphenols are normally quantified according to the Folin–Ciocalteu method calibrated to either gallic acid or phloroglucinol. The results therefore are quoted as gallic acid/phloroglucinol equivalents. The lack of analytical standards for phlorotannins limits the possibility of their characterisation by HPLC. If a standard does not exist, mass spectrometry may prove useful in elucidating the structure. However, HPLC and MS are constrained by the huge molecular weight and polymer type diversity in the compounds although a recent paper has reported some improvements to characterisation methods by HPLC–MS (Steevensz et al. 2012). In general, polyphenols can be extracted using aqueous/solvent systems, sometimes with precipitation of carbohydrates and dialysis to remove salts. More information on extraction methods can be found in Ragan and Glombitza (1986). Bromophenols are polyphenols with one or more bromine substitutions. Marine algae, in particular red and brown seaweeds, are a common source of bromophenolic compounds. Those studied in the literature tend to be smaller phenolic compounds which are well characterised and purified by the authors.

Table 5 Total polyphenol levels in three different seaweeds (García-Casal et al. 2009)

Species	Classification	Total polyphenols (gallic acid equivalents g^{-1} dry algae)
Ulva sp.	Green	10.84
Porphyra sp.	Red	18.43
Sargassum sp.	Brown	80.39

Polyphenols as anti-cancer agents

Seaweed polyphenols are being investigated for their potential utility in two different anti-cancer roles. The first focusses on their ability to directly inhibit cancer cell proliferation and promote cell death. The second is as a cytoprotective agent, which can protect cells against DNA damage and thus reduce the incidence of tumours. To complicate this matter still further, in most studies, the extracts investigated are polyphenol rich with the polyphenol content varying from >1 to >99 % purity. This means that authors in most cases can only tentatively attach a claim of efficacy to the polyphenols in the extract and indeed most acknowledge this. To date, all studies reporting on pure extracts have been carried out on phlorotannins (Hwang et al. 2006; Zhang et al. 2010; Kong et al. 2009; Oh et al. 2011; Li et al. 2011). One example of the cytoprotective effect of polyphenols was shown in a study of extracts from *Fucus vesiculosus* and *Fucus serratus*. The Comet Assay was used to measure DNA damage on Caco-2 cells exposed to H_2O_2; when the cells were exposed to the polyphenol extracts, this reduced the level of DNA damage suggesting cytoprotection, although the effect was small (O'Sullivan et al. 2011).

The direct cytotoxicity of several algal extracts on HeLa cell growth was positively correlated with polyphenol content (Yuan and Walsh 2006). However, no correlation between growth inhibition and total phenolic content was found when extracts from three red seaweeds were tested against cancer cells, although there was a correlation with anti-oxidant effect (Zubia et al. 2009a, b). The growth of two tumour cell lines was inhibited and apoptosis increased by phlorotannin-rich extracts from *Saccharina* (*Laminaria*) *japonica*; anti-oxidant activity against several free radicals was also found (Yang et al. 2010a). Polyphenol-rich extracts were also found to inhibit the growth of colon cancer cells although there was no correlation with the phenolic content (Nwosu et al. 2011). Currently the evidence to support a correlation between the phenolic content of crude extracts and anti-cancer effects is limited, and claims should be made with care.

Induction of apoptosis by polyphenols

Although the cytotoxic effect of polyphenols is far from clear, some studies have shown that polyphenol-rich extracts can induce apoptosis in breast (MCF-7 and MDA-MB-231), colon (CT-26) and lung (A549) cancer cells. For example, a crude polyphenol extract induced apoptosis in colon cancer cells but had little effect on the viability of normal cells (Athukorala et al. 2006). In a study of three pure phlorotannin extracts, it was found that dioxinodehydroeckol showed the best dose-dependent cytotoxic effect against MCF7 and MDA-MB231 breast cancer cell lines. In MCF-7 cells, a number of pro-apoptotic effects were found including increases in PARP cleavage, p53, Bax and the activity of caspases 3 and 9. There was also a down-regulation of Bcl-2 nuclear factor kappa B (NF-κB) (Kong et al. 2009). Recently, a study of a crude polyphenol extract from the red seaweed *Eucheuma cottonii* (now *Kappaphycus alverezii*) has shown no effect against normal Vero cells. However, a dose-dependent decrease in proliferation and increase in apoptosis was found against MCF7 and MD-MBA-132 cells. In LA7 tumours grown subcutaneously in rats, the polyphenol-rich fraction also confirmed an anti-tumour effect; this included induction of apoptosis, down-regulation of endogenous oestrogen production and improvement of the anti-oxidative status of the rats (Namvar et al. 2012). In a review of the mechanisms underlying the role of polyphenols to TRAIL-induced apoptosis, it was claimed that polyphenols can restore tumour cell sensitivity to TRAIL-induced cell death with no apparent toxicity towards normal cells. There is evidence that both extrinsic and intrinsic pathways of apoptosis can be modulated by polyphenols, with activity depending on cell type, polyphenolic compound and experimental conditions (Jacquemin et al. 2010).

Anti-metastatic effect of extracts

There are few studies on the anti-metastatic effects of seaweed polyphenols on cancer cells. In one study of the polyphenolic compound 6,6′-bieckol extracted from *E. cava*, no significant inhibition of growth was found in HT1080 human fibrosarcoma cells. However, there was a change in cell morphology and reduced invasiveness that was accompanied by a reduction in matrix metalloproteinase-2 (MMP), MMP-9 and NF-κB (Zhang et al. 2010). MMP production is often deregulated in malignant tumours and is thought to influence tumour invasion and metastasis. Controlling its expression is therefore of interest since the results suggest that the compound may act to inhibit cell metastasis and migration, processes which are a main cause of morbidity and mortality in cancer patients.

Bromophenols

Work on bromophenols has been carried out on purified extracts as a rule, rather than on ‘phenol-rich’ crude extracts. Their bioactivity has been reviewed by Liu et al. (2011). An in vivo study of a crude extract from *Leathesia nana*, which was also purified to yield bromophenols, reduced S-180 tumour growth in Kumming mice (Shi et al. 2009). These results may provide a basis for further in vivo work with purified bromophenol compounds. Some mechanistic work has been recently published regarding a bis (2,3-dibromo-4,5-dihydroxybenzyl) ether, showing a possible pathway of action and binding site (Liu et al. 2012b).

Conclusions

The dual character of polyphenols as cytotoxic and anti-oxidant may explain why some researchers find that seaweed ingestion is cytoprotective since this could act to protect against DNA damage by free radicals. Attempting to elucidate the primary activity of polyphenols is therefore very difficult as the in vitro models are of limited value in elucidating the relevance of small effects and the in vivo models are difficult to study since the cancer protective effect will be small. The evidence suggests that depending on the extract, the dose and the model, polyphenols can be shown to exhibit both effects. It is unlikely that clear evidence on the anti-cancer properties of polyphenols will be available until the effects of purified extracts are investigated and even then the experimental model may be crucial. Human dietary trials could provide more

evidence, but this approach has its own limitations (discussed in more detail below).

Carotenoids

Structure and occurrence

Carotenoids are natural pigment isoprenoid compounds found in both plants and animals. They are biosynthesised by tail to tail linkage of two C20 molecules to give a C40 molecule from which all carotenoid structures are derived (Britton 1995). In general, carotenoids are relatively easy to extract using a solvent and then saponification to remove impurities; they may then be purified by chromatography and are therefore often studied as pure or nearly pure extracts (Rodriguez 2001). However, isomerisation is common in carotenoids due to the presence of conjugated double bonds. In theory, every double bond in the chain may exist in the *cis* or *trans* form, giving rise to a huge number of possible configurations which provides an extra level of complexity even when the extracts are pure (Britton 1995). For example, the mixture of 13-*cis* and 13′-*cis* isomers of fucoxanthin extracted from *U. pinnatifida* had the greatest anti-proliferative effect compared to the other isomers tested; this was attributed to an increase in apoptosis induced in both HL-60 cells and Caco-2 cells (Nakazawa et al. 2009). The carotenoids astaxanthin and peridinin are found in microalgae and dinoflagellates and are not discussed here (for more information, see Palozza et al. 2009 and Sugawara et al 2007.)

Bioactivity

Various carotenoids have been shown to have both anti-cancer (Nishino et al. 1999) and/or anti-oxidant activity, whilst in certain conditions they may also show pro-oxidant effects (Young and Lowe 2001). The evidence for the bioactivity of carotenoids is primarily based on in vitro studies. However, it is likely that a number of factors reduce their effectiveness in vivo, making it difficult to extrapolate from in vitro studies (Young and Lowe 2001). Nevertheless, carotenoids including lutein, zeaxanthin, lycopene and β-cryptoxanthin have been shown to reduce carcinogenesis in vivo, and fucoxanthin has been shown to cause a marked reduction in tumour formation in mice (Nishino et al. 1999; Okuzumi et al. 1993).

Fucoxanthin is the most widely studied macroalgal carotenoid, and although it is found in many brown algae species, the majority of studies have investigated fucoxanthin extracted from one species *U. pinnatifida* (Table 7). Siphonaxanthin is found in siphonaceous green algae; to date, only two studies have reported on the bioactivity of this compound (Ganesan et al. 2010, 2011). Both fucoxanthin and siphonaxanthin have been found to induce cell cycle arrest and/or cell death via apoptosis in a variety of tumour cell lines derived from liver, prostate, colon, white cells and cervix; further characterisation has identified a range of pro- and anti-apoptotic mechanisms to be involved (summarised in Table 7). For example, fucoxanthin was found to cause DNA fragmentation and apoptosis in the prostate cancer cell lines, PC-3, DU145 and LNCaP (Kotake-Nara et al. 2001). In colorectal cancer cells, fucoxanthin induced a significant increase in apoptosis coupled with a decrease in Bcl-2 expression, and the viability of Caco-2 cells was synergistically reduced in combination with troglitazone, an inhibitor of the peroxisome proliferator-activated receptor γ (Hosokawa et al. 2004). In HL-60 leukaemic cells, fucoxanthin-induced apoptosis was linked to activation of caspases 3 and 9 with no effect on Bcl-xl, Bcl-2 or Bax (Kotake-Nara et al 2005a). However, in prostate cancer cells, fucoxanthin caused DNA fragmentation, caspase-3 activation and reduction in Bcl-2 and Bax (Kotake-Nara et al 2005b). In HepG2 and DU145 cells, fucoxanthin caused G_1 cell cycle arrest which was later confirmed in LNCaP cells (Satomi and Nishino 2007; Satomi 2012).

It has been shown that fucoxanthin can be hydrolysed to fucoxanthinol during absorption both in colorectal adenocarcinoma cells (Caco-2) and in vivo in male ICR mice (Sugawara et al. 2002). A few studies have compared the effect of both compounds (Table 7). For example, treatment with either compound caused apoptosis and caspases 3, 8 and 9 activation in human T cell lymphotropic virus infected leukaemic cells (HTLV-1); however, neither affected uninfected cells (Ishikawa et al. 2008). Both compounds reduced proliferation in several tumour cell lines without blocking the toxicity of cisplatin (Mise and Yasumoto 2011), and both were also shown to induce apoptosis and cell cycle arrest (Yamamoto et al. 2011; Tafuku et al. 2012). When HL-60 cells were treated with either siphonaxanthin or fucoxanthin, apoptosis was increased accompanied by changes in GADD45α, DR5 and Bcl-2; the former caused more chromatin condensation and caspase activation (Ganesan et al. 2011). Only two studies have reported on the effect of macro-algal carotenoids on angiogenesis. Fucoxanthin and fucoxanthinol were found to suppress proliferation of HUVECs and decrease microvessel growth in ex vivo rat aortic rings (Sugawara et al. 2006). A similar study confirmed this result for fucoxanthin, and it also showed siphonaxanthin to have a comparable effect (Ganesan et al. 2010).

Conclusions

Clearly macroalgal carotenoids have potential as anti-cancer agents eliciting their effect primarily through a

variety of apoptotic pathways and possibly in vivo through additional inhibition of tumour angiogenesis. One recent in silico study has suggested that fucoxanthin may cause cytotoxicity through a tubulin binding action (Januar et al. 2012).

Small molecules and lipids

Terpenes and derivatives

Terpenes are a large group of organic chemicals often found in plants that are composed of isoprene units arranged as chains or rings. In vitro studies have shown that terpenoid compounds often have good cytotoxicity towards tumour cell lines (Fuller et al. 1992; Ji et al. 2008), but normal cells are often also affected (Pereira et al. 2011; Campos et al. 2012) (see Table 8 for more examples). This shows the importance of testing the toxicity of compounds on normal as well as tumour cells. There have been few in vivo studies of terpenes and their derivatives; however, studies have been carried out on *Caulerpa taxifola.* One of the active compounds extracted from this seaweed, 10,11 epoxycaulerpenyne, was found to be toxic both to normal hamster kidney cells (BHK 21/C13) and Swiss mice (Lemée et al. 1993). An in vivo study of the sesquiterpenoid, elatol, showed that it could reduce growth of melanoma cells (B16F10) inoculated in C57BL6 mice (Campos et al. 2012).

Lactones and derivatives

Macrolides are a group of natural compounds characterised by the presence of a macrocyclic lactone ring. Details on their identification, isolation and cytotoxicity have previously been published (Kobayashi and Tsuda 2004; Tsuda et al. 2005). To the authors' knowledge, no in vivo studies or assays on normal cells have been reported. However, the action of several macrolides on tumour cells in vitro has been reported, with many compounds showing promising IC_{50} values (see Table 8).

Steroids

Steroids are a class of organic compound characterised by a four-carbon ring structure. Sterols and stanols are subdivisions of steroids. No in vivo studies have been carried out in this sub-group of chemicals, but cytotoxicity against many tumour cell lines and some normal cell lines has been reported (see Table 8).

Alkaloids

Alkaloids are organic compounds which contain a basic nitrogen. Caulerpin has been isolated from several species of green and red algae (see review on alkaloids from marine algae, Güven et al. 2010). Lophocladines and caulerpin have shown cytotoxicity against a variety of tumour cell lines; however, caulerpin has also been shown to affect the growth of normal cells (Rocha et al. 2007; Liu et al. 2009a, b). When the crude extract, which was mostly composed of caulerpin, was compared to purified caulerpin from *Caulerpa racemosa*, only the crude extract showed cytotoxicity to melanoma cells; the authors suggested that this might be due to a synergistic effect (Rocha et al. 2007).

Quinones

Quinones have been mostly found in brown algae, although a few have been isolated from green algae. Their cytotoxicity has been recently reviewed (Sunassee and Davies-Coleman 2012). Quinone compounds have been found to be cytotoxic to tumour cells, with some cytotoxicity seen in normal cells where tested (Perry et al. 1991; Iwashima et al. 2005). A mechanistic study has shown that sargachromanol E, a compound with a quinone moiety, caused apoptosis in HL-60 cells.

Lipids

Some uncharacterised lipids, as well as fully characterised molecules, have been extracted from macroalgae. Cytotoxicity was found against a variety of tumour cell lines, although no comparisons to normal cells have been reported (see Table 8). One in vivo study of uncharacterised lipid fractions showed good anti-tumour activity against Meth A fibrosarcoma implanted in BALB/c mice (Noda et al. 1989).

Conclusions

Molecules in this category are usually very well characterised, but in most studies the anti-cancer cytotoxicity is mainly studied as part of a screen when testing for other bioactivities, e.g. anti-microbial, anti-inflammatory etc. Molecules which have provided promising results require further experimentation to determine the mechanism of their cytotoxicity and also if they have any effect on normal cells. In vivo studies should then be carried out to identify differential toxicity, an essential step in the development of anti-cancer drugs for humans.

Protein and peptides

A recent review has emphasized the potential of peptides, proteins and amino acids from macroalgae as a rich source of bioactive molecules (Harnedy and FitzGerald 2011). However, there are currently only a limited number of studies on proteinaceous extracts as a potential source of anti-cancer agents (Table 9). In general, these extracts show good activity

against tumour cells with little or no activity against normal cells (Sugahara et al. 2001; Go et al. 2009; Kim et al. 2012b). One early study showed toxicity against the 'normal' CV1 monkey fibroblast cells of kahalalide F, a peptide isolated from the seaweed *Bryopsis pennata* and in greater quantities from the mollusk *Elysia rufescens* which feeds on it. However, kahalalide F also showed efficacy against a number of tumour cell lines (Hamann and Scheuer 1993), and this potency resulted in it entering clinical trial. The drug was well tolerated and showed a good safety profile (Pardo et al. 2008) underlining the limitations of extrapolating from normal cell line toxicity data to animal models and human trials. The drug was then tested in a phase II trial of cutaneous malignant melanoma; it was again well tolerated but showed no significant anti-tumour activity resulting in early closure of the trial (Martín-Algarra et al. 2009). A new phase I trial to determine the safety of prolonged infusions in order to achieve longer exposure time was carried out. A dose with an acceptable safety profile was found, and this will allow a phase II trial to be carried out in the future (Salazar et al. 2013). Clearly peptide/protein fractions of macroalgae are under-researched despite their potential exemplified by kahalalide F which is the only macroalgal product to have entered clinical trials.

Crude extracts

In vitro studies

There have been many studies of the anti-cancer properties of seaweeds using unpurified fractions from a variety of solvent/water combinations; these have shown a range of anti-tumour effects (Table 10). For example, in a study of several seaweed species, dichloromethane/methanol extracts were found to be more cytotoxic than water extracts (Moo-Puc et al. 2009). Methanol, rather than water extracts, had the most potent telomerase inhibiting activity (Kanegawa et al. 2000). Methanol extracts of the brown seaweeds *Sargassum swartzii*, *Cystoseira myrica* and *Colpomenia sinuosa* were partitioned to obtain different fractions in hexane, chloroform, ethylacetate and methanol/water; the hexane fractions were found to be the most effective (Khanavi et al. 2010). Hexane extracts from *Laurencia* sp. were also found to be most cytotoxic to uterine and cervical cancer cell lines (chloroform and methanol extracts were also tested) (Stein et al. 2011). In a recent study, the ethyl acetate fraction of *Cytoseira compressa* was shown to be the most cytotoxic, followed by the chloroform and methanol fractions (Mhadhebi et al. 2012).

Enzyme targets in cancer cells have also been investigated. A comprehensive screen of 304 seaweed samples, collected from diverse sites around the Japanese archipelago, investigated their ability to inhibit telomerase in MOLT-4 cells using methanol and water-based extracts. Twelve samples showed inhibitory activity with a methanol extract from the green alga *Caulerpa sertularioides* being the most effective (Kanegawa et al. 2000). Telomerase is recognised as an attractive target in anti-cancer therapy as the enzyme is frequently up-regulated in cancer cells, a characteristic associated with cells that can proliferate indefinitely (Shay and Wright 2006). Protein kinase A is another enzyme which has potential as a target for inhibiting cancer cells. In a pilot screen of marine macroalgae collected in Australia, uncharacterised ethanol extracts of *Porphyra* sp., *Ecklonia radiata* and *Sargassum vestitum* were shown to be potent inhibitors of protein kinase A (Winberg et al. 2011). Other in vitro studies are summarised in Table 10.

In vivo studies

Early in vivo studies using crude preparations from a variety of seaweed species, including *Laminaria* species, showed anti-tumour efficacy as shown by decreases in tumour size and incidence (Yamamoto and Maruyama 1985; Yamamoto et al. 1986). A study on 7,12-dimethylbenz(α)anthracene (DMBA)-induced skin tumours in ICR mice showed that a dichloromethane extract from the brown seaweed *U. pinnatifida* reduced the number of tumours compared to the control (Ohigashi et al. 1992). When the toxicity of crude water and methanol extracts from *Caulerpa taxifolia* was studied on Swiss mice, seasonality was found to have an effect. Water extracts were found to be more toxic when isolated in the winter and spring, and methanol extracts were more toxic in summer (Lemée et al. 1993). The development of chemically induced skin tumours was reduced in ICR mice by a methanol/acetone extract from the green seaweed *Enteromorpha prolifera* (Higashi-Okai et al. 1999). Inhibition of metastasis was demonstrated in vivo with a water extract from the red algae *Marginisporum crassissimum* (Hiroishi et al. 2001). Ethanol extracts from *L. nana* were able to reduce growth of S-180 tumours in mice (Shi et al. 2009), and ethanol extracts from *Acanthophora spicifera* were able to decrease the volume and weight of Erlich ascites carcinoma in mice (Lavakumar et al. 2012). A study on gastric cancer induced in rats showed anti-oxidant activity and immune stimulation on treatment with a water extract from *S. pallidum* (Zhang et al. 2012).

Effect on normal cells

In general, where normal cells have been studied in vitro, crude extracts have been shown to be less toxic to normal cells than to tumour cells (Funahashi et al. 2001; Lee et al. 2004; Moo-Puc et al. 2011b; Rocha et al. 2007; Lin et al. 2012). An extract from *Ulva lactuca* was found to stimulate growth of splenocytes, whilst inhibiting tumour cell growth,

indicating the possibility of an anti-cancer agent with potential to stimulate the immune system (Lee et al. 2004).

Conclusion

Clearly many seaweeds show potential as a source of novel anti-cancer agents, and in some cases, specific targets have been identified. However, studies with crude extracts need refining if the active compound(s) are to be identified, and in many cases, further purification can be problematic.

Raw/processed seaweed

Animal nutrition studies

The majority of studies that involve feeding seaweed to animals have investigated the putative chemoprotective effect of raw seaweed when the animals are exposed to carcinogenic agents. In many studies, it has not been noted whether fresh or dried seaweed has been used. A number of these studies are summarised in Table 11; studies that involve investigation of the therapeutic potential of seaweed and seaweed extracts have been discussed above (also see Tables 4, 5, 6, 7, 8, 9 and 10).

U. pinnatifida (wakame) suppressed the growth of chemically induced mammary tumours in mice. It was fed to the mice at levels of 1 and 5 % in normal feed. The authors suggest a connection between iodine content and reduction in proliferation of cancer cells. Iodine had previously been found to reduce the proliferation of breast cancer cells in vitro and in vivo (Funahashi et al. 1999). In a letter to the editor, Tokudome et al. (2001) emphasise that caution should be exercised in hypothesising which component has the anti-cancer effect. In addition, they point out that excessive consumption of seaweed can lead to an excess of iodine in the diet, which can cause diseases such as thyrotoxicosis in humans.

Human nutrition studies

Most human studies have involved epidemiological analysis of cancer rates in populations eating seaweed as a part of their standard diet. In most of these studies, there is no further clarification as to the seaweed species eaten, or indeed the method of processing which can vary considerably and may also include further cooking by the consumer; all of these will affect the bioactive components. For example, an investigation of *Himanthalia elongata* (B) showed how drying affected its anti-oxidant profile (Gupta et al. 2011).

Along with preparation and cooking, it is well recognised that there are many factors that can influence dietary studies which makes interpretation difficult. There is also an important dichotomy of effect that needs to be considered when investigating the effects of seaweed ingestion. Firstly, they can potentially act in a protective manner to stop initiation or promotion of tumours, and in addition, the presence of natural cytotoxins could kill small foci of latent tumours either directly or by enhancing immune surveillance mechanisms. This is highlighted in a review on the effect of *Laminaria* on breast cancer in which the author discusses a number of mechanisms through which *Laminaria* can affect breast cancer rates. For example, the seaweed is a good source of fibre which increases faecal bulk and decreases bowel transit time, and it contains anti-bacterial activity that will influence faecal microflora. It also affects sterol metabolism, and it stimulates the host-mediated immune response all of these have the potential to reduce cancer rates (Teas et al. 1982).

One of the early reports on the influence of diets high in seaweed was a study of a group (>8,000) of native-born and first-generation Japanese men living in Hawaii. In a later sub-analysis of the wives of these men, it was found that 86 had a confirmed diagnosis of breast cancer and that there was a significantly lower incidence of breast cancer in the wives who ate a more Japanese style diet which was high in seaweed. However, this interpretation is based on a reasonable, but unproven, assumption that the women ate a similar diet to the men who were the study respondents (Nomura et al. 1978). In another population of ethnic Japanese living in Hawaii, the incidence of prostate cancer was found to be increased in those eating five or more helpings of seaweed per week suggesting that moderation in seaweed ingestion might be a better option (Severson et al. 1989). A study has been reported from the Saitama Prefecture in Japan where lifestyle and dietary interviews were carried out with 181 patients recently diagnosed with colorectal cancer and 653 controls obtained from the local population. A few significant correlations were found including an independent inverse association between seaweed consumption and both colon and rectal cancer (Hoshiyama et al. 1993).

The JACC study investigated a very large cohort of Japanese men (n=42,940) and women (n=55,308) aged 40 to 79 years during 1990–1997. Seaweed consumption, amongst many other foods, was assessed using a self-administered food frequency questionnaire. During this period, 446 males and 126 females died from lung cancer (information obtained from death certificates). Several associations were found including an inverse correlation between lung cancer and seaweed consumption in men, although this was not significant for women possibly due to the small reported incidence. This underlines the difficulty in obtaining clear information from dietary studies. Even in this study over 7 years and nearly 100,000 participants, only a few trends were found and they varied by gender (Ozasa et al. 2001). As discussed above, excessive seaweed consumption can increase iodine levels, and this can cause diseases such as thyrotoxicosis which is especially true for individuals who are unaccustomed to a high iodine diet (Tokudome et al. 2001).

Table 6 Polyphenols and brominated phenols from seaweeds with anti-cancer potential

Seaweed	Component	Study model	Notes	Reference
Dictyota dichotoma, *Hormophysa triquetra*, *Spatoglossum asperum*, *Stoechospermum marginatum*, *Padina tetrastromatica* (B)	Hexane, dichloromethane-, ethyl acetate and methane fractions	Tumour cells: MiaPaCa-2, Panc-1, BXPC-3, Panc-3.27 Normal cells In vivo	Dose-dependent inhibition of cell growth, induction of apoptosis. Inhibition of NF-κB. Modulated EGFR phosphorylation, kRas, AurKb and Stat3 (see paper for details on extract/cell line efficacy). Little characterisation carried out; authors recommend more to aid discovery of active compounds	Aravindan et al. (2013)
Laurencia obusta (R)	Methanol extract and fractions	Tumour cells: A549, HCT15, MCF7 Normal cells In vivo	Higher phenolic and flavonoid contents found in fraction than crude extract. Cytotoxicity is the highest in extract with the highest flavonoids and polyphenol content. Further characterisation recommended to identify bioactive compounds	Dellai et al. (2013)
Turbinaria ornata (B), *Kappaphycus alvarezii* (R), *Acanthophora spicifera* (R), *Gracilaria corticata* (R)	Methanol, chloroform, ethyl acetate and aqueous extracts. Highest PP content 1.3 μg/mL, the highest flavonoid content 88 μg/mL	Tumour cells: A549, HCT-15, MG-63, PC-3 Normal cells In vivo	Although some association was found between inhibition of proliferation of A549 and MG-63 cells with higher values of total flavonoid content (see paper for details), authors suggest many bioactive molecules in extract could be responsible for growth inhibition effect	Murugan and Iyer (2013)
Leathesia nana (B)	bis(2,3-Dibromo-4,5-dihydroxybenzyl) ether	Tumour cells: A549, HCT-116, HeLa, HCT-8, K562, SMMC-7721 Normal cells: MCF-10A In vivo	IC_{50}, approximately 14–36 μg mL^{-1} for tumour cells, 50 μg mL^{-1} for normal cells. K562 most sensitive (IC_{50}, 14 μg mL^{-1}) and further work carried out on these cells. Induced apoptosis by a mitochondrial-mediated pathway. Induced ROS generation and arrested the cell cycle in the S phase. Inhibits topoisomerase I activity. Modelling showed that it may bind to the minor groove of DNA	Liu et al. (2012b)
Eucheuma cottonii (R)	Crude extract, PP content 2 %. Identification attempt using HPLC; catechin, rutin and quercetin were found. No quantitative information given	Tumour cells: MCF-7, MB-MDA-431 Normal cells: Vero In vivo: female Sprague-Dawley rats inoculated SC with LA7 cells into the mammary fat pad	In vitro: MCF-7: IC_{50} 20 μg mL^{-1}, MB-MDA-431: IC_{50} 42 μg mL^{-1}. No toxicity to Vero cells. Apoptosis was observed in cancer cells. In vivo: tumour incidence and volume was reduced by extract. Tumours showed apoptosis and rats had better anti-oxidative status. Authors propose that the anti-cancer effect may be related to a number of extract components	Namvar et al. (2012)
Ecklonia cava (B)	Crude ethyl acetate extract. PP content 30 %	Tumour cells: A549 Normal cells In vivo	Extract showed a significant inhibition of migration and invasion of A549 cells in a concentration-dependent manner. It strongly inhibited MMP-2, Akt and p38, but not JNK and ERK. No significant cytotoxicity was observed. Link between polyphenol content and anti-cancer activity could not be made	Lee et al. (2011)
Ecklonia cava (B)	Fucodiphlorethol G, eckol, dieckol, phlorofucofuroeckol A and a complex 1,4-dioxin analogue	Tumour cells: HeLa, HT1080, A549 and HT-29 Normal cells: MRC-5 In vivo	IC_{50} values of compounds against cancer cell lines were in the range of 180–360 μM. The extracts were less cytotoxic to MRC-5 cells (IC_{50} not specified but above 400 μM)	Li et al. (2011)

Table 6 (continued)

Seaweed	Component	Study model	Notes	Reference
Udotea flabellum (G)	Crude extract. PP content 1.7–3.4 %	Tumour cells: Hep-2, HeLa, SiHa and KB Normal cells: MDCK In vivo	Cytotoxic to cancerous cells, much less cytotoxic to normal cells. Authors do not link anti-cancer activity and PP content, but discuss the possibility that purified PP extracts may have anti-cancer activity. Also found link between increasing light exposure and increasing cytotoxicity	Moo-Puc et al. (2011a)
Ulva lactuca (G), *Palmaria palmata* (R), *Alaria esculenta* (B)	Crude extract. Extract standardised to percentage PP, PP content of 0–50 μg mL^{-1} tested	Tumour cells: Caco-2 Normal cells In vivo	Extracts reduced viability of Caco-2 cells	Nwosu et al. (2011)
Ecklonia cava (B)	Phlorotannin: Dieckol	Tumour cells: SK Hep-1 Normal cells In vivo	TPA induced cell motility was decreased by Dieckol. Decreased AP-1 in MAPK signalling pathways and MMP-9 activity	Oh et al. (2011)
Ascophyllum nodosum, *Pelvetia canaliculata*, *Laminaria hyperborea*, *Fucus vesiculosus*, *Fucus serratus* (all B)	Crude extract. PP content 0.2–0.5 %	Tumour cells: Caco-2 Normal cells In vivo	Anti-oxidant and anti-proliferative activity of the extracts was examined. *A. nodosum*, *F. vesiculosus*, *P. canaliculata* and *F. serratus* extracts had anti-proliferative effects (dose 0.55–5.5 mg mL^{-1} tested). Good anti-oxidant activity in vitro. Caco-2 cells used as a model for anti-oxidant effect rather than anti-cancer model	O'Sullivan et al. (2011)
Laminaria japonica Aresch (B)	Crude extract. PP content 200 μg/mL of extract. Fractions of this also studied, no characterisation	Tumour cells: BEL-7402, P388 Normal cells In vivo	Extract inhibited growth of cells and had free radical scavenging effect. Caused apoptosis in 1 of the fractions. Links anti-cancer effect and PP content, but limited evidence for this claim	Yang et al. (2010a)
Ecklonia cava (B)	6,6′-Bieckol, a phlorotannin	Tumour cells: HT1080 Normal cells In vivo	Cell viability in HT1080 cells not affected (dose: up to 250 μM). Reduced tumour invasion and migration by matrigel assay. Inhibited expression of MMP-2 and MMP-9, which are both expressed in malignant tumours. No clear effect on AP-1 but NF-κB was reduced	Zhang et al. (2010)
Ecklonia cava (B)	Phlorotannins: (1) dioxinodehydroeckol, (2) complex dioxin analogue structure provided	Tumour cells: MCF-7, MDA-MB-231 Normal cells In vivo	Compound (1) had the greatest cytotoxic effect on both MCF-7 and MDA-MB-231 cells. It induced apoptosis, increased Bax, p53, caspases 3 and 9 and PARP cleavage. Bcl2 and NF-κB were down-regulated	Kong et al. (2009)
Osmundaria colensoi (R)	Bromophenols, structures (7) given in paper	Tumour cells: HL-60 Normal cells In vivo	One of the isolated compounds, lanosol butenone, had moderate cytotoxic activity against leukaemia cells (IC_{50} 8 μM)	Popplewell and Northcote (2009)
Leathesia nana (B)	Bromophenols (and crude ethanolic extract). Structure given in paper	Tumour cells: A549, BGC-823, MCF-7, B16-BL6, HT-1080, A2780, Bel7402, HCT-8 Normal cells In vivo: S-180 cells inoculated SC in the right axilla of Kunming mice	Most compounds had IC_{50} values below 10 μg mL^{-1} against the cell lines tested. Caused a decrease in PTK and increase in c-kit expression. In vivo: crude extract reduced tumour growth	Shi et al. (2009)

Table 6 (continued)

Seaweed	Component	Study model	Notes	Reference
10 brown seaweeds	Crude (DCM/MeOH) extract. PP content 1.0–10.9 %	Tumour cells: Daudi, Jurkat, K562 Normal cells In vivo	*Bifurcaria bifurcata*, *Cystoseira tamariscifolia*, *Desmarestia ligulata*, *Dictyota dichotoma* and *Halidrys siliquosa* had good cytotoxic effects on all cell lines tested. An extract from *F. ceranoides* increased cell viability in Daudi cells (dose 100 μg mL^{-1}). Link between cytotoxicity and anti-oxidant activity discussed	Zubia et al. (2009b)
24 red seaweeds	Crude (DCM/MeOH) extract. PP content 0.5–5.7 %	Tumour cells: Daudi, Jurkat, K562 Normal cells In vivo	*Asparagopsis armata*, *B. byssoides* and *H. plumosa* extracts had strong cytotoxic activities against Daudi and Jurkat cells (dose 100 μg mL^{-1}). No correlation was found between cytotoxic activities, and polyphenol content was found in any of the cell lines tested	Zubia et al. (2009a)
Caulerpa sertularioides (G), *Halimeda macroloba* (G), *Ulva reticulata* (G), *Padina australis* (B), *Sargassum polycystum* (B), *Turbinaria conoides* (B)	Crude extract (ethanol or acetone)	Tumour cells: Caco-2 Normal cells In vivo	Both ethanol and acetone extracts of the 6 Indonesian seaweeds decreased Caco-2 viability when cells were treated with 600 μM hydrogen peroxide. However, when Caco-2 cells were treated with 700 or 800 μM hydrogen peroxide, the ethanol and acetone extracts from *P. australis* increased cell viability significantly more than those from the other seaweeds	Gunji et al. (2007)
Callophycus serratus (R)	Callophycoic acids A–H, brominated diterpene-benzoic acids and phenols	Tumour cells: Panel of 11 cancer cell lines Normal cells In vivo	$IC_{50\ values}$ of >25 μM for 7 of the 11 cell lines; IC_{50} for other 4 had range 20.6–24.5 μM	Lane et al. (2007)
Ecklonia cava (B)	Crude extract	Tumour cells: CT-26, THP 1, B-16, U-937 Normal cells: V79-4 In vivo	Toxic against all cancer cell lines tested, low cytotoxicity against the normal cell line, V79-4. Extract induced apoptosis in CT-26 cells and had good anti-oxidant activity. More toxic than polysaccharide fraction. Also looked at carbohydrate rich fractions (see polysaccharide table)	Athukorala et al. (2006)
Supplied commercially, brown seaweed extract	>99 % phlorotannins: contained complex mix of 10 phlorotannins (63.8 %) plus minor homologues (37.2 %) as determined by HPLC	Tumour cells Normal cells In vivo: effect of feeding and topical application on UVB radiation induced skin carcinogenesis in SKH-1 mice	Both administration methods reduced tumour number and volume; tumour incidence also decreased but not significantly. Both methods inhibited COX-2 and cell proliferation. Shows brown algae PPs have an anti-photocarcinogenic effect—may be associated with prevention of UVB-induced oxidative stress, inflammation and cell proliferation in skin. Caused no reduction in body weight or food consumption	Hwang et al. (2006)
Ecklonia cava (B)	Crude extract (ethanol) 58 % polyphenols	Tumour cells: HT1080 Normal cells: HDF In vivo	No cytotoxic effect on HT1080 or HDF cells (doses up to 100 μg mL^{-1}). Inhibited MMP-2 and MMP-9 activity. Link proposed between polyphenols and anti-cancer activity	Kim et al. (2006)

Table 6 (continued)

Seaweed	Component	Study model	Notes	Reference
Rhodomela confervoides (R)	Bromophenols, structures (8) given in paper	Tumour cells: HCT-8, Bel7402, BGC-823, A549, A2780 Normal cells In vivo	Analysis of bromophenols from red algae. Pilot cytotoxicity study showed 4 out of 8 novel bromopolyphenols had moderate cytotoxicity compared to 5FU	Ma et al. (2006)
Palmaria palmata (R), *Laminaria setchellii* (B), *Macrocystis integrifolia* (B), *Nereocystis luetkeana* (B)	Crude extract, PP content 0.2–1.3 %	Tumour cells: HeLa Normal cells In vivo	Crude extracts tested for cytotoxicity, inhibited HeLa cell growth at 5 mg/mL for all extracts. Little or no effect seen at lower concentrations. Significant positive correlation was found between anti-proliferative activity and polyphenol content	Yuan and Walsh (2006)
Palmaria palmata (R)	Crude extract, PP content 1.3 %	Tumour cells: HeLa Normal cells In vivo	Extract produced from sample which received low UV exposure exhibited lower anti-oxidant activity compared to high UV exposure sample. Extracts showed dose-dependent inhibition of HeLa cell proliferation. No direct link was made between anti-cancer activity and polyphenol content	Yuan et al. (2005)
Rhodomela confervoides (R)	Bromophenols, structures given in paper	Tumour cells: A549, BGC-823, MCF-7, Bel7402, HCT-8 Normal cells In vivo	No cytotoxicity at 10 μg mL^{-1}	Zhao et al. (2005)
Polysiphonia lanosa (R)	Bromophenols, structures (19) given in paper	Tumour cells: DLD-1, HCT-116 Normal cells In vivo	Several compounds were tested but lanosol *n*-propyl ether was the most active compound from the algae—IC_{50} 12.4 μM (DLD-1) and 1.32 μM (HCT-116). Other synthesised isomers were also tested and reported here	Shoeib et al. (2004)
Leathesia nana (B)	Bromophenols, structures (19) given in paper	Tumour cells: A549, BGC-823, MCF-7, Bel7402, HCT-8 Normal cells In vivo	Four compounds toxic to cell lines, with IC_{50} values in range 0.001–0.020 μM mL^{-1}	Xu et al. (2004)

Table 7 Carotenoids from seaweeds with anti-cancer potential

Seaweed	Component	Study Model	Notes	Reference
Undaria pinnatifida (B)	Fucoxanthin	Tumour cells: HepG2 Normal cells In vivo	Was found to improve efficacy of cisplatin treatment. Reduced cell viability. Increased Bax/Bcl-2 ratio, probably through inhibition of NF-κB, and inhibited ERCC1 expression through ERK and PI3K/AKT pathways	Liu et al. (2013)
Unknown (B)	Fucoxanthin	Tumour cells: HepG2 Normal cells In vivo	Inhibited the activity of CYP1A2 and CYP3A4	Satomi (2013)
N/A	Fucoxanthin	Tumour cells Normal cells In vivo	A computer-based study suggested that fucoxanthin's main mode of action is as a tubulin binder	Januar et al. (2012)
Unknown (B)	Fucoxanthin	Tumour cells: LNCaP Normal cells In vivo	Inhibited growth of LNCaP cells in a dose-dependent manner. Caused G_1 cell cycle arrest, but no increase in apoptosis was seen. Results suggested that GADD45A and SAPK/JNK might be involved in these effects	Satomi (2012)
Unknown (B)	Fucoxanthin, fucoxanthinol	Tumour cells: B cell malignancies, e.g. Burkitt's lymphoma, Hodgkin's lymphoma and Epstein–Barr virus-immortalized B cells Normal cells: PBMC In vivo	Both showed dose-dependent reduction in cell viability, G_1 cell cycle arrest and caspase-dependent apoptosis in tumour cells but not PBMC. Fucoxanthinol was ~2× more potent; it suppressed NF-κB and related anti-apoptotic and cell cycle genes, e.g. Bcl-2, cIAP-2, XIAP, cyclin D1 and D2. Proposed as a treatment for B cell malignancies	Tafuku et al. (2012)
Codium fragile (G), *Undaria pinnatifida* (B)	Siphonaxanthin, fucoxanthin	Tumour cells: HL-60 Normal cells In vivo	Both induced apoptosis through caspase-3 activation (dose range 5–20 μM), but siphonaxanthin was most cytotoxic. It increased expression of GADD45α and DR5 and suppressed Bcl-2	Ganesan et al. (2011)
Padina australis (B)	Fucoxanthin	Tumour cells: H1299 Normal cells In vivo	IC_{50} 2.45 mM	Jaswir et al. (2011)
Undaria pinnatifida (B)	Fucoxanthin, fucoxanthinol	Tumour cells: Caco-2, HepG2, Neuro2a Normal cells In vivo	Both reduced proliferation of tumour cells in a dose-dependent manner; on combining with cisplatin, neither reduced the effect of cisplatin	Mise and Yasumoto (2011)
Cladosiphon okamuranus Tokida (B)	Fucoxanthin, fucoxanthinol	Tumour cells: BCBL-1; HeLa; TY-1 infected with human herpes virus 8 Normal cells: PBMC In vivo: female C.B-17/Icr-SCID mice injected i.p. with BCBL-1 cells	In vitro: both caused cell cycle arrest in G_1 and caspase-dependent apoptosis; also reduced NF-κB, AP-1 and Akt and down-regulated anti-apoptotic proteins and cell cycle regulators. Proteasome degradation was responsible for the low levels of proteins after fucoxanthinol treatment. In vivo: reduction in tumours in mice treated with fucoxanthin	Yamamoto et al. (2011)
Undaria pinnatifida (B)	Fucoxanthin	Tumour cells: MGC-803 Normal cells	Fucoxanthin down-regulated the expression of CyclinB1 and survivin, induced G_2/M arrest and	Yu et al. (2011)

Table 7 (continued)

Seaweed	Component	Study Model	Notes	Reference
		In vivo	apoptosis in cells. The reduction of CyclinB1 by fucoxanthin was associated with the JAK/STAT pathway	
Codium fragile (G)	Siphonaxanthin	Tumour cells Normal cells: HUVEC In vivo: ex vivo aortic segments from Wister rats	Siphonaxanthin suppressed tube formation (>10 μM), HUVEC proliferation and microvessel growth (2.5 μM); there was no effect on HUVEC chemotaxis	Ganesan et al. (2010)
Ishige okamurae (B)	Fucoxanthin	Tumour cells: HL-60, HT-29, HepG-2 Normal cells In vivo	IC_{50}s: HL-60 (12.1 μM) HT-29 and HepG-2 (>30 μM). Apoptosis induced through ROS generation; Bcl-XL was down-regulated and caspases 3 and 7 and PARP cleavage was increased	Kim et al. (2010b)
Undaria pinnatifida (B)	Fucoxanthin	Tumour cells: SK-Hep-1 Normal cells: BNL CL.2 In vivo	Tumour cells: induced cell cycle arrest in G_0/G_1 and apoptosis (at 5–20 μM). BNL CL.2 cells: slight effect on proliferation. Enhanced gap junction intercellular communication of cancerous but not normal cells. Increased expression of Cx43 and Cx32 and intracellular calcium	Liu et al. (2009a)
Undaria pinnatifida (B)	Fucoxanthin, purified isomeric fractions	Tumour cells: HL-60, PC-3, LNCaP, Caco-2 Normal cells In vivo	The all-trans fucoxanthin was the major isomer (>88 %) extracted from *U. pinnatifida*. The highest anti-proliferative effect in HeLa cells: in order 13′-*cis*>13-*cis*>all-*trans*>other isomers. The effects were linked to higher apoptosis inducing activity	Nakazawa et al. (2009)
Not specified	Fucoxanthin	Tumour cells: HepG2, DU145 Normal cells In vivo	HepG2 cells: fucoxanthin inhibited p38 MAPK and increased gadd45a and G_1 arrest. DU145 cells: fucoxanthin inhibited SAPK/JNK, suppressing gadd45a and G_1 arrest. Study shows gadd45a is closely related to fucoxanthin-induced G_1 arrest; MAPK involvement is cell type specific	Satomi and Nishino (2009)
Laminaria japonica (B)	Fucoxanthin	Tumour cells: HepG2 Normal cells In vivo	Cytotoxic to HepG2 with cell cycle arrest during the G_0/G_1 phase of cell cycle (dose 25 μM). Down-regulated cyclin D	Das et al. (2008)
Undaria pinnatifida (B)	Fucoxanthin, fucoxanthinol	Tumour cells: Jurkat, K562, MT-2, MT-4, HUT-102, ED-40515(−) Normal cells: PBMC In vivo: female C.B-17/Icr-SCID mice; HUT-102 cells injected SC in postauricular region	In vitro: inhibited proliferation by inducing GI cell cycle arrest and apoptosis in HTLV-1 infected lines and primary adult T cell leukaemia cells, but not uninfected cell lines at doses ≤10 μM. Showed increased caspases 3, 8 and 9 and decreased Bcl-2, XIAP, cIAP2, survivin, NF-κB and AP-1. In vivo: fucoxanthinol significantly reduced tumour weight and volume	Ishikawa et al. (2008)
Laminaria japonica (B)	Fucoxanthin	Tumour cells: EJ-1 Normal cells In vivo	Reduced cell viability was dose and time dependent. Increases in DNA ladder, hypodiploid cells and caspase 3 were found. Apoptotic cells were >93 % after 72 h in 20 μM fucoxanthin	Zhang et al. (2008)

Table 7 (continued)

Seaweed	Component	Study Model	Notes	Reference
Not specified	Fucoxanthin	Tumour cells: HepG2 and DU145 Normal cells In vivo	IC_{50} of 3 μM, but apoptosis was not induced. In both cell lines caused G_1 arrest and induction of GADD45A, PIM1 and GADD153. CYP1A1 was increased in HepG2 only	Satomi and Nishino (2007)
Undaria pinnatifida (B)	Fucoxanthin, fucoxanthinol	Tumour cells: HUVEC Normal cells In vivo: ex vivo aortic segments from male Wister rats	Fucoxanthin (>10 μM) suppressed HUVEC proliferation; there was no effect on HUVEC chemotaxis. Microvessel (CD31+ve) formation suppressed (10–20 μM). Both chemicals suppressed microvessel growth in rat aortic rings	Sugawara et al. (2006)
Not specified	Fucoxanthin	Tumour cells: WiDr, HCT116 wild type and HCT116 p21(−/−) Normal cells In vivo	Reduced viability of WiDr cells. Cell cycle arrest during G_o/G_1 mediated through up-regulation of p21	Das et al. (2005)
Not specified	Fucoxanthin	Tumour cells: PC-3 Normal cells In vivo	Apoptosis was induced with DNA fragmentation and caspase 3 activation at doses of 20 μM. Bcl-2 and Bax, but not Bcl-X_L, were reduced	Kotake-Nara et al. (2005a)
Undaria pinnatifida (B)	Fucoxanthin	Tumour cells: HL-60 and H_2O_2 resistant HL-60 variants (HP50-2, HP100-1) Normal cells In vivo	Fucoxanthin induced apoptosis through loss of mitochondrial membrane potential. Caspases 3 and 9 were activated, Bcl-2, Bcl-X_L or Bax were unchanged, no evidence found for ROS involvement	Kotake-Nara et al. (2005b)
Undaria pinnatifida (B)	Fucoxanthin	Tumour cells: Caco-2, HT-29 and DLD-1 Normal cells In vivo	Reduced cell viability (test doses 7.6, 15.2 μM); Bcl-2 expression decreased and apoptosis increased. A greater effect on Caco-2 cell viability was seen when combined with troglitazone	Hosokawa et al. (2004)
Undaria pinnatifida (B)	Fucoxanthin	Tumour cells: Caco-2 Normal cells In vivo: Male ICR mice	Showed that fucoxanthin is hydrolysed to fucoxanthinol during absorption both in vitro and in vivo	Sugawara et al. (2002)
Undaria pinnatifida (B)	Fucoxanthin	Tumour cells: PC-3, DU 145, LNCaP Normal cells In vivo	Fucoxanthin reduced cell viability of PC-3 (>5 μM) and DU 145 and LNCaPs (>10 μM); showed DNA fragmentation and reduce cell viability through increased apoptosis	Kotake-Nara et al. (2001)
Undaria pinnatifida (B)	Fucoxanthin	Tumour cells: HL-60 Normal cells In vivo	Fucoxanthin reduced cell viability and induced apoptosis	Hosokawa et al. (1999)
Hizikia fusiforme (B)	Fucoxanthin	Tumour cells Normal cells In vivo: B6C3F1 mice: SC injection of DMH 6× over 3 weeks; then fucoxanthin treatment for 7 weeks	Colonic crypt epithelial cells showed reduced proliferation and number of aberrant crypt foci; no liver or kidney toxicity seen	Kim et al. (1998)

Table 7 (continued)

Seaweed	Component	Study Model	Notes	Reference
Not specified	Fucoxanthin	Tumour cells Normal cells In vivo: ENN induced duodenal tumours in mice	Fucoxanthin (0.005 %) significantly reduced number of tumour-bearing mice and average number of tumours per mouse	Okuzumi et al. (1993)
Not specified	Fucoxanthin	Tumour cells: GOTO Normal cells In vivo	Fucoxanthin (10 μg mL^{-1}) reduced growth rate of cells to 38 % of control; caused cell-cycle arrest in G_0–G_1; expression of N-myc gene decreased	Okuzumi et al. (1990)

Recently, a significant inverse correlation was found between breast cancer rates and *Porphyra* (gim or nori) consumption in Korean women, whereas no significant correlation was observed with *U. pinnatifida* (miyeok or wakame) intake. However, the authors recommend further work and point out the limitations of the study including low consumption in the groups and low variation between cases (Yang et al. 2010b). In a large, recently reported prospective study (n= 52,679) supported by the Japan Public Health Centre, a positive association was found between seaweed consumption and thyroid cancer risk (especially papillary carcinoma) in postmenopausal but not premenopausal women. Hazard ratio for almost daily consumption compared with 2 days/week or less was 1.71; 95 % CI 1.01–2.90; trend P=0.04.

The difficulty of interpretation of dietary studies has been further emphasised by an interventional study of breast cancer risks in American women. The study was designed to investigate the potential effect of seaweed on soy-associated increases in IGF-1 since increased IGF-1 is associated with an increased risk of post-menopausal breast cancer. The study confirmed that soy significantly increases serum IGF-1 levels; however, combination with seaweed reduced this increase by about 40 %. This suggests that concurrent seaweed and soy consumption may be important in modifying the potential deleterious effect of soy-induced increases in serum IGF-1 (Teas et al. 2011). A further preliminary dietary study showed that seaweed supplementation (*U. pinnatifida* capsules) reduced the concentration of urinary human urokinase-type plasminogen activator receptor (uPAR) in postmenopausal American women, an effect that was reversible after seaweed supplementation ended. It is suggested that this may explain the reduced prevalence of breast cancer in Japanese women, where seaweed is frequently consumed, as a raised uPAR level is known to be associated with a higher incidence of breast cancer and an unfavourable prognosis (Teas et al. 2013). This is an important finding as to the potential of seaweed in protecting against BC; however, this study was not designed to identify any potential of the *Undaria* capsules as a source of novel CCT.

Conclusions

Dietary studies provide a unique challenge when trying to identify the efficacy of individual components. In animals, these studies have primarily been confined to situations where seaweed has been tested as a means to reduce tumour development in response to toxic levels of tumour initiators and/or promoters. In humans, tumours develop at a very much reduced rate and over a longer timespan. Human dietary studies do show, on average, trends in favour of seaweed ingestion in the protection from cancer development but the effect is small. Caution must also be exercised since too much seaweed in the diet can increase iodine ingestion to toxic levels. Also there is

Table 8 Small molecules from seaweeds with anti-cancer potential

Seaweed	Chemical	Class	Study model	Notes	Reference
Terpenes and derivatives					
Laurencia microcladia (R)	Elatol	Sesquiterpenoid	Tumour cells: B16F10, A549, DU145, MCF-7, L929 Normal cells: L929 In vivo: C57BL6 mice were injected SC with B16F10 cells	In vitro: reduced viability of all cell lines. B16F10 cells: G_1 and sub-G_1 cell cycle arrest with reduction in cyclin D1, cyclin E, cdk2 and cdk4. Increased apoptosis was accompanied by a decrease in Bcl-xl and increase in Bak, caspase 9 and p53. In vivo: both oral (3, 10 and 30 mg kg^{-1}) and IP (1, 3 and 10 mg kg^{-1}) administration reduced tumour growth	Campos et al. (2012)
Plocamium suhrii and *Plocamium cornutum* (R)	Structures provided	Halogenated monoterpenes	Tumour cells: WHCO1 Normal cells In vivo	IC_{50} values range 6.6–87.6 μM	Antunes et al. (2011)
Laurencia viridis (R)	Structures given in paper	Polyether triterpenoids	Tumour cells: Jurkat, MM144, HeLa, CADO-ES1 Normal cells In vivo	IC_{50} values of 2.0–34.5 μM depending on compound and cell line. Jurkat and CADO-ES1 cells particularly sensitive	Pacheco et al. (2011)
Stypopodium flabelliforme (B)	Structures given in paper (6 in total)	Mero-diterpenoids	Tumour cells: Caco-2, SH-SY5Y, RBL-2H3, RAW.267 Normal cells: V79 In vivo	Concentrations tested ≤50 μM. Non-cancerous V79 cells: 3 compounds had no/little effect, but 3 inhibited proliferation significantly. Cancer cells: some compounds showed selective toxicity, e.g. stypodiol—had little effect on V79 cells but toxic to SH-SY5Y cells	Pereira et al. (2011)
Sargassum fallax (B)	Fallahydroquinone, fallaquinone, fallachromenoic acid, sargaquinone, sargahydroquinoic acid, sargaquinoic acid, sargachromenol	Mero-diterpenoids	Tumour cells: P388 Normal cells In vivo	IC_{50}: sargaquinoic acid (17 μM) and sargahydroquinoic acid (14 μM). Remainder were less active (IC50s >27–32 μM)	Reddy and Urban (2009)
Laurencia mariannensis (R)	Laurenmariannol, (21α)-21-hydroxythyrsiferol and thyrsiferol	Triterpenoids	Tumour cells: P-388 Normal cells In vivo	IC_{50}: laurenmariannol (0.60 μg mL^{-1}), (21α)-21-hydroxythyrsiferol (6.60 μg mL^{-1}) and thyrsiferol (0.30 μg mL^{-1})	Ji et al. (2008)
Cystophora moniliformis (B)	Structures given in paper (9 in total)	Linear and cyclic C18 terpenoids	Tumour cells: P-388 Normal cells In vivo	Most compounds (7) showed little anti-tumour activity (IC_{50s} >40 μM). An inseparable mixture of 2 compounds (3:1 ratio) displayed moderate anti-tumour activity (IC_{50} of 45 μM)	Reddy and Urban (2008)
Laurencia microcladia (R)	Structures (6) given in paper	Sesquiterpenes	Tumour cells: HT29, MCF7, PC3, HeLa, A431 Normal cells In vivo	Bulkiest compound (a dimer) had no cytotoxicity (IC_{50} >300 μM). Others had IC_{50} ranging from 75 to 288 μM	Kladi et al. (2007)

Table 8 (continued)

Seaweed	Chemical	Class	Study model	Notes	Reference
Caulerpa racemosa (G)	Caulerpenyne	Sesquiterpenoid	Tumour cells: SHSY5Y, Kelly Normal cells In vivo	Cytotoxic to both cell lines, induces apoptosis	Cavas et al. (2006)
Laurencia obtusa, *Laurencia microcladia* (R)	12 novel and known sesquiterpenes	Sesquiterpenes	Tumour cells: K562, MCF7, PC3, HeLa, A431, A549, NSCLC-N6 Normal cells: CHO In vivo	Cytotoxic activity ranged between 15.8 and 320 μM. Compounds were nearly always more cytotoxic to cancer than normal cells	Kladi et al. (2006)
Caulerpa taxifolia (G)	Caulerpal A and B	Sesquiterpenes	Tumour cells: HL-60, MCF-7 Normal cells In vivo	No significant cytotoxicity was found against these cell lines	Mao et al. (2006)
Taonia atomaria (B)	Atomarianone A and B	Mero-diterpenoids	Tumour cells: NSCLC-N6, A549 Normal cells In vivo	IC_{50} values of <7.35 μM	Abatis et al. (2005)
Stypopodium flabelliforme (B)	(1) 2β,3α-epitaondiol, (2) flabellinol, (3) flabellinone, (4) stypotriolaldehyde, (5) stypohydroperoxide	Mero-diterpenoid	Tumour cells: NCI-H460, Neuro-2a Normal cells In vivo	(1), (2) and (3) were moderately cytotoxic to neuro-2a cells (LC_{50} ranges from 2 to 11 μM) and to NCI-H460 cells (LC_{50} of 9–24 μM)	Sabry et al. (2005)
Plocamium cartilagineum (R)	Furoplocamioid C, pre-furoplocamioid, pirene, others including halogenated cyclohexanes mertensene, violacene and lindane	Halogenated monoterpenes	Tumour cells: CT26, SW480, HeLa, SkMel28 Normal cells: CHO In vivo	Some compounds had good inhibitory potential; for most compounds, the cytotoxic effect was reversible	De Ines et al. (2004)
Caulerpa taxifolia (G)	Caulerpenyne	Sesquiterpene	Tumour cells: SK-N-SH Normal cells In vivo	IC_{50} of 10 μM. No blockage in G_2/M phase. Induced aggregation of tubulin may inhibit microtubule polymerisation and bundling of residual microtubules	Barbier et al. (2001)
Sargassum hemiphyllum (B)	Hedaol A, B and C	Terpene	Tumour cells: P-388 Normal cells In vivo	IC_{50} of 5.1, 2.2 and 50 μg mL^{-1} to P-388 cells for Heladaol A, B and C, respectively	Takada et al. (2001)
Laurencia majuscula (R)	Majapolene A, B, majapolone, majapols A–D	Sesquiterpenes	Tumour cells: NCI 60-cell in vitro tumour panel Normal cells In vivo	Majapolene A displayed modest cytotoxic activity in NCI panel screen	Erickson et al. (1995)
Caulerpa taxifolia (G)	Caulerpenyne	Sesquiterpene	Tumour cells: several colorectal tumour cell lines and CAL 27 Normal cells In vivo	IC_{50}: colorectal cancer cells (approximately 7 μM). Cells exhibited early shift into S phase followed by a blockade in G_2/M phase	Fischel et al. (1995)
Portieria hornemannii (R)	Structures (6) given in paper	Halogenated monoterpenes	Tumour cells: NCI in vitro tumour panel Normal cells In vivo	Structure activity study. Results expressed as panel average cytotoxicity. 4 compounds had good cytotoxicities (GI_{50} of 0.7–1.3 μM)	Fuller et al. (1994)

Table 8 (continued)

Seaweed	Chemical	Class	Study model	Notes	Reference
Caulerpa taxifolia (G)	(1) 10,11-epoxycaulerpenyne, (2) taxifolial A, (3) taxifolial D, (4) caulerpenyne	Monoterpene, sesquiterpene	Tumour cells Normal cells: BHK 21/C13 In vivo: Swiss mice	IC_{50} in BHK21/C13 cells: (1) 11 μg mL^{-1}, (4) 15 μg mL^{-1}, (2) and (3) both non-toxic at 20 μg mL^{-1}. In vivo: lethality: (1) 75 mg kg^{-1}, (2) and (4) both non-toxic at 100 mg kg^{-1}, (3) not determined	Lemée et al. (1993)
Portieria hornemannii (R)	(3S,6*R*)-6-Bromo-3-(bromomethyl)-2,3,7-trichloro-7-methyloct-1-ene (holomon)	Halogenated monoterpene	Tumour cells: NCI in vitro tumour panel Normal cells In vivo	Cytotoxic to chemoresistant cell lines. Selected for preclinical drug development by NCI; this was limited due to lack of supply (Fuller et al. 1994); synthesis of the compound has since been published	Fuller et al. (1992)
Cystoseira mediterranea (B)	Mediterraneols, structures of 11 compounds provided	Diterpenoid derivative	Tumour cells Normal cells In vivo: P388 mouse leukaemia screen	Range of novel structures reported. They inhibited mitotic division of fertilized urchin eggs with an ED_{50} in the range 2 μg mL^{-1} and also showed in vivo activity. Detailed results not given as compounds were screened by NCI, presumably unpublished. Treatment/control of 128 % at dose of 32 mg kg^{-1}	Francisco et al. (1986)
Lactone derivatives					
Callophycus serratus (R)	Bromophycolide R, S, T U	Bromophycolides, lactones	Tumour cells: cell panel similar to Kubanek 2005 above Normal cells In vivo	Mean IC_{50} of 16–19 μM across the cell lines studied	Lin et al. (2010)
Callophycus serratus (R)	Bromophycolides J-Q	Brominated diterpene–benzoate macrolides	Tumour cells: cell panel as above Normal cells In vivo	Range of IC_{50} in the 11 cell lines was 3.1–10 μM	Lane et al. (2009)
Neurymenia fraxinifolia (R)	Neurymenolide A and B	Macrolides	Tumour cells: DU4475 Normal cells In vivo	IC_{50}: neurymenolide A (3.9 μM) and neurymenolide B (19.0 μM)	Stout et al. (2009)
Callophycus serratus (R)	Bromophycolides C-I	Mostly brominated diterpene-benzoate macrolides	Tumour cells: cell panel as above Normal cells In vivo	Range of IC_{50} in the 11 cell lines was 9 to 42.6 μM	Kubanek et al. (2006)
Plocamium corallorhiza (R)	Plocoralides A–C	Polyhalogenated monoterpenes	Tumour cells: WHCO1 Normal cells In vivo	IC_{50} range 9.3–34.8 μM	Knott et al. (2005)
Callophycus serratus (R)	Bromophycolides A and B; debromophycolide A	Diterpene–benzoate macrolides	Tumour cells: BT-549, DU4475, MDA-MD-468, NCI-H446, PC-3, SHP-77, LNCaP-FGC, HCT116, MDA-MB-231, A2780/DDP-S, DU145 Normal cells In vivo	Mean anti-cancer activity across the cell lines studied was 6.9, 27.7 and >76 μM for bromophycolides A, B and debromophycolide A, respectively. Bromophycolides A caused apoptosis in A2780 with data indicating cell cycle arrest in G_1	Kubanek et al. (2005)

Table 8 (continued)

Seaweed	Chemical	Class	Study model	Notes	Reference
Stanols/sterols/steroids					
Porphyra dentata	Sterol fraction (cholesterol-15 %, β-sitosterol-55 %, campesterol-30 %) (crude fractions also studied)	Sterol	Tumour cells: 4T1 Normal cells In vivo: female BALB/c mice injected with 4T1 cells SC in mammary fat pads. Injected IP with 20 μL of sterol at dosages of 5, 10 or 25 mg kg^{-1} day^{-1} every 3 days for 18 consecutive days	In vitro: reduced cell viability and induced apoptosis. In vivo: reduced tumourigenesis and increased survival. Did not inhibit MDSC. Decrease in ROS levels in MDSC	Kazłowska et al. (2013)
Sargassum angustifolium (B)	Fucosterol (crude fractions also studied)	Sterol	Tumour cells: HT-29, Caco-2, T47D Normal cells: NIH 3T3 In vivo	IC_{50} (μg mL^{-1}): 28 (T47D), >70 (Caco-2), 70 (HT-29), >70 (NIH 3T3)	Khanavi et al. (2012)
Cystoseira myrica (B)	(1) 3-Keto-22-epi-28-nor-cathasterone; (2) cholest-4-ene-3,6-dione	Brassinosteroid	Tumour cells: HEPG-2 and HCT116 Normal cells In vivo	IC50 for (1): HEPG-2 (2.96 μM) and HCT116 (12.38 μM). IC_{50} for (2): HEPG-2 (5.63 μM) and HCT116 (1.16 μM)	Hamdy et al. (2009)
23 seaweeds were tested incl. *Sargassum thunbergii* (B)	Possibly fucosterol	Sterol	Tumour cells: HL-60, HT-29 Also tested: B-16, A-549 Normal cells: HaCaT In vivo	HL60: most seaweeds were toxic at 100 μg mL^{-1}. HT29: *H. fusiformis* and *S. thunbergii* were toxic at 100 μg mL^{-1}. Normal cells: mostly low cytotoxicity, however *H. fusiformis* inhibited growth up to 65.6 %	Kim et al. (2009)
Sargassum carpophyllum (B)	Structures given in paper (7 in total)	Steroids	Tumour cells: HL-60, P-388, MCF-7, HCT-8, 1A9, HOS, PC-3 Normal cells In vivo	Fucosterol and 24-ethylcholesta-4,24(28)-dien-3,6-dione have excellent cytotoxicity towards P-388 cells; IC50s of 0.7 and 0.8 mg mL^{-1}, respectively. 24R,28R- and 24S,28*S*-epoxy-24-ethylcholesterol was active against MCF-7, HCT-8, 1A9, HOS and PC-3 with IC_{50}s of 4–10 mg mL^{-1}	Tang et al. (2002)
Jania rubens (R)	16β-Hydroxy-5α-cholestane-3,6-dione	Sterol	Tumour cells: KB Normal cells In vivo	IC_{50} value of 0.5 μg mL^{-1}	Ktari et al. (2000)
Tydemania expeditionis (G)	3 sulphated cycloartanes, structures given in paper	Stanols		IC_{50} values of 100, 32 and 39 μM. Activity mediated through inhibition of protein kinase	Govindan et al. (1994)
Alkaloids					
Caulerpa spp. (G)	Caulerpin	Alkaloid	Tumour cells: T47D, MCF-7, MDA-MB-231, DU145, PC-3 Normal cells: HMEC In vivo	Cytotoxic to all cell lines, PC-3 most sensitive, DU145 least. Studied HIF-1 inhibition: under hypoxic conditions, caulerpin may disrupt mitochondrial ROS-regulated HIF-1 activation and HIF-1 downstream target gene expression through inhibition of the transport or delivery of electrons to mitochondrial complex III	Liu et al. (2009b)

Table 8 (continued)

Seaweed	Chemical	Class	Study model	Notes	Reference
Lobophora variegata (B), *Caulerpa racemosa* (G), *Spatoglossum schroederi* (B), *Stypopodium zonale* (B)	Caulerpin (acetone/dichloromethane/chloroform crude extracts)	Alkaloid	Tumour cells: C32 Normal cells: FEK4 In vivo	IC_{50} values for C32 cells were >100 μg mL^{-1}. Caulerpin was cytotoxic to FEK4 cells	Rocha et al. (2007)
Lophocladia sp. (R)	Lophocladines A and B	Alkaloids	Tumour cells: NCI-H460, neuro-2a, MDA-MB-435 Normal cells In vivo	IC_{50} values: lophocladine A NCI-H460 and neuro-2a (>45 μM), MDA-MB-435 (>450 μM). Lophocladine B, MDA-MB-435 (3.1 μM), NCI-H460 (64.6 μM), neuro-2a cells (>45 μM). Lophocladine B caused microtubule depolymerisation and cell cycle arrest in G_2/M	Gross et al. (2006)
Quinones					
Sargassum siliquastrum (B)	Sargachromanol E	Meroditerpenoid with a hydroquinone ring	Tumour cells: HL-60 Normal cells In vivo	Caused caspase 3-mediated apoptosis in HL-60 cells	Heo et al. (2011)
Perithalia capillaris (B)	Structures (3) given in paper	bis-Prenylated quinone and phenols	Tumour cells: HL-60 Normal cells In vivo	IC_{50} of quinone (5-(1,1-dimethylprop-2-enyl)-2-(3-methylbut-2-enyl)cyclohexa-2,5-diene-1,4-dione), 0.34 μM. Other compounds less active	Sansom et al. (2007)
Sargassum micracanthum (B)	Structures given in paper	Plastoquinones	Tumour cells: colon 26-L5 Normal cells In vivo	IC_{50} values 1.5–17.5 μg mL^{-1}	Mori et al. (2005)
Sargassum micracanthum (B)	Structures (3) given in paper	Plastoquinones	Tumour cells: HeLa 229, MDCK Normal cells: Vero In vivo	IC_{50} values 8–35 μM, with similar cytotoxicities to normal cells	Iwashima et al. (2005)
Landsburgia quercifolia (B)	Deoxylapachol, 2-(3-methyl-2-butenyl)-2,3-epoxy-1,4-naphthalenedione	Quinones	Tumour cells: P-388 Normal cells: BSC In vivo	IC_{50}: deoxylapachol, P388 cells (0.6 μg mL^{-1}), BSC cells (10 μg mL^{-1}). 2-(3-methyl-2-butenyl)-2,3-epoxy-1,4-naphthalenedione, P388 cells (0.8 μg mL^{-1}). BSC cells (10 μg mL^{-1}). Other molecules tested were found to be much less cytotoxic than the 2 cited	Perry et al. (1991)
Lipids					
Haliclona cymaeformis/*Ceratodictyon spongiosum* (Red Algae sponge assemblage)	Ceratodictyols A–F	Glyceryl ethers	Tumour cells: HeLa Normal cells In vivo	IC_{50} value of 67 μM each	Akiyama et al. (2009)

Table 8 (continued)

Seaweed	Chemical	Class	Study model	Notes	Reference
Laurencia glandulifera (R)	Structures given in paper	Tetrahydrofuran acetogenins	Tumour cells: HT-29, MCF-7, PC-3, HeLa and A431 Normal cells In vivo	No significant cytotoxicity was found against the 5 cell lines at 10 μM	Kladi et al. (2009)
Tydemania expeditionis (G), *Hydrolithon reinboldii* (R)	Structures given in paper	Unsaturated fatty acids	Tumour cells: BT-549, DU4475, MDA-MB-468, MDA-MB-231, HCT116, NCI-H446, SHP-77, PC-3, LNCaP-FGC, DU145, A2780/DDP-S, CCRF-CEM Normal cells In vivo	IC_{50} values from 1.3 to 14.4 μM	Jiang et al. (2008)
Gracilaria asiatica (R)	Gracilarioside, gracilamides	Ceramide	Tumour cells: A375-S2 Normal cells In vivo	Gracilarioside induced 18.2 % cell death at 20.0 μg mL^{-1}. Two gracilamides tested showed weak toxicity (11.7 % cell death at 30.0 μg mL^{-1})	Sun et al. (2006)
Porphyra yezoensis (R)	Sulfoquinovosyl-diacylglycerol with acyl chains of different lengths and degrees of unsaturation	Sulpholipid	Tumour cells Normal cells In vivo	100 μg L^{-1} caused cytotoxicity; 5–50 μg L^{-1} did not. Telomerase inhibition was found at IC_{50} of 22 μM	Eitsuka et al. (2004)
46 samples of air dried algae (B, R, G)	24 lipid extracts	Variety of molecules including lipids	Tumour cells: Ehrlich carcinoma and Meth A fibrosarcoma Normal cells In vivo	Several glycolipid and phospholipid fractions from brown and red algae were effective against Meth A fibrosarcoma (also see Table 4)	Noda et al. (1990)
24 lipid extracts from 8 species of seaweeds (R, G and B)		Lipid	Tumour cells Normal cells In vivo: male ddY and BALB/c mice implanted with Meth A fibrosarcoma IC on flank	Lipids were admin by IP injection 7–19 days after tumour implantation. In general, phospholipid fractions had the highest activity, in particular for *Sargassum*, *Laminaria* and *Porphyra* spp. Also examined effects of carbohydrate extracts (see Table 4)	Noda et al. (1989)

Table 9 Proteins and peptides from seaweeds with anti-cancer potential

Seaweed	Chemical	Class	Study model	Notes	Reference
Capsosiphon fulvescens (B)		Glycoprotein	Tumour cells: AGS Normal cells In vivo	Showed dose-dependent inhibition of growth and cell invasion. Expression of TJ proteins, MMP-2 and MMP-9 decreased	Kim et al. (2013)
Synthesised, originally extracted from *Bryopsis* spp.	Kahalalide F	Cyclic depsipeptide	Tumour cells Normal cells In vivo: phase I clinical trial, 106 patients with advanced solid tumours. Dose: up to 1,200 μg m^{-2}, 3–24 h weekly infusion	Aimed to determine recommended dose for further phase II studies of a prolonged weekly intravenous infusions of KF. 3 and 24 h infusion times were found to have an acceptable safety profile	Salazar et al. (2013)
Capsosiphon fulvescens (B)		Glycoprotein	Tumour cells: AGS Normal cells: IEC-6 In vivo	Reduced cell viability to 68 % in AGS (dose 1–3 μg mL^{-1}), no effect on IEC-6. Induced apoptosis and sub-G1 arrest. Increased levels of Fas, FADD, cleaved caspases 3, 8 and 9, cleaved PARP, Bcl-2 family proteins, cytochrome C and Apaf-1	Kim et al. (2012b)
Laminaria japonica (B)	Crude extract	Glycoprotein	Tumour cells: HT-29, AGS, HepG2 Normal cells In vivo	Cytotoxic to all cell lines especially HT-29. Induced apoptosis which may be mediated via more than 1 pathway, including the Fas signalling pathway, the mitochondrial pathway and cell cycle arrest	Go et al. (2010)
Bryopsis pennata (G)	5-OHKF (a kahalalide derivative)	Cyclic depsipeptide	Tumour cells: SK-N-SH Normal cells *In vivo*	5-OHKF showed no anti-tumour effects	Gao et al. (2009)
Laminaria japonica (B)	Crude extract	Glycoprotein	Tumour cells: IEC-6 Normal cells In vivo	Stimulates growth of these normal gastrointestinal cells by activating the epidermal growth factor receptor signalling pathway	Go et al. (2009)
Synthesised, originally extracted from *Bryopsis* spp.	Kahalalide F	Cyclic depsipeptide	Tumour cells Normal cells In vivo: phase II clinical trial, 24 patients with advanced malignant melanoma. dose 650 μg m^{-2}, 1 h weekly infusion	Good safety profile, but no anti-tumour response. Trial closed	Martín-Algarra et al. (2009)
Synthesised, originally extracted from *Bryopsis* spp.	Kahalalide F	Cyclic depsipeptide	Tumour cells Normal cells In vivo: phase I clinical trial, 38 patients with advanced solid tumours. Dose 266–1,200 μg m^{-2}, 1-h weekly infusion	Recommended dose 650 μg m^{-2}, good safety profile	Pardo et al. (2008)

Table 9 (continued)

Seaweed	Chemical	Class	Study model	Notes	Reference
Galaxaura filamentosa (R)	Galaxamide	Cyclic peptide	Tumour cells: GRC-1, HepG2 Normal cells In vivo	Anti-tumour effects were reported with IC_{50} values of 4.26 μg mL^{-1} (GRC-1) and 4.63 μg mL^{-1} (HepG2)	Xu et al. (2008)
Eucheuma serra (R)	*Eucheuma serra* agglutinin	Lectin	Tumour cells: Colon26 Normal cells In vivo: Colon26: mouse colon adenocarcinoma cells in BALB/c mice	In vitro: induced cell death; the increased expression of caspase 3 and translocation of phosphatidylserine in lectin-treated Colon26 cells suggested cell death was induced through apoptosis. In vivo: intravenous injection of extract significantly inhibited growth of tumours; DNA fragmentation, indicating apoptosis, was detected in tumour cells following treatment. Small decrease in body weight in treated animals	Fukuda et al. (2006)
Eucheuma serra (R)	*Eucheuma serra* agglutinin	Lectin	Tumour cells: Colo201, HeLa, MCF-7, HB4C5 Normal cells: MCF10-2A In vivo	Cytotoxic to Colo201 and HeLa, not to malignant (MCF-7) or non-tumourigenic (MCF10-2A) breast cancer cells. Induced apoptosis by caspase 3 activation. Lipid vesicles as a drug delivery system were investigated, with promising results	Sugahara et al. (2001)
Bryopsis sp. (G)	Kahalalide O	Cyclic depsipeptide	Tumour cells: P-388, A549, HT29, MEL28 Normal cells In vivo	Did not inhibit growth of cell lines at concentration of 10 μg mL^{-1}	Horgen et al. (2000)
Bryopsis sp. (G)	Kahalalide K	Cyclic depsipeptide	Tumour cells: CCL131 Normal cells In vivo	Showed no cytotoxic effect against neuroblastoma cells at concentration of 100 μg mL^{-1}	Kan et al. (1999)
Bryopsis sp. (G)	Kahalalide F	Cyclic depsipeptide	Tumour cells: A-549, HT-29, LOVO, P-388, KB Normal cells: CV-1 In vivo	IC_{50} values against A-549, HT-29 and LOVO are 2.5,0.25 and <1.0 μg mL^{-1}, respectively; against P-388 and KB, 10 and >10 μg mL^{-1}. Also active against CV-1 cells with an IC50 of 0.25 μg mL^{-1}	Hamann and Scheuer (1993)

Table 10 Crude extracts from seaweeds with anti-cancer potential

Seaweed	Extract Type	Cancer cells	Notes	Ref
Eucheuma cottonii (R)	Ethanol extract	Tumour cells Normal cells In vivo: female Sprague-Dawley rats injected SC with LA-7 cells	Oral supplementation of powdered extract (100 mg kg^{-1}), or oral treatment with TAM (10 mg kg^{-1}) for 28 days. Suppressed tumour growth more effectively than TAM, no visible side effects for extract, slight liver and kidney lesions for TAM-treated. Extract decreased MDA, increased GSH.	Shamsabadi et al. (2013)
Polyopes lancifolius (R)	Methanol extract	Tumour cells: T24 Normal cells In vivo	Doses of up to 150 μg mL^{-1} did not affect cell viability. Decreased MMP-9 and decreased cell invasion by matrigel assay	Jayasooriya et al. (2012)
Hydroclathrus clathratus (B)	Ethyl acetate portion of ethanol extract	Tumour cells: HL-60 Normal cells In vivo	Induced apoptosis, activated caspases 3 and 9, up-regulated Bax and down-regulated Bcl-xL, increased ROS	Kim et al. (2012a)
Acanthophora spicifera (R)	Crude ethanol extract	Tumour cells Normal cells In vivo: Ehrlich ascites carcinoma implanted IP in Swiss albino mice	Extract decreased tumour volume and weight and increased survival compared to the saline treated control. Decreased haemoglobin and packed cell volume, increased white blood cell and SOD and CAT levels	Lavakumar et al. (2012)
Caulerpa microphysa (G)	Pepsin-digested extracts	Tumour cells: WEHI-3, HL-60 Normal cells: RAW 264.7 In vivo	Cytotoxic effect seen at ≥25 μg mL^{-1} for both tumour cell lines. Little effect on RAW 264.7. Increased DNA damage in tumour cell lines	Lin et al. (2012)
Cystoseira compressa (B)	Methanol and chloroform, ethyl acetate and methanol fractions	Tumour cells: A549, HCT15, MCF7 Normal cells In vivo	IC_{50} for chloroform fraction (78–80 μg mL^{-1}), ethyl acetate fraction (27–50 μg mL^{-1}) and methanol fraction (110–130 μg mL^{-1})	Mhadhebi et al. (2012)
Mekabu (sporophyll of *Undaria pinnatifida*) (B)	Ethanol extract	Tumour cells: HCT116 Normal cells In vivo	Extract induced apoptosis through a different mechanism from 5FU and CPT-11; this suggests Mekabu could be a useful adjunct to chemotherapy in colorectal cancer	Nishibori et al. (2012)
Gracilaria tenuistipitata (B)	Crude aqueous extract	Tumour cells: H1299 Normal cells In vivo	The extract reduced H_2O_2-induced oxidative damage of DNA in H1299 and protected the cells against H_2O_2-induced cytotoxicity. The extract itself was not found to be cytotoxic. H_2O_2-induced G_2/M cell cycle arrest was reduced when cells were co-treated with the extract (1–4 mg mL^{-1} tested)	Yang et al. (2012)
Gracilaria tenuistipitata	Methanol extract	Tumour cells: Ca9-22 Normal cells In vivo	IC_{50} 0.326 mg mL^{-1}. Caused apoptosis, increased ROS and DNA damage	Yeh et al. (2012)

Table 10 (continued)

Seaweed	Extract Type	Cancer cells	Notes	Ref
Sargassum pallidum (B)	Crude aqueous extract	Tumour cells Normal cells In vivo: gastric cancer induced by MNNG in male Wistar rats	Serum IL-2, 4 and 10 increased and IL-6, IL-1β, TNF-α decreased in rats receiving extract. Gastric mucosa and serum MDA decreased, gastric mucosa and serum GSH decreased, anti-oxidant enzymes (SOD, CAT, GSH-Px) increased	Zhang et al. (2012)
Bifurcaria bifurcata (B)	Crude chloroform/methanol extract	Tumour cells: NSCLC-N6 Normal cells In vivo	The extract has an IC_{50} of 4 μg mL^{-1} after 72 h of treatment on this particularly chemoresistant cell line and induced G_1 cell cycle arrest	Moreau et al. (2006)
Hizikia fusiforme (B)	Ethyl alcohol extract	Tumour cells: U937 Normal cells In vivo	Doses of 30–50 μg mL^{-1} reduced viability to 50–60 %. Treatment with extract increased the cleaved forms of caspases 3, 8 and 9 and PARP and decreased Bcl-2, IAP-1, IAP-2 and XIAP	Kang et al. (2011)
Penicillus dumetosus (G)	DCM/methanol crude extract	Tumour cells: Hep-2, HeLa, SiHa, KB Normal cells: MDCK In vivo	Effect of light on extract IC_{50} was studied. In general, increased light exposure led to decreased IC_{50} values. Light treatment also increased cytotoxicity in normal cells, although the extract was less cytotoxic to normal cells	Moo-Puc et al. (2011b)
Laurencia spp. (R)	Hexane, chloroform, methanol extract	Tumour cells: MES-SA and the doxorubicin-resistant mutant, MES-SA/Dx5, HeLa Normal cells In vivo	Hexane extracts most toxic. Example IC_{50}s: *L. translucida* hexane extract ~16 μg mL^{-1}. *L. dendroidea* hexane ~91 μg mL^{-1}	Stein et al. (2011)
2 green, 3 brown and 6 red	Methanol extracts	Tumour cells Normal cells: L6 In vivo	IC_{50} for *Dasya pedicellata* extract was 14.7 μg mL^{-1}. >90 μg mL^{-1} for all other extracts studied (*Codium*, *Cystoseira*, *Corallina*, *Ceramium*, *Gracilaria* and *Gelidium*)	Süzgeç-Selçuk et al. (2011)
12 species tested including: *Porphyra* sp. (R), *Ecklonia radiata* (B), *Sargassum vestitum* (B)	Ethanol extract	Tumour cells Normal cells In vivo	Inhibition of kinase A was assayed. *Porphyra* sp. (R), *Ecklonia radiata* (B) and *Sargassum vestitum* (B) showed the highest levels of inhibition	Winberg et al. (2011)
Sargassum swartzii (B), *Cystoseira myrica* (B), *Colpomenia sinuosa* (B)	Crude methanol (70 %) extract and hexane, chloroform, ethylacetate and MeOH–H_2O fractions of this	Tumour cells: HT-29, Caco-2, T47D, T47D-T.R, MDA-MB468 Normal cells: NIH 3T3 In vivo	Hexane fractions of *S. swartzii* and *C. myrica* had good cytotoxic action and induced apoptosis in Caco-2 and T47D cells. Mechanism was found to be oestrogen receptor independent by testing oestrogen receptor negative and positive breast cancer cells. Was also cytotoxic to normal cells, but at higher IC_{50}s	Khanavi and Nabavi (2010)
Laminaria cichorioides, *Costaria costata*, *Fucus evanescens* (all B)	Water: ethanol extracts	Tumour cells: DLD-1, HT-29 Normal cells In vivo	All extracts worked in soft agar assay (reduced colony formation); *Fucus evanescens* was the best. Seasonal differences were seen	Imbs et al. (2009)

Table 10 (continued)

Seaweed	Extract Type	Cancer cells	Notes	Ref
27 species were studied:14 red, 5 brown and 8 green	DCM: methanol (7:3) and water extracts	Tumour cells: Hep-2, HeLa, KB Normal cells: MDCK In vivo	In general, green seaweeds were the most cytotoxic, with organic extracts having the best cytotoxic activity	Moo-Puc et al. (2009)
Leathesia nana (B)	Ethanol extract	Tumour cells: A549, BGC-823, MCF-7, B16-BL6, HT-1080, A2780, Bel7402, HCT-8 Normal cells In vivo: S-180 cells inoculated SC in the right axilla of Kunming mice	In vivo: crude extract reduced tumour growth. Purified bromophenols also studied (see Table 8)	Shi et al. (2009)
Lobophora variegata (B), *Caulerpa racemosa* (G), *Spatoglossum schroederi* (B), *Stypopodium zonale* (B),	Acetone/DCM/chloroform crude extracts and purified caulerpin	Tumour cells: C32 Normal cells: FEK4 In vivo	IC_{50} values between 14.9 and >100 μg mL^{-1}. Extracts, except caulerpin, were less cytotoxic to normal cells	Rocha et al. (2007)
Eisenia arborea, *Ecklonia cava*, *Ishige foliacea*, *Ishige okamurai*, *Sargassum micracanthum*, *S. ringgoldianum*, *S. thunbergii* (all B)	Methanol/water	Tumour cells: RBL-2H3 Normal cells In vivo	Almost all extracts (1 mg/mL) were cytotoxic with a reduction in cell viability of ≥55 % (*E. arborea* and *S. thunbergii* had no effect)	Sugiura et al. (2006)
Colpomenia sinuosa (B), *Halimeda discoidea* (G), *Galaxaura oblongata* (R)	Ethyl acetate extracts	Tumour cells: U937, HL-60, HuH-7 Normal cells In vivo	Extracts inhibited growth of all cell lines in a time- and dose-dependent manner. Apoptosis seen in U937 and HL-60 cells. ROS were increased in U937 cells. The anti-oxidant *N*-acetylcysteine blocked extract-induced apoptosis; suggests that ROS is a key mediator in the apoptotic signalling pathway	Huang et al. (2005)
Mekabu (sporophyll of *Undaria pinnatifida*) (B)	Water extract	Tumour cells: MDA-MB231 Normal cells In vivo	DNA fractionation was seen, confirming the extract induced apoptosis. This was associated with activation of caspases 3, 6 and 8; caspase 9 and Bid were unaffected	Sekiya et al. (2005)
Ulva lactuca (G)	Water soluble from methanol extract	Tumour cells: U937, RAW 264.7 Normal cells: splenocytes In vivo	Inhibited tumour cell growth whilst stimulating splenocytes (dose 25–100 μg mL^{-1}); extract increased NO production in RAW 264.7 cells	Lee et al. (2004)
Mekabu (sporophyll of *Undaria pinnatifida*) (B)	Water extract	Tumour cells: MCF-7, T-47D and MDA-MB-231 Normal cells: MCF-10A In vivo: DMBA-induced mammary tumours in Sprague-Dawley rats	In vivo: strong suppressive effect on mammary carcinogenesis (given daily in drinking water, without toxicity). In vitro: strongly induced apoptosis in 3 human breast cancer cell lines. No induction of apoptosis was seen in normal human mammary cells	Funahashi et al. (2001)
Marginisporum crassissimum (R)	Water extract	Tumour cells: B16-BL6, JYG-B, KPL-1 Normal cells In vivo: female C57BL/6J mice inoculated in the tail vein with B16-BL6 cells	In vitro: extracts inhibited growth of all tumour cell lines and also invasion of B16-BL6 cells. In vivo: lung metastasis of B16-BL6 cells was inhibited by IP	Hiroishi et al. (2001)

Table 10 (continued)

Seaweed	Extract Type	Cancer cells	Notes	Ref
			administration of extract; also increase survival time	
Screened 304 species of algae	Crude methanol and water extracts	Tumour cells: MOLT-4, K562, HeLa, KB Normal cells In vivo	10 methanol extracts and 2 water extracts from those algal samples showed telomerase inhibiting activity; most effective: methanol extract from *Caulerpa sertularioides*. K562, HeLa and KB cells showed little or no telomerase inhibiting activity	Kanegawa et al. (2000)
Enteromorpha prolifera (G)	Methanol/acetone extraction	Tumour cells Normal cells In vivo: ICR mice with DMBA-induced skin tumours; after 1 week TPA applied twice-weekly for 20 weeks	Skin application of extract significantly reduced tumourigenesis. 4 treatment combinations were tested; the largest reduction was seen when extract was applied before each application of both DMBA and TPA	Higashi-Okai et al. (1999)
Caulerpa taxifolia (G)	Crude water and methanol (plus 10,11-epoxycaulerpenyne, taxifolial A and D, caulerpenyne)	Tumour cells Normal cells: BHK 21/C13 In vivo: Swiss, female	In vitro: seasonal differences found, IC_{50}: water/winter (800 μg mL^{-1}), methanol/winter (250 μg mL^{-1}), methanol/summer (150 μg mL^{-1}). In vivo: toxicity on mice was tested. Water extracts in summer/autumn was not toxic at 2 g kg^{-1}. In winter/spring, they were lethal at 1 g kg^{-1}. Methanol extracts from summer were lethal at 1 g/kg but not lethal at 1.5 g kg^{-1} in winter	Lemée et al. (1993)
Undaria pinnatifida (B)	Dichloromethane crude extract	Tumour cells Normal cells In vivo: skin tumours in ICR mice initiated with DMBA and promoted with TPA	Variety of seaweeds screened. *U. pinnatifida* was most potent and used for in vivo testing. 15 weeks of topical treatment with extract: number of mice with tumours and no. of tumours per mouse was reduced	Ohigashi et al. (1992)
13 species were assayed	Water, ethanol and chloroform	Tumour cells: KB Normal cells In vivo	*Dictyopteris membranacea* in particular exhibited excellent cytotoxic activity. All 3 extracts significantly inhibited the growth of the cell cultures. They were screened in different seasons for cytotoxicity	Kosovel et al. (1988)
16 extracts/powdered preparations from 9 species of seaweeds		Tumour cells: S-180 inoculated SC into mice Normal cells In vivo	Diets containing *Laminaria angustata*, *L. angustata* and *L. japonica* gave tumour inhibition ratios of 70.3 to 83.6 %. IP injection of 10 preparations from 6 edible seaweeds, including the 3 listed, was also effective with inhibition ratios of 61.9 to 95.2 %	Yamamoto et al. (1986)
19 preparations from 8 species of edible seaweeds, sodium alginate and cellulose powder	Crude extract	Tumour cells Normal cells In vivo: rats with intestinal tumours induced by 1,2-dimethyl-hydrazine	There was a significant decrease in tumour incidence in rats fed 6 preparations from *Eisenia bicyclis*, *Laminaria angustata*, *L. angustata* var. *longissima* and *Porphyra tenera*	Yamamoto and Maruyama (1985)

some evidence that prostate cancer rates may be increased in men eating high levels (≥5 portions/week) of seaweed; thus, moderation may be the best policy. In view of the considerable limitations on the type of studies possible in animal models and particularly humans, it may always be difficult to draw conclusions on the potential use of seaweed as a source of novel anti-cancer agents. The only exception to this would be a fully powered phase 3 clinical trial of a potentially effective cancer drug that has progressed over all of the hurdles to this final stage before licensing.

Overall conclusions

Over the last 40 years, there has been an increasing interest in the identification of novel drugs isolated from natural compounds including macroalgae. The papers identified in this review (Tables 4, 5, 6, 7, 8, 9, 10, 11 and 12) show that many different seaweeds have been investigated, primarily sourced from the seas off the coasts of Asia but including diverse sites from around the world. To fully identify the potential of macroalgae, there is a need to expand these studies to seaweeds collected in the seas off other continents since it is known that there is great spatial diversity in both species of seaweed and the bioactive molecules they contain.

Many of the studies discussed have identified good to excellent potential of the macroalgae as sources for anti-cancer drugs; this has been proven in a range of different models both in vitro and in vivo. However, very few preparations, from any marine sources, have made it to clinical trial, and only one seaweed-derived drug, kahalalide F, has been tested (currently in clinical trials, see "Protein and peptides").

One of the problems of natural product research is the purification and identification of the active compound(s). Most studies use crude extracts or partially purified fractions. This approach is useful when screening for bioactivity, and any activity found is frequently attributed to the predominant component of the extracts. However, this cannot be confirmed since there may be other less abundant, but more potent compounds, in the extract. Clearly, when potent effects are found, there is a need for further work to fully purify and characterise the extracts so that activity can be attributed to a specific class of compounds or a molecule and the mechanism of action identified. However, this is not a simple matter and takes considerable levels of investment

Table 11 Raw seaweeds with anti-cancer potential

Seaweed	In vivo model	Notes	Ref
Laminaria japonica (B)	AOM-induced colon tumours in male Sprague-Dawley rats	All seaweed feeding regimens reduced aberrant intestinal crypt formation. Suggests anti-carcinogenic effects mediated through both the blocking of initiation and the suppression of cell proliferation in initiated cells	Lee and Sung (2003)
Undaria pinnatifida (B)	DMBA-induced mammary tumours in female Sprague-Dawley rats	Weights of mammary tumours were significantly lower and serum total iodine concentration was significantly higher than in control group	Funahashi et al. (1999)
(1) *Porphyra tenera* (B), (2) *Laminaria religiosa* (B), (3) *L. japonica var. ochotensis* (B)+3 others	DMBA-induced tumours in rats	1, 2 and 3 showed an inhibitory effect on tumourigenesis. Tumour incidence was lower. A significant delay in the time to first noticeable tumour in (2) and (3) fed rats. Tumour weight per rat in each group was significantly lower in the (2) fed rats	Yamamoto et al. (1987)
Laminaria angustata (B)	AOM-induced intestinal carcinogenesis in male F344 rats	The incidence and multiplicity of intestinal tumours did not vary between control and seaweed groups. The incidence and multiplicity of colon adenomas and the size of colon tumours increased in rats fed the seaweed containing diet compared to control. No effect on faecal bile acids and faecal cholesterol, total neutral sterols decreased in the seaweed group. Authors suggested that dietary seaweed increases the risk for colon tumours	Reddy et al. (1985)
Laminaria angustata (B)	DMBA-induced mammary tumours in female Sprague-Dawley rats	Causes delay in time for tumour to appear and a reduction in the number of histologically confirmed tumours	Teas et al. (1984)

Table 12 The effect of seaweed ingestion in humans, using epidemiological and interventional methodology

Seaweed	Experimental design	Notes	Ref
Epidemiology			
General seaweed consumption	Japanese women (n=52,679; age 40–69 years) followed up for 14.5 years. Seaweed consumption was assessed using a food frequency questionnaire: 2 days/week or less (baseline), 3–4 days/week, or almost daily	Showed a positive association between seaweed consumption and thyroid cancer risk (especially papillary carcinoma) in postmenopausal but not premenopausal women	Michikawa et al. (2012)
Undaria pinnatifida (B) and *Porphyra* spp. (R)	Korean women (n=362) aged 30–65 years old, with histologically confirmed breast cancer, paired with control cases according to age and menopausal status. Seaweed consumption, and other foods, was assessed using a food frequency questionnaire	Case–control study of seaweed consumption and cancer risk in Korean women. Inverse associations were found between gim (*Porphyra*) intake and the risk of breast cancer in pre- and post-menopausal women. Miyeok (*Undaria*) consumption did not have any significant associations with breast cancer	Yang et al. (2010b)
General seaweed consumption	Title: JACC study. Japanese males (n=42,940) and females (n=55,308) aged 40 to 79 years followed 1990–1997). Seaweed consumption, amongst other foods, was assessed using a food frequency questionnaire: scarcely any, 1–2 times/month, 1–2 times/week, 3–4 times/week and almost every day	Inverse association between lung cancer risk and seaweed consumption in men. No significant trend for women	Ozasa et al. (2001)
General seaweed consumption	Lifestyle questionnaire including diet of 181 individuals newly diagnosed with colorectal cancer and 653 general population controls	An inverse association between seaweed consumption and both colon and rectal cancer was found	Hoshiyama et al. (1993)
General seaweed consumption	Men of Japanese ancestry, residing on the Hawaiian island of Oahu (n=7,999, age 46–68, followed 1968–1986). Seaweed consumption, amongst other foods, was assessed using a food frequency questionnaire: almost never, <2/week, 2–4 times/week, daily, >once a day	Men who consumed at least 5 servings/week had a significantly increased risk of prostate cancer compared to those who consumed one serving/week or less	Severson et al. (1989)
General seaweed consumption	From a dietary study of 6,860 Japanese men aged 46–68 living in Hawaii 86 indicated they had spouses who had breast cancer. A wide ranging food frequency questionnaire was used assessing seaweed consumption defined as: almost never, < 2/week, 2-4 times/week, almost daily. Study carried out on the assumption that men's dietary data from an existing survey would be similar to their spouses	Compared American and Japanese style diet, found link between American style diet and increased risk of breast cancer. Japanese style diet included seaweed items	Nomura et al. (1978)
Intervention			
Undaria pinnatifida (B)	American healthy postmenopausal women (n=15, African American and European American, 10 breast cancer (BC) survivors, 5 no history of BC). 3 month single-blinded placebo-controlled clinical trial. Consumed 10 capsules daily (5 g day^{-1}) of placebo for 4 weeks, seaweed for 4 weeks, then placebo for 4 weeks	Blood and urine samples were collected after each treatment period. Reversable reduction in levels of uPAR after treatment period. UPAR is associated with unfavourable prognosis in BC patients	Teas et al. (2013)
Alaria esculenta (B)	American postmenopausal women (n=30; mean age 58 years; all Caucasian). 14-week double-blinded, randomized, placebo-controlled crossover clinical trial. Consumed 5 g day^{-1} placebo or seaweed in capsules for 7 weeks. In the 7th week, a high-soy protein isolate powder was added	Soy was found to significantly increase serum IGF-1 concentrations compared to the placebo. Combining seaweed and soy reduced the increase ~40 %	Teas et al. (2011)

which perhaps explains why so many apparently effective crude fractions have failed to be developed.

An additional complication is the potential for synergistic and/or antagonistic effects of crude extracts to be lost on purification, and this may not become apparent until complex purification has taken place. Also when testing for compounds that have cytotoxic effects on cancer cells, it is essential that there is tumour specificity; this requires the concurrent study of normal cells and evaluation of side effects in animal models and humans. In addition, in recent years, the regulatory authorities require more specific information as to how a new drug works, and this involves carrying out mechanistic studies to identify the specific targets in cancer cells which are less affected in normal cells. Some studies have attempted to do this, and a variety of pathways have been implicated most frequently those controlling apoptosis.

As discussed above, human dietary studies suggest that seaweed in the diet has a protective effect against tumour development, although there are some suggestions that too much can have deleterious effects in some situations. The human studies primarily measure the protective effect of dietary seaweed on humans, and they do not really inform as to whether they contain potential cytotoxic compounds. However, this may be one of the mechanisms through which they may work, by reducing the viability of micro-tumours or enhancing the immune system's ability to eradicate small, invisible clusters of tumour cells before they become clinically demonstrable; currently, it is not possible to test this.

This review has compiled considerable evidence that marine-derived macroalgae are an excellent source of compounds with the potential to be developed into drugs for treating cancer. However, considerable investment is required if this valuable resource is to be utilised to its full potential.

Acknowledgments This study was supported by the FUSION programme, Intertrade Ireland.

Glossary

4T1	Murine mammary tumour
13762 MAT	Rat mammary adenocarcinoma
1301	Human T cell leukaemia
A20	Murine reticulum cell sarcoma
A549	Human lung adenocarcinoma
AAPH	2,2-Azobis(2-amidinopropane) dihydrochloride
AGS	Human gastric adenocarcinoma
AIF	Apoptosis inducing factor
AMVN	2,2-Azobis(2,4-dimethylvaleronitrile)
B-16	Murine melanoma
B16-BL6	Murine melanoma
B16-F10	Murine melanoma
BCNU	Carmustine
BEL-7402	Human hepatocellular carcinoma
BSC	Monkey kidney cells
BXPC3	Human primary pancreatic adenocarcinoma
C32	Human melanoma
Caco-2	Human epithelial colorectal adenocarcinoma
CCL39	Chinese hamster fibroblasts
Cdk	Cyclin-dependent kinases
CHO	Chinese hamster ovary
Colo320DM	Human colon adenocarcinoma
COX-2	Cyclooxygenase-2
CT-26	Murine colon cancer
Cx	Connexin
Daudi	Human Burkitt's lymphoma
DC	Dendritic cells
DLD-1	Human colorectal adenocarcinoma
DU-145	Human prostate cancer
ED-40515(−)	Human leukaemia T cell line
ENN	*N*-Ethyl-*N*′-nitro-*N*-nitrosoguanidine
ERCC1	Excision repair cross complementation 1
ERK	Extracellular signal-regulated kinases
FBHE	Foetal bovine heart endothelial
FGF	Fibroblast growth factor
FHC	Human colon epithelial
FHs 74 Int	Human normal intestinal
GADD45A	Growth arrest and DNA-damage-inducible protein
GCSF	Granulocyte colony-stimulating factor
GOTO	Human neuroblastoma cells
GSH	Glutathione
GSH-PX	Glutathione peroxidase
H22	Murine hepatoma
HCT-116	Human colon cancer cells
HCT-15	Human colorectal adenocarcinoma cells
HCT-8	Human colon cancer cells
HeLa	Human cervical cancer cells
HEp-2	Epidermoid carcinoma cells
HepG2	Liver cancer cells
HL-60	Human leukaemia
HMEC-1	Human microvascular endothelial cells
HOS	Human osteosarcoma cells
HT1080	Human fibrosarcoma cells
HT-29	Human colon adenocarcinoma cells
HTLV-1	Human T cell leukaemia virus type 1
HS-Sultan cells	Human lymphoma
Hs 677.st	Human stomach fibroblasts
HUT-102	Human cutaneous T lymphocytes
HUVEC	Human umbilical vein endothelial cells
H1299	Non-small cell lung cancer cells
ICR	Imprinting control region mice

IEC-6	Rat normal intestinal epithelial cells
IGF-IR	Insulin-like growth factor-I receptor
JAK/STAT	Janus kinase/signal transducer and activator of transcription
JB6 Cl41	Normal murine epidermis
Jurkat	Human T cell leukaemia
K562	Human chronic myelogenous leukaemia
KB	Human nasopharynx carcinoma
L-1210	Mouse lymphocytic leukaemia
L929	Murine fibrosarcoma
LLC	Lewis lung carcinoma
LNCaP	Human prostate adenocarcinoma
LOVO	Human colorectal adenocarcinoma
LS-174	Human colonic adenocarcinoma cells
MiaPaCa-2	Human pancreatic carcinoma
MAPK	Mitogen-activated protein kinase
MCF-7	Human breast adenocarcinoma
MDA	Malondialdehyde, an oxidative stress marker
MDA-MB-231	Human mammary adenocarcinoma
MDA-MB-435	Human mammary carcinoma
MDCK	Madine–Darby canine kidney
MDSC	Myeloid-derived suppressor cells
MEL-28	Human melanoma
MG-63	Human osteosarcoma
MGC-803	Human gastric cancer
MKN-45	Human gastric adenocarcinoma
MMP	Matrix metalloproteinase
MOLT-4	Human lymphoblastic leukaemia
MRC-5	Human lung fibroblast
MT-2	Human lymphocyte infected with HTLV-1
MT-4	Human T cell leukaemia
NF-κB	Nuclear factor κB
NSCLC-N6	Human non-small cell bronchopulmonary carcinoma line
P-388	Murine leukaemic cells
Panc-1	Human pancreatic carcinoma
Panc-3.27	Human pancreatic cancer
PAI-1	Plasminogen activator inhibitor-1
PBMC	Peripheral blood mononuclear cells
PCNA	Proliferating cell nuclear antigen
PC-3	Human prostate cancer
PtK1	*Potorous tridactylis* normal kidney cells
RAW264.7	Mouse leukaemic monocyte macrophage cell line
RIF-1	Radiation-induced fibrosarcoma
RPMI-7951	Human malignant melanoma obtained from the lymph node
S-180	Sarcoma 180
SAPK/JNK	Stress-activated protein kinase/Jun-amino-terminal kinase
SF-295	Brain
SK-MEL-28	Human malignant melanoma
SF-295	Human glioblastoma
SK-MEL-28	Human malignant melanoma
SK Hep-1	Human hepatocellular carcinoma
SMMC-7721	Human hepatocellular carcinoma
SW-480	Human colon carcinoma
THP 1	Human leukaemia
TJ	Tight junction (proteins)
TNF-α	Tumour necrosis factor-alpha
TPA	12-*O*-Tetradecanoylphorbol-13-acetate
TRAIL	TNF-related apoptosis-inducing ligand
uPAR	Urinary human urokinase-type plasminogen activator receptor
U-937	Human leukaemic monocyte lymphoma
V79-4	Chinese hamster lung fibroblasts
VEGF	Vascular endothelial growth factor
Vero	African green monkey kidney
WHCO1	Human oesophageal cancer
WiDr	Colon adenocarcinoma cell
XC	Rat sarcoma
YAC-1	Murine lymphoma

References

Abatis D, Vagias C, Galanakis D, Norris JN, Moreau D, Roussakis C, Roussis V (2005) Atomarianones A and B: two cytotoxic meroditerpenes from the brown alga *Taonia atomaria*. Tetrahedron Lett 46:8525–8529

Abdala-Díaz R, Cabello-Pasini A, Pérez-Rodríguez E, Álvarez R, Figueroa F (2006) Daily and seasonal variations of optimum quantum yield and phenolic compounds in *Cystoseira tamariscifolia* (Phaeophyta). Mar Biol 148:459–465

Aisa Y, Miyakawa Y, Nakazato T, Shibata H, Saito K, Ikeda Y, Kizaki M (2005) Fucoidan induces apoptosis of human HS-sultan cells accompanied by activation of caspase-3 and down-regulation of ERK pathways. Am J Hematol 78:7–14

Akiyama T, Ueoka R, van Soest RWM, Matsunaga S (2009) Ceratodictyols, 1-glyceryl ethers from the red alga-sponge association *Ceratodictyon spongiosum/Haliclona cymaeformis*. J Nat Prod 72:1552–1554

Ale MT, Maruyama H, Tamauchi H, Mikkelsen JD, Meyer AS (2011a) Fucoidan from *Sargassum* sp. and *Fucus vesiculosus* reduces cell viability of lung carcinoma and melanoma cells in vitro and activates natural killer cells in mice in vivo. J Biol Macromol 49:331–336

Ale MT, Maruyama H, Tamauchi H, Mikkelsen JD, Meyer AS (2011b) Fucose-containing sulfated polysaccharides from brown seaweeds inhibit proliferation of melanoma cells and induce apoptosis by activation of caspase-3 in vitro. Mar Drugs 9:2605–2621

Ale MT, Mikkelsen JD, Meyer AS (2012) Designed optimization of a single-step extraction of fucose-containing sulfated polysaccharides from *Sargassum* sp. J Appl Phycol 24:715–723

Alekseyenko TV, Zhanayeva SY, Venediktova AA, Zvyagintseva TN, Kuznetsova TA, Besednova NN, Korolenko TA (2007) Antitumor and antimetastatic activity of fucoidan, a sulfated polysaccharide isolated from the Okhotsk Sea *Fucus evanescens* brown alga. Bull Exp Biol Med 143:730–732

Alfadda AA, Sallam RM (2012) Reactive oxygen species in health and disease. J Biomed Biotechnol. doi:10.1155/2012/936486

Andreasen P (2007) PAI-1 - A potential therapeutic target in cancer. Curr Drug Targets. 8:1030–1041

Antunes EM, Afolayan AF, Chiwakata MT, Fakee J, Knott MG, Whibley CE, Hendricks DT, Bolton JJ, Beukes DR (2011) Identification and

in vitro anti-esophageal cancer activity of a series of halogenated monoterpenes isolated from the South African seaweeds *Plocamium suhrii* and *Plocamium cornutum*. Phytochemistry 72:769–772

Aravindan S, Delma CR, Thirugnanasambandan SS, Herman TS, Aravindan N (2013) Anti-pancreatic cancer deliverables from sea: first-hand evidence on the efficacy, molecular targets and mode of action for multifarious polyphenols from five different brown-algae. PloS One 8:e61977. doi:10.1371/journal.pone.0061977

Athukorala Y, Kim K, Jeon Y-J (2006) Antiproliferative and antioxidant properties of an enzymatic hydrolysate from brown alga, *Ecklonia cava*. Food Chem Toxicol 44:1065–1074

Athukorala Y, Ahn GN, Jee Y-H, Kim G-Y, Kim S-H, Ha J-H, Kang J-S, Lee K-W, Jeon Y-J (2009) Antiproliferative activity of sulfated polysaccharide isolated from an enzymatic digest of *Ecklonia cava* on the U-937 cell line. J Appl Phycol 21:307–314

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

Benard C, Cultrone A, Michel C, Rosales C, Segain J-P, Lahaye M, Galmiche J-P, Cherbut C, Blottière HM (2010) Degraded carrageenan causing colitis in rats induces TNF secretion and ICAM-1 upregulation in monocytes through NF-κB activation. PLoS One 5:e8666

Berteau O, Mulloy B (2003) Sulfated fucans, fresh perspectives: structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. Glycobiology 13:29R–40R

Bocanegra A, Bastida S, Benedí J, Ródenas S, Sánchez-Muniz FJ (2009) Characteristics and nutritional and cardiovascular-health properties of seaweeds. J Med Food 12:236–258

Boo H-J, Hong J-Y, Kim S-C, Kang J-I, Kim M-K, Kim E-J, Hyun J-W, Koh Y-S, Yoo E-S, Kwon J-M, Kang H-K (2013) The anticancer effect of fucoidan in PC-3 prostate cancer cells. Mar Drugs 11:2982–2999

Bourgougnon N, Roussakis C, Kornprobst J-M, Lahaye M (1994) Effects in vitro of sulfated polysaccharide from *Schizymenia dubyi* (Rhodophyta, Gigartinales) on a non-small-cell bronchopulmonary carcinoma line (NSCLC-N6). Cancer Lett 85:87–92

Britton G (1995) Structure and properties of carotenoids in relation to function. FASEB J 9:1551–1558

Burges Watson D (2008) Public health and carrageenan regulation: a review and analysis. J Appl Phycol 20:505–513.

Campos A, Souza CB, Lhullier C, Falkenberg M, Schenkel EP, Ribeiro-do-Valle RM, Siqueira JM (2012) Anti-tumour effects of elatol, a marine derivative compound obtained from red algae *Laurencia microcladia*. J Pharm Pharmacol 64:1146–54

Carthew P (2002) Safety of carrageenan in foods. Env Health Perspect 110:176–177

Cavas L, Baskin Y, Yurdakoc K, Olgun N (2006) Antiproliferative and newly attributed apoptotic activities from an invasive marine alga: *Caulerpa racemosa* var. *cylindracea*. J Exp Mar Biol Ecol 339:111–119

Cho M, Lee B-Y, You S-G (2011) Relationship between oversulfation and conformation of low and high molecular weight fucoidans and evaluation of their in vitro anticancer activity. Molecules 16:291–297

Colegate SM, Molyneux RJ (2008) Bioactive natural products: detection, isolation, and structural determination, 2nd edn. CRC, Boca Raton, 624 pp

Costa LS, Fidelis G, Cordeiro S, Oliveira R, Sabry D, Câmara R, Nobre L, Costa MSSP, Almeida-Lima J, Farias E, Leite E, Rocha H (2010) Biological activities of sulfated polysaccharides from tropical seaweeds. Biomed Pharmacother 64:21–28

Costa LS, Fidelis G, Telles C, Dantas-Santos N, Camara R, Cordeiro S, Costa MSSP, Almeida-Lima J, Melo-Silveira R, Oliveira R, Albuquerque I, Andrade G, Rocha H (2011a) Antioxidant and antiproliferative activities of heterofucans from the seaweed *Sargassum filipendula*. Mar Drugs 9:952–966

Costa LS, Telles C, Oliveira R, Nobre L, Dantas-Santos N, Camara R, Costa MSSP, Almeida-Lima J, Melo-Silveira R, Albuquerque I, Leite E, Rocha H (2011b) Heterofucan from *Sargassum filipendula* induces apoptosis in HeLa cells. Mar Drugs 9:603–614

Cox S, Abu-Ghannam N, Gupta S (2010) An assessment of the antioxidant and antimicrobial activity of six species of edible Irish seaweeds. Int Food Res J 17:205–220

Cragg GM, Newman DJ (2009) Nature: a vital source of leads for anticancer drug development. Phytochem Rev 8:313–331

Croci D, Cumashi A, Ushakova N et al (2011) Fucans, but not fucomannoglucuronans, determine the biological activities of sulfated polysaccharides from *Laminaria saccharina* brown seaweed. PloS One 6:e17283. doi:10.1371/journal.pone.0017283

Cumashi A, Ushakova N, Preobrazhenskaya M, D'Incecco A, Piccoli A, Totani L, Tinari N, Morozevich G, Berman A, Bilan M, Usov A, Ustyuzhanina N, Grachev A, Sanderson C, Kelly M, Rabinovich G, Iacobelli S, Nifantiev N (2007) A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds. Glycobiology 17:541–552

Das SK, Hashimoto T, Shimizu K, Yoshida T, Sakai T, Sowa Y, Komoto A, Kanazawa K (2005) Fucoxanthin induces cell cycle arrest at G0/G1 phase in human colon carcinoma cells through up-regulation of p21WAF1/Cip1. Biochim Biophys Acta 1726:328–335

Das SK, Hashimoto T, Kanazawa K (2008) Growth inhibition of human hepatic carcinoma HepG2 cells by fucoxanthin is associated with down-regulation of cyclin D. Biochim Biophys Acta 1780:743–9

De Ines C, Argandona V, Rovirosa J, San-Martin A, Diaz-Marrero A, Cueto M, Gonzalez-Coloma A (2004) Cytotoxic activity of halogenated monoterpenes from *Plocamium cartilagineum*. Z Naturforsch 59:339–344

De Sousa A, Torres M, Pessoa C, de Moraes M, Filho F, Alves A, Costa-Lotufo L (2007) In vivo growth-inhibition of Sarcoma 180 tumor by alginates from brown seaweed. Carbohydr Polym 69:7–13

Dellai A, Laajili S, Le Morvan V, Robert J, Bouraoui A (2013) Antiproliferative activity and phenolics of the Mediterranean seaweed *Laurencia obusta*. Ind Crops Prod 47:252–255

Dias PF, Siqueira JM, Vendruscolo LF, de Jesus NT, Gagliardi AR, Maraschin M, Ribeiro-do-Valle RM (2005) Antiangiogenic and antitumoral properties of a polysaccharide isolated from the seaweed *Sargassum stenophyllum*. Cancer Chemother Pharmacol 56:436–446

Dias PF, Siqueira JM, Maraschin M, Ferreira AG, Gagliardi AR, Ribeiro-do-Valle RM (2008) A polysaccharide isolated from the brown seaweed *Sargassum stenophyllum* exerts antivasculogenic effects evidenced by modified morphogenesis. Microvasc Res 75:34–44

Du B, Zhong X-Y, Liao X-J, Xu W-J, Zhou X-L, Xu S-H (2010) A new antitumor arabinopyranoside from *Laurencia majuscula* induces G2/M cell cycle arrest. Phytother Res 24:1447–1450

Eitsuka T, Nakagawa K, Igarashi M, Miyazawa T (2004) Telomerase inhibition by sulfoquinovosyldiacylglycerol from edible purple laver (*Porphyra yezoensis*). Cancer Lett 212:15–20

Ellouali M, Boisson-Vidal C, Durand P, Jozefonvicz J (1993) Antitumor activity of low molecular weight fucans extracted from brown seaweed *Ascophyllum nodosum*. Anticancer Res 13:2011–2019

Erickson KL, Beutler JA, Gray GN, Cardellina JH, Boyd MR (1995) Majapolene A, a cytotoxic peroxide, and related sesquiterpenes from the red alga *Laurencia majuscula*. J Nat Prod 58:1848–1860

Ermakova SP, Sokolova R, Kim S-M, Um B-H, Isakov V, Zvyagintseva TN (2011) Fucoidans from brown seaweeds *Sargassum horneri, Ecklonia cava, Costaria costata*: structural characteristics and anticancer activity. Appl Biochem Biotechnol 164:841–580

Fan Y, Wang W, Song W, Chen H, Teng A, Liu A (2012) Partial characterization and anti-tumor activity of an acidic polysaccharide from *Gracilaria lemaneiformis*. Carbohydr Polym 88:1313–1318

Fernández L, Valiente O, Mainardi V, Bello JL, Vélez H, Rosado A (1989) Isolation and characterization of an antitumor active agar-type polysaccharide of *Gracilaria dominguensis*. Carbohydr Res 190:77–83

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

Francisco C, Banaigs B, Teste J, Cave A (1986) Mediterraneols: a novel biologically active class of rearranged diterpenoid metabolites from *Cystoseira mediterranea* (Pheophyta). J Org Chem 51:1115–1120

Freile-Pelegrín Y, Robledo D, Azamar JA (2006) Carrageenan of *Eucheuma isiforme* (Solieriaceae, Rhodophyta) from Yucatán, Mexico. I. Effect of extraction conditions. Bot Mar 49:65–71

Fujihara M, Iizima N, Yamamoto I, Nagumo T (1984) Purification and chemical and physical characterisation of an antitumour polysaccharide from the brown seaweed *Sargassum fulvellum*. Carbohydr Res 125:97–106

Fukuda Y, Sugahara T, Ueno M, Fukuta Y, Ochi Y, Akiyama K, Miyazaki T, Masuda S, Kawakubo A, Kato K (2006) The anti-tumor effect of *Euchema serra* agglutinin on colon cancer cells in vitro and in vivo. Anticancer Drugs 17:943–947

Fuller RW, Cardellina JH, Kato Y, Brinen LS, Clardy J, Snader KM, Boyd MR (1992) A pentahalogenated monoterpene from the red alga *Portieria hornemannii* produces a novel cytotoxicity profile against a diverse panel of human tumor cell lines. J Med Chem 35: 3007–3011

Fuller RW, Cardellina JH, Jurek J, Scheuer PJ, Alvarado-Lindner B, McGuire M, Gray GN, Steiner JR, Clardy J, Menez E (1994) Isolation and structure/activity features of halomon-related antitumor monoterpenes from the red alga *Portieria hornemannii*. J Med Chem 37:4407–4411

Funahashi H, Imai T, Tanaka Y, Tsukamura K, Hayakawa Y, Kikumori T, Mase T, Itoh T, Nishikawa M, Hayashi H, Shibata A, Hibi Y, Takahashi M, Narita T (1999) Wakame seaweed suppresses the proliferation of 7,12-dimethylbenz(a)-anthracene-induced mammary tumors in rats. Jpn J Cancer Res 90:922–7

Funahashi H, Imai T, Mase T, Sekiya M, Yokoi K, Hayashi H, Shibata A, Hayashi T, Nishikawa M, Suda N, Hibi Y, Mizuno Y, Tsukamura K, Hayakawa A, Tanuma S (2001) Seaweed prevents breast cancer? Jpn J Cancer Res 92:483–7

Furusawa E, Furusawa S (1989) Anticancer potential of Viva-Natural, a dietary seaweed extract, on Lewis lung carcinoma in comparison with chemical immunomodulators and on cyclosporine-accelerated AKR leukemia. Oncology 46:343–348

Furusawa E, Furusawa S (1990) Antitumor potential of low-dose chemotherapy manifested in combination with immunotherapy of Viva-Natural, a dietary seaweed extract, on Lewis lung carcinoma. Cancer Lett 50:71–78

Gamal-Eldeen AM, Ahmed EF, Abo-Zeid MA (2009) In vitro cancer chemopreventive properties of polysaccharide extract from the brown alga, *Sargassum latifolium*. Food Chem Toxicol 47:1378–1384

Ganesan P, Matsubara K, Ohkubo T, Tanaka Y, Noda K, Sugawara T, Hirata T (2010) Anti-angiogenic effect of siphonaxanthin from green alga, *Codium fragile*. Phytomedicine 17:1140–1144

Ganesan P, Noda K, Manabe Y, Ohkubo T, Tanaka Y, Maoka T, Sugawara T, Hirata T (2011) Siphonaxanthin, a marine carotenoid from green algae, effectively induces apoptosis in human leukemia (HL-60) cells. Biochim Biophys Acta 1810:497–503

Gao J, Caballero-George C, Wang B, Rao KV, Shilabin AG, Hamann MT (2009) 5-OHKF and NorKA, depsipeptides from a Hawaiian collection of *Bryopsis pennata*: binding properties for NorKA to the human neuropeptide Y Y1 receptor. J Nat Prod 72:2172–6

García-Casal M, Ramírez J, Leets I, Pereira A, Quiroga M (2009) Antioxidant capacity, polyphenol content and iron bioavailability from algae (*Ulva* sp., *Sargassum* sp. and *Porphyra* sp.) in human subjects. Br J Nutr 101:79–85

Go H, Hwang H-J, Nam T (2009) Glycoprotein extraction from *Laminaria japonica* promotes IEC-6 cell proliferation. Int J Mol Med 24:819–824

Go H, Hwang H-J, Nam T-J (2010) A glycoprotein from *Laminaria japonica* induces apoptosis in HT-29 colon cancer cells. Toxicol In Vitro 24:1546–1553

Govindan M, Abbas SA, Schmitz FJ, Lee RH, Papkoff JS, Slate DL (1994) New cycloartanol sulfates from the alga *Tydemania expeditionis*: inhibitors of the protein tyrosine kinase pp60v-src. J Nat Prod 57:74–78

Gross H, Goeger DE, Hills P, Mooberry SL, David L, Murray TF, Valeriote FA, Gerwick WH (2006) Lophocladines, bioactive alkaloids from the red alga *Lophocladia* sp. J Nat Prod 69:640–644

Gu Q, Fang Y, Wang C, Li B, Wenjun M (1998) Studies on the chemical composition and antitumor activity of the acid polysaccharide from alga *Sargassum fusiforme*. Nat Prod Sci 4:88–90

Gunji S, Santoso J, Yoshie-Stark Y, Suzuki T (2007) Effects of extracts from tropical seaweeds on DPPH radicals and Caco-2 cells treated with hydrogen peroxide. Food Sci Technol Res 13:275–279

Gupta S, Cox S, Abu-Ghannam N (2011) Effect of different drying temperatures on the moisture and phytochemical constituents of edible Irish brown seaweed. Food Sci Technol 44:1266–1272

Güven KC, Percot A, Sezik E (2010) Alkaloids in marine algae. Mar Drugs 8:269–284

Hamann M, Scheuer P (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

Hamdy A-HA, Aboutabl EA, Sameer S, Hussein AA, Díaz-Marrero AR, Darias J, Cueto M (2009) 3-Keto-22-epi-28-nor-cathasterone, a brassinosteroid-related metabolite from *Cystoseira myrica*. Steroids 74:927–930

Harnedy P a., FitzGerald RJ (2011) Bioactive proteins, peptides, and amino acids from macroalgae. J Phycol 47:218–232

Hanahan D, Weinberg R (2011) Hallmarks of cancer: the next generation. Cell 144:646–674

Heo S-J, Kim K, Yoon W-J, Oh C, Choi Y-U, Affan A, Lee Y-J, Lee H-S, Kang D-H (2011) Chromene induces apoptosis via caspase-3 activation in human leukemia HL-60 cells. Food Chem Toxicol 49: 1998–2004

Higashi-Okai K, Otani S, Okai Y, Hiqashi-Okaj K (1999) Potent suppressive effect of a Japanese edible seaweed, *Enteromorpha prolifera* (Sujiao-nori) on initiation and promotion phases of chemically induced mouse skin tumorigenesis. Cancer Lett 140:21–25

Hiroishi S, Sugie K, Yoshida T, Morimoto J, Taniguchi Y, Imai S, Kurebayashi J (2001) Antitumor effects of *Marginisporum crassissimum* (Rhodophyceae), a marine red alga. Cancer Lett 167:145–150

Hoffman R, Paper DH, Donaldson J, Vogl H (1996) Inhibition of angiogenesis and murine tumour growth by laminarin sulphate. Br J Cancer 73:1183–1186

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

Hornsey IS, Hide D (1974) The production of antimicrobial compounds by British marine algae I. Antibiotic-producing marine algae. Br Phycol J 9:353–361

Hoshiyama Y, Sekine T, Sasaba T (1993) A case–control study of colorectal cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. Tohoku J Exp Med 171:153–165

Hosokawa M, Wanezaki S, Miyauchi K, Kurihara H, Kohno H, Kawabata J, Odashima S, Takahashi K (1999) Apoptosis-inducing

effect of fucoxanthin on human leukemia cell line HL-60. Food Sci Technol Res 5:243–246
Hosokawa M, Kudo M, Maeda H, Kohno H, Tanaka T, Miyashita K (2004) Fucoxanthin induces apoptosis and enhances the antiproliferative effect of the PPARgamma ligand, troglitazone, on colon cancer cells. Biochim Biophys Acta 1675:113–119
Huang H-L, Wu S-L, Liao H-F, Jiang C-M, Huang R-L, Chen Y-Y, Yang Y-C, Chen Y-J (2005) Induction of apoptosis by three marine algae through generation of reactive oxygen species in human leukemic cell lines. J Agric Food Chem 53:1776–1781
Hwang H, Chen T, Nines RG, Shin H-C, Stoner GD (2006) Photochemoprevention of UVB-induced skin carcinogenesis in SKH-1 mice by brown algae polyphenols. Int J Cancer 119:2742–2749
Hyun J-H, Kim S-C, Kang J-I, Kim M-K, Boo H-J, Kwon J-M, Koh Y-S, Hyun J-W, Park D-B, Yoo E-S, Kang H-K (2009) Apoptosis inducing activity of fucoidan in HCT-15 colon carcinoma cells. Biol Pharmacol Bull 32:1760–1764
Imbs TI, Krasovskaya NP, Ermakova SP, Makarieva TN, Shevchenko NM, Zvyagintseva TN (2009) Comparative study of chemical composition and antitumor activity of aqueous-ethanol extracts of brown algae *Laminaria cichorioides*, *Costaria costata*, and *Fucus evanescens*. Russ J Mar Biol 35:164–170
Ishikawa C, Tafuku S, Kadekaru T, Sawada S, Tomita M, Okudaira T, Nakazato T, Toda T, Uchihara J-N, Taira N, Ohshiro K, Yasumoto T, Ohta T, Mori N (2008) Anti-adult T-cell leukemia effects of brown algae fucoxanthin and its deacetylated product, fucoxanthinol. Int J Cancer 123:2702–2712
Itoh H, Noda H, Amano H, Zhuaug C, Mizuno T, Ito H (1993) Antitumor activity and immunological properties of marine algal polysaccharides, especially fucoidan, prepared from *Sargassum thunbergii* of Phaeophyceae. Anticancer Res 13:2045–2052
Itoh H, Noda H, Amano H, Ito H (1995) Immunological analysis of inhibition of lung metastases by fucoidan (GIV-A) prepared from brown seaweed *Sargassum thunbergii*. Anticancer Res 15:1937–47
Iwashima M, Mori J, Ting X, Matsunaga T, Hayashi K, Shinoda D, Saito H, Sankawa U, Hayashi T (2005) Antioxidant and antiviral activities of plastoquinones from the brown alga *Sargassum micracanthum*, and a new chromene derivative converted from the plastoquinones. Biol Pharmacol Bull 28:374–377
Jacquemin G, Shirley S, Micheau O (2010) Combining naturally occurring polyphenols with TNF-related apoptosis-inducing ligand: a promising approach to kill resistant cancer cells? Cell Mol Life Sci 67:3115–3130
Januar HI, Dewi AS, Marraskuranto E, Wikanta T (2012) In silico study of fucoxanthin as a tumor cytotoxic agent. J Pharm Bioallied Sci 4: 56–59
Jaswir I, Noviendri D, Salleh HM, Taher M (2011) Isolation of fucoxanthin and fatty acids analysis of *Padina australis* and cytotoxic effect of fucoxanthin on human lung cancer (H1299) cell lines. Afr J Biotechnol 10:18855–18862
Jayasooriya RGPT, Nam T-J, Kim G-Y, Choi H (2012) Methanol extract of *Polyopes lancifolius* suppresses tumor necrosis factor-α-induced matrix metalloproteinase-9 expression in t24 bladder carcinoma cells. Trop J Pharm Res 13:405–412
Jeong B-E, Ko E-J, Joo H-G (2012) Cytoprotective effects of fucoidan, an algae-derived polysaccharide on 5-fluorouracil-treated dendritic cells. Food Chem Toxicol 50:1480–1484
Ji NY, Li XM, Xie H, Ding J, Li K, Ding LP, Wang BG (2008) Highly oxygenated triterpenoids from the marine red alga *Laurencia mariannensis* (Rhodomelaceae). Helv Chim Acta 91:1940–1946
Jiang R-W, Hay ME, Fairchild CR, Prudhomme J, Le Roch K, Aalbersberg W, Kubanek J (2008) Antineoplastic unsaturated fatty acids from Fijian macroalgae. Phytochemistry 69:2495–2500
Jiang Z, Okimura T, Yokose T, Yamasaki Y, Yamaguchi K, Oda T (2010) Effects of sulfated fucan, ascophyllan, from the brown alga *Ascophyllum nodosum* on various cell lines: a comparative study on ascophyllan and fucoidan. J Biosci Bioeng 110:113–117
Jiao L, Li X, Li T, Jiang P, Zhang L, Wu M, Zhang L (2009) Characterization and anti-tumor activity of alkali-extracted polysaccharide from *Enteromorpha intestinalis*. Int Immunopharmacol 9: 324–329
Jiao G, Yu G, Zhang J, Ewart HS (2011) Chemical structures and bioactivities of sulfated polysaccharides from marine algae. Mar Drugs 9:196–223
Jiménez-Escrig A, Jiménez-Jiménez I, Pulido R, Saura-Calixto F (2001) Antioxidant activity of fresh and processed edible seaweeds. J Sci Food Agric 81:530–534
Jin Z, Han Y-X, Han X-R (2013) Degraded iota-carrageenan can induce apoptosis in human osteosarcoma cells via the Wnt/β-catenin signaling pathway. Nutr Cancer 65:126–131
Jolles B, Remington M, Andrews PS (1963) Effects of sulphated degraded laminarin on experimental tumour growth. Br J Cancer 17:109–115
Joyce JA (2005) Therapeutic targeting of the tumor microenvironment. Cancer Cell 7:513–520
Kan Y, Fujita T, Sakamoto B, Hokama Y, Nagai H (1999) Kahalalide K: a new cyclic depsipeptide from the Hawaiian green alga *Bryopsis* species. J Nat Prod 62:1169–1172
Kanegawa K, Harada H, Myouga H, Katakura Y, Shirahata S, Kamei Y (2000) Telomerase inhibiting activity in vitro from natural resources, marine algae extracts. Cytotechnology 33:221–227
Kang C, Kang S, Boo S, Choi YH, Moon D, Kim G (2011) Ethyl alcohol extract of *Hizikia fusiforme* induces caspase-dependent apoptosis in human leukemia U937 cells by generation of reactive oxygen species. Trop J Pharmaceut Res 10:739–746
Karnjanapratum S, You S-G (2011) Molecular characteristics of sulfated polysaccharides from *Monostroma nitidum* and their in vitro anticancer and immunomodulatory activities. Int J Biol Macromol 48: 311–318
Kaufman HL, Wadler S, Antman K (2008) Molecular targeting in oncology. Springer, Berlin, p 748
Kawamoto H, Miki Y, Kimura T, Tanaka K, Nakagawa T, Kawamukai M, Matsuda H (2006) Effects of fucoidan from Mozuku on human stomach cell lines. Food Sci Technol Res 12:218–222
Kazłowska K, Lin H-TV, Chang S-H, Tsai G-J (2013) In vitro and in vivo anticancer effects of sterol fraction from red algae *Porphyra dentata*. Evid Based Complement Alternat Med 2013:1–10. doi:10.1155/2013/493869
Khanavi M, Nabavi M (2010) Cytotoxic activity of some marine brown algae against cancer cell lines. Biol Res 43:31–37
Khanavi M, Gheidarloo R, Sadati N, Ardekani MRS, Nabavi SMB, Tavajohi S, Ostad SN (2012) Cytotoxicity of fucosterol containing fraction of marine algae against breast and colon carcinoma cell line. Pharmacogn Mag 8:60–64
Kim JM, Araki S, Kim DJ, Park CB, Takasuka N, Baba-Toriyama H, Ota T, Nir Z, Khachik F, Shimidzu N, Tanaka Y, Osawa T, Uraji T, Murakoshi M, Nishino H, Tsuda H (1998) Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1,2-dimethylhydrazine initiation. Carcinogenesis 19:81–85
Kim M-M, Van Ta Q, Mendis E, Rajapakse N, Jung W-K, Byun H-G, Jeon Y-J, Kim S-K (2006) Phlorotannins in *Ecklonia cava* extract inhibit matrix metalloproteinase activity. Life Sci 79:1436–1443
Kim K, Ham Y, Moon J, Kim M (2009) In vitro cytotoxic activity of *Sargassum thunbergii* and *Dictyopteris divaricata* (Jeju Seaweeds) on the HL-60 tumour cell line. Int J Pharmacol 5:298–306
Kim EJ, Park SY, Lee J-Y, Park JHY (2010a) Fucoidan present in brown algae induces apoptosis of human colon cancer cells. BMC Gastroenterol 10:96. doi:10.1186/1471-230X-10-96
Kim K-N, Heo S-J, Kang S-M, Ahn G, Jeon Y-J (2010b) Fucoxanthin induces apoptosis in human leukemia HL-60 cells through a ROS-mediated Bcl-xL pathway. Toxicol In Vitro 24:1648–1654

Kim K, Yang M-S, Kim G-O, Lee WJ, Lee NH, Hyun C-G (2012a) *Hydroclathrus clathratus* induces apoptosis in HL-60 leukaemia cells via caspase activation, upregulation of pro-apoptotic Bax/Bcl-2 ratio and ROS production. J Med Plant Res 6:1497–1504

Kim Y-M, Kim I-H, Nam T-J (2012b) Induction of apoptosis signaling by glycoprotein of *Capsosiphon fulvescens* in human gastric cancer (AGS) cells. Nutr Cancer 64:761–769

Kim Y-M, Kim I-H, Nam T-J (2013) Inhibition of AGS human gastric cancer cell invasion and proliferation by *Capsosiphon fulvescens* glycoprotein. Mol Med Rep 8:11–16. doi:10.3892/mmr.2013.1492

King RJB, Robins MW (2006) Cancer biology. Pearson Education, Harlow, p 292

Kintzios SE (2004) What do we know about cancer and its therapy? In: Kintzios SE, Berberaki MG (eds) Plants that fight cancer. CRC, New York, pp 1–14

Kladi M, Xenaki H, Vagias C, Papazafiri P, Roussis V (2006) New cytotoxic sesquiterpenes from the red algae *Laurencia obtusa* and *Laurencia microcladia*. Tetrahedron 62:182–189

Kladi M, Vagias C, Papazafiri P, Furnari G, Serio D, Roussis V (2007) New sesquiterpenes from the red alga *Laurencia microcladia*. Tetrahedron 63:7606–7611

Kladi M, Vagias C, Papazafiri P, Brogi S, Tafi A, Roussis V (2009) Tetrahydrofuran acetogenins from *Laurencia glandulifera*. J Nat Prod 72:190–193

Knott MG, Mkwananzi H, Arendse CE, Hendricks DT, Bolton JJ, Beukes DR (2005) Plocoralides A–C, polyhalogenated monoterpenes from the marine alga *Plocamium corallorhiza*. Phytochemistry 66:1108–1112

Ko S-C, Lee S-H, Ahn G, Kim K, Cha S-H, Kim S-K, Jeon B-T, Park P-J, Lee K-W, Jeon Y-J (2012) Effect of enzyme-assisted extract of *Sargassum coreanum* on induction of apoptosis in HL-60 tumor cells. J Appl Phycol 24:675–684

Kong C-S, Kim J-A, Yoon N-Y, Kim S-K (2009) Induction of apoptosis by phloroglucinol derivative from *Ecklonia cava* in MCF-7 human breast cancer cells. Food Chem Toxicol 47:1653–1658

Kobayashi J, Tsuda M (2004) Amphidinolides, bioactive macrolides from symbiotic marine dinoflagellates. Nat Prod Rep 21:77–93

Kono S, Toyomura K, Yin G, Nagano J, Mizoue T (2004) A case–control study of colorectal cancer in relation to lifestyle factors and genetic polymorphisms: design and conduct of the Fukuoka colorectal cancer study. Asian Pac J Cancer Prev 5:393–400

Kosovel V, Avanzini A, Scarcia V, Furlani A (1988) Algae as possible sources of antitumoural agents. Preliminary evaluation of the "in vitro" cytostatic activity of crude extracts. Pharmacol Res Commun 20:27–31

Kotake-Nara E, Kushiro M, Zhang H, Sugawara T, Miyashita K, Nagao A (2001) Carotenoids affect proliferation of human prostate cancer cells. J Nutr 131:3303–3306

Kotake-Nara E, Asai A, Nagao A (2005a) Neoxanthin and fucoxanthin induce apoptosis in PC-3 human prostate cancer cells. Cancer Lett 220:75–84

Kotake-Nara E, Terasaki M, Nagao A (2005b) Characterization of apoptosis induced by fucoxanthin in human promyelocytic leukemia cells. Biosci Biotechnol Biochem 69:224–227

Koyanagi S, Tanigawa N, Nakagawa H, Soeda S, Shimeno H (2003) Oversulfation of fucoidan enhances its anti-angiogenic and antitumor activities. Biochem Pharmacol 65:173–179

Ktari L, Blond A, Guyot M (2000) 16β-Hydroxy-5α-cholestane-3,6-dione, a novel cytotoxic oxysterol from the red alga *Jania rubens*. Bioorg Med Chem Lett 10:2563–2565

Kubanek J, Jensen PR, Keifer PA, Sullards MC, Collins DO, Fenical W (2003) Seaweed resistance to microbial attack: a targeted chemical defense against marine fungi. Proc Natl Acad Sci U S A 100:6916–6921

Kubanek J, Prusak A, Snell T, Giese R, Kenneth I, Fairchild C, Aalbersberg W, Raventos-Suarez C, Hay M (2005) Antineoplastic diterpene–benzoate macrolides from the Fijian red alga *Callophycus serratus*. Org Lett 7:5261–5264

Kubanek J, Prusak A, Snell T, Giese R, Fairchild C, Aalbersberg W, Hay M (2006) Bromophycolides C-I from the Fijian red alga *Callophycus serratus*. J Nat Prod 69:731–735

Kwon M, Nam T-J (2006) Porphyran induces apoptosis related signal pathway in AGS gastric cancer cell lines. Life Sci 79:1956–1962

Kwon M, Nam T (2007) A polysaccharide of the marine alga *Capsosiphon fulvescens* induces apoptosis in AGS gastric cancer cells via an IGF-IR-mediated PI3K/Akt pathway. Cell Biol Int 31:768–775

Lahaye M, Robic A (2007) Structure and functional properties of ulvan, a polysaccharide from green seaweeds. Biomacromolecules 8:1765–1774

Lane A, Stout E, Hay M, Prusak A, Hardcastle K, Fairchild C, Franzblau S, Le Roch K, Prudhomme J, Aalbersberg W, Kubanek J (2007) Callophycoic acids and callophycols from the Fijian red alga *Callophycus serratus*. J Org Chem 72:7343–7351

Lane AL, Stout EP, Lin A, Prudhomme J, Le K, Fairchild CR, Franzblau SG, Hay ME, Aalbersberg W, Kubanek J (2009) Antimalarial bromophycolides J–Q from the Fijian red alga *Callophycus serratus*. J Org Chem 74:2736–2742

Lavakumar V, Ahamed KFHN, Ravichandiran V (2012) Anti cancer and antioxidant effect of *Acanthophora spicifera* against EAC induced carcinoma in mice. J Pharm Res 5:1503–1507

Lee E, Sung M (2003) Chemoprevention of azoxymethane-induced rat colon carcinogenesis by seatangle, a fiber-rich seaweed. Plant Foods Human Nutr 58:1–8

Lee DG, Hyun J-W, Kang KA, Lee JO, Lee S-H, Ha BJ, Ha JM, Lee EY, Lee JH (2004) *Ulva lactuca*: a potential seaweed for tumor treatment and immune stimulation. Biotechnol Bioproc Eng 9:236–238

Lee NY, Ermakova SP, Choi H-K, Kusaykin MI, Shevchenko NM, Zvyagintseva TN, Choi HS (2008) Fucoidan from *Laminaria cichorioides* inhibits AP-1 transactivation and cell transformation in the mouse epidermal JB6 cells. Mol Carcinog 47:629–37

Lee H, Kang C, Jung E, Kim J-S, Kim E (2011) Antimetastatic activity of polyphenol-rich extract of *Ecklonia cava* through the inhibition of the Akt pathway in A549 human lung cancer cells. Food Chem 127:1229–1236

Lemée R, Pesando D, Durand-Clement M, Dubreuill A, Meinesz A, Guerriero A, Pietra F (1993) Preliminary survey of toxicity of the green alga *Caulerpa taxifolia* introduced into the Mediterranean. J Appl Phycol 5:485–493

Li Y, Qian Z-J, Kim M-M, Kim S-K (2011) Cytotoxic activities of phlorethol and fucophlorethol derivatives isolated from Laminariaceae *Ecklonia cava*. J Food Biochem 35:357–369

Lin A, Stout E, Prudhomme J, Le Roch K, Craig R, Franzblau S, Aalbersberg W, Hay M, Kubanek J (2010) Bioactive bromophycolides R–U from the Fijian red alga *Callophycus serratus*. J Nat Prod 73:275–278

Lin H-C, Chou S-T, Chuang M-Y, Liao T-Y, Tsai W-S, Chiu T-H (2012) The effects of *Caulerpa microphysa* enzyme-digested extracts on ACE-inhibitory activity and in vitro anti-tumour properties. Food Chem 134:2235–2241

Lins K, Bezerra D, Alves A, Alencar N, Lima M, Torres V, Farias W, Pessoa C, de Moraes M, Costa-Lotufo L (2009) Antitumor properties of a sulfated polysaccharide from the red seaweed *Champia feldmannii* (Diaz-Pifferer). J Appl Toxicol 29:20–26

Liu Q, Meng Q-Y (2004) In vivo anti-tumor effect of polysaccharide from *Sargassum confusum* and the mechanisms. Di Yi Jun Yi Da Xue Xue Bao 24:434–6

Liu Q, Meng Q-Y (2005) Therapeutic effect of seaweed polysaccharide from *Sargassum confusum* on sarcoma S180 in mice and its mechanism. Chin Cancer 24:1469–1473

Liu C-L, Huang Y-S, Hosokawa M, Miyashita K, Hu M-L (2009a) Inhibition of proliferation of a hepatoma cell line by fucoxanthin in relation to cell cycle arrest and enhanced

gap junctional intercellular communication. Chem Biol Interact 182:165–172
Liu Y, Morgan J, Coothankandaswamy V, Liu R, Jekabsons M, Mahdi F, Nagle D, Zhou Y-D (2009b) The *Caulerpa* pigment caulerpin inhibits HIF-1 activation and mitochondrial respiration. J Nat Prod 72:2104–2109
Liu M, Hansen PE, Lin X (2011) Bromophenols in marine algae and their bioactivities. Mar Drugs 9:1273–1292
Liu F, Wang J, Chang A, Liu B, Yang L, Li Q, Wang P, Zou X (2012a) Fucoidan extract derived from *Undaria pinnatifida* inhibits angiogenesis by human umbilical vein endothelial cells. Phytomedicine 19:797–803
Liu M, Zhang W, Wei J, Qiu L, Lin X (2012b) Marine bromophenol bis(2,3-dibromo-4,5-dihydroxybenzyl) ether, induces mitochondrial apoptosis in K562 cells and inhibits topoisomerase I in vitro. Toxicol Lett 211:126–134
Liu C-L, Lim Y-P, Hu M-L (2013) Fucoxanthin enhances cisplatin-induced cytotoxicity via NFκB-mediated pathway and downregulates DNA repair gene expression in human hepatoma HepG2 cells. Mar Drugs 11:50–66
Ma M, Zhao J, Wang S, Li S, Yang Y, Shi J, Fan X, He L (2006) Bromophenols coupled with methyl gamma-ureidobutyrate and bromophenol sulfates from the red alga *Rhodomela confervoides*. J Nat Prod 69:206–210
Magalhaes K, Costa LS, Fidelis G, Oliveira R, Nobre L, Dantas-Santos N, Camara R, Albuquerque I, Cordeiro S, Sabry D, Costa MSSP, Alves L, Rocha H (2011) Anticoagulant, antioxidant and antitumor activities of heterofucans from the seaweed *Dictyopteris delicatula*. Int J Mol Sci 12:3352–3365
Mao S-C, Guo Y-W, Shen X (2006) Two novel aromatic valerenane-type sesquiterpenes from the Chinese green alga *Caulerpa taxifolia*. Bioorg Med Chem Lett 16:2947–2950
Marinho-Soriano E, Bourret E (2003) Effects of season on the yield and quality of agar from *Gracilaria* species (Gracilariaceae, Rhodophyta). Bioresour Technol 90:329–333
Martín-Algarra S, Espinosa E, Rubió J, López López JJ, Manzano JL, Carrión LA, Plazaola A, Tanovic A, Paz-Ares L (2009) Phase II study of weekly Kahalalide F in patients with advanced malignant melanoma. Eur J Cancer 45:732–735
Maruyama H, Yamamoto I (1984) An antitumor fucoidan fraction from an edible brown seaweed, *Laminaria religiosa*. Hydrobiologia 116–117:534–536
Maruyama H, Tamauchi H, Hashimoto M, Nakano T (2003) Antitumor activity and immune response of Mekabu fucoidan extracted from sporophyll of *Undaria pinnatifida*. In Vivo 17:245–249
Maruyama H, Tamauchi H, Iizuka M, Nakano T (2006) The role of NK cells in antitumor activity of dietary fucoidan from *Undaria pinnatifida* sporophylls (Mekabu). Planta Med 72:1415–1417
Maschek JA, Baker BJ (2008) The chemistry of algal secondary metabolism. In: Amsler CD (ed) Algal chemical ecology. Springer, Berlin
Mayer AMS, Gustafson KR (2008) Marine pharmacology in 2005–2006: antitumour and cytotoxic compounds. Eur J Cancer 44:2357–2387
Mayer AMS, Glaser KB, Cuevas C, Jacobs RS, Kem W, Little RD, McIntosh JM, Newman DJ, Potts BC, Shuster DE (2010) The odyssey of marine pharmaceuticals: a current pipeline perspective. Trends Pharmacol Sci 31:255–265
McHugh D (1987) Production, properties and uses of alginates. http://www.fao.org/docrep/x5822e/x5822e04.htm
McKeown SR, Cowen RL, Williams KJ (2007) Bioreductive drugs: from concept to clinic. Clin Oncol 19:427–442
Mhadhebi L, Dellai A, Clary-Laroche A, Ben Said R, Robert J, Bouraoui A (2012) Anti-inflammatory and antiproliferative activities of organic fractions from the Mediterranean brown seaweed, *Cystoseira compressa*. Drug Dev Res 73:82–89
Miao HQ, Elkin M, Aingorn E, Ishai-Michaeli R, Stein CA, Vlodavsky I (1999) Inhibition of heparanase activity and tumor metastasis by laminarin sulfate and synthetic phosphorothioate oligodeoxynucleotides. Int J Cancer 83:424–431
Michikawa T, Inoue M, Shimazu T, Sawada N, Iwasaki M, Sasazuki S, Yamaji T, Tsugane S (2012) Seaweed consumption and the risk of thyroid cancer in women: the Japan Public Health Center-based Prospective Study. Eur J Cancer Prev 21:254–260
Mise T, Yasumoto T (2011) Simultaneous treatment of cancer cells lines with the anticancer drug cisplatin and the antioxidant fucoxanthin. Br J Pharmacol 2:127–131
Moo-Puc R, Robledo D, Freile-Pelegrin Y (2009) In vitro cytotoxic and antiproliferative activities of marine macroalgae from Yucatán, Mexico. Cien Mar 35:345–358
Moo-Puc R, Robledo D, Freile-Pelegrin Y (2011a) Enhanced antitumoral activity of extracts derived from cultured *Udotea flabellum* (Chlorophyta). Evid Based Complement Alternat Med 2011:969275. doi:10.1155/2011/969275
Moo-Puc R, Robledo D, Freile-Pelegrin Y (2011b) Improved antitumoral activity of extracts derived from cultured *Penicillus dumetosus*. Trop J Pharmaceut Res 10:177–185
Moreau D, Thomas-Guyon H, Jacquot C, Jugé M, Culioli G, Ortalo-Magné A, Piovetti L, Roussakis C (2006) An extract from the brown alga *Bifurcaria bifurcata* induces irreversible arrest of cell proliferation in a non-small-cell bronchopulmonary carcinoma line. J Appl Phycol 18:87–93
Mori J, Iwashima M, Wakasugi H, Saito H, Matsunaga T, Ogasawara M, Takahashi S, Suzuki H, Hayashi T (2005) New plastoquinones isolated from the brown alga, *Sargassum micracanthum*. Chem Pharmaceut Bull 53:1159–1163
Murugan K, Iyer VV (2013) Antioxidant and antiproliferative activities of extracts of selected red and brown seaweeds from the Mandapam Coast of Tamil Nadu. J Food Biochem. doi:10.1111/jfbc.12029
Nakayasu S, Soegima R, Yamaguchi K, Oda T (2009) Biological activities of fucose-containing polysaccharide ascophyllan isolated from the brown alga *Ascophyllum nodosum*. Biosci Biotechnol Biochem 73:961–964
Nakazawa Y, Sashima T, Hosokawa M, Miyashita K (2009) Comparative evaluation of growth inhibitory effect of stereoisomers of fucoxanthin in human cancer cell lines. J Funct Foods 1:88–97
Namvar F, Mohamed S, Fard SG, Behravan J, Mustapha NM, Alitheen NBM, Othman F (2012) Polyphenol-rich seaweed (*Eucheuma cottonii*) extract suppresses breast tumour via hormone modulation and apoptosis induction. Food Chem 130:376–382
Newman DJ, Cragg GM, Snader KM (2000) The influence of natural products upon drug discovery (Antiquity to late 1999). Nat Prod Rep 17:215–234
Nishibori N, Itoh M, Kashiwagi M, Arimochi H, Morita K (2012) In vitro cytotoxic effect of ethanol extract prepared from sporophyll of *Undaria pinnatifida* on human colorectal cancer cells. Phytother Res 26:191–196
Nishino H, Tokuda H, Satomi Y, Masuda M, Bu P, Onozuku M, Yamaguchi S, Okuda Y, Takayasu J, Tsuruta J, Okuda M, Ichiishi E, Murakoshi M, Kato T, Misawa N, Narisawa T, Takasuka N, Yano M (1999) Cancer prevention by carotenoids. Pure Appl Chem 71:2273–2278
Noda H, Amano H, Arashima K, Hashimoto S, Nisizawa K (1989) Antitumour activity of polysaccharides and lipids from marine algae. Nippon Suisan Gakkaishi 55:1265–1271
Noda H, Amano H, Arashima K, Nisizawa K (1990) Antitumor activity of marine algae. Hydrobiologia 204–205:577–584
Nomura A, Henderson BE, Lee J (1978) Breast cancer and diet among the Japanese in Hawaii. Am J Clin Nutr 31:2020–2025
Nwosu F, Morris J, Lund VA, Stewart D, Ross HA, McDougall GJ (2011) Anti-proliferative and potential anti-diabetic effects of phenolic-rich extracts from edible marine algae. Food Chem 126:1006–1012

O'Sullivan AM, O'Callaghan YC, O'Grady MN, Queguineur B, Hanniffy D, Troy DJ, Kerry JP, O'Brien NM (2011) In vitro and cellular antioxidant activities of seaweed extracts prepared from five brown seaweeds harvested in spring from the west coast of Ireland. Food Chem 126:1064–1070

Oh S-M (2011) Dieckol inhibits 12-*O*-tetradecanoylphorbol-13-acetate-induced SK-Hep1 human hepatoma cell motility through suppression of matrix metalloproteinase-9 activity. J Korean Soc Appl Biol Chem 54:376–381

Ohigashi H, Sakai Y, Yamaguchi K, Umezaki I, Koshimizu K (1992) Possible anti-tumor promoting properties of marine algae and in vivo activity of Wakame seaweed extract. Biosci Biotechnol Biochem 56:994–995

Okuzumi J, Nishino H, Murakoshi M, Iwashima A, Tanaka Y, Yamane T, Fujita Y, Takahashi T (1990) Inhibitory effects of fucoxanthin, a natural carotenoid, on N-myc expression and cell cycle progression in human malignant tumor cells. Cancer Lett 55:75–81

Okuzumi J, Takahashi T, Yamane T, Kitao Y, Inagake M, Ohya K, Nishino H, Tanaka Y (1993) Inhibitory effects of fucoxanthin, a natural carotenoid, on *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine-induced mouse duodenal carcinogenesis. Cancer Lett 68:159–168

Ozasa K, Watanabe Y, Ito Y, Suzuki K, Tamakoshi A, Seki N, Nishino Y, Kondo T, Wakai K, Ando M, Ohno Y (2001) Dietary habits and risk of lung cancer death in a large-scale cohort study (JACC Study) in Japan by sex and smoking habit. Jpn J Cancer Res 92:1259–69

Pacheco FC, Villa-Pulgarin JA, Mollinedo F, Martín MN, Fernández JJ, Daranas AH (2011) New polyether triterpenoids from *Laurencia viridis* and their biological evaluation. Mar Drugs 9:2220–2235

Palozza P, Torelli C, Boninsegna A, Simone R, Catalano A, Mele MC, Picci N (2009) Growth-inhibitory effects of the astaxanthin-rich alga *Haematococcus pluvialis* in human colon cancer cells. Cancer Lett 283:108–117

Pardo B, Paz-Ares L, Tabernero J, Ciruelos E, García M, Salazar R, López A, Blanco M, Nieto A, Jimeno J, Izquierdo MA, Trigo JM (2008) Phase I clinical and pharmacokinetic study of kahalalide F administered weekly as a 1-hour infusion to patients with advanced solid tumors. Clin Cancer Res 14:1116–1123

Park H-K, Kim I-H, Kim J, Nam T-J (2013) Induction of apoptosis and the regulation of ErbB signaling by laminarin in HT-29 human colon cancer cells. Int J Mol Med 32:291–295

Pavia H, Brock E (2000) Extrinsic factors influencing phlorotannin production in the brown alga *Ascophyllum nodosum*. Mar Ecol Prog Ser 193:285–294

Pereira D, Cheel J, Areche C, San-Martin A, Rovirosa J, Silva L, Valentao P, Andrade P (2011) Anti-proliferative activity of meroditerpenoids isolated from the brown alga *Stypopodium flabelliforme* against several cancer cell lines. Mar Drugs 9:852–62

Perron NR, García CR, Pinzón JR, Chaur MN, Brumaghim JL (2011) Antioxidant and prooxidant effects of polyphenol compounds on copper-mediated DNA damage. J Inorg Biochem 105:745–753

Perry N, Blunt J, Munro M (1991) A cytotoxic and antifungal 1,4-naphthoquinone and related compounds from a New Zealand brown alga, *Landsburgia quercifolia*. J Nat Prod 54:978–985

Philchenkov A, Zavelevich M, Imbs T, Zvyagintseva TN, Zaporozhets T (2007) Sensitization of human malignant lymphoid cells to etoposide by fucoidan, a brown seaweed polysaccharide. Exp Oncol 29:181–185

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

Popplewell WL, Northcote PT (2009) Colensolide A: a new nitrogenous bromophenol from the New Zealand marine red alga *Osmundaria colensoi*. Tetrahedron Lett 50:6814–6817

Ragan M, Glombitza K (1986) Phlorotannins, brown algal polyphenols. Prog Phycol Res 4:129–241

Reddy P, Urban S (2008) Linear and cyclic C18 terpenoids from the southern Australian marine brown alga *Cystophora moniliformis*. J Nat Prod 71:1441–1446

Reddy P, Urban S (2009) Meroditerpenoids from the southern Australian marine brown alga *Sargassum fallax*. Phytochemistry 70:250–255

Reddy BS, Numoto S, Choi CI (1985) Effect of dietary *Laminaria angustata* (brown seaweed) on azoxymethane-induced intestinal carcinogenesis in male F344 rats. Nutr Cancer 7:59–64

Reichelt JL, Borowitzka MA (1984) Antibiotics from algae: results of a large scale screening programme. Hydrobiologia 116/117:158–168

Riou D, Colliec-Jouault S, Pinczon du Sel D, Bosch S, Siavoshian S, Le Bert V, Tomasoni C, Sinquin C, Durand P, Roussakis C (1996) Antitumor and antiproliferative effects of a fucan extracted from *Ascophyllum nodosum* against a non-small-cell bronchopulmonary carcinoma line. Anticancer Res 16:1213–1218

Rioux L-E, Turgeon SL, Beaulieu M (2007) Characterization of polysaccharides extracted from brown seaweeds. Carbohydr Polym 69: 530–537

Rocha F, Soares A, Houghton P, Pereira R, Coelho Kaplan M, Teixeira V (2007) Potential cytotoxic activity of some Brazilian seaweeds on human melanoma cells. Phytother Res 175:170–175

Rodriguez G (2001) Extraction, isolation, and purification of carotenoids. Curr Protocols Food Anal Chem 1–8

Rodríguez-Bernaldo de Quirós A, Lage-Yusty MA, López-Hernández J (2010) Determination of phenolic compounds in macroalgae for human consumption. Food Chem 121:634–638

Roussis V, Vagias C, Tziveleka LA (2004) Cytotoxic metabolites from marine algae. In: Kintzios SE, Barberaki MG (eds) Plants that fight cancer. CRC, Boca Raton, pp 195–240

Sabry OMM, Andrews S, McPhail KL, Goeger DE, Yokochi A, LePage KT, Murray TF, Gerwick WH (2005) Neurotoxic meroditerpenoids from the tropical marine brown alga *Stypopodium flabelliforme*. J Nat Prod 68:1022–30

Salazar R, Cortés-Funes H, Casado E, Pardo B, López-Martín A, Cuadra C, Tabernero J, Coronado C, García M, Soto Matos-Pita A, Miguel-Lillo B, Cullell-Young M, Iglesias Dios JL, Paz-Ares L (2013) Phase I study of weekly kahalalide F as prolonged infusion in patients with advanced solid tumors. Cancer Chemother Pharmacol 72:75–83

Sansom C, Larsen L, Perry N, Berridge M, Chia E, Harper J, Webb V (2007) An antiproliferative bis-prenylated quinone from the New Zealand brown alga *Perithalia capillaris*. J Nat Prod 70:2042–2044

Satomi Y (2012) Fucoxanthin induces GADD45A expression and G1 arrest with SAPK/JNK activation in LNCap human prostate cancer cells. Anticancer Res 32:807–813

Satomi Y (2013) Inhibition of the enzyme activity of cytochrome P450 1A1, 1A2 and 3A4 by fucoxanthin, a marine carotenoid. Oncol Lett 6:860–864

Satomi Y, Nishino H (2007) Fucoxanthin, a natural carotenoid, induces G1 arrest and GADD45 gene expression in human cancer cells. In Vivo 21:305–309

Satomi Y, Nishino H (2009) Implication of mitogen-activated protein kinase in the induction of G1 cell cycle arrest and gadd45 expression by the carotenoid fucoxanthin in human cancer cells. Biochim Biophys Acta 1790:260–266

Sekiya M, Funahashi H, Tsukamura K, Imai T, Hayakawa A, Kiuchi T, Nakao A (2005) Intracellular signaling in the induction of apoptosis in a human breast cancer cell line by water extract of Mekabu. Int J Clin Oncol 10:122–126

Senthilkumar K, Manivasagan P, Venkatesan J, Kim S-K (2013) Brown seaweed fucoidan: biological activity and apoptosis, growth signaling mechanism in cancer. Int J Biol Macromol 60:366–74

Severson R, Nomura A, Grove J (1989) A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Res 49:1857–1860

Shamsabadi FT, Khoddami A, Fard SG, Abdullah R, Othman HH, Mohamed S (2013) Comparison of tamoxifen with edible seaweed (*Eucheuma cottonii* L.) extract in suppressing breast tumor. Nutr Cancer 65:255–262

Shay JW, Wright WE (2006) Telomerase therapeutics for cancer: challenges and new directions. Nat Rev Drug Discov 5:577–584

Shi D, Li J, Guo S, Su H, Fan X (2009) The antitumor effect of bromophenol derivatives in vitro and *Leathesia nana* extract in vivo. Chin J Oceanol Limnol 27:277–282

Shoeib NA, Bibby MC, Blunden G, Linley PA, Swaine DJ, Wheelhouse RT, Wright CW (2004) In-vitro cytotoxic activities of the major bromophenols of the red alga *Polysiphonia lanosa* and some novel synthetic isomers. J Nat Prod 67:1445–1449

Sokolova RV, Ermakova SP, Awada SM (2011) Composition, structural characteristics, and antitumor properties of polysaccharides from the brown algae *Dictyopteris polypodioides* and *Sargassum* sp. Chem Nat Compd 47:297–301

Steevensz AJ, Mackinnon SL, Hankinson R, Craft C, Connan S, Stengel DB, Melanson JE (2012) Profiling phlorotannins in brown macroalgae by liquid chromatography–high resolution mass spectrometry. Phytochem Anal 23:547–553

Stein E, Andreguetti D, Rocha C, Fujii M, Baptista M, Colepicolo P, Indig G (2011) Search for cytotoxic agents in multiple *Laurencia* complex seaweed species (Ceramiales, Rhodophyta) harvested from the Atlantic Ocean with emphasis on the Brazilian State of Espírito Santo. Rev Bras Farmacognos 21:239–243

Stengel DB, Connan S, Popper Z (2011) Algal chemodiversity and bioactivity: sources of natural variability and implications for commercial application. Biotechnol Adv 29:483–501

Stevan F, Oliveira M, Bucchi D, Noseda M, Iacomini M, Duarte M (2001) Cytotoxic effects against HeLa cells of polysaccharides from seaweeds. J Submicrosc Cytol Pathol 33:477–484

Stout E, Hasemeyer A, Lane A, Davenport T, Engel S, Hay M, Fairchild C, Prudhomme J, Le Roch K, Aalbersberg W, Kubanek J (2009) Antibacterial neurymenolides from the Fijian red alga *Neurymenia fraxinifolia*. Org Lett 11:225–228

Sugahara T, Ohama Y, Fukuda A, Hayashi M, Kawakubo A, Kato K (2001) The cytotoxic effect of *Eucheuma serra* agglutinin (ESA) on cancer cells and its application to molecular probe for drug delivery system using lipid vesicles. Cytotechnology 36:93–99

Sugawara T, Baskaran V, Tsuzuki W, Nagao A (2002) Brown algae fucoxanthin is hydrolyzed to fucoxanthinol during absorption by Caco-2 human intestinal cells and mice. J Nutr 132:946–951

Sugawara T, Matsubara K, Akagi R, Mori M, Hirata T (2006) Antiangiogenic activity of brown algae fucoxanthin and its deacetylated product, fucoxanthinol. J Agric Food Chem 54:9805–9810

Sugawara T, Yamashita K, Sakai S, Asai A, Nagao A, Shiraishi T, Imai I, Hirata T (2007) Induction of apoptosis in DLD-1 human colon cancer cells by peridinin isolated from the dinoflagellate, *Heterocapsa triquetra*. Biosci Biotechnol Biochem 71:1069–1072

Sugiura Y, Takeuchi Y, Kakinuma M, Amano H (2006) Inhibitory effects of seaweeds on histamine release from rat basophile leukemia cells (RBL-2H3). Fish Sci 72:1286–1291

Sun Y, Xu Y, Liu K, Hua H, Zhu H, Pei Y (2006) Gracilarioside and gracilamides from the red alga *Gracilaria asiatica*. J Nat Prod 69:1488–1491

Sunassee SN, Davies-Coleman MT (2012) Cytotoxic and antioxidant marine prenylated quinones and hydroquinones. Nat Prod Rep 29:513–535

Süzgeç-Selçuk S, Meriçli AH, Güven KC, Kaiser M, Casey R, Hingley-Wilson S, Lalvani A, Tasdemir D (2011) Evaluation of Turkish seaweeds for antiprotozoal, antimycobacterial and cytotoxic activities. Phytother Res 25:778–783

Synytsya A, Kim W-J, Kim S-M, Pohl R, Synytsya A, Kvasnička F, Čopíková J, Il Park Y (2010) Structure and antitumour activity of fucoidan isolated from sporophyll of Korean brown seaweed *Undaria pinnatifida*. Carbohydr Polym 81:41–48

Tafuku S, Ishikawa C, Yasumoto T, Mori N (2012) Anti-neoplastic effects of fucoxanthin and its deacetylated product, fucoxanthinol, on Burkitt's and Hodgkin's lymphoma cells. Oncol Rep 28:1512–1518

Takada N, Watanabe R, Suenaga K, Yamada K, Uemura D (2001) Isolation and structures of hedaols A, B, and C, new bisnorditerpenes from a Japanese brown alga. J Nat Prod 64:653–5

Tang H-F, Yi Y-H, Yao X-S, Xu Q-Z, Zhang S-Y, Lin H-W (2002) Bioactive steroids from the brown alga *Sargassum carpophyllum*. J Asian Nat Prod Res 4:95–101

Tanniou A, Vandanjon L, Incera M, Serrano Leon E, Husa V, Grand J, Nicolas JL, Poupart N, Kervarec N, Engelen A, Walsh R, Guerard F, Bourgougnon N, Stiger-Pouvreau V (2013) Assessment of the spatial variability of phenolic contents and associated bioactivities in the invasive alga *Sargassum muticum* sampled along its European range from Norway to Portugal. J Appl Phycol. doi:10.1007/s10811-013-0198-x

Teas J (1982) The dietary intake of laminaria, a brown seaweed, and breast cancer prevention. Nutr Cancer. doi:10.1080/01635588209513760

Teas J, Harbison M, Gelman R (1984) Dietary seaweed (*Laminaria*) and mammary carcinogenesis in rats. Cancer Res 44:2758–2761

Teas J, Irhimeh M, Druker S, Hurley T, Hébert J, Savarese T, Kurzer M (2011) Serum IGF-1 concentrations change with soy and seaweed supplements in healthy postmenopausal American women. Nutr Cancer 63:743–748

Teas J, Vena S, Cone D, Irhimeh M (2013) The consumption of seaweed as a protective factor in the etiology of breast cancer: proof of principle. J Appl Phycol 25:771–779

Teruya T, Konishi T, Uechi S, Tamaki H, Tako M (2007) Anti-proliferative activity of oversulfated fucoidan from commercially cultured *Cladosiphon okamuranus* TOKIDA in U937 cells. Int J Biol Marcromol 41:221–226

Thinh PD, Menshova RV, Ermakova SP, Anastyuk SD, Ly BM, Zvyagintseva TN (2013) Structural characteristics and anticancer activity of fucoidan from the brown alga *Sargassum mcclurei*. Mar Drugs 11:1456–1476

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

Tobacman JK (2002) Carrageenan in foods: response. Env Health Perspect 110:176–177

Tokudome S, Kuriki K, Moore MA (2001) Seaweed and cancer prevention. Jpn J Cancer Res 92:1008–1009

Tsuda M, Kariya Y, Iwamoto R, Fukushi E, Kawabata J, Kobayash J (2005) Amphidinolides B4 and B5, potent cytotoxic 26-membered macrolides from *Dinoflagellate amphidinium* species. Mar Drugs 3:1–8

Usui T, Asari K, Mizuno T (1980) Isolation of highly purified "Fucoidan" from *Eisenia bicyclis* and its anticoagulant and antitumor activities. Agric Biol Chem 44:1965–1966

Van Alstyne K (1988) Herbivore grazing increases polyphenolic defenses in the intertidal brown alga *Fucus distichus*. Ecology 69:655–663

Wang H, Chiu L, Ooi VEC, Ang PO (2010) A potent antitumor polysaccharide from the edible brown seaweed *Hydroclathrus clathratus*. Bot Mar 53:265–274

Watt J, Marcus R (1971) Carrageenan-induced ulceration of the large intestine in the guinea pig. Gut 12:164–171

Weinberg RA (2007) The biology of cancer, vol 2. Garland Science, London, 796

Winberg PC, Skropeta D, Ullrich A (2011) Seaweed cultivation pilot trials—towards culture systems and marketable products. Australian Government Rural Industries Research and Development Corporation, RIRDC publication no. 10/184. PRJ-000162

Wu JM, Staton CA (2012) Anti-angiogenic drug discovery: lessons from the past and thoughts for the future. Expert Opin Drug Discov 7:723–743

Xu X, Song F, Wang S, Li S, Xiao F, Zhao J, Yang Y, Shang S, Yang L, Shi J (2004) Dibenzyl bromophenols with diverse dimerization patterns from the brown alga *Leathesia nana*. J Nat Prod 67:1661–1666

Xu W-J, Liao X-J, Xu S-H, Diao J-Z, Du B, Zhou X-L, Pan S-S (2008) Isolation, structure determination, and synthesis of galaxamide, a rare cytotoxic cyclic pentapeptide from a marine algae *Galaxaura filamentosa*. Org Lett 10:4569–4572

Xue M, Ge Y, Zhang J, Wang Q, Hou L, Liu Y, Sun L, Li Q (2012) Anticancer properties and mechanisms of fucoidan on mouse breast cancer in vitro and in vivo. PloS One 7:e43483. doi:10.1371/journal.pone.0043483

Yamamoto I, Maruyama H (1985) Effect of dietary seaweed preparations on 1,2-dimethylhydrazine-induced intestinal carcinogenesis in rats. Cancer Lett 26:241–251

Yamamoto I, Nagumo T, Fujihara M, Takahashi M, Ando Y (1977) Antitumor effect of seaweeds. II. Fractionation and partial characterization of the polysaccharide with antitumor activity from *Sargassum fulvellum*. Jpn J Exp Med 47:133–140

Yamamoto I, Takahashi M, Suzuki T, Seino H, Mori H (1984a) Antitumor effect of seaweeds. IV. Enhancement of antitumor activity by sulfation of a crude fucoidan fraction from *Sargassum kjellmanianum*. Jpn J Exp Med 54:143–51

Yamamoto I, Takahashi M, Tamura E, Maruyama H, Mori H (1984b) Antitumor activity of edible marine algae: effect of crude fucoidan fractions prepared from edible brown seaweeds against L-1210 leukemia. Hydrobiologia 116/117:145–148

Yamamoto I, Maruyama H, Takahashi M, Komiyama K (1986) The effect of dietary or intraperitoneally injected seaweed preparations on the growth of Sarcoma-180 cells subcutaneously implanted into mice. Cancer Lett 30:125–131

Yamamoto I, Maruyama H, Moriguchi M (1987) The effect of dietary seaweeds on 7,12-dimethylbenz[a]anthracene-induced mammary tumorigenesis in rats. Cancer Lett 35:109–118

Yamamoto K, Ishikawa C, Katano H, Yasumoto T, Mori N (2011) Fucoxanthin and its deacetylated product, fucoxanthinol, induce apoptosis of primary effusion lymphomas. Cancer Lett 300:225–234

Yamasaki Y, Yamasaki M, Tachibana H, Yamada K (2012) Important role of 1-integrin in fucoidan-induced apoptosis via caspase-8 activation. Biosci Biotechnol Biochem 76:1163–1168

Yang C, Chung D, Shin I-S, Lee H, Kim J, Lee Y, You S (2008) Effects of molecular weight and hydrolysis conditions on anticancer activity of fucoidans from sporophyll of *Undaria pinnatifida*. Int J Biol Macromol 43:433–437

Yang H, Zeng M, Dong S, Liu Z, Li R (2010a) Anti-proliferative activity of phlorotannin extracts from brown algae *Laminaria japonica* Aresch. Chin J Oceanol Limnol 28:122–130

Yang YJ, Nam S-J, Kong G, Kim MK (2010b) A case–control study on seaweed consumption and the risk of breast cancer. Br J Nutr 103: 1345–1353

Yang J-I, Yeh C-C, Lee J-C, Yi S-C, Huang H-W, Tseng C-N, Chang H-W (2012) Aqueous extracts of the edible *Gracilaria tenuistipitata* are protective against H_2O_2-induced DNA damage, growth inhibition, and cell cycle arrest. Molecules 17:7241–7254

Yang L, Wang P, Wang H, Li Q, Teng H, Liu Z, Yang W, Hou L, Zou X (2013) Fucoidan derived from *Undaria pinnatifida* induces apoptosis in human hepatocellular carcinoma SMMC-7721 cells via the ROS-mediated mitochondrial pathway. Mar Drugs 11:1961–1976

Ye H, Wang K, Zhou C, Liu J, Zeng X (2008) Purification, antitumor and antioxidant activities in vitro of polysaccharides from the brown seaweed *Sargassum pallidum*. Food Chem 111:428–432

Yeh C-C, Yang J-I, Lee J-C, Tseng C-N, Chan Y-C, Hseu Y-C, Tang J-Y, Chuang L-Y, Huang H-W, Chang F-R, Chang H-W (2012) Anti-proliferative effect of methanolic extract of *Gracilaria tenuistipitata* on oral cancer cells involves apoptosis, DNA damage, and oxidative stress. BMC Complement Altern Med 12:142. doi:10.1186/1472-6882-12-142

Yoshie Y, Wang W, Petillo D, Suzuki T (2000) Distribution of catechins in Japanese seaweeds. Fish Sci 66:998–1000

Young A, Lowe G (2001) Antioxidant and prooxidant properties of carotenoids. Arch Biochem Biophys 385:20–27

Yu R-X, Hu X-M, Xu S-Q, Jiang Z-J, Yang W (2011) Effects of fucoxanthin on proliferation and apoptosis in human gastric adenocarcinoma MGC-803 cells via JAK/STAT signal pathway. Eur J Pharmacol 657:10–19

Yuan YV, Walsh NA (2006) Antioxidant and antiproliferative activities of extracts from a variety of edible seaweeds. Food Chem Toxicol 44: 1144–1150

Yuan YV, Carrington MF, Walsh NA (2005) Extracts from dulse (*Palmaria palmata*) are effective antioxidants and inhibitors of cell proliferation in vitro. Food Chem Toxicol 43:1073–1081

Yuan Y (2008) Marine algal constituents. In: Shahidi F and Barrow C (eds) Marine nutraceuticals and functional foods. CRC, Florida

Zhang Z, Zhang P, Hamada M, Takahashi S, Xing G, Liu J, Sugiura N (2008) Potential chemoprevention effect of dietary fucoxanthin on urinary bladder cancer EJ-1 cell line. Oncol Rep 20:1099–1103

Zhang C, Li Y, Shi X, Kim S (2010) Inhibition of the expression on MMP-2, 9 and morphological changes via human fibrosarcoma cell line by 6,6′-bieckol from marine alga *Ecklonia cava*. BMB Rep 43: 62–68

Zhang R-L, Luo W-D, Bi T-N, Zhou S-K (2012) Evaluation of antioxidant and immunity-enhancing activities of *Sargassum pallidum* aqueous extract in gastric cancer rats. Molecules 17:8419–8429

Zhang Z, Teruya K, Yoshida T, Eto H, Shirahata S (2013) Fucoidan extract enhances the anti-cancer activity of chemotherapeutic agents in MDA-MB-231 and MCF-7 breast cancer cells. Mar Drugs 11:81–98

Zhao J, Ma M, Wang S, Li S, Cao P, Yang Y, Lü Y, Shi J, Xu N, Fan X, He L (2005) Bromophenols coupled with derivatives of amino acids and nucleosides from the red alga *Rhodomela confervoides*. J Nat Prod 68:691–694

Zhou G, Sun Y-P, Xin H, Zhang Y, Li Z, Xu Z (2004) In vivo antitumor and immunomodulation activities of different molecular weight lambda-carrageenans from *Chondrus ocellatus*. Pharmacol Res 50: 47–53

Zhou G, Xin H, Sheng W, Sun Y, Li Z, Xu Z (2005) In vivo growth-inhibition of S180 tumor by mixture of 5-Fu and low molecular lambda-carrageenan from *Chondrus ocellatus*. Pharmacol Res 51: 153–157

Zhou G, Sheng W, Yao W, Wang C (2006) Effect of low molecular lambda-carrageenan from *Chondrus ocellatus* on antitumor H-22 activity of 5-Fu. Pharmacol Res 53:129–134

Zhu C, Cao R, Zhang S-X, Man Y-N, Wu X-Z (2013) Fucoidan inhibits the growth of hepatocellular carcinoma independent of angiogenesis. Evid Based Complement Alternat Med 2013:692549. doi:10.1155/2013/692549

Zhuang C, Itoh H, Mizuno T, Ito H (1995) Antitumor active fraction from the brown seaweed, Umitoranoo (*Sargassum thunbergii*). Biosci Biotechnol Biochem 59:563–567

Zou M-C, Cui F-L, Sheng Y-Q, Qiu Z (2010) Effects of laminarin sulphate on the expressions of PTEN and P271kip1 in prostate cancer PC-3 cells. Zhonghua Nan Ke Xue 16:498–503

Zubia M, Fabre M, Kerjean V, Deslandes E (2009a) Antioxidant and cytotoxic activities of some red algae (Rhodophyta) from Brittany coasts (France). Bot Mar 52:268–277

Zubia M, Fabre M, Kerjean V, Le Lann K, Stiger-Pouvreau V, Fauchon M, Deslandes E (2009b) Antioxidant and antitumoural activities of some Phaeophyta from Brittany coasts. Food Chem 116:693–701