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REVIEW

Components of brown seaweeds are potential candidate for cancer therapy - a review

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Finding novel anticancer agents is very important for the treatment of cancer, and marine organisms are a valuable source for developing novel agents for the clinical applications. Isolation and identification of the novel anticancer components from the brown seaweeds and study their mode of action is very attractive in current scenario and unexplored source for pharmacological applications. This review will reveal active components of brown algae with their antitumor potential towards the cancer treatment according to their structures, which might provide useful information for medicinal chemists in developing potent anticancer agents.

1 Introduction

Cancer known as malignant tumor is a group of diseases involving abnormal cell growth having potential to kill the normal cells or spread rapidly to all parts of body. Cancers can be classified on the basis of type of cell such as carcinoma (Cancers derived from the epithelial cells and most common in aged group people), sarcoma (cancers originates from connective tissues), lymphoma and leukemia (These both classes of cancer derived from hematopoietic cells such as blood cancer), germ cell tumor (cancers arise from pluripotent cells such as dysgerminoma and seminoma) blastoma (cancer originates from immature embryos and most common in childrens).[1] There are about 100 known kinds of cancer so far that affect humans. There are many causes of cancer, tobacco contributes 25-30%, obesity, poor diet and excessive use of alcohol 30-35%, genetic defects 15-20% and 10% is followed by radiations.[2] Chemotherapy or (CTX), is considered the novel strategy to treat the cancer cells today, which is defined as the use of chemical substances, anticancer drugs especially one or more chemotherapeutic agents (alone or combined) to stop the growth of cancer cells. There is a tremendous increase in use of herbal drugs by the cancer patients all around the world which are being chosen due to their potential effects against cancer diagnosis and easy excess[3-6] and which they mostly take as part of regime comprising of multiple complementary and alternative medicine modalities.[7,8]

Natural products from the marine source having strong medicinal potential had gained a much interest in the field of cancer research and the development of novel anticancer drugs.[9] So far, 15,000 novel compounds have been discovered from seaweeds, and several antitumor compounds are being investigated through clinical trials.[10,11] Seaweed consumption and health benefits are correlated and considered potential source for the development of anticancer drugs, functional foods and pharmacological products.[12-17] In the current scenario, the pharmaceutical companies are gaining much interest to those compounds (sulphated polysaccharides, halogenated furanones, kahalalide F, lectins, kainoidsfucoidans and aplysiatoxins)，which are being used in drug development isolated from marine algae especially Phaeophyta.[12] Phyto-chemical constituents of brown seaweeds such as carbohydrates, flavonoid, phenols, alkaloids and proteins play a key role against pathogens. These compounds also have significant potential against the antitumor, antioxidants, anticoagulant and immunomodulating activities.[18-22] In this review, we will discuss the detailed structural composition of different components of brown algae with their antitumor potential towards the cancer treatment.

2 Categorize of anticancer compounds isolated from brown seaweeds

2.1. Polysaccharides

Polysaccharides are the main components of the brown algae rather than green and red algae and composed of alginate **1** (Fig. **1**), laminarin **2** (Fig. **1**), Fucoidan **3** (Fig. **1**), and their derivatives. Some constituents of Porphyran **4** (Fig. **1**), and alginic acid **5** (Fig. **1**), were also reported in some species of brown algae.[23] The polysaccharides regulate the primary functions of brown algae like strength and flexibility to cell wall; prevent desiccation and keeps ionic equilibrium. Polysaccharide contents in brown algae, their structural composition, functional and anticancer properties have been

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reported.[24-33] Polysaccharides are extensively studied for novel antitumor agents especially found in brown seaweeds such as 8 to 12% compound **3** (Fig. **1**) present in *sargassum sp* and *Fucus sp* on their dry weight basis.[34] Compound **3** (Fig. **1**) are complex sulfated polysaccharides and accounts 10-20% Dw in brown algae and considered as unique polymer with heterogeneous composition and structure,

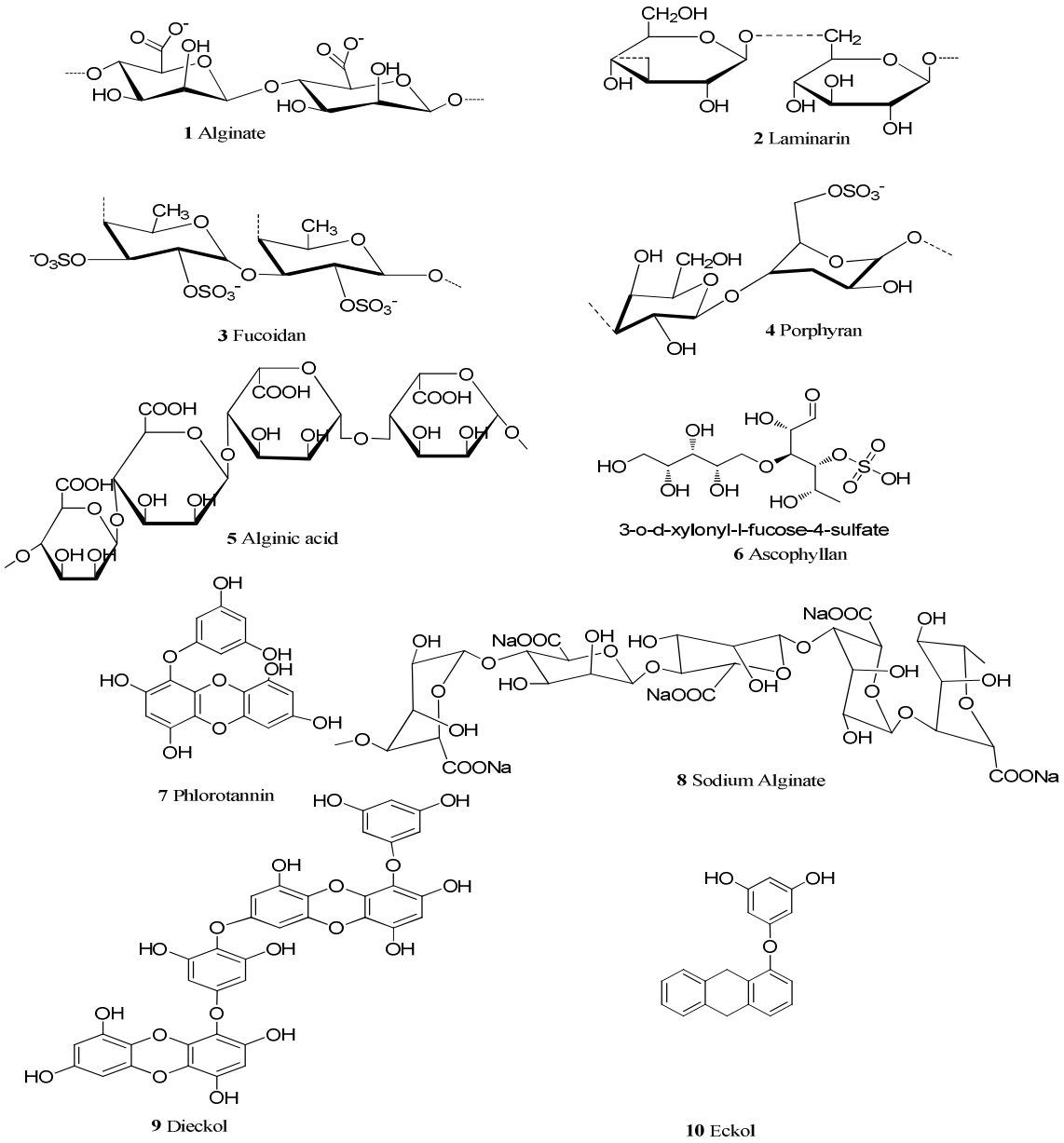


Fig. 1 Structures of compounds **1-10**.

mainly composed of sulfated L-fucose and small fractions of mannose, rhamnose, xylose and glucose.[35,36] The polysaccharides isolated from brown seaweeds contained similar repeating sugars but different in sulphation and molecular weights due to different isolation techniques and geographical locations.[37-40] Compound **3** (Fig. 1) isolated from five different brown seaweeds consist of 13 to 36 % contents of fucose and 8 to 25% variation in degrees of sulphation.[41] The several studies has been carried out about sulphation variation in polysaccharides of brown seaweeds affects their quality against antitumor activity.[42,43] Marine algae phaeophyta possess sulfated polysaccharides as major components of their cell wall and considered as valuable bioactive compound having several beneficial biological activities such as antitumor,[44] anticoagulant,[45] antiviral,[46,47] antiinflammatory,[48,49] and immunomodulating activities.[50] Marine macro algae especially phaeophyceae a class of brown seaweeds contain, fucoidan complex polysaccharides (FCSPs), and their specific biological activities depends on the source of seaweed, method of extraction, their compositional and

structural traits.[34] Ye *et al*. isolated highly sulphated polysaccharide fractions, SP-1, SP-2 and SP-3, from *Sargassum pallidum* and *in vitro*, results showed significant cytotoxicity against the A549 cells, HepG2 cells, and MGC-803 cells.[51] Compound **3** (Fig. 1) fractions from *Dictyopteris delicatula* and *Dictyopteris polypodioides* induced the 60-90% and 28% tumor growth inhibition for Hela and RPMI-7951 cancer cells respectively.[52,53] The polysaccharides extracted from Quebec's *Ascophyllum nodosum*, *Fucus vesiculosus* and *Saccharina longicruris* contain significant constituents of sulphates, total sugars and uronic acids that have diverse industrial and pharmacological applications.[54] Compound **3** (Fig. 1) increased IFN gama T cells production and significant increase in NK cells activity when treated to mice inoculated with P-388 tumour cells.[55] Compound **3** (Fig. 1) fractions isolated from *Sargassum hornery*, *Eclonia cava and Costaria costata* induced inhibition of colony formation in human melanoma and colon cancer cells and may be effective antitumor agents.[56] Compound **3** (Fig. 1) and fucose isolated from brown seaweeds are rich in sulfated polysaccharides which have potential biomedical properties as immunostimulatory,[57] immunomodulation, anti-inflammatory, anticoagulant,[58] antithrombotic, anticancer and anti-proliferative activities.[59] Compound **3** (Fig. 1) isolated from *Undaria Pinnatifida* have potential to repress the differentiation of adipose cells by inhabiting inflammatory cytokines and considered as a potent therapeutic agent against obesity and diabetes.[60-63] There are authentic reports that low molecular weight Compound **3** (Fig. 1) have better antitumor activity than high molecular weight of Compound **1** (Fig. 1).[64] O-acetylated sulphated galactofucan polysaccharide isolated from brown seaweed *Undaria pinnatifida* suppresses proliferation of PC-3 (prostate cancer), A549 (alveolar carcinoma), Hela (Cervical cancer) and HepG2 (heptacellular carcinoma) cells, in such a way to that of commercial fucoidan.[65] Ascophyllan (**6**, Fig. 1), extracted from brown alga *Ascophyllum nodosum* reduced the growth of U937 cells and also induced apoptosis and DNA fragmentation.[66,67] Compound **3** (Fig. 1) isolated from brown seaweed *Undaria pinnatifida* was tested against AGS stomach cancer cells and found low molecular fraction is more effective i.e. <30 kDa compared to >30 kDa fraction.[68] Compound **3** (Fig. 1) from *Laminaria brasiliensis* found cytotoxic to Hela cells at doses 2.5-40 µg/mL.[69] Polysaccharide fractions extracted from brown alga *Coccophora langsdorfii,* with similar linear backbone to compound **3** (Fig. 1) exhibited significant colony formation of SK-ML-5 and SK-ML-28 Melanoma cells (the percentage of inhibition was 28 and 76, respectively).[70] *In Vitro* and *In Vivo* studies of polysaccharides and sulfated polysaccharides proved their significance to be a novel source of anticancer agents and most studied group of macromolecules but still none of any agent entered into clinical trials, which may be related to purifying and identifying issues of their specific structure. Polysaccharides are a diverse group of molecules even pure fractions contains a diversity of sugar units and it's difficult to find a specific administrative route. Polysaccharides from brown seaweeds which have provided promising results requires identifying and formulating their molecular structures and determining the mechanism of their administration route is an essential step in the development of anticancer drugs for human deadly diseases.

Table 1 Anticancer components and their efficacy against cancer cells isolated from brown algae

Seaweed	Active agent(s)	Activity	Test type (s)	References
Esenia bicycles	Laminarian, EBL 1:3:1:6-B.D-Glucan (**2**, Fig. 1)	Anticancer activity at 200 ug/mL, Human melanoma SK-MEL-28 cells and colon cancer DLD1-cells	*In vitro*	(58)
Coccophoa langsdorfii	α-L-fucoidan (**3**, Fig. 1)	28 and 78 % anticancer activity at 100 µg/mL on SK-ML-5 and SK-ML-28 Melanoma cells	*In vitro*	(70)
Ishigeo kamurae	Diphlorethohydroxycarmalol (DPHC) (**50**, Fig. 5)	75% anticancer activity at 100 µg/mL on HL60 cancer cells	*In vitro*	(143)
Saccharina gurjanovae	sulfated galactofucan SgF (MW 123 kDa) (**3**, Fig. 1)	21% anticancer activity at 800 µg/mL on colon cancer DLD-1 cells	*In vitro*	(144)
Turbinaria conoides	Fucoidan (**3**, Fig. 1)	73.5% anticancer activity at 500 µg/mL on A549 cell line	*In vitro*	(145)
Fucus evanescens	Fucoidan (**3**, Fig. 1)	70% ,63% anticancer activity at 400 µg/mL on SK-MEL-28 and SK-MEL-5 cells	*In vitro*	(146)
Alaria angusta	Fucoidan AaF3 (**3**, Fig. 1) Laminaran AaL	29% and 22% anticancer activity at 400 µg/mL on HT29	*In vitro*	(58)

	(**2**, Fig. 1)	cells respectively.		
Ecklonia cava	8,8-bieckol (**11**, Fig. 2) (phlorotannins)	Anti-inflammatory	*In vivo*	(147)
Ecklonia Cava	Phloroglucinol (PG) (**14**, Fig. 2)	Decrease the CD44+ cancer cell population and expression of CSC regulatorssuch as Sox2, CD44, Oct4, Notch2 and β-catenin.	*In vitro* and *In vivo*	(90)
Stoechospermum marginatum	Spatane derivatives compounds 4 (**51**, Fig. 5), 1b (**52**, Fig. 5) 2a (**53**, Fig. 5), and 4a (**54**, Fig. 5)	Anticancer activity on B16F10 cancer cell line with IC_{50} values of 3.28, 3.45, 3.62 and 4.11 µg/ml respectively as compared to standard drug etoposide IC50 = 4.12 µg/ml	*In vitro*	(148)
Sargassum cichorioides *F.evanescens* *U.pinnatifida*	Fucoidan ScF2, (**55**, Fig. 5) Fucoidan FeF2 (**56**, Fig. 6), Galactofucan UpF2 (**57**, Fig. 6),	26% anti-proliferation activity at 200 µg/mL on DLD-1 cells 46% anti-proliferation activity at 200µg/mL on RPMI-7951 cells 60% Inhibition activity at 200 µg/mL on T-47D cells	*In vitro*	(59)
Fucus vesiculosus	Fucoidan (**3**, Fig. 1)	Inhibit growth and apoptosis of HT-29 and HCT116 cells	*In vitro*	(149)
Ecklonia *cava*	Dieckol (**9**, Fig. 1)	50% anticancer activity at 84.3 µg/mL and 99.6 µg/mL on A2780 and SKOV3 cells	*In vitro*	(91)
Laminaria japonica	Phlorotannins (**7**, Fig. 1)	30% and 43% anti-proliferation activity at 100 µg/mL on BEL-7402 and P388 cells	*In vitro*	(92)
Lobophora variegata	Fraction rich in fucans (FRF) (**3**, Fig. 1)	54% anticancer activity at 25 µg mL^{-1} on HepG2 cells	*In vitro*	(150)
Sargassum heterophyllum	Sargaquinoic acid (SQA) (**28**, Fig. 3)	SQA displayed an IC_{50} of 67.4±5.9 µM against MDA-MB-231cells via caspase-3activity and down-regulation of Bcl-2,cell cycle arrest in G1 phase.	*In vitro*	(151)
Sargassum wightii	Methanolic extract	29% and 41% anticancer activity at 200 µg/mL onHeLa and MDA-MB 231 cell lines	*In vitro*	(152)
Pylaiella littoralis	PLE extract	67.9%, 37%, 21.9%, and 20.2% anti-proliferative activity at 100µg/mL on HT-29, AGS, SK-HEP, NCI-H1299 cell lines	*In vitro*	(153)
Laminaria japonica	Fucoidan (**3**, Fig. 1)	2% osteoblast differentiation at 10	*In vitro*	(154)

		µg/mL in hABM-MSCs		
Sargassummacrocarpum	Sargafuran (**58**, Fig. 6)	At 15 µg ml^{-1} kills completely P. acnes	*In Vitro*	(155)
D.polypodioides and Sargassum sp	Fucoidan (**3**, Fig. 1)	44% and 28% anticancer activity at 200µg ml^{-1} on RPMI-7951 cells	*In vitro*	(53)
Fucus serratus Laminaria digitate, Ascophyllmnodosum, Pelvetia canaliculata	Astaxanthin (**59**, Fig. 6), β-carotene (**25**, Fig.3), zeaxanthin (**22**, Fig. 3)	Improves immune system, protect against eye diseases and anticancer effects	*In vivo*	(156,157)
Leathesia difformes	Methanolic extract	IC50 of 12.6 µgmL−1 and 40.6 µgmL−1 against KB and HT-29 cells	*In vitro*	(158)
Turbinaria ornata	Sulfated fucan-like polysaccharide (**3**, Fig. 1)	50%antiproliferative effect at 6.7µg/mL on NSCLC-N6 cell line	*In vitro*	(61)
Leathesia nana	six bromophenol derivatives 6-(2,3-dibromo-4,5-dihydroxybenzyl)-2,3-dibromo-4,5-dihydroxybenzyl methyl ether (**16**, Fig. 2**)**, (+)-3-(2,3-dibromo-4,5-dihydroxyphenyl)-4-bromo-5,6-dihydroxy-1,3-dihydroisobenzofuran (**17**, Fig. 2), 3-bromo-4-(2,3-dibromo-4,5-dihydroxybenzyl)-5-methoxymethyl-pyrocatechol **(18**, Fig. 2), 2,2,3,3 -tetrabromo-4,4,5,5-tetrahydroxy-diphenylmethane (**19**, Fig. 2), bis (2,3-dibromo-4,5-dihydroxybenzyl)ether (**20**, Fig. 3), 2,2,3-tribromo-3,4,4,5-tetrahydroxy-6-ethyloxymethyldiphenylmethane (**21**, Fig. 3) **17**, **19**, **20** (Fig. 2,3) compounds ethanolic extract of *Leathesia nana* (EELN)	All six exhibited 50% anticancer activity at 10 µg/mL on A549, BGC-823, MCF-7, B16-BL6, HT-1080, A2780, Bel7402 and HCT-8 cell lines 77.5%, 80.1% and 71.4% protein tyrosine kinase (PTK) inhibition activity. Inhibit the growth of Sarcoma 180 tumor cells and increase the indices of thymus and spleen to improve the immune system	*In vitro* *In vivo* *In vivo*	(98)
Sargassum vulgare C.	Alginates (SVHV and SVLV) (**1**, Fig. 1)	51.8%,74.8%,66.2% and 88.8% inhibition of	*In vivo*	(30,31)

Agardh, Laminaria digitat		Sarcoma 180 cells in mice at the doses of 50 and 100 mg/m^2/day for SVLV and SVHV, respectively		
Sargassum fulvellum	Pheophytin a (**26**, Fig. 3)	Enhances the neuro differentiation of PC12 cells at 3.9 µg/ml concentration.	*In vivo*	(159)
Undaria pinnatifida and *Hijikia fusiformis*	Fucoxanthin, 5,6-epoxy-3'-ethanoyloxy-3,5'-dihydroxy-6',7'-didehydro-5,6,7,8,5',6'-hexahydro-β,β-caroten-8-one (**23**, Fig. 3)	Regulates the white adipose tissue (WAT) weight gain and hyperglycemia in diabetic/obese KK-A^y mice	*In vivo*	(62)
Eisenia bicyclis	Pyropheophytin a (**60**, Fig. 6)	Antioxidant activity	*In vitro*	(111)
Undaria pinnatifida	Fucoxanthin and its metabolite, fucoxanthinol (**23**, Fig. 3)	Inhibits adipocyte differentiation in 3T3-L1 cells	*In vitro*	(160)
Undaria pinnatifida	Fucoidan (**3**, Fig. 1)	15.2%, 29.8%, 39.3%; 45.1% Inhibited growth of PC-3 cells and induced apoptosis at 10 µg/mL 50 µg/mL, 100 µg/mL, and 200 µg/mL respectively.	*In vivo*	(161)
Fucus vesiculosus	Fucoidan-Sulfated polysaccharides (**3**, Fig. 1)	80% anticancer activity at 100 µg/mL on DC cells and it has dose dependent cytoprotective activity.	*In vitro*	(63)
Sargassum mcclurei	Fucoidan Polysacchrides SmF1, SmF2, SmF3, and SmF3-DS (**3**, Fig. 1)	17, 48, 20, and 18% inhibited the colony formation of DLD-1 colon cancer cells at100 µg/mL respectively.	*In vitro*	(162)
Sargassum sp. Fucus vesiculosus	Crude Fucoidan MTA and SIG (**3**, Fig. 1)	40 and 36% reduction in viability of LLC and B16 cells at 1µg/mL in dose dependent manner respectively.	*In vitro*	(34)
Sargassum filipendula	SF-0.7v fucoidan (**3**, Fig. 1)	38.1% and 31.0%, growth inhibition at 2.0 mg/mL on HepG2 and PC3 respectively.	*In vitro*	(163)
Dictyopteris polypodioides	Fucoidan (**3**, Fig. 1)	44 and 28 % growth inhibition at 200 µgmL−1 on RPMI-7951 cells respectively	*In vitro*	(53)
Ecklonia cava, Sargassum horneri, Costaria costata	Fucoidan (**3**, Fig. 1)	8-55 % anticancer activity at 1-200 µgmL−1on SK-ML-28, DLD-1 cells.	*In vitro*	(56)
Undaria pinnatifida	Fucoidan of sporophyll (**3**, Fig. 1)	10-20% antitumor activity at 0-0.8 mg/ ml on PC-3, HeLa, A549, HepG2 cancer cells	*In vitro*	(65)

Dictyopteris delicatula	Fucoidan (**3,** Fig. 1)	60-90 % inhibition in tumor growth at 2 mg mL−1 on Hela cancer cells	*In vitro*	(52)
Sargassum stenophyllum	Sarg A Fucoidan polysaccharides (**3**, Fig. 1)	40% and 80% decrease in B16F10 melanoma cell tumors with the dose of 1.5 or 150 µg per animal per day for 3 days	*In vivo*	(164)
Laminaria digitata	Fucoidan (**3**, Fig. 1)	Inhibited inflammation and heterotypic tumour cell adhesions on MDA-MB-231 tumor cells at significant level	*In vitro*	(165)
Sargassum thunbergii	Fucoidan fractions (**3**, Fig. 1)	Injection of 20 mg kg−1 per day for 10 days increases the survival of Ehrlich carcinoma implanted IP in ICR/Slc mice as compared to control	*In vivo*	(166)
Alaria esculenta	Crude extract	Crude extract reduced viability of Caco-2 cancer cells	*In vivo*	(167)
Laminaria digitata	Laminarin (**2**, Fig. 1)	Induced tumor growth HT-29 Bcl-2 cells by decrease in cytochrome c expression and increase in Bad and Bax, restrict phosphorylation of ErbB2 and accumulation of cells in sub-G1 and G2-M phase.	*In vivo*	(93)
Ascophyllum nodosum	Ascophyllan (**6**, Fig. 1)	Reduced the growth of U937 cells and also induced apoptosis and DNA fragmentation.	*In vivo*	(66)
Ascophyllum nodosum	Ascophyllan (**6**, Fig. 1)	Inhibited tumour growth of Vero and XC cells and increases the growth of MDCK cells at concentrations 0-1,000 µg/mL	*In vivo*	(67)
Leathesia nana	bis(2,3-Dibromo-4,5-dihydroxybenzyl) ether (**20**, Fig. 3)	Induced apoptosis in mouse breast cancer by a mitochondrial mediated pathway and ROS generation. Inhibits topoisomerase I and cell cycle activity in the S phase.	*In vivo*	(168)
Undaria pinnatifida	Fucoidan extract (**3**, Fig. 1)	Inhibits the angiogenesis by human umbilical vein endothelial cells.	*In vivo*	(116)
Fucus vesiculosus	Fucoidan (**3**, Fig. 1)	Induces apoptosis of human lymphoma HS-Sultan cancer cells by down-regulation of ERK and activation of caspase-3 pathways	*In vivo*	(169)

Cladosiphon okamuranus	Fucoidan (**3**, Fig. 1)	Inhibited cell growth in MKN-45 cancer cells at 1mg/mL	*In vitro*	(170)
Sargassum hemiphyllum	Hedaol A, B, and C(**61**, **62**, **63**, Fig. 6)	50% anticancer activity at 50 µg/mLto P-388 cells for Heladaol A, B and C, respectively	*In vitro*	(171)
Hizikia fusiforme	Ethanolic extract	50-60 % inhibition in tumour growth with dose of 30-50 µg/mL. Increased caspased 3, 8,9 PARP and decreased IAP-2, Bcl-2, IAP-1 and XIAP	*In vivo*	(172)
Ecklonia cava	Dieckol (**9**, Fig. 1)	Induced SK-Hep1 human hepatoma cell motility through suppression of matrix metalloproteinase-9 pathwayS	*In vivo*	(85)
Sargassum fulvellum	Sodium alginate (**8**, Fig. 1)	Inhibited the tumor growth of S-180 in mice	*In vivo*	(83)
Stypopodim flabelliforme	Stypodiol (**38**, Fig. 4)	Induced anti-proliferation activity to SH-SY5Y cells with IC value of $\leqslant$50 µM and non-toxic to V79 normal cells	*In vitro*	(123).
Stypopodim flabelliforme	Two Mero-diterpenoids derivatives2β,3α-epitaondiol (**41**, Fig. 4), and flabellinol (**42**, Fig. 4)	All three showed cytotoxic to neuro-2a cells at 2-11 µMand 9-24µM to NCI-H460 cells respectively	*In vivo*	(122)
Bifurcaria bifurcata	Elaganolone (**64**, Fig. 6)	Strong antiprotozoal activity against T. bruceirhodesiense and a selective SI of 12.4 in LC6 cells	*In vitro*	(173)

2.2. Phenolic compounds

Polyphenols act as anti-oxidants and ability to scavenge free radicals and up-regulate certain metal chelation reactions and improves the body's own anti-oxidant system.[71] Phenolics are secondary metabolites of seaweeds composed of aromatic rings bearing one or more hydroxyl groups and include flavonoids, lignans, tannins and phlorotannins and may affect *In vivo* as receptor sensitivity,[28,72] cell signaling pathways and gene regulation or inflammatory enzyme activity.[73] Phlorotannins (**7**, Fig. 1), are produced in abundant through secondary

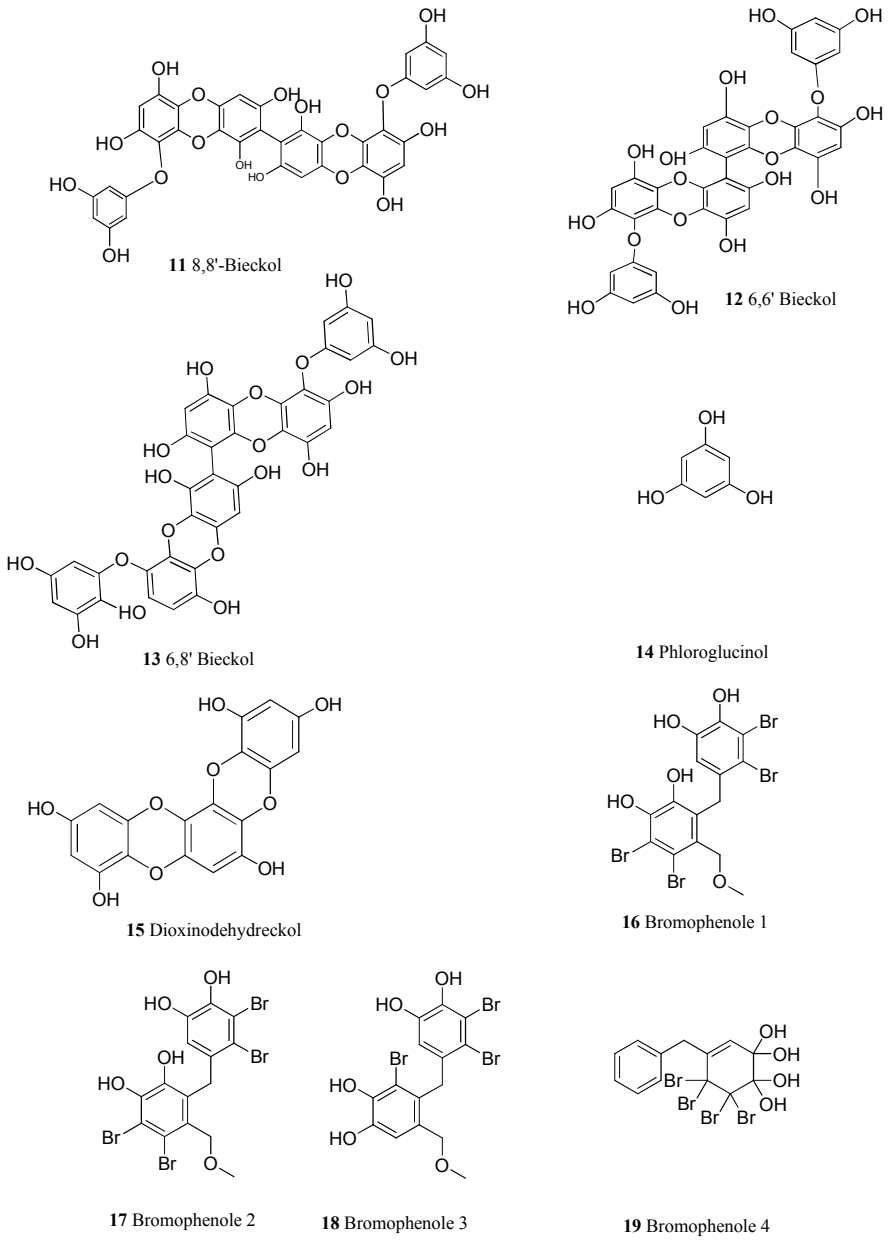
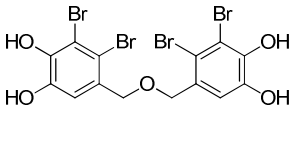
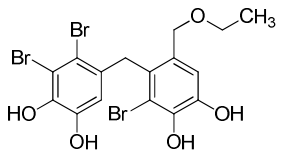


Fig. 2 Structures of compounds **11-19**

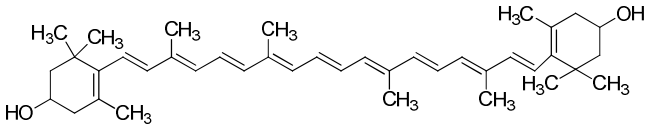
metabolism in Phaeophyceae.[74-76] Compound **7** (Fig. 1) consists of different molecular sizes (400-400,000 Da) and accounts (0.5-20%dw) in brown algae. The phenolic content quantitative analysis and comparative studies of *Fucaceae*, *Sargassaceae*, *Cystoseiraceae* and *Laminariaceae* have been reported. [77-81] The flavonoid content 88 µg/mL have been isolated from methanol extract of brown alga *Turbinaria ornate* which exhibited significant anti-proliferation activity on A549, PC-3, HCT-15 and MG-63 tumor cells *In vivo*.[82] Sodium alginate (**8**, Fig. 1), isolated from *Sargassum fulvellum* inhibited the tumor growth of S-180 in mice.[83,84] Dieckol (**9**, Fig. 1), from brown alga when treated to SK Hep-1 cells decreased TPA cell motility and MMP-9 activity which was associated to AP-1 in MAPK signalling pathways.[85] Methanol extracts of *Sargassum fulvellum* and *Sargassum thunbergii* inhibited 79.1% and 72.1% an inflammatory symptom of mouse ear edema without toxicity respectively.[74] Polyphenolic crude ethanolic extract from *Ecklonia cava* induced inhibition of MMP-2 and MMP-9activity and the link to be associated between polyphenols and anticancer activity.[86]



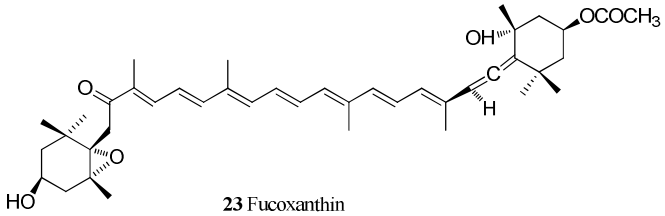
20 Bromophenole 5



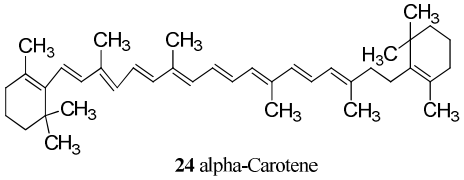
21 Bromophenole 6



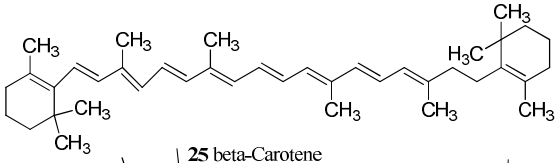
22 Zeaxanthin



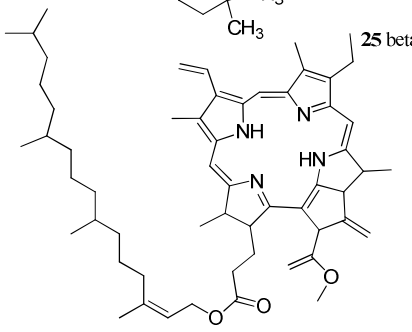
23 Fucoxanthin



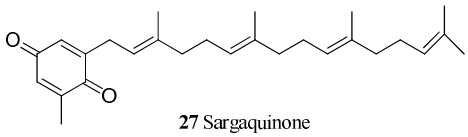
24 alpha-Carotene



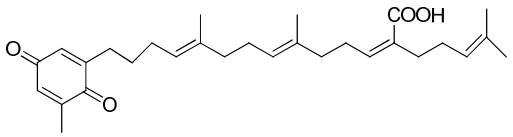
25 beta-Carotene



26 Phaeophytin a



27 Sargaquinone



28 Sargaquinoic acid

Fig. 3 Structures of compounds **20-28**

Sargassum muticum, *Fucus vesiculosus*, *Gelidium sesquipedale* and *Cystoseira compressa* extracts were evaluated to find out the total flavonoid and phenolic contents to investigate the cytotoxic and mutagenic potential. Hexane extracts of these isolates have no significant cytotoxic and mutagenic activity against human hepatocellular carcinoma Hep 3B cell line when applied as 5-50 µg/mL. The finding results suggested that the phytochemical constituent of brown seaweeds might be suitable agents for the control of human deadly diseases.[87-89] The Phlorotannin compounds such as eckol (**10**, Fig. 1), 8,8'-bieckol (**11**, Fig. 2), 6,6'-bieckol (**12**, Fig. 2), and 6,8'-bieckol (**13**, Fig. 2), have been isolated from several brown algae *Sargassum fulvellum*, *Sargassum thunbergii*, *Ecklonia cava*, *Hizikia fusiformis*, *Ishige okamurae*, *Ecklonia cava*, *Eisenia arborea* and *Eisenia arborea*.[74] Phloroglucinol (**14**, Fig. 2), isolated from *Ecklonia cava* decreases the CD44+ cancer cell population and expression of CSC regulators such as Sox2, CD44, Oct4, Notch2 and β-catenin.[90] Compound **9** (Fig. 1) from *Ecklonia cava* exhibited 50% anticancer activity at 84.3 µg/mL and 99.6 µg/mL on A2780 and SKOV3 cells respectively.[91] The

growth of two tumour cell lines BEL-7402 and P388 cells was inhibited to 30 to 43% at 100 µg/mL of compound **7** (Fig. 1) rich extracts from *Laminaria japonica* and apoptosis also observed.[92] Compound **2** (Fig. 1) isolated from brown alga *Laminaria digitata* induced apoptosis in HT-29 Bcl-2 cells in a dose dependent manner, via increased the percentage of cells in the sub-G1, G2-M phase and inhibited the heregulin-stimulated phosphorylation of ErbB2.[93] Similarly, a compound **1** (Fig. 1) was isolated from brown alga *Sargassum vulgare* and studied *In vivo* which exhibited 27 to 88 % inhibition in tumour growth of Swiss mice with S-180 implanted SC supplemented dose 50 and 100 mg m-2 per Day for 10 days.[94] kimiya *et al*. studied various extracts of brown algae *In vivo* and *In vitro* including *Ecklonia cava*, *Codium fragile*, *Ulva japonica*, *Undarina pinnatifida* and *P.Binghamiae* against RBL-2H3 cells at 100 to 200 ug/ml among them, *P.binghamia* exhibited highest degranulation of both RBL-2H3 cells and as well mouse esinophils.[95] A Phlorotannin compound dioxinodehydroeckol (**15**, Fig. 2), induced apoptosis in MCF-7, MDA-MB-231 cells and increased the activities of caspases 3 and 9, Bax, p53, PARP pathways via down regulation of the NF-kB and Bcl2.[20,28] Bromophenol compounds from marine organisms especially from brown algae have proved to be valuable characteristic natural products with potential biological activities including antioxidant, antidiabetic, anticancer and α-glucosidase inhibitor activities.*Leathesia nana* a marine brown seaweed possess six unique bromophenols compounds (**16**-**21**, Fig. 2,3), derivatives and all six exhibited 50% anticancer activity at 10 µg/mL on A549, BGC-823, MCF-7, B16-BL6, HT-1080, A2780, Bel7402 and HCT-8 cell lines respectively.[96,99]

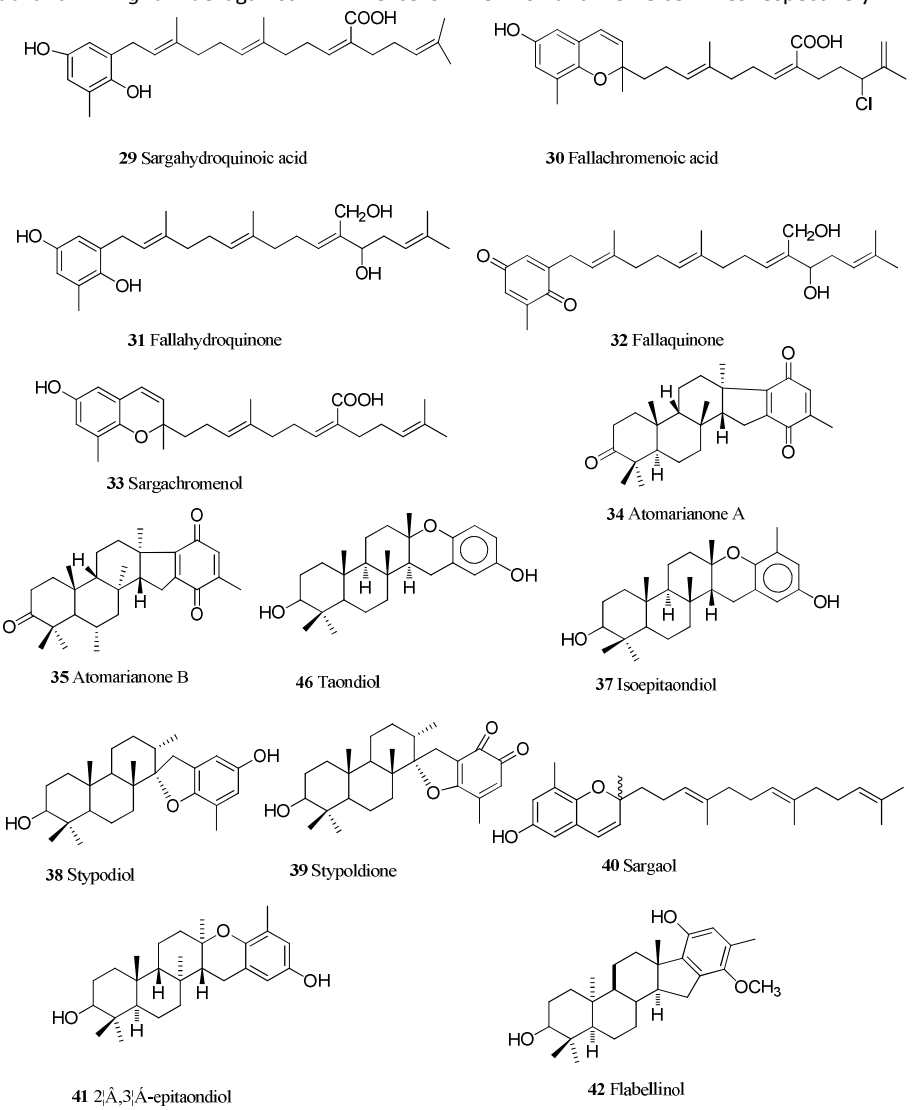


Fig. 4 Structures of compounds **29-42**

2.3. Carotenoids

Carotenoids are natural pigments, dietary fibers and having functional compounds primarily found in both plants and animals. Brown seaweed cell wall contains catatonic compounds including lutein, zeaxanthin (**22**, Fig. 3), and fucoxanthin (**23**, Fig. 3).[100,101] Brown algae is considered as a rich marine reservoir of secondary metabolites especially carotenoids and possess bioactivities including, antioxidant,

anticancer, anti-inflammatory and anti-viral.[102] Epidemiological investigations have evidenced that there is a clear link between seaweed carotenoids diet and cancer risk and considered most important pharmaceutical compounds, which might be a promising anticancer marine drug.[103] Carotenoids are coloured terpenes produced by secondary metabolism in brown algae with abundant structural variety, such as a-carotene (**24**, Fig. 3), and b-carotene (**25**, Fig. 3), chlorophyll a, phaeophytin a, (**26**, Fig. 3), lutein, zeaxanthin (**22**, Fig. 3), and fucoxanthin (**23**, Fig. 3), and play a key role in human nutrition, providing provitamin A, hormone synthesis, photomorphogenesis, photoprotection and cerebrovascular diseases.[104-107] Compound **23** (Fig. 3) content values in the range 1-6 mg/g,[15,18] structural variability,[108,109] and bioactivity of some brown seaweeds have been reported up to 16 mg/g for *Turbinaria sp*,[106] and higher for *Laminaria sp* and *Undaria pinnatifida*.[105] Compound **23** (Fig. 3) and Fucoxanthinol both reduced proliferation of HUVECs without affecting their chemotaxis and inhibits the growth in *ex vivo* rat aortic rings through suppression of micro vessel (CD31+ve) formation.[110] Compound **23** (Fig. 3) derivative from two brown algae *Undaria pinnatifida* and *Hijikia fusiformis* regulates the white adipose tissue (WAT) weight gain and hyperglycemia in diabetic/obese KK-Ay mice In Vivo.[62] Similarly, compound **23** (Fig. 3) and its metabolite, fucoxanthinol was isolated from brown alga *Undaria pinnatifida* exhibited significant Inhibition to adipocyte differentiation in 3T3-L1cells.[111] Compound **23** (Fig. 3) induced apoptosis via activation of caspases 3 and 9, and reduced the expression of Bax and Bcl-2 proteins, but not Bcl-X(L).[112] However, apoptosis, DNA fragmentation, reduction in Bcl-2, Bax and caspase3-activation has been observed in DU145,PC-3 and LNCaP prostate cancer cell lines.[113,114] Compound **23** (Fig. 3) reduced cell viability and induced apoptosis via decrease to Bcl-2 expression on HT-29 and DLD-1 cells.[115] Compound **23** (Fig. 3) increased the NFκB-regulated Bax/Bcl-2 mRNA ratio, via inhibition of ERCC1 and NF-kB expression through blocking the P13K/AKT pathways. Also, induced cell inhibition of human hepatoma HepG2 cells and improve the activity of cisplatin treatment.[116] Compound **23** (Fig. 3) induced apoptosis G2/M1cell cycle arrest via down regulate the expression of CyclinB1, which was linked with the JAK/STAT pathway.[117] Compound **23** (Fig. 3) induced apoptosis via reduction of cell viability in EJ-1 cancer cells and increased hypodiploid cells, DNA ladder and caspase 3 activities.[118]

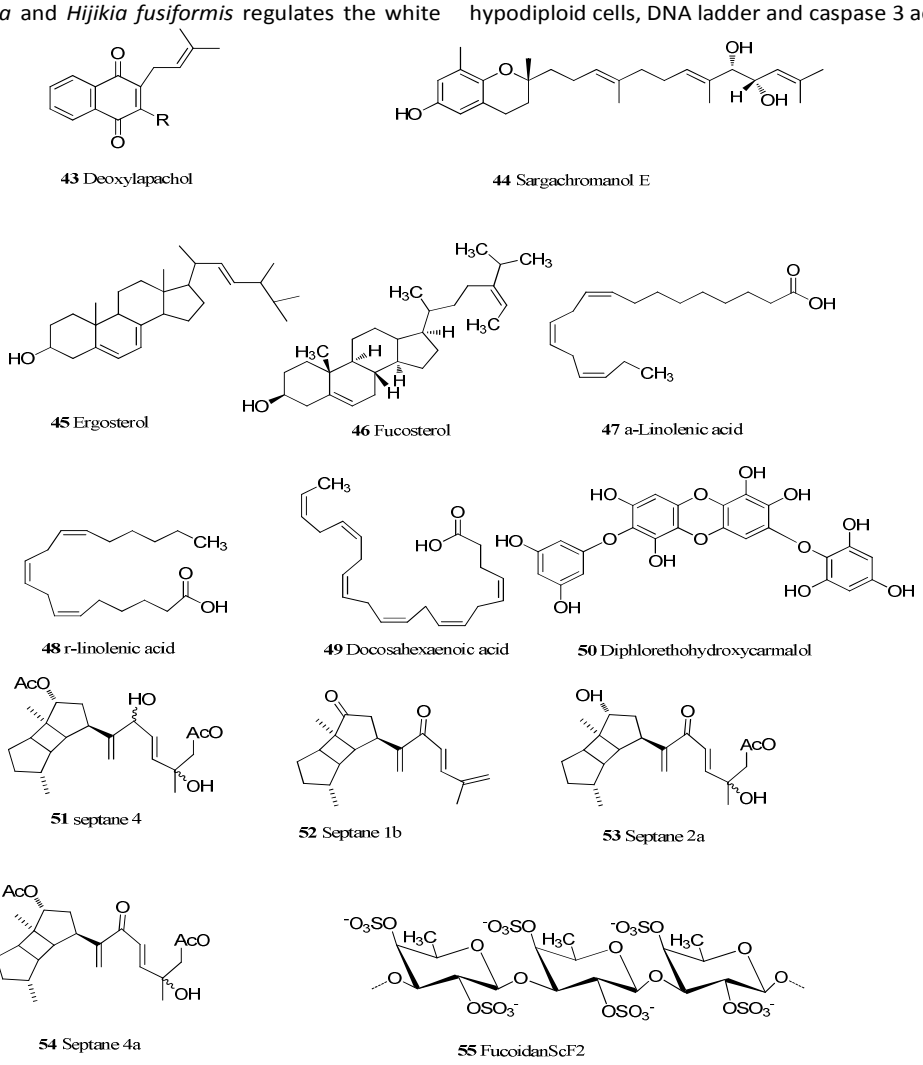


Fig. 5 Structures of compounds **43-55**

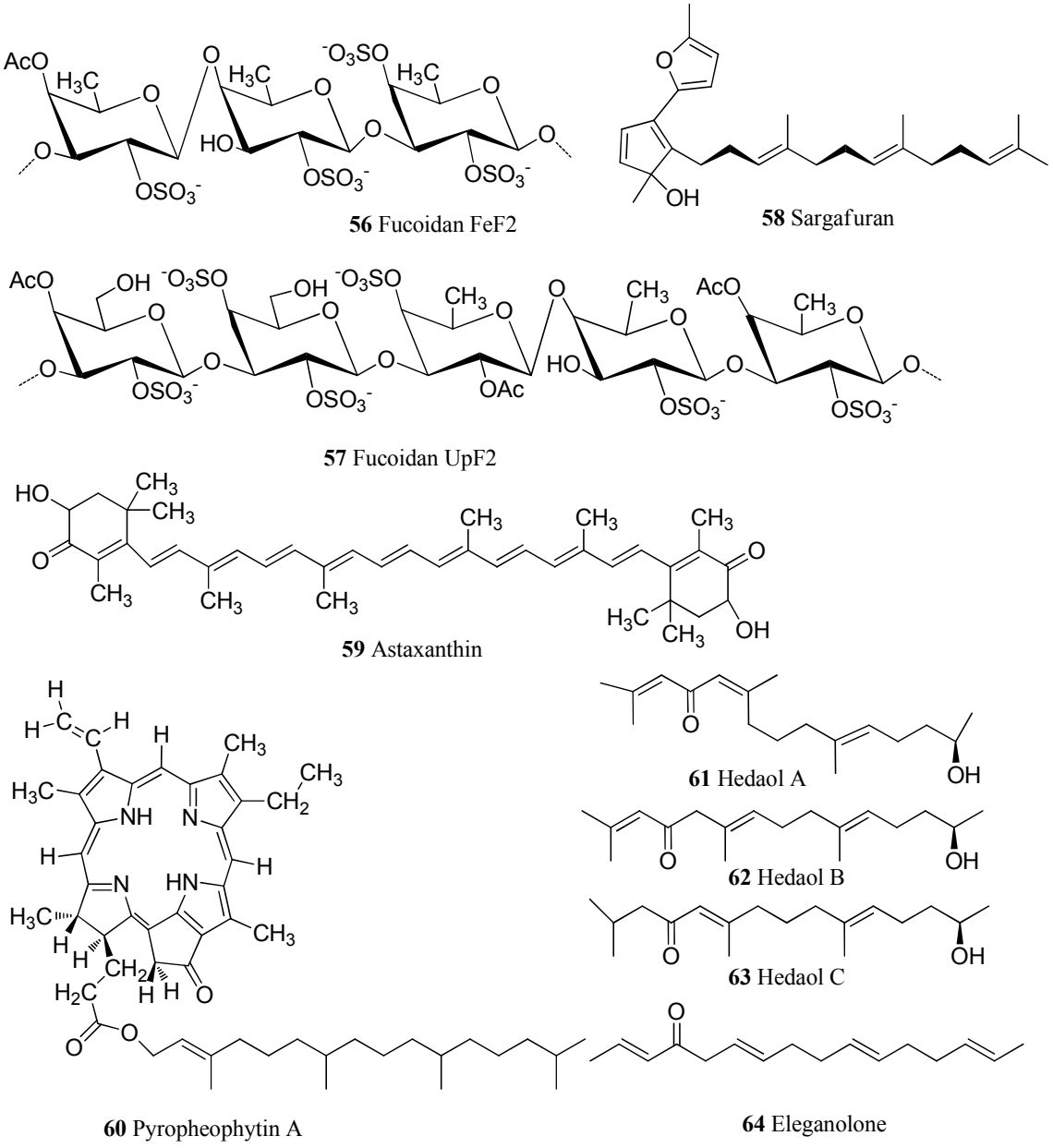


Fig. 6 Structures of compounds **56-64**

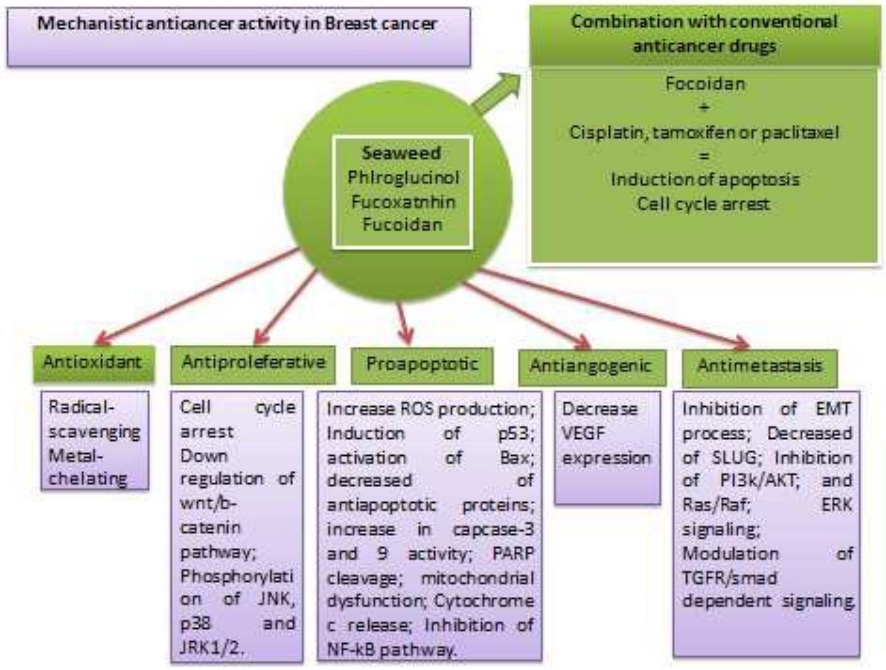


Fig. 7 Molecular mechanisms and targets of phloroglucinol, fucoxanthin and fucoidan mediating the anticancer activity in breast cancer.[192]

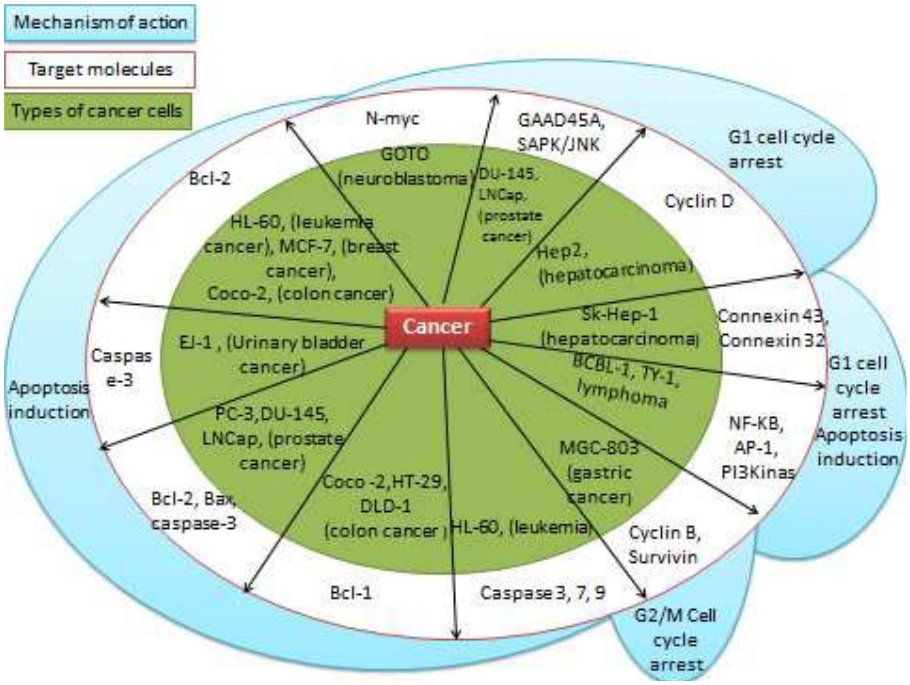


Fig. 8 Anti-cancer effects of fucoxanthin and fucoxanthinol on various types of cancer cells and their mechanism of action.[193]

2.4. Terpenoids

Terpenes and polyketides for example, account most of the secondary metabolites and can be recognized as oligomers of the primary metabolites isoprene and acetate respectively. Terpenes and polyketides in brown algae frequently occur as secondary metabolites and their structure go to acyclic entities with a linear chain to complex polycyclic molecules, which are considered as main component for cancer treatment.[119] Antitumor activity of meroterpenoids metabolites isolated from *Sargassum fallax* against p388 human cancer cells were found IC_{50} of 17, 14, 32 and >27-29 µM when treated with 1 mg/mL for Sargaquinone (**27**, Fig. 3), sargaquinoic acid **(28**, Fig. 3), sargahydroquinoic acid (**29**, Fig. 4), and Fallachromonoic acid (**30**, Fig. 4), fallahydroquinone (**31**, Fig. 4), fallaquinone (**32**, Fig. 4), Sargachromenol (**33**, Fig. 4), respectively.[120]

Atomarianone A (**34**, Fig. 4), and B (**35**, Fig. 4), compounds were isolated from *Taonia atomaria* and both found cytotoxic to NSCLC-N6, A549 cell lines with IC_{50} values of <7.35µM.[121] Diterpenoid metabolites isolated from a brown alga *Cystoseira mediterranea* tested *In vivo* against in mouse P388 leukaemia cells and found significant cell inhibition activity.[122] The isolated terpenoid derivatives sargaquinone (**27**, Fig. 4), taondiol (**36**, Fig. 4), isoepitaondiol (**37**, Fig. 4), stypodiol (**38**, Fig. 4), stypoldione (**39**, Fig. 4), and sargaol (**40**, Fig. 4), were found strong antioxidant potential with specific biological activities such as, compound **39** (Fig. 4) which inhibits the microtubule polymerization, compound **36** (Fig. 4**)** exhibited anticancer activity, compound **37** (Fig. 4) related to insecticidal activity and cytotoxicity against P-388 lymphocytic cells related to metabolites compounds **27**and **40** (Fig. 4). Two Mero-diterpenoids including, 2β, 3α-epitaondiol (**41**, Fig. 4), flabellinol (**42**, Fig. 4), were isolated from *Stypopodium flabelliforme* and *In vivo* studied showed all three were cytotoxic to neuro-2a cells at 2-11 µM and 9-24 µM to NCI-H460 cells respectively.[123] Compound **38** (Fig. 4) induced anti-proliferation activity to SH-SY5Y cells with IC value of ≤50 µMand was also found non-toxic to V79 normal cells.[124]

2.5. Proteins, Lipids, Sterols and Quinones, vitamins, fatty acids and amino acids

The protein structure of brown seaweeds and their biological potential are still poorly studied so far, but the amino acid composition is well documented by several studies.[125] The protein contents in the brown seaweed are usually considered small and different from species to species such as, *Undaria sp* has the highest ratio of 24% dry weight, followed by 17-21% for *Fucus*, *Sargassum*, *Laminaria* and lowest content 10% is for *Ascophyllum sp*. Brown seaweed proteins generally contains highest content of threonine, alanine, valine, glycine, leucine and lysine with several amino acids such as histidine, tryptophan, cysteine, methionine and tyrosine with lower levels.[126,127] The combined glutamic acid and aspartic acid level 22-44%, 39-41% and 18% wet weight of the total amino acid fraction is reported for *Fucus sp*, *Sargassum sp* and *Laminaria digitata* respectively.[128-130] Amino acids isolated from brown seaweeds *Sargassum vulgare (C.Agardh)* and *Sargassum thunbergii* extracts have been considered as potential source of new treatments for parasitic diseases such as anti-helmintics.[131] Ishihara *et al*. isolated two polyunsaturated fatty acids 18:4n-3 and 16:4n-3 from two brown marine algae *Ulva pertusa* and *Ulva pinnatifida* and extensively studied *In vivo* which exhibited strong inhibition on Lekotrien B4, 5-hydroxyeicosatetraenoic acid and leukotriene C4 in MC/9 mice mast cells.[132] Deoxylapachol a 1, 4-Naphthoquinone (**43**, Fig. 5), derivative isolated from *Landsburgia quercifolia* induced apoptosis to p-388 human cancer cells (IC> 0.6 pg/ml).[133] Sargachromanol E (**44**, Fig. 5), from *Sargassum Siliquastrum* induced caspase 3-mediated apoptosis in HL-60 cancer cells.[134] Two steroidal compounds named 3-Keto-22-epi-28-nor-cathasterone and cholest-4-ene-3, 6-dion were isolated from *Cystoseira myrica* which induced cytotoxicity to HEPG-2 and HCT116 cells in the range of 12.38-1.16 µM in selective patterns.[135] Ergosterols (**45**, Fig. 5), isolated from brown alga *Lyengaria stellata* exhibited noticeable hematopoietic effect when it was applied orally at the doses of 10 mg/200 g body weight to rabbits for 30 days.[136,137] Another compound, Fucosterol (**46**, Fig. 5), isolated from brown seaweeds *Pelvetia siliquosa*, *Cystoseira foeniculacea* and *Sargassum angustifolium* exhibited significant cytotoxic effect to HT-29, Caco-2 and T47D cells.[138,139] *Laminaria japonica* glycoprotein (LJGP), induced apoptosis and cell cycle arrest in AGS, HepG2, HT-29 cancer cells in a dose-dependent manner via mediated by Fas signalling pathway, caspas-3 activation and mitochondrial pathway.[140] The PGE2 production and histamine release were lowered in the canine mastocytoma cell line C2 and RBL-2H3 cells treated with alpha-linolenic acid (**47**, Fig. 5), γ -Linolenic acid (**48**, Fig. 5), and docosahexaenoic acid (**49**, Fig. 5), respectively.[141,142]

3 Mechanisms of action and comparison of toxicity of compounds with other chemotherapeutic drugs

In recent decades, the scientists have had much attention to know the nature of initialization and progression of malignant tumors through the advancement of genetics and molecular biology. In some papers, there are some mechanistic studies proved the role of these compounds to regulate the biological and physiological processes of the cell and got much attention of the researchers around the chemotherapeutic world.[20,65,66,138] In some reports, the researchers identified specific inhibitory activity of natural compounds from brown seaweeds, on a number of key cellular processes including, antimetastatic, antiangiogenic, telomerase, proapoptotic, tumor angiogenesis and apoptosis pathways.[174,175] Compound **6** (Fig.1) has been reported to induce cytokine release TNF and granulocyte colony-stimulating factor (GCSF) from macrophage-derived RAW264.7 cells though apoptosis and DNA fragmentation,[66] and a sulphated polysaccharide compound **3** (Fig. 1) extracted to *Hydroclathrus clathratus* was found to increase tumor necrosis factor (TNF-α) in mouse serum.[64] Compound **14** (Fig. 2) has been evidenced to inhibit the epithelial-mesenchymal cell transition (EMT) process and suppression of metastatic ability of breast cancer cells through decrease in expression of SNAIL-related zinc-finger transcription factors and inhibition of PI3K/AKT and Ras/Raf-1/ERK signaling pathways.[176] Compound 22 (Fig. 3) proved its anti-carcinogenic activity to interrelated with mutagens such as 1-nitropyrene,[177] and aflatoxin B1 (AFB1),[178] by regulating specific genes involved in T-cell transformations.[179] Compound **23** (Fig. 3) has been evidenced to induce the apoptosis through caspase-3, 7, 9 activation and suppress the Bax and Bcl-2 proteins expression through inhibition of NF-kB pathway in several cancer cell lines including, HL-60 cell line,[114] MDA-MB-231,[180] MCF-7 breast cancer cells,[181] Caco-2 colon cancer cells,[182] Caco-2, HT-29, DLD-1 cells,[115] prostate cancer cell line [112] and urinary bladder cancer EJ-1 cell line.[118] Compound **25** (Fig. 3) prevents the carcinogenesis by preventing DNA damage,[183] onset of cancers, especially lung cancer,[184] and regulates several biological functions including, hormones, tissue growth and differentiation, mediators of cell signalling and regulators of cells.[104] Compound **59** (Fig. 6) rich algal extract has been evidenced potent protection against UVA-induced DNA damage to melanocytes, intestinal CaCo-2 cells,[185] and inhibition of androgen-induced proliferation of human prostate cancer cells.[113,186] In current scenario of chemotherapy, there are several studies have been proved the synergistic effects of natural bioactive compounds when in

combination with complementary or conventional anticancer drugs.[187, 188, 189] The chemotherapeutics have been received promising results for application of natural compounds when combination with commonly used anticancer drugs such as, activation of different molecular mechanistic pathways, improve drug absorption, enhance anticancer drug efficiency and increase the clinical responses.[175,27,190] Compound **7** (Fig. 1) rich extract exhibited significant anti-proliferative effect than that of 5-fluorouracil (a commercial chemotherapy drug), against P388 and BEL-7402 cancer cells with the doses of 120 µg/ml and >200 µg /ml, respectively.[92] A recent finding for compound **22** (Fig. 3) has been evidenced the significant antiproliferative effect against MCF-7 and MDA-MB-231 cells, through apoptosis and cell cycle arrest, when co-treated with cisplatin, tamoxifen and paclitaxel. Suppression of Bcl-2 proteins expression, ERK and AKT signalling pathway, regulation of estrogen receptors and production of oxidative stress would be the possible mechanisms.[27] Compound **23** (Fig. 3) has been found promising results when combine treatment with oxaliplatin/5-fluorouracil/leucovorin or irinotecan/ fluorouracil/leucovorin, such as decrease in fatigue, and increase the survival rate of patients that received co-treatment.[191] Compound **50** (Fig. 5) has been found more potent than that of acarbose, a commercial carbohydrate digestive enzyme inhibitor, against alpha-glucosidase and alpha-amylase with IC_{50} values of 0.16mM and 0.53mM, respectively. It can be considered as potent chemotherapeutic drug for treating diabetes.[143] However, despite the strong potential of these studies, the natural compounds needs more comprehensive study before translation into useful modern chemotherapeutic drugs.

4 Conclusions and prospective

Cancer is a multi-faceted molecular disease that is undrugable to date. The academic and research institutes after their intensive efforts are still unable to find potential antitumor compounds rather than few products.[194] Hence, there is growing trend by the scientist to find out a novel compound to treat the cancer. Although, few marine antitumor compounds are being practiced to treat the human deadly diseases like cancer but they are known to have some side effects such as sleepiness, nervousness, tiredness and drowsiness. To eliminate these side effects, the scientists had paid a great attention to find out the potential drugs from marine source with potent efficacy and specificity for the treatment of cancer. Brown seaweeds have a diversity of compounds and novel entities such as polysaccharides, polyphenolic contents, carotenoids, terpenoids, bromophenols, proteins, lipids, amino acids, vitamins, sterols and quinines. Therefore, *In vitro* and *In vivo* studies of these compounds have proved their strong potential against cancer cells without toxicity. Considerably, there are still many issues persist to develop a marine drug such as toxic side effects and large scale production. However, biochemical combinatorial genetic and metabolic engineering can be helpful for the development of natural drugs by the modification or eliminating the toxic groups from these natural compounds to obtain a pure compound which are more specific and less cytotoxic. In addition, the anticancer activity and specificity of active compounds can be increased to find out the exact mechanism of action, structural activity relationship, synthetic method and drug metabolism. There is need for extensive study to overcome the issues related to find out the desired compounds such as large scale production and it can be improved through aquaculture and fermentation processes. Brown seaweeds studied so far, exhibited strong potential against various cancer cells without producing toxicity, therefore, there is a need to explore the marine brown algae for the development of new pharmaceutical products. Thus, this review might be useful for developing potential anticancer drugs from brown seaweeds.

Abbreviations

1 IFN- Interferon factor
2 NK - Natural killer
3 FCSPs-Fucoidan complex sulphated polysaccharides
4 AGS- human stomach cancer cell line
5 RPMI-7951- Human malignant melanoma obtained
6 P-388- Murine leukaemic cells
7 Pc-3-prostate cancer
8 A549-alveolar carcinoma
9 Hela-Cervical cancer
10 HepG2-heptacellular carcinoma
11 U937- Human leukaemic monocyte lymphoma
12 kDa-Kilo Dalton
13 SK-ML-5- Human malignant melanoma
14 SK-ML-28- Human malignant melanoma
15 HCT-15- human colon cancer cell line
16 MG-63- Human osteosarcoma
17 MCF-7- Breast cancer
18 Hep-2- Liver Cancer
19 S-180- Sarcoma 180
20 Dw-Dry weight
21 MAPK-Mitogen-Activated Protein Kinase
22 TPA-Tetradecanoylphorbol acetate
23 MMP-9- Matrix metalloproteinase-9
24 AP-1- Activator Protein -1
25 Hep 3B- human hepatoma cell line
26 BGC-823- human gastric cancer cell line
27 B16-BL6- Murine melanoma
28 HT-1080- Human fibrosarcoma cells
29 A2780- human ovarian cancer cell line
30 Bel7402- human hepatocellular carcinoma
31 HCT-8- Human colon cancer cells-
32 CSCs- cancer stem-like cells
33 SKOV3- human ovarian carcinoma cell line
34 P388-human leukaemia cells
35 HT-29- Human colon adenocarcinoma cells
36 RBL-2H3- basophilic leukemia cell line
37 MDA-MB-231- Human mammary adenocarcinoma
38 WAT-white adipose tissues
39 HUVECs- Human umbilical vein endothelial cells
40 3T3-L1- mouse adipose tissue cell line
41 DU145- human prostate cancer cell line
42 LNCaP- human prostate adenocarcinoma cell line

43 DLD-1- Human colorectal adenocarcinoma
44 ERCC1- Expression of excision repair cross complementation 1
45 PI3K/AKT- Phosphatidylinositol 3-kinase
46 NF κ B- Nuclear transcription factor kappa B
47 EJ-1- human bladder cancer cells
48 MGC-803- Human gastric adenocarcinoma cancer cells
49 JAK/STAT- Janus Kinase/Signal transducer and activator of transcription
50 neuro-2a- mouse neuroblastoma cell line
51 V79- Chinese Hamster Lung Fibroblast Cell Line
52 MC/9-mice mast cells
53 HCT116- Human colon cancer cells
54 Caco-2 - Human epithelial colorectal
55 T47D- Breast cancer cell line
56 LJGP- *Laminaria japonica* glycoprotein
57 EBL- *Eiseniabicyclis*laminaran
58 SgF-Sulfatedglactofucan
59 AaF-*Alariaagusta*fucoidan
60 AaL-*Alariaagusta*laminaran
61 ScF-*Sargassumcichorioides*fucoidan
62 FeF-*Ficusevanescens*fucoidan
63 UpF-*Undariapinnatifida*galactofucan
64 FRF-Fraction rich in fucans
65 SQA-Sargaquinoic acid
66 PLE-*Pylaiellalittoralis* extract
67 NCI-H1299-Human lung cancer cell line
68 hABM-MSCs- human alveolar bone marrow-derived mesenchymal stem cells
69 ERK- Extracellular signal-related kinase
70 JNK- c-Jun N-terminal kinase
71 KB- Human leukemia-lymphoma cell line
72 NSCLC-N6- Human non-small cell bronchopulmonary carcinoma line
73 PTK- protein tyrosine kinase
74 SVLV-*Sargassum vulgare* low viscosity
75 SVHV- *Sargassum vulgare* high viscosity
76 PC12- Clonal rat pheochromocytoma cell line
77 DC - Dendritic cells
78 SmF- *Sargassummcclureif*ucoidan
79 LCC-Lewis lung carcinoma cells
80 MCB16- melanoma cells B16
81 MDCK- Madine – Darby canine kidney
82 ROS-Reactive oxygen species
83 MKN-45- Human gastric adenocarcinoma
84 SK-Hep1- Human hepatoma cell line
85 LC6- large cell lung cancer cell line
86 SH-SY5Y- Human neuroblastoma cell line
87 NCI-H460-Lung cancer cell line
88 EELN- Ethanolic extract of *Leathesia nana*
89 GCSF- Granulocyte colony-stimulating factor
90 EMT-Epithelial-mesenchymal cell transition

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Components of brown seaweeds are potential candidate for cancer therapy - a review

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Brown seaweeds had opened new opportunities for the development of novel anticancer agents due to their diverse structural composition and mode of action.