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Algal Terpenoids: A Potential Source of Antioxidants for Cancer Therapy

Umme Tamanna Ferdous and Zetty Norhana Balia Yusof

Abstract

In cancer treatment, increase in drug resistance and decrease in new chemotherapeutic drugs have become a pressing problem. Hence, searching for novel anticancer agents with less toxicity and high sensitivity is expanding gradually. Many preclinical and clinical studies indicate that natural antioxidants can help combating carcinogenicity and reduce the adverse effects on cancer therapy, when used alone or as adjuvant in chemotherapy. Consequently, marine algae pave the way for exploring more potential antioxidant compounds which have pharmaceutical importance. Algal terpenoids comprise a large group of bioactive compounds that have excellent antioxidative property and can be used as source of antioxidant in cancer therapy. This chapter summarizes the potential role of terpenoids from algal sources in inhibiting cancer cells, blocking cell cycle, hindering angiogenesis and metastasis as well as in inducing apoptosis.

Keywords: algal terpenoids, antioxidant, cancer, chemotherapy, marine algae

1. Introduction

Though cancer is the prime reason for the premature death and responsible for more than nine million death globally in 2018, cancer treatments are still facing challenges in terms of their potency and safety [1]. Over fifty percent of the existing cancer drugs are from natural origin, therefore, exploration of cancer therapeutics from natural reservoir has been escalated currently [2]. In accordance with this natural anti-cancer drug discovery, natural antioxidants can be considered as an alternative source of cancer therapeutics. Many antioxidants, for instance, vitamins, carotenoids, genistein, curcumin, resveratrol, gingerol etc. exhibited promising outcomes in preclinical and clinical studies [3]. Currently, researchers are looking for more novel phytochemicals that can be further used as cancer drug discovery.

Terpenoids are the broadest class of diverse phytochemicals which are widely available in marine algae. These secondary metabolites have excellent antioxidative property and exerted *in vitro* as well as *in vivo* anticancer activity [4]. Algal terpenoids mainly comprised of mono-, di-, tri-, tetra-, mero- and sesquiterpenoids. Tetraterpenoid which is mostly carotenoid, is widely studied algal terpenoid. Carotenoids isolated from macro- and microalgae have been used widely in health-related industries and they have been reported to display strong anticancer activity

against different cancer cells [5]. Besides these tetraterpenoids, other terpenes and terpenoids have also significant anticancer property. This chapter focus on the usage of antioxidants in cancer therapy, presenting the anticancer property of algal terpenoids with their mechanism of action in cancer cells.

2. Role of antioxidant in cancer therapy

Antioxidants are molecules which can detoxify the reactive species (reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive sulfur species (RSS), reactive carbonyl species (RCS) and reactive selenium species (RSeS)), that are generated through body's normal metabolism or can be obtained from environment [6]. These reactive species give rise to oxidative stress which is of two types, oxidative eustress and oxidative distress. Oxidative eustress is considered as good stress, which under basal intensity, maintains redox homeostasis, responsible for controlled cell growth and reversible oxidative modification which ensure normal physiology. On the other hand, oxidative distress is known as bad stress, that in higher intensity, damage biomolecules and consequently disrupt redox signaling and give rise to different diseases, e.g. cancer [7].

Antioxidants protect cellular damage from free radicles through their organized defense mechanism (**Figure 1**), where they either inhibit new free radicle formation or scavenge the formed free radicles. They can also repair the damaged DNA and biomolecules [8]. In cancer cells, ROS level is excessively high which helps in pro-tumorigenic cell signaling while prolonging the cell death. Some chemotherapeutic agents also can induce production of high amount of ROS, which is often considered as one of the main reasons for chemotherapeutic treatment side effects. However, antioxidants, when used in therapeutic dose in adjuvant chemotherapy, can hinder this high production of ROS and thus, potentiate the efficacy of cancer treatments, reduce the adverse effects of the therapy and improves the overall health status of the cancer patients. Antioxidants can inhibit cancer proliferation, angiogenesis and metastasis [9]. Dietary antioxidants supplements are frequently in cancer treatment. About 20–80% of the cancer patients use antioxidant supplements after cancer diagnosis [10]. The efficacy of using antioxidants in adjuvant chemotherapy has been assessed in many clinical trials. The clinical studies of antioxidant administration, especially vitamin, glutathione, melatonin, Coenzyme Q10, during chemotherapy have been revealed the reduction of chemotherapy induced toxicity and improvement of patient health [11].

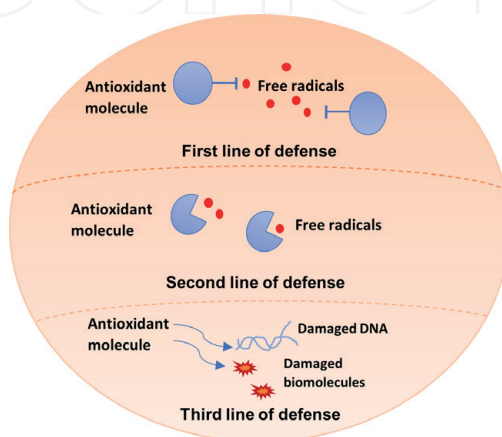


Figure 1.
Three lines of defense system of antioxidant in cell.

3. Algal terpenoids as prospective candidate in cancer therapy

Seaweed are more studied, in terms of their terpenoid profile, compared to marine microalgae. Though the anticancer activity of tetraterpenoids from marine microalgae has been reported broadly, brown macroalgae are good source of carotenoids. Anticancer activity of carotenoids (zeaxanthin, lutein, β -carotene, violaxanthin) was reported in Malaysian green and brown macroalgae [12].

3.1 Monoterpenoids

Monoterpenoids, found in different plant parts, like in bark, root, seeds or leaves, have antioxidant and anticancer activity. For instance, carvacrol, thymol, linalool as well as eugenol are good antioxidant and at the same time, exert antitumor activity against liver, prostate and breast cancer cells [13, 14]. Limonene and perillyl alcohol were subjected to phase I clinical trials in cancer patients [15].

Plocamium cartilagineum, a red alga, produces halogenated monoterpenes like furoplocamioid C, prefuroplocamioid, pirene and cyclohexane which have selective cytotoxicity against human melanoma, human and murine colon cancer cells as well as HeLa cells [16]. Similarly, *Plocamium sp.* from Namibia possesses halogenated monoterpene that have better antioxidant property than that of standard antioxidant [17]. *Sargassum ringgoldianum*, Korean brown seaweed, showed antioxidative activity through monoterpene lactone, that also gave protection against H_2O_2 -induced damage in Vero cells [18].

3.2 Diterpenoids

A new diterpenoid has been isolated from green alga *Gracilaria Salicornia*, which displays antioxidant activity equivalent to α -tocopherol [19]. Brown alga *Bifurcaria bifurcate* has been reported to produce diterpenes, namely eleganolone and eleganol which have better antioxidant activity in comparison to standard antioxidant, as well as exert neuroprotective effect on neuroblastoma [20]. Likewise, diterpenes from brown seaweed *Dictyota dichotoma* has good antioxidant capacity and shows cytotoxicity to liver and breast cancer cell lines [21]. Rodrigues et al., isolated a new diterpene sphaerodactylomelol from *Sphaerococcus coronopifolius* which blocked proliferation of human liver cancer cells at an IC_{50} of 280 μM , while killed the cancer cells at IC_{50} of 720 μM [22].

However, diterpenoids can induce apoptosis in cancer cells through downregulating Bcl2 and regulatory pathways like, JAK2/STAT3, PI3K/Akt and NF- κ B. They can arrest cell cycle at G1 and G2-M checkpoint. Besides, diterpenoids can also inhibit metastasis and angiogenesis by hindering PI3K/Akt/mTOR and VEGFR-2 signaling pathways [23].

3.3 Triterpenoids

Triterpenoid (benzene dicarboxylic acid, diisooctyl ester) from the dichloromethane extract of *Sargassum wightii* displayed excellent radical scavenging and reducing activity [24]. Similarly, triterpenoids from the methanolic extracts of *Sargassum sp.* and *Eucheuma cottonii* could be responsible for their strong antioxidant activity [25]. Methanolic extract of *Gracilaria salicornia*, isolated from Persian Gulf, has inhibited human colon cancer cells at an IC_{50} of 58.6 $\mu g/mL$ and also has good antioxidant property. Phytochemical analysis has been revealed that

triterpenes are present in ample amount in that extract which could be attributed for these activities [26]. On the other hand, Indonesian seaweed *Eucheuma cottonii* contains triterpenoid which exhibited cytotoxicity against lung cancer cells at an IC₅₀ of 251.73 µg/mL [27]. *Padina boergesenii* has been reported to produce triterpenes that have antiangiogenic activity against renal carcinoma [28]. Ethanolic extract of edible seaweed *Kjellmaniella crassifolia* has been reported to contain three terpenoids, namely dihydrocimicifugenol, 3-epicyclomusalenol and cyclosadol with chemo-preventive property [29]. Anti-cancerous triterpenoids can also be found in *Laurencia mariannensis*, *L. viridis* and *L. obtuse* [30].

3.4 Tetraterpenoids

Algal tetraterpenoids mainly consist of carotenoids, namely, β-carotene, lutein, fucoxanthin, astaxanthin, canthaxanthin, zeaxanthin, cryptoxanthin, violaxanthin, neoxanthin and siphonaxanthin (**Figure 2**). These carotenoids have both antioxidative and anticancer activity with other pharmaceutical importance.

3.4.1 Lutein

Lutein from *Botryococcus braunii* has been reported to exhibit both *in vitro* and *in vivo* antioxidant activity [31].

3.4.2 β-carotene

β-Carotene from *Dunaliella salina* is responsible for apoptotic cell death in human prostate carcinoma [32].

3.4.3 Fucoxanthin

Phaeodactylum tricornutum, *Odontella aurita*, *I. galbana*, *C. calcitrans*, *D. salina*, *C. gracilis*, *Navicula sp.*, *Thalassiosira sp.*, *Pavlova lutheri*, *Cylindrotheca closterium* can produce ample amount of fucoxanthin with antioxidative property [33–36]. *P. tricornutum* and *C. calcitrans* possess fucoxanthin which exhibits strong anticancer activity [33, 37]. Fucoxanthin, obtained from brown macroalgae *Padina tetrastromatica*, exhibited cytoprotective effect against oxidative damage [38].

3.4.4 Zeaxanthin

Zeaxanthin separated from *Nannochloropsis oculata*, *Scenedesmus obliquus*, *Porphyridium aerugineum* has showed antioxidative property [39, 40]. Zeaxanthin from *Porphyridium purpureum* induced apoptosis human melanoma. Moreover, ZX from this *P. purpureum* potentiates the efficacy of chemotherapeutic drug, vemurafenib towards human melanoma [41].

3.4.5 Violaxanthin

Violaxanthin with antioxidative and anti-inflammatory activities has been isolated from *Chlorella vulgaris*, *N. oceanica*, *Dunaliella salina*, *Tetraselmis spp.*, *Isochrysis galbana*, *Pavlova lutheri*, *P. salina* and *Chaetoceros spp.* *Eustigmatos cf. polyphem* [42–46]. Violaxanthin from *Dunaliella tertiolecta* and *Chlorella ellipsoidea* inhibited breast and colon carcinoma, respectively [47].

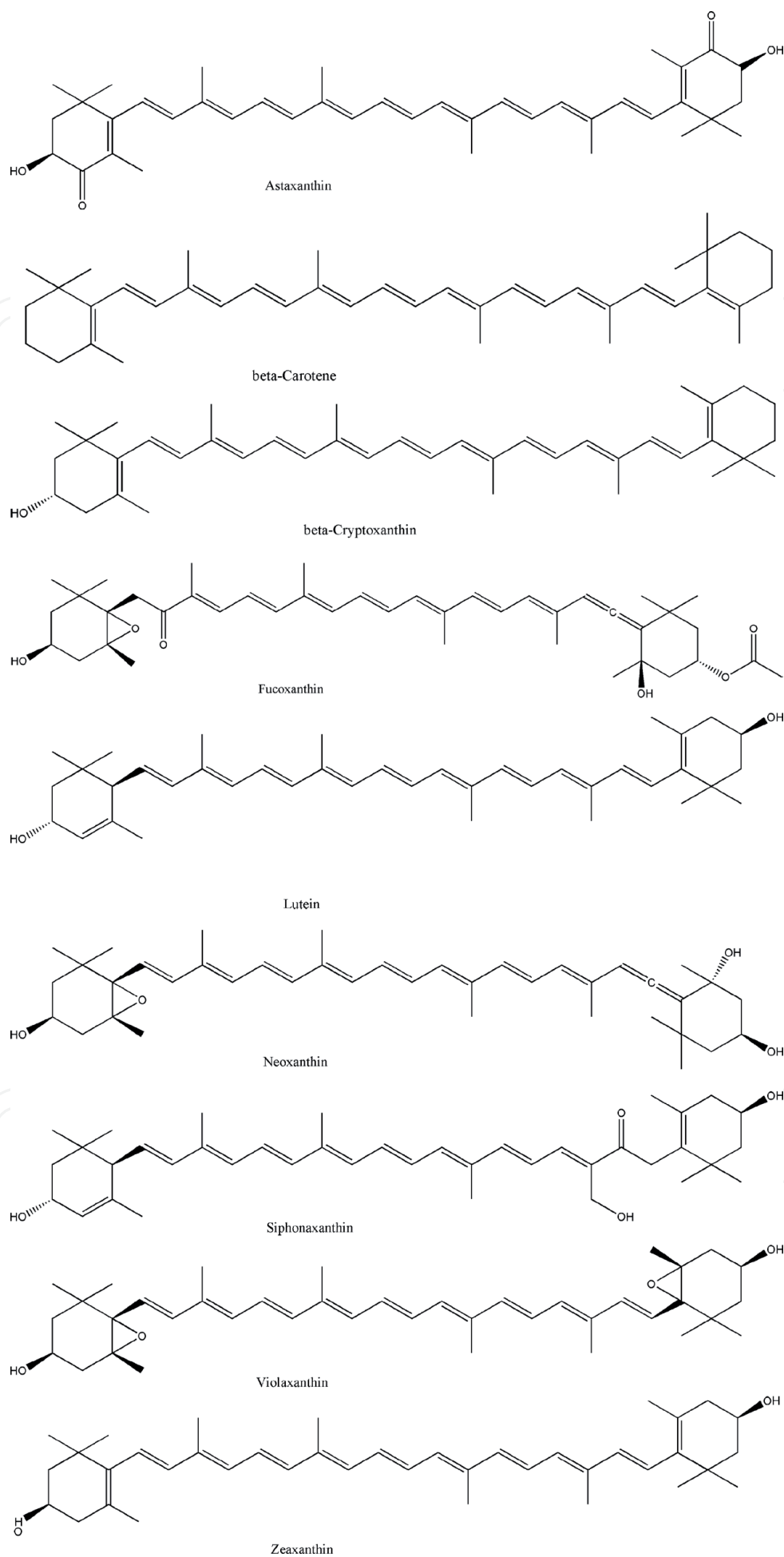


Figure 2.
Chemical structure of some algal tetraterpenoids.

3.4.6 Neoxanthin

The antioxidative property of neoxanthin was found in *Scenedesmus sp.*, *Chlorella sp.* and *Tetraselmis suecica* [48, 49].

3.4.7 Astaxanthin

Astaxanthin from *H. pluvialis* inhibits the oxidative stress inside the cells [50].

3.4.8 β -Cryptoxanthin

β -Cryptoxanthin obtained from *Cyanophora paradoxa* exerted cytotoxicity against human skin, breast and lung cancer cells [51].

3.4.9 Siphonaxanthin

Siphonaxanthin from green microalgae *Codium fragile* exhibited apoptosis in human leukemia cells through TRAIL induction with the augmentation of GADD45a and DR5 expression and reduced Bcl-2 and thus, showed more effective anticancer property compared to FX [52].

3.5 Sesquiterpenoids

Sesquiterpenoids have also high antioxidative and anticancer properties. Green seaweed *Ulva fasciata*, isolated from south Indian rocky shore, produced five sesquiterpenoids with radical scavenging activity and among them, 3,4,5,5-tetramethyl-4-(30-oxopentyl)-2-cyclohexen-1-one was revealed as one of the most potent radical scavengers [53]. Isozonarol, a sesquiterpenoid, has been identified from *Dictyopteris undulata* that can scavenge DPPH with an EC_{50} of 71 μ M which is similar to α -tocopherol [54].

Sesquiterpenoids from *Laurencia composita* Yamada, namely compositacin D and G, as well as cycloelatanene A and B inhibited the growth of lung cancer cells at IC_{50} values ranging from 48.6 to 85.2 μ M [55]. *Laurencia spp.* are good sources of anti-cancer sesquiterpenoids [56]. For instance, *Laurencia okamurai* produced laurinterol which inhibited melanoma cells by causing apoptosis via p53-dependent pathway and caspase activation [57]. Likewise, teuhetenone from *Laurencia obtuse* has been reported to display anticancer property against breast cancer cell line with an IC_{50} of 22 μ M which is more effective in inhibiting breast cancer cells compared to chemotherapeutic drug, cisplatin (59 μ M) [58]. Another major sesquiterpene, caulerpenyne was separated from *Caulerpa taxifolia*, that hindered human neuroblastoma cells (IC_{50} = 10 μ M), while blocked cell cycle at G2/M phase [59].

3.6 Meroterpenoids

Cystoseira usneoides, brown macroalgae, is a rich source of meroterpenoids. Eight meroterpenoids have been isolated from this seaweed which have anti-colon and anti-lung cancer activity. These meroterpenoids can hinder growth and migration of colon cancer cells by suppressing ERK/JNK/AKT pathways, as well as can arrest cells at G2/M phase [60]. Similarly, these meroterpenoids displayed anticancer effect against lung carcinoma, while blocks lung cancer cells at G2/M and S phases [61]. Another brown seaweed *Stypopodium flabelliforme* produced meroterpenoids, namely epitaondiol, epitaondiol monoacetate and stypotriol triacetate which exhibited anticancer property against human colon and brain carcinoma [62].

Sargassum muticum can produce tetraprenyltoluquinol meroterpenoid that has antioxidant activity and can give protection against oxidative damage [63]. Likewise, highly oxygenated meroterpenoids with antioxidant property have been found from *Kappaphycus alvarezii*, a red macroalgae [64]. *Hypnea musciformis* has meroterpenoid like 2-(tetrahydro-5-(4-hydroxyphenyl)-4-pentylfuran-3-yl)-ethyl-4-hydroxy benzoate which shows antioxidative properties comparable to gallic acid [65]. Meroterpenoids from ethanolic extract of *Sargassum serratifolium* have the capability to protect liver from the oxidative damage generated from pro-oxidant tert-butyl hydroperoxide [66].

4. Conclusion

The investigation on the anticancer properties of algal terpenoids is still in its infancy, albeit the anticancer efficacy of these phytochemicals is quite persuasive. Marine algae contain a wide array of promising terpenes and terpenoids that can strongly inhibit the proliferation of cancer cells. Extensive research on these algal terpenoids regarding their mechanism of action in the cancer cells and more clinical studies will open the door to develop novel drugs for treating cancer.

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