Chapter

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 protumorigenic 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].

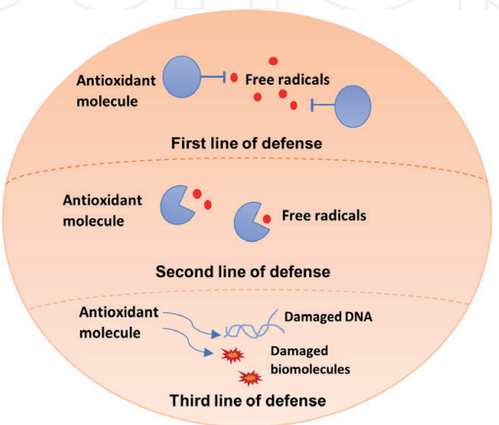

Figure 1.
Three lines of defense system of antioxidant in cell.

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 eleganonal 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-κB. 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 μg/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 IC_{50} 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**). Theses 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*, *Dunaniella 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].

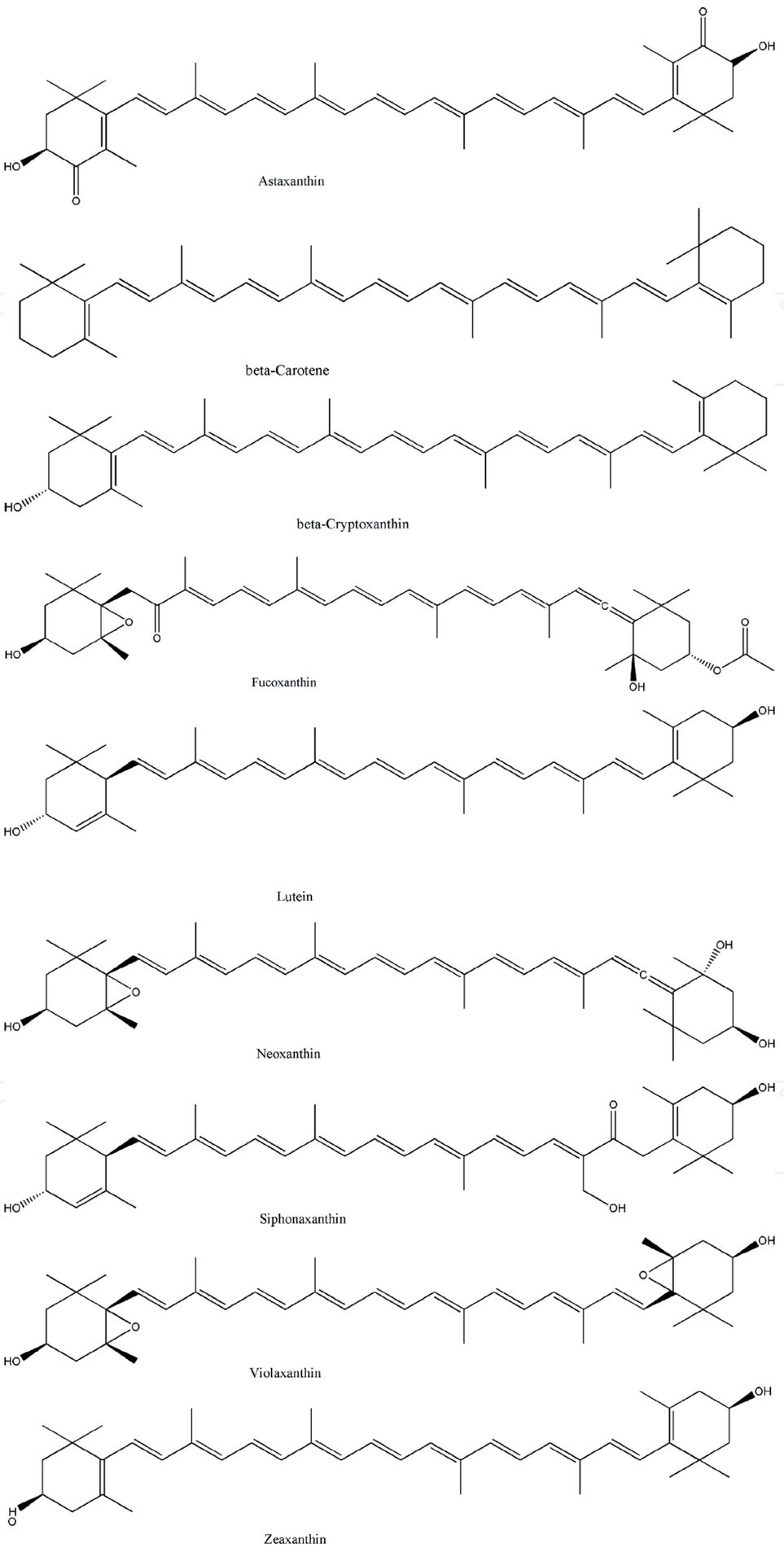

Figure 2.
Chemical structure of some algal tetraterpenoids.

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 μM 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 μM [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 μM which is more effective in inhibiting breast cancer cells compared to chemotherapeutic drug, cisplatin (59 μM) [58]. Another major sesquiterpene, caulerpenyne was separated from *Caulerpa taxifolia,* that hindered human neuroblastoma cells (IC_{50} = 10 μM), 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.

Author details

Umme Tamanna Ferdous[2] and Zetty Norhana Balia Yusof[1,2,3]*

1 Department of Biochemistry, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

2 Aquatic Animal Health and Therapeutics Laboratory (AquaHealth), Institute of Bioscience, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

3 Bioprocessing and Biomanufacturing Research Center, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

*Address all correspondence to: zettynorhana@upm.edu.my

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018;*68*(6):394-424. DOI: 10.3322/caac.21492

[2] Ovadje P, Roma A, Steckle M, Nicoletti L, Arnason JT, Pandey S. Advances in the research and development of natural health products as main stream cancer therapeutics. *Evidence-Based Complementary and Alternative Medicine*. 2015;*2015*. DOI: 10.1155/2015/751348

[3] Calvani M, Pasha A, Favre C. Nutraceutical boom in cancer: Inside the labyrinth of reactive oxygen species. *International Journal of Molecular Sciences*. 2020;*21*(6). DOI: 10.3390/ijms21061936

[4] Huang M, Lu JJ, Huang MQ, Bao JL, Chen XP, Wang YT. Terpenoids: Natural products for cancer therapy. *Expert Opinion on Investigational Drugs*. 2012;*21*(12):1801-1818. DOI: 10.1517/13543784.2012.727395

[5] Sathasivam R, Ki JS. A review of the biological activities of microalgal carotenoids and their potential use in healthcare and cosmetic industries. *Marine Drugs*. 2018;*16*(1). DOI: 10.3390/md16010026

[6] Borek C. Dietary Antioxidants and Human Cancer. *Journal of Restorative Medicine*. 2017;*6*(1):53-61 https://doi.org/10.14200/jrm.2017.6.0105

[7] Sies, H. (2019). Oxidative Stress: Eustress and Distress in Redox Homeostasis. In *Stress: Physiology, Biochemistry, and Pathology*. doi:10.1016/B978-0-12-813146-6.00013-8

[8] Mut-Salud N, Álvarez PJ, Garrido JM, Carrasco E, Aránega A, Rodríguez-Serrano F. Antioxidant Intake and Antitumor Therapy: Toward Nutritional Recommendations for Optimal Results. *Oxidative Medicine and Cellular Longevity*. 2016;*2016*. DOI: 10.1155/2016/6719534

[9] Ilghami R, Barzegari A, MashayekhiMR, LetourneurD, CrepinM, Pavon-Djavid G. The conundrum of dietary antioxidants in cancer chemotherapy. *Nutrition Reviews*. 2020;*78*(1):65-76. DOI: 10.1093/nutrit/nuz027

[10] Marian MJ. Dietary Supplements Commonly Used by Cancer Survivors: Are There Any Benefits? *Nutrition in Clinical Practice*. 2017;**32**:607-627. DOI: 10.1177/0884533617721687

[11] Singh K, Bhori M, Kasu YA, Bhat G, Marar T. Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity – Exploring the armoury of obscurity. *Saudi Pharmaceutical Journal*. 2018;*26*(2):177-190. DOI: 10.1016/j.jsps.2017.12.013

[12] Othman, R., Amin, N. A., Sani, M. S. A., Fadzillah, N. A., & Jamaludin, M. A. (2018). Carotenoid and chlorophyll profiles in five species of Malaysian seaweed as potential Halal Active Pharmaceutical Ingredient (API). *International Journal on Advanced Science, Engineering and Information Technology*, *8*(4-2), 1610-1616. https://doi.org/10.18517/ijaseit.8.4-2.7041

[13] Rajput JD, Bagul SD, Pete UD, Zade CM, Padhye SB, Bendre RS. Perspectives on medicinal properties of natural phenolic monoterpenoids and their hybrids. *Molecular Diversity*. 2018;*22*(1):225-245. DOI: 10.1007/s11030-017-9787-y

[14] Sun XB, Wang SM, Li T, Yang YQ. Anticancer activity of linalool

terpenoid: Apoptosis induction and cell cycle arrest in prostate cancer cells. *Tropical Journal of Pharmaceutical Research*. 2015;*14*(4):619-625. DOI: 10.4314/tjpr.v14i4.9

[15] Gould MN. Cancer chemoprevention and therapy by monoterpenes. *Environmental Health Perspectives*. 1997;*105*:977-979. DOI: 10.2307/3433313

[16] De Inés C, Argandoña VH, Rovirosa J, San-Martín A, Díaz-Marrero AR, Cueto M, et al. Cytotoxic activity of halogenated monoterpenes from Plocamium cartilagineum. *Zeitschrift Fur Naturforschung - Section C Journal of Biosciences*. 2004;*59*(5-6):339-344. DOI: 10.1515/znc-2004-5-609

[17] Shapumba CW, Knott M, Kapewangolo P. Antioxidant activity of a halogenated monoterpene isolated from a Namibian marine algal Plocamium species. *Journal of Food Science and Technology*. 2017;*54*(10):3370-3373. DOI: 10.1007/s13197-017-2784-4

[18] Yang X, Kang M-C, Lee K-W, Kang S-M, Lee W-W, Jeon Y-J. Antioxidant activity and cell protective effect of loliolide isolated from Sargassum ringgoldianum subsp. coreanum. *Algae*. 2011;*26*(2):201-208. DOI: 10.4490/algae.2011.26.2.201

[19] Antony T, Chakraborty K. First report of antioxidant abeo-labdane type diterpenoid from intertidal red seaweed Gracilaria salicornia with 5-lipoxygenase inhibitory potential. *Natural Product Research*. 2020;*34*(10):1409-1416. DOI: 10.1080/14786419.2018.1508150

[20] Silva J, Alves C, Freitas R, Martins A, Pinteus S, Ribeiro J, et al. Antioxidant and neuroprotective potential of the brown seaweed bifurcaria bifurcata in an in vitro Parkinson's disease model. *Marine Drugs*. 2019;*17*(2):1-16. DOI: 10.3390/md17020085

[21] Ayyad SEN, Makki MS, Al-Kayal NS, Basaif SA, El-Foty KO, Asiri AM, et al. Cytotoxic and protective DNA damage of three new diterpenoids from the brown alga Dictoyota dichotoma. *European Journal of Medicinal Chemistry*. 2011;*46*(1):175-182. DOI: 10.1016/j.ejmech.2010.10.033

[22] Rodrigues D, Alves C, Horta A, Pinteus S, Silva J, Culioli G, et al. Antitumor and antimicrobial potential of bromoditerpenes isolated from the Red Alga, Sphaerococcus coronopifolius. *Marine Drugs*. 2015;*13*(2):713-726. DOI: 10.3390/md13020713

[23] Jian B, Zhang H, Han C, Liu J. Anti-cancer activities of diterpenoids derived from euphorbia fischeriana steud. *Molecules*. 2018;*23*(2):1-11. DOI: 10.3390/molecules23020387

[24] Syad AN, Shunmugiah KP, Kasi PD. Antioxidant and anti-cholinesterase activity of Sargassum wightii. *Pharmaceutical Biology*. 2013;*51*(11):1401-1410. DOI: 10.3109/13880209.2013.793721

[25] Nurjanah, Nurilmala M, Anwar E, Luthfiyana N, Hidayat T. Identification of bioactive compounds of seaweed sargassum sp. and eucheuma cottonii doty as a raw sunscreen cream. *Proceedings of the Pakistan Academy of Sciences: Part B*. 2017;*54*(4):311-318

[26] Ghannadi A, Shabani L, Yegdaneh A. Cytotoxic, antioxidant and phytochemical analysis of Gracilaria species from Persian Gulf. *Advanced Biomedical Research*. 2016;*5*(1):139. DOI: 10.4103/2277-9175.187373

[27] Arsianti A, Kurniawan G, Tejaputri NA, Qorina F, Fithrotunnisa Q, Azizah NN, et al. Phytochemical Profile, Antioxidant

Activity and Cell Line Study of Marine Red Macroalgae Eucheuma cottonii on Lung A-549 Cancer Cells. *Pharmacognosy Journal*. 2020;*12*(2):276-281. DOI: 10.5530/pj.2020.12.43

[28] Rajamani K, Balasubramanian T, Thirugnanasambandan SS. Bioassay-guided isolation of triterpene from brown alga Padina boergesenii possess anti-inflammatory and anti-angiogenic potential with kinetic inhibition of β-carotene linoleate system. *LWT - Food Science and Technology*. 2018. DOI: 10.1016/j.lwt.2018.04.010

[29] Wu ZH, Liu T, Gu CX, Shao CL, Zhou J, Wang CY. Steroids and triterpenoids from the brown alga Kjellmaniella crassifolia. *Chemistry of Natural Compounds*. 2012;*48*(1):158-160. DOI: 10.1007/s10600-012-0190-8

[30] Li YX, Himaya SWA, Kim SK. Triterpenoids of marine origin as anti-cancer agents. *Molecules*. 2013;*18*(7):7886-7909. DOI: 10.3390/molecules18077886

[31] Rao AR, Sarada R, Baskaran V, Ravishankar GA. Antioxidant activity of Botryococcus braunii extract elucidated in vitro models. *Journal of Agricultural and Food Chemistry*. 2006;*54*(13):4593-4599. DOI: 10.1021/jf060799j

[32] Jayappriyan KR, Rajkumar R, Venkatakrishnan V, Nagaraj S, Rengasamy R. In vitro anticancer activity of natural β-carotene from Dunaliella salina EU5891199 in PC-3 cells. *Biomedicine and Preventive Nutrition*. 2013;*3*(2):99-105. DOI: 10.1016/j.bionut.2012.08.003

[33] Neumann U, Derwenskus F, Flister VF, Schmid-Staiger U, Hirth T, Bischoff SC. Fucoxanthin, a carotenoid derived from Phaeodactylum tricornutum exerts antiproliferative and antioxidant activities in vitro. *Antioxidants*. 2019;*8*(6):1-11. DOI: 10.3390/antiox8060183

[34] Peraman M, Nachimuthu S. Bioautography-based Identification of Antioxidant Metabolites of Solanum nigrum L. and Exploration Its Hepatoprotective Potential agChester, K. et al. (2017) 'Bioautography-based Identification of Antioxidant Metabolites of Solanum nigrum L. and Explorati. *Pharmacognosy Magazine*. 2019;*15*:S243-S249. DOI: 10.4103/pm.pm

[35] Rijstenbil JW. Effects of UVB radiation and salt stress on growth, pigments and antioxidative defence of the marine diatom Cylindrotheca closterium. *Marine Ecology Progress Series*. 2003;*254*(June 2003):37-48. DOI: 10.3354/meps254037

[36] Xia S, Wang K, Wan L, Li A, Hu Q, Zhang C. Production, characterization, and antioxidant activity of fucoxanthin from the marine diatom odontella aurita. *Marine Drugs*. 2013;*11*(7):2667-2681. DOI: 10.3390/md11072667

[37] Foo SC, Yusoff FM, Imam MU, Foo JB, Ismail N, Azmi NH, et al. Increased fucoxanthin in Chaetoceros calcitrans extract exacerbates apoptosis in liver cancer cells via multiple targeted cellular pathways. *Biotechnology Reports*. 2018;*20*(e00296). DOI: 10.1016/j.btre.2018.e00296

[38] Raguraman VLSA, MubarakAli D, Narendrakumar G, ThirugnanasambandamR,KirubagaranR, Thajuddin N. Unraveling rapid extraction of fucoxanthin from Padina tetrastromatica: Purification, characterization and biomedical application. *Process Biochemistry*. 2018;*73*:211-219. DOI: 10.1016/j.procbio.2018.08.006

[39] Banskota AH, Sperker S, Stefanova R, McGinn PJ, O'Leary SJB. Antioxidant properties and lipid composition of selected microalgae. *Journal of Applied Phycology*. 2019;*31*(1):309-318. DOI: 10.1007/s10811-018-1523-1

[40] Cho YC, Cheng JH, Hsu SL, Hong SE, Lee TM, Chang CMJ. Supercritical carbon dioxide anti-solvent precipitation of anti-oxidative zeaxanthin highly recovered by elution chromatography from Nannochloropsis oculata. *Separation and Purification Technology*. 2011;*78*(3):274-280. DOI: 10.1016/j.seppur.2011.02.017

[41] Juin, C., Oliveira Junior, R. G. de, Fleury, A., Oudinet, C., Pytowski, L., Bérard, J. B., ... Picot, L. (2018). Zeaxanthin from Porphyridium purpureum induces apoptosis in human melanoma cells expressing the oncogenic BRAF V600E mutation and sensitizes them to the BRAF inhibitor vemurafenib. *Brazilian Journal of Pharmacognosy*, *28*(4), 457-467. doi:10.1016/j.bjp.2018.05.009

[42] Ahmed F, Fanning K, Netzel M, Turner W, Li Y, Schenk PM. Profiling of carotenoids and antioxidant capacity of microalgae from subtropical coastal and brackish waters. *Food Chemistry*. 2014;*165*:300-306. DOI: 10.1016/j.foodchem.2014.05.107

[43] Kim HM, Jung JH, Kim JY, Heo J, Cho DH, Kim HS, et al. The Protective Effect of Violaxanthin from Nannochloropsis oceanica against Ultraviolet B-Induced Damage in Normal Human Dermal Fibroblasts. *Photochemistry and Photobiology*. 2019;*95*(2):595-604. DOI: 10.1111/php.13030

[44] Kim J, Kim M, Lee S, Jin ES. Development of a Chlorella vulgaris mutant by chemical mutagenesis as a producer for natural violaxanthin. *Algal Research*. 2020;*46*(September 2019):101790. DOI: 10.1016/j.algal.2020.101790

[45] Soontornchaiboon W, Joo SS, Kim SM. Anti-inflammatory effects of violaxanthin isolated from microalga Chlorella ellipsoidea in RAW 264.7 macrophages. *Biological and Pharmaceutical Bulletin*. 2012;*35*(7):1137-1144. DOI: 10.1248/bpb.b12-00187

[46] Wang F, Huang L, Gao B, Zhang C. Optimum production conditions, purification, identification, and antioxidant activity of violaxanthin from microalga eustigmatos cf. Polyphem (eustigmatophyceae). *Marine Drugs*. 2018;*16*(6). DOI: 10.3390/md16060190

[47] Pasquet V, Morisset P, Ihammouine S, Chepied A, Aumailley L, Berard JB, et al. Antiproliferative activity of violaxanthin isolated from bioguided fractionation of Dunaliella tertiolecta extracts. *Marine Drugs*. 2011;*9*(5):819-831. DOI: 10.3390/md9050819

[48] Patias LD, Fernandes AS, Petry FC, Mercadante AZ, Jacob-Lopes E, Zepka LQ. Carotenoid profile of three microalgae/cyanobacteria species with peroxyl radical scavenger capacity. *Food Research International*. 2017;*100*:260-266. DOI: 10.1016/j.foodres.2017.06.069

[49] Sansone C, Galasso C, Orefice I, Nuzzo G, Luongo E, Cutignano A, et al. The green microalga Tetraselmis suecica reduces oxidative stress and induces repairing mechanisms in human cells. *Scientific Reports*. 2017;*7*(December 2015):1-12. DOI: 10.1038/srep41215

[50] Régnier P, Bastias J, Rodriguez-Ruiz V, Caballero-Casero N, Caballo C, Sicilia D, et al. Astaxanthin from Haematococcus pluvialis prevents oxidative stress on human endothelial cells without toxicity. *Marine Drugs*. 2015;*13*(5):2857-2874. DOI: 10.3390/md13052857

[51] Baudelet PH, Gagez AL, Bérard JB, Juin C, Bridiau N, Kaas R, et al. Antiproliferative activity of Cyanophora paradoxa pigments in melanoma, breast and lung cancer cells.

Marine Drugs. 2013;*11*(11):4390-4406. DOI: 10.3390/md11114390

[52] Ganesan P, Noda K, Manabe Y, Ohkubo T, Tanaka Y, Maoka T, et al. Siphonaxanthin, a marine carotenoid from green algae, effectively induces apoptosis in human leukemia (HL-60) cells. *Biochimica et Biophysica Acta - General Subjects*. 2011;*1810*(5):497-503. DOI: 10.1016/j.bbagen.2011.02.008

[53] Chakraborty K, Paulraj R. Sesquiterpenoids with free-radical-scavenging properties from marine macroalga Ulva fasciata Delile. *Food Chemistry*. 2010;*122*(1):31-41. DOI: 10.1016/j.foodchem.2010.02.012

[54] Kumagai M, Nishikawa K, Matsuura H, Umezawa T, Matsuda F, Okino T. Antioxidants from the brown alga dictyopteris undulata. *Molecules*. 2018;*23*(5):1-8. DOI: 10.3390/molecules23051214

[55] Yu XQ, Jiang CS, Zhang Y, Sun P, Kurtán T, Mándi A, et al. Compositacins A–K: Bioactive chamigrane-type halosesquiterpenoids from the red alga Laurencia composita Yamada. *Phytochemistry*. 2017;*136*:81-93. DOI: 10.1016/j.phytochem.2017.01.007

[56] Rocha DHA, Seca AML, Pinto DCGA. Seaweed secondary metabolites in vitro and in vivo anticancer activity. *Marine Drugs*. 2018;*16*(11):1-27. DOI: 10.3390/md16110410

[57] Kim MM, Mendis E, Kim SK. Laurencia okamurai extract containing laurinterol induces apoptosis in melanoma cells. *Journal of Medicinal Food*. 2008;*11*(2):260-266. DOI: 10.1089/jmf.2007.575

[58] Alarif WM, Al-Footy KO, Zubair MS, Halid Ph M, Ghandourah MA, Basaif SA, et al. The role of new eudesmane-type sesquiterpenoid and known eudesmane derivatives from the red alga Laurencia obtusa as potential antifungal-antitumour agents. *Natural Product Research*. 2016;*30*(10):1150-1155. DOI: 10.1080/14786419.2015.1046378

[59] Barbier P, Guise S, Huitorel P, Amade P, Pesando D, Briand C, et al. Caulerpenyne from Caulerpa taxifolia has an antiproliferative activity on tumor cell line SK-N-SH and modifies the microtubule network. *Life Sciences*. 2001;*70*(4):415-429. DOI: 10.1016/S0024-3205(01)01396-0

[60] Zbakh H, Zubía E, de Los Reyes C, Calderón-Montaño JM, Motilva V. Anticancer Activities of Meroterpenoids Isolated from the Brown Alga Cystoseira usneoides against the Human Colon Cancer Cells HT-29. *Foods*. 2020b;*9*:300. DOI: 10.3390/foods9030300

[61] Zbakh H, Zubía E, de los Reyes C, Calderón-Montaño JM, López-Lázaro M, Motilva V. Meroterpenoids from the brown alga cystoseira usneoides as potential anti-inflammatory and lung anticancer agents. *Marine Drugs*. 2020a;*18*(4). DOI: 10.3390/md18040207

[62] Pereira DM, Cheel J, Areche C, San-Martin A, Rovirosa J, Silva LR, et al. Anti-proliferative activity of meroditerpenoids isolated from the brown alga Stypopodium flabelliforme against several cancer cell lines. *Marine Drugs*. 2011;*9*(5):852-862. DOI: 10.3390/md9050852

[63] Balboa EM, Li YX, Ahn BN, Eom SH, Domínguez H, Jiménez C, et al. Photodamage attenuation effect by a tetraprenyltoluquinol chromane meroterpenoid isolated from Sargassum muticum. *Journal of Photochemistry and Photobiology B: Biology*. 2015;*148*:51-58. DOI: 10.1016/j.jphotobiol.2015.03.026

[64] Makkar F, Chakraborty K. Antioxidant and anti-inflammatory oxygenated meroterpenoids from the

thalli of red seaweed Kappaphycus alvarezii. *Medicinal Chemistry Research*. 2018;*27*(8):2016-2026. DOI: 10.1007/s00044-018-2210-0

[65] Chakraborty K, Joseph D, Joy M, Raola VK. Characterization of substituted aryl meroterpenoids from red seaweed Hypnea musciformis as potential antioxidants. *Food Chemistry*. 2016;*212*:778-788. DOI: 10.1016/j.foodchem.2016.06.039

[66] Lim S, Kwon M, Joung EJ, Shin T, Oh CW, Choi JS, et al. Meroterpenoid-Rich fraction of the ethanolic extract from sargassum serratifolium suppressed oxidative stress induced by tert-butyl hydroperoxide in HepG2 cells. *Marine Drugs*. 2018;*16*(10). DOI: 10.3390/md16100374