Beneficial potency of algae-based polyunsaturated fatty acids (PUFAs) for cancer therapy

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Abstract. Algae species is a promising sustainable source of polyunsaturated fatty acids (PUFAs) in the marine ecosystem. The composition of the essential fatty acids is varied between the algae species. Most of the algal species are rich in EPA except for Chlorophyta and Heterokontophyta that are rich in DHA. The dietary intake of PUFAs, such as EPA and DHA, could prevent the inflammation by limiting the biosynthesis of pro-inflammatory mediator associated with cancer development. This review highlights the importance and function of algae-based PUFAs as the inflammatory inhibitor furthermore as a potential pharmaceutical for cancer therapy.

Keyword: Algae, PUFAs, Inflammation, Cancer

1. Introduction
Algae is a diverse group of aquatic photosynthetic organisms, range from unicellular to multicellular. The phylum of algae is Bacillariophyta (Diatom), Dinophyta (Dinoflagellate), Chlorophyta (green algae), Euglenophyta, Chrysophyta (golden algae), Phaeophyta (brown algae), Xanthophyta, Eustigmatophyta, Raphidophyta, Haptophyta, and Rhodophyta (red algae). Cyanophyta (cyanobacteria) is also considered as algae, but they have a typical structure of prokaryote organism [1-2]. Algae, as the basis of the aquatic trophic chain, known as a source for nutritional ingredients and have been widely consumed as human food and supplements. The average composition of proteins, fats, and carbohydrates in microalgae could be varied among species that influenced by the nutrition, environment, and growth phase [3-4]. Algae species are abundant in PUFAs and are of a promising alternative source of essential fatty acids regarding the decreasing of fish stock due to overfishing. Algae could be a more sustainable resource of PUFAs rather than fish and fish oil.

PUFAs have a potential for pharmaceutical purposes to reduce the number of free radical in cells. Several studies reported that dietary intake of n-3 and n-6 PUFAs could prevent the inflammatory process suggesting the pharmaceutical application to treat the inflammation furthermore for cancer prevention and treatment. Omega-3 is proposed to avoid and treat tumor cell by various mechanisms such as induction of cell mortality through apoptosis, enhancement of cell sensitivity to cancer cell therapies, and efficient selective cytotoxicity to tumor cell [5-6].

Cancer is the primary disease that ranks the second most common cause of death in the world [7]. Cancer-associated with an inflammatory process that plays a decisive role at the different stage of tumorigenesis, especially for initiation and promotion [8-10]. Polyunsaturated fatty acid (PUFA) influences the inflammation through a variety of mechanism, mostly related to the alteration of fatty
Acid composition in the cell membrane [11-12]. Omega-3 (n-3 PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) works as anti-inflammation by resolving the inflammatory effect [11-13]. In this paper, we discuss the benefits and the detail of the mechanisms of algal-based PUFAs, for treating the inflammation associated with cancer therapy.

2. Algae-based Polyunsaturated Fatty Acids (PUFAs)
Polyunsaturated fatty acids (PUFAs) are the essential elements of the cell membranes phospholipids. PUFAs play essential roles to maintain the membrane fluidity and lipid raft formation for assuring the function of membrane protein. The modification of the composition of fatty acids in the cell membrane could induce the inflammation process [11-12].

Omega-3 (ω-3 or n-3 PUFA) and Omega-6 (ω-6 or n-6 PUFA) are the structural descriptors for polyunsaturated fatty acid family. There are three types of n-3 PUFAs such as α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA, the precursor of EPA and DHA, is the simplest omega-3 that only found in plant and categorized as an essential fatty acid. Linoleic acid (LA), the shortest n-6 PUFA, is the precursor for inflammatory mediators such as prostaglandin and leukotrienes. The ratio of n-6/n-3 PUFAs has affected the health effects, that are recommended to be lower than ten based on the World Health Organization. Therefore, the health benefit of n-3 PUFAs is suggested because of its properties as a competitive substrate for n-6 PUFAs metabolism so it can inhibit the inflammation. Most of PUFAs from algae has a ratio of n-3/n-6 PUFAs between 0.29 and 6.79 that can be regarded as a wholesome source of dietary PUFAs [5-6, 14-15].

In recent years, studies of algae-based PUFAs were increased because of the need for an alternative and a sustainable source of PUFAs. Most of the studies were focused on the exploration of the pharmaceutical potency and health benefit of PUFAs from the diverse species of algae (Table 1). The composition of fatty acid between algae species is different. For example, Chlorophyta and Cryptophyta have a high proportion of PUFAs, that about 50%-60% of total fatty acids, comparing to Ochrophyta, Cyanobacteria, and Diatom, that about 20%-30% [16]. Macroalgae species of Phaeophyta and Rhodophyta produced a higher concentration of C20 PUFAs comparing to macroalgae species of Chlorophyta. Rhodophytes are commonly reported rich in EPA. Phaeophytes are produced high C18 and C20 fatty acids such as LA (C18:2n-6), arachidonic acid (AA; C20:4n-6), and EPA. DHA is commonly exhibited in high concentration in Chlorophytes, but not in Rhodophytes and Phaeophytes [17]. Moreover, the studies of microalgae species of Rhodophytes, Phaeophytes, and Chlorophytes showed a similar result of macroalgae species, in which the Chlorophytes produced higher DHA while Rhodophytes and Phaeophytes produced higher EPA [16-17].

Linoleic acid (LA; C18:2n-6) was the predominant PUFAs of macroalgae species of Chlorophytes, except Ulva sp., irrespective to three different orders: Bryopsidales, Cladophorales, and Ulvales. ALA is the most detected PUFAs in Ulva sp. that considered as the characteristic of Ulvales (Table 1) [17]. Other study reported that Ulva lactuca and Enteromorpha compressa (order: Ulvales) from the coast of California were rich in Octadecatetraenoic acid and α-linolenic acid as the predominant n-6 PUFAs. While, Chaetomorpha linum (order: Siphonocladales) had a different composition of FAs compared to Ulvales, although this species is also from the coast of California. C. linum was rich in LA but poor in octadecatetraenoic acid and α-linolenic acid [18]. The composition of PUFAs of macroalgae of Chlorophytes was different between species. DHA was the most abundant PUFAs in Chlorella vulgaris that made up 21% of total fatty acids. Chlamydomonas reinhardtii and Haematococcus pluvialis are rich in octadecatetraenoic acid [19].

Most of macroalgae species of Phaeophyta (Brown Algae) contain a higher concentration of PUFAs, that made up 30-57% of total fatty acid, compared to Chlorophytes and Rhodophytes. Study on six species of macroalgae of Phaeophytes showed that C18 and C20 fatty acids are the most detected fatty acid in these species with LA (C18:2n-6), AA (C20:4n-6), and EPA was abundantly available. DHA was also detected but in a deficient concentration that was 0.8%-1.5% of total FA [17]. Heterosigma akashiwo (class: Raphidophyceae) and Nannochloropsis oculata (class: Eustigmatophyceae) contained 38-48% of PUFAs from the total fatty acids that were rich in C16 fatty acids.
acid and EPA but poor in DHA. Both of microalgae species of Ochrophyta showed a noticeable amount of AA [16,20-21].

Table 1. Overview of algal species producing poly-unsaturated fatty acids (PUFAs)

| Phylum          | Species                           | Major fatty acids | References |
|-----------------|-----------------------------------|-------------------|------------|
| Chlorophyta     | Chlamydomonas variabilis          | EPA, GLA          | 19         |
|                 | Haematococcus pluvialis           |                   |            |
|                 | Chlorella vulgaris                 | DHA, GLA          | 17         |
|                 | Codium fernandezianum             |                   | 17         |
|                 | Codium dimorphum                  | LA, GLA, EPA      |            |
|                 | Codium fragile                    |                   |            |
|                 | Ulva lactuca                      | ALA, EPA          | 17-18      |
|                 | Enteromorpha compressa            | ALA, EPA          | 18         |
|                 | Chaetomorpha linum                | LA, GLA, EPA      | 18         |
|                 | Cladophora albida                 | LA, GLA, DHA      | 17         |
| Phaeophyta      | Cystoseira barbata                | LA, AA, EPA       | 17-18      |
|                 | Cystoseira osmundaceae            |                   |            |
|                 | Analipus japonicus                |                   |            |
|                 | Laminaria dentigeria             |                   |            |
|                 | Hedophyllum integrifolium         |                   |            |
|                 | Postelia palmeformis             |                   |            |
|                 | Alaria marginata                 |                   |            |
|                 | Egregia menziessi                |                   |            |
|                 | Fucus ditichus                   |                   |            |
| Rhodophyta      | Porphyridium cruentum             | AA, EPA           | 17         |
|                 | Jania sp.                         |                   |            |
|                 | Pterocladiella capillacea        |                   |            |
|                 | Aspatagopsis armata              |                   |            |
|                 | Peyssonnelia sp.                 |                   |            |
|                 | Bornetia secundiflora            |                   |            |
| Dinoflagellata  | Amphidium carterae                | DHA               | 26         |
|                 | Cystodium sp.                    |                   |            |
|                 | Peridinium aciculiferum           |                   |            |
|                 | Gymnodium fuscum                 |                   |            |
| Ochrophyta      | Heterosigma akashiwo             | EPA               | 16         |
|                 | Phaeodactylum tricornutum         |                   | 22         |
| Haptophyta      | Isochrysis galbana                | EPA               | 22         |
|                 | Emiliana huxleyi                 |                   | 16         |
| Eustigmatophyta | Nannochloropsis sp.              | EPA               | 29         |
| Heterokontophyta| Schyzochtrium sp.                | DHA               | 30-31      |
| Cyanophyta      | Microcystis aeruginosa            | ALA, GLA          | 28         |
|                 | Spirulina platensis              | GLA               | 19, 27     |

Pereira [17] reported that five macroalgae species of Rhodophyta contained the abundant proportion of AA (18:2n-6) and EPA (20:5n-3) as the predominant PUFAs. Rhodophytes exhibited higher concentrations of C20 PUFAs and EPA but lacked to DHA. The study of *Porphyridium cruentum* showed that this algae species produced high amount of C16, C18, and C20 fatty acid with EPA was the most abundant PUFAs in this species. The proportion of AA and EPA in *Porphyridium*
cruentum was changed due to nitrogen concentration, light intensity, and temperature that important for scaling up the production of PUFAs [22-24].

Diatom, Dinoflagellates, and Haptophytes produced PUFAs that composed 20-40% of total fatty acids. Diatom is rich in C16 fatty acid. Haptophytes contains the high concentration of C16 fatty acids besides contains C18 and longer chain PUFAs in the lower level [16,21]. Both Diatom and Haptophytes have EPA as the predominant PUFAs. Phaeodactylum tricornutum (Diatom) contained EPA in the percentage of 29% of total fatty acids, while Isochrysis galbana contained EPA in the proportion of 23% of total fatty acids [22]. Emiliania huxleyi had a different of the composition of fatty acid compared to other Haptophytes, that contained a higher percentage of n-6 PUFA and contained DHA in a notable amount. In Dinoflagellates, C16, C18 fatty acids, and DHA are the predominant fatty acids [16]. Rezanka [25] reported that three species of Dinoflagellates, those are Amphidinium carterae, Cystodinium sp., and Peridinium aciculiferum, were abundant in C16 and C22 fatty acids. Gymnodinium fuscum K-1836 contained n-3 PUFA in the percentage of 30% of the total fatty acid that DHA proportion is 60% of the total PUFA. Peridinium cinctum K-1721 contained DHA, as the most abundant PUFA, in the ratio of 18.7% of total fatty acids [26].

Los [27] reported that the fatty acids composition on cyanobacteria species is conserved. The investigation on 17 species of cyanobacteria showed that most of the species were abundant in C14 and C18 fatty acid. Study on freshwater cyanobacteria showed that the C18 PUFA such as ALA and GLA were detected in Microcystis aeruginosa [28]. The long-chain PUFA were almost undetected in the cyanobacteria species. Some species of cyanobacteria were produced longer-chain PUFA (C20 or C>20) at a minor concentration. Spirulina plantesis produced omega-9 and gamma-linolenic acid in a small ratio [19,27].

Nannochloropsis sp. (phylum: Eustigmatophyta) and Schyzochytrium sp. (phylum: Heterokontophyta) have been commercially developed as the substitute of fish omega-3. Both species are commercially marketed as the vegan omega-3 or algae-based omega-3 supplement with the health benefits for supporting immune and preventing inflammation. Nannochloropsis sp. is abundant with C16, C18 PUFA, and EPA. The content of EPA is variable between species, ranging from 1.1%-12%, that makes this genus as the promising source for EPA production. The manipulation of the culture condition, such as nitrogen concentration and salinity, is suggested for increasing the production of lipid of Nannochloropsis sp. [29]. Schyzochytrium sp. is contained a high proportion of DHA that reached to 30-40% of total fatty acids. The ratio of C and N in the culture media determines the lipid accumulation. In Schyzochytrium sp., the production of DHA and total lipid could be optimized by adding the various carbon source such as glucose, fructose, and glycerol [30-31].

3. Potential therapeutic activity of PUFAs for cancer

Inflammation is a part of the defense mechanism as the initial response for pathogen killing to protect the cells from the infection. Besides, inflammation works to repair and maintain the homeostasis condition of infected cells. Tumor development was suggested to have an association with environmental and dietary exposure that could induce chronic inflammation. Modulation in cellular inflammatory response could potentially induce the development of pro-tumorigenic microenvironment [8,32-33].

Recent extensive studies proposed the potential therapeutic activity of n-3 PUFAs against tumors by suppressing the biosynthesis of the pro-inflammatory mediator. Omega-3 or purified EPA and DHA can execute the antineoplastic activity, playing an essential role to prevent and treat cancer. Besides, EPA and DHA inhibit the metastasis of tumor cells by inducing the apoptosis, either alone or in combination with conventional anticancer therapies [12-13, 34-36].

Multiple mechanisms appear to underlie the benefit potential of n-3 PUFAs for cancer prevention and treatment by inhibiting the angiogenic signal, suppressing the invasion-metastasis cascade, modulating the cell-cycle components, limiting the potential of replicative tumor growth, and activating the apoptosis and autophagy signal. Angiogenesis is required for the tumor to expand beyond 2 mm. Tumor cells activate the angiogenic switch, a controller of angiogenesis, by modulating
the balance of angiogenesis inducers and countervailing inhibitors [35, 37]. Several studies showed that Omega-3 or n-3 PUFAs has an intense suppressing effect on angiogenesis. In vitro study showed that EPA reduces the proliferation of endothelial cell by suppressing the VEGF-receptor. Moreover, n-3 PUFAs inhibit the production of platelet-derived growth factors (PDGF), a mediator involved in angiogenesis [38-39]. DHA has been demonstrated to inhibit nitric oxide (NO) production. NO has been known to inhibit the apoptosis and induce cell survival and proliferation [40].

Metastasis requires a loss of cell-cell adhesion and cell-ECM interaction regulated by cell adhesion molecules (ECM) and integrin. DHA has a role in cell-cell adhesion modulation by reducing the expression of ECM. Besides, EPA and DHA reduce the production of NO preventing the tumor cell migration. Laboratory-based studies showed that Omega-3 could act as the COX inhibitor causing the prevention of metastasis. COX-2 pathway plays an essential role in tumorigenesis. COX-2 reduces cell-cell and cell-matrix interaction leading to increased metastasis [41-42].

In the normal cell, the homeostasis of the cell number and normal tissue structure is regulated by the complex series of proliferation and apoptosis signal. The malfunction of cell regulatory process causes uncontrolled cell proliferation leads to promote cancer. The cell cycle is modulated by the binding of cyclin-dependent kinases inhibitors (CKIs) to inactivate the cyclin-CDK complex. The high intake of Omega-3 such as DHA increased the expression of p21 proteins, a CKI protein that responsible for cell resting before apoptosis induction of cancer [43].

The evasion of apoptosis is an essential phenomenon that induces tumorigenesis. The previous result of H-29 colon cell lines showed that omega-3 successfully increased the induction of apoptosis [44]. DHA induces the releasing of cytochrome C that leads to cancer cell apoptosis by binding to apoptotic protease signaling [45]. Moreover, EPA and DHA affected the expression of Bcl-2 family that responsible for the downregulation of anti-apoptotic proteins of Bcl-2 and Bcl-xL and the upregulation of pro-apoptotic proteins of Bak and Bcl-xS. In the in-vivo study in a mouse model, the supplementation of EPA and DNA restricted the initiation of colon tumor by increased the apoptotic rate [46-47]. Omega-3 is proposed to repress the COX-2 leading the repression of the expression of Bcl-2 and other anti-apoptotic proteins [41]. Autophagy is a natural-conserved of regulated mechanism to disassemble the unnecessary or unfunctional component of the cell. Autophagy-associated cell death is a form of programmed cell death that autophagy serves as a cell mortality mechanism. A study reported that DHA increased a remarkable accumulation of cytosolic autophagic vacuoles suggesting that anti-cancer activity of omega-3 associated with autophagy [48].

Several studies also suggested that omega-3 has the potential to increase the sensitivity of cancer cells to the cytotoxicity therapy and to increase the specificity between cancer and normal cell to the treatment [43]. For example, the experiment in the animal model showed that enriched n-3 PUFAs-diet could enhance the efficiency of doxorubicin and mitomycin to inhibit tumor growth. A therapeutic study in breast cancer patient showed a delayed time in tumor development and longer survival time when the consumption of chemotherapeutic drugs such as doxorubicin, epirubicin, and cyclophosphamide was combined with the use of DHA. This result suggested that DHA, in combination with chemotherapeutic drugs, showed a synergistic interaction [34-35, 48-50].

The health benefit of algae-based PUFAs associate to the anti-inflammatory mechanism. The consumption of algae-based PUFAs shows a reduction of a chronic complication caused by inflammation. Therefore, algae-based PUFAs may have a therapeutic effect to prevent the tumorigenesis furthermore to treat cancer. The in vitro study was conducted by assessing the extract of red seaweeds and Pavlova lutheri human THP-1 macrophages. The lipid extracts, containing 32%-42% of n-3 PUFAs, inhibited the production of cytokines interleukin (IL)-6, a pro-inflammatory protein [51]. Supplementation of n-3 PUFAs of Chlorophyceae and Eustigmatophyceae to the wild types and diabetic mice showed a reduction of IFN-γ and TNF-α and an increment of IL-17A. Those three proteins are the inflammatory cytokines involved in the acute and chronic states of inflammation. The changes in the inflammatory cytokines after supplementation were similar to the effect of fish-oil consumption [52]. Other study showed that the consumption of Schyzochytrium sp. reduced the risk of colitis in the mouse model. It is suggested that DHA of Schyzochytrium sp. increased the induction of
anti-inflammatory cytokines and inhibited the production of pro-inflammatory cytokines [30].

4. Conclusion
The composition of PUFAs plays an important role to modulate the cell homeostasis by maintaining the cell membrane fluidity and lipid raft formation. Recently, the exploration of PUFAs from algae were increased because of the need for a sustainable source of PUFAs. Moreover, the algae-based PUFAs have a beneficial effect of preventing the inflammation associated with the potential therapeutic of PUFAs for cancer therapy. The modification in the fatty acid composition affects the inflammatory microenvironment that leads to tumor development by promoting mutations, genomic instability, and epigenetic modifications. Omega-3, such as EPA and DHA, could prevent tumorigenesis most probably by limiting the biosynthesis of the pro-inflammatory mediator, an inducer for the cell proliferation.

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