CHAPTER 9

Biological Activities and Potential Health Benefits of Fucoxanthin Derived from Marine Brown Algae

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Abstract

The importance of marine algae as sources of functional ingredients has been well recognized due to their valuable health beneficial effects. Therefore, isolation and investigation of novel bioactive ingredients with biological activities from marine algae have attracted great attention. Among functional ingredients identified from marine algae, fucoxanthin has received particular interest.

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Fucoxanthin has been attributed with extraordinary potential for protecting the organism against a wide range of diseases and has considerable potential and promising applications in human health. Fucoxanthin has been reported to exhibit various beneficial biological activities such as antioxidant, anticancer, anti-inflammatory, antiobesity, and neuroprotective activities. In this chapter, the currently available scientific literatures regarding the most significant activities of fucoxanthin are summarized.

I. INTRODUCTION

Ninety percent of the world's living biomass is found in the oceans with marine species comprising approximately half of the total global biodiversity (Kim and Wijesekara, 2010; Swing, 2003). Therefore, the wide diversity of marine organisms is being recognized as rich sources of functional materials, including polyunsaturated fatty acids (PUFA), polysaccharides, essential minerals and vitamins, enzymes, and bioactive peptides (Shahidi, 2008; Shahidi and Alasalvar, 2011; Shahidi and Janak Kamil, 2001). Among marine organisms, marine algae or sometimes referred as seaweeds have long been used in food diets as well as traditional remedies in Eastern hemisphere (Heo *et al.*, 2009). The term marine algae, as used herein, generally refer to marine macroalgae or sometimes referred as seaweeds.

Marine algae were mainly classified into three major classes based on their pigmentation, namely brown, red, and green algae, which are referred to as Phaeophyceae, Rhodophyceae, and Chlorophyceae, respectively (Khan *et al.*, 2010). The amount and type of pigments present is found to differ according to the algae classes. Three basic classes of pigments found in marine algae are chlorophylls, carotenoids, and phycobiliproteins. Various pigments isolated from marine algae have shown to possess several biological activities and potential health benefits. Therefore, a great attention has been arisen to isolate marine algal pigments and identify their biological activities and potential health benefit effects. Lutein and β-carotene, a family of carotenoids which isolated from *Porphyra tenera* displays strong suppressive effect against mutagen-induced *umu C* gene expression in *Salmonella typhimurium* (Okai *et al.*, 1996). Phycoerythrin, one of phycobiliproteins which are the light-harvesting accessory pigments present in red algae, cyanobacteria, and cryptomonads, has been demonstrated to possess strong antioxidant activity *in vitro* and hepatoprotective properties *in vivo* (Soni *et al.*, 2008; Yabuta *et al.*, 2010). Pheophytin *a*, a chlorophyll-related compound isolated from *Sargassum fulvellum*, has been demonstrated to promote neurite outgrowth in PC12 cells (Ina *et al.*, 2007). Further, recent studies have

TABLE 9.1 Potential health beneficial effects of marine brown algae-derived fucoxanthin

Health beneficial effects	Source	References
Antioxidant	*Hijikia fusiformis, Undaria pinnatifida, Fucus serratus, Padina tetrastromatic*	Nomura *et al.* (1997), Sasaki *et al.* (2008), Yan *et al.* (1999)
Anticancer	*Undaria pinnatifida*	Hosokawa *et al.* (1999), Kotake Nara *et al.* (2005a,b)
Anti-inflammatory	*Myagropsis myagroides*	Heo *et al.* (2010)
Antiobesity	*Undaria pinnatifida*	Maeda *et al.* (2005, 2007a,b, 2008)
Antiangiogenic	*Undaria pinnatifida*	Sugawara *et al.* (2006)
Neuroprotective	*Hijikia fusiformis*	Okuzumi *et al.* (1990)
Prevent osteoporosis	*Laminaria japonica*	Das *et al.* (2010)
Photoprotective	*Laminaria japonica*	Heo and Jeon (2009), Shimoda *et al.* (2010)

demonstrated the correlation between a diet rich in carotenoids and diminishing risk of cardiovascular disease, cancers, opthalmological diseases as well as photoaging (Burtin, 2003). Compared with other pigments isolated from marine algae, fucoxanthin has attracted greater attention. It has been reported that fucoxanthin provide a myriad of health benefits effect. The health benefit effects of fucoxanthin are presented in Table 9.1. This contribution provides an overview on biological activities of fucoxanthin derived from marine brown algae and their potential health beneficial and applications in food, pharmaceutical industries.

II. PROFILES AND BIOAVAILABILITY OF FUCOXANTHIN

Fucoxanthin (Fig. 9.1) is one of the most abundant carotenoids contributing around 10% estimated total production of carotenoids in nature (Matsuno, 2001). It has a unique structure including an unusual allenic bond and a 5,6-monoepoxide in its molecule. For different brown algal strains, the compositions and profile of fucoxanthin were found to be different. Tsukui *et al.* reported that *Sargassum horneri* had a remarkably higher level of fucoxanthin content (3.7 mg/g) in comparison with other

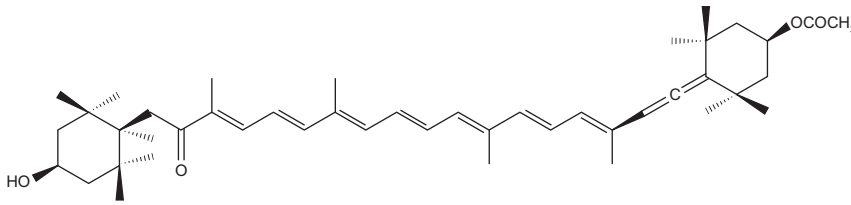

FIGURE 9.1 Chemical structures of fucoxanthin derived from marine brown algae.

Sargassum species tested in their study (Tsukui *et al.*, 2009). Moreover, fucoxanthin was reported as the major carotenoid in *Hizikia fusiformis* (Yan *et al.*, 1999). In addition, Kanazawa *et al.* reported high fucoxanthin level in two edible marine algae species, *Laminaria japonica* and *Undaria pinnatifida* (Kanazawa *et al.*, 2008). Fucoxanthin is widely available in various species of marine brown algae; hence, more and more fucoxanthin has been investigated in recent years for applications in foods, nutraceutical pharmaceutical, and cosmeceutical industries.

In our body, fucoxanthin absorption strongly depends on a number of factors which are not entirely understood. Numerous factors can impact fucoxanthin absorption, including the amount and possibly the type of dietary lipids consumed, the stability of the matrix to which the carotenoid was bound, and additional dietary factors such as dietary fiber (Bohn, 2008). Bioavailability of fucoxanthin seems to be very low; however, there is a scientific controversy about it. Strand *et al.* (1998) found that fucoxanthin metabolites but not fucoxanthin were transferred to the egg yolks of laying hens fed a diet supplemented with 15% *Fucus serratus* (Strand *et al.*, 1998). Hashimoto *et al.* (2009) reported that fucoxanthin and its metabolites show better bioavailability than astaxanthin. More recently, Asai *et al.* (2008) revealed that bioavailability of fucoxanthin human is very low. The mechanism underlying the poor incorporation of fucoxanthin from diets into human plasma remains to be clarified. In a serial studies, Sugawara *et al.* reported that esterification of fucoxanthin in human intestinal caco-2 cells and mice was mediated by enzymatic activity after intestinal absorption (Sugawara *et al.*, 2002, 2009). The esterified fucoxanthin was likely to be incorporated into the lipid core in chylomicron and carried into a variety of tissues including the skin. In addition, by esterifying fucoxanthin into highly nonpolar products, intestinal cells might be protected from the cytotoxic effects of fucoxanthin (Sugawara *et al.*, 2009). Fucoxanthinol was identified as a prime metabolite of fucoxanthin in mice and rats (Asai *et al.*, 2004; Sangeetha *et al.*, 2010). Interestingly, amarouciaxanthin A was found as a major metabolite of fucoxanthin in rat liver, suggesting that liver enzymes may play a role in hydrolyzing fucoxanthin into amarouciaxanthin A (Sangeetha *et al.*, 2010). In contrast,

dietary fucoxanthin was accumulated in the mice heart and liver as fucoxanthinol and in adipose tissue as amarouciaxanthin A (Hashimoto *et al.*, 2009). However, fucoxanthinol was further converted into amarouciaxanthin A by short-chain dehydrogenase or reductase in the mice liver within 24 h and rapidly transported to other tissues.

No adverse side effects of fucoxanthin were reported in the mice study. Notably, in animal studies, fucoxanthin also appeared to stimulate liver to produce docosahexaenoic acid (DHA), a type of omega-3 fatty acid, at levels comparable to fish oil supplementation. The animal experiments with fucoxanthin stimulated researchers to recommend human clinical trials. In placebo-controlled trials, a supplement containing a 5% fucoxanthin (daily dosage 10 mg) did not reveal any harmful effects (Holt, 2008). Therefore, fucoxanthin may be considered as nontoxic, nonallergenic, biocompatible, bioactive materials.

III. BIOLOGICAL ACTIVITIES OF FUCOXANTHIN

A. Antioxidant activity

Oxidation of biomolecules has been identified as a free radical-mediated process (Mendis *et al.*, 2004). Formation of free radicals is an unavoidable consequence in aerobic organisms during the oxygen metabolism, thus believed to be involved in many pathological diseases such as cancer, diabetes mellitus, aging, and Alzheimer's disease (AD; Johansen *et al.*, 2005; Kong *et al.*, 2010; Rattan, 2006; Valko *et al.*, 2006). In addition, deterioration of some foods, development of undesirable off-flavor and potentially toxic reaction compounds in food, has been identified as a result of free radical-mediated oxidation of fatty acids and lipids. Oxidation of lipids by reactive oxygen species (ROS) such as superoxide anion and hydroxyl radicals which shorten the shelf life of foods is attracting great concern in food and pharmaceutical industry; hence, several synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), *tert*-butylhydroquinone (TBHQ) are widely used to retard the oxidation and peroxidation processes (Je *et al.*, 2005; Kim *et al.*, 2001; Ni *et al.*, 2000). However, the use of these synthetic antioxidants must be under strict regulation due to potential health hazards (Park *et al.*, 2001; Safer and Al-Nughamish, 1999). Hence, the search for natural antioxidants as safe alternatives is important in food industry (Pena-Ramos and Xiong, 2001). Recently, there is a considerable interest in the food industry as well as pharmaceutical industry for the development of antioxidants from natural sources. Among marine organism, marine algae represent one of the richest sources of natural antioxidants (Cornish and Garbary, 2010).

Yan *et al.* (1999) identified that fucoxanthin is the major antioxidant of *H. fusiformis* and investigated the radical scavenging activity. Although it has been previously reported by Nomura *et al.* that carotenoids such as zeaxanthin, β-carotene, and lutein did not show DPPH scavenging activity, Yan *et al.* showed that fucoxanthin has a strong radical scavenging activity (Nomura *et al.*, 1997; Yan *et al.*, 1999). The potential involvement of fucoxanthin in radical scavenging activity may correlate to the presence of unusual double allenic bonds at C-7′ position. These findings were confirmed in a recent study carried by Sachindra *et al.* which isolated fucoxanthin from *U. pinnatifida* and prepared two fucoxanthin metabolites, fucoxanthinol and halocynthiaxanthin (Sachindra *et al.*, 2007). The antioxidant activities of these three carotenoids were assessed by DPPH and hydroxyl radicals scavenging activities and singlet oxygen quenching activity. The order of scavenging activity of each carotenoid followed a pattern of fucoxanthin > fucoxanthinol > halocynthiaxanthin (Sachindra *et al.*, 2007). The major structural differences in these three carotenoids are the presence of an allenic bond in fucoxanthin and fucoxanthinol, suggesting that the allenic bond is responsible for the higher scavenging activity of fucoxanthin and fucoxanthinol. Therefore, fucoxanthin may have great potential for use as a nutraceutical and a pharmaceutical and a substitute for synthetic antioxidants. In addition, Sasaki *et al.* demonstrated that fucoxanthin when added to ground chicken meat at a level of 200 mg/kg reduced the formation of secondary oxidation products including TBA reactive substances in the same level as α-tocopherol (Sasaki *et al.*, 2008). Oral administration of fucoxanthin has been reported to improve plasma antioxidant status and meat color in broiler chicks (Sasaki *et al.*, 2010). Moreover, fucoxanthin obtained from *Padina tetrastromatic* has shown higher potential to be used as antioxidant in rats induced by vitamin A deficiency, followed by retinol and β-carotene (Ravi Kumar *et al.*, 2008; Sangeetha *et al.*, 2009). However, the exact mechanism of action as to how fucoxanthin exerts antioxidative effect in rats induced by vitamin A deficiency is not yet completely understood. In addition, cytoprotective effect of fucoxanthin against ROS formation induced by H_2O_2 has been observed *in vitro* (Heo *et al.*, 2008). The presence of two hydroxyl groups in the ring structure of fucoxanthin may correlate to the inhibition of ROS formation. Notably, several studies have indicated that the number of hydroxyl groups on the ring structure of fucoxanthin is correlated with the effects of ROS suppression.

These evidences suggest that among various naturally occurring substances in marine organisms, fucoxanthin proves to be one of the useful candidates in search for effective, nontoxic substances with potential antioxidant activity. Moreover, fucoxanthin is one of the most abundant carotenoid in the nature and could be used as a rich source of natural antioxidants with potential application in the food industry as well as cosmetic and pharmaceutical areas.

B. Anticancer activity

Cancers can be defined as diseases in which unremitting clonal expansion of somatic cells kills by invading, subverting, and eroding normal tissues (Evan and Vousden, 2001). It has been documented that apoptosis (programmed cell death) is a key process in cancer development and progression. Inactivation of apoptosis is considered to be one of the six fundamental hallmarks of cancer, and therefore, apoptosis is a major target of cancer therapy development (Brown and Attardi, 2005). Hence, developing novel molecules that promote apoptosis by targeting both the intrinsic and extrinsic apoptotic pathways may lead to the development of effective cancer therapies.

Fucoxanthin is known to be important free-radical scavengers and antioxidants for the prevention of oxidative damage, which is an important contributor in carcinogenesis. Therefore, it might be suggested that fucoxanthin has potent capacities for new anticancer product developments in the food industries as well as in pharmaceuticals as novel chemopreventing agents for cancer therapy.

Exciting research studies have been published regarding carotenoids and its anticancer qualities. Ishikawa *et al.* showed anti-adult T-cell leukemia effects of fucoxanthin and its deacetylated metabolite, fucoxanthinol (Ishikawa *et al.*, 2008). The inhibitory activities of fucoxanthin and fucoxanthinol were stronger than those of β-carotene and astaxanthin. Adult T-cell leukemia is a fatal malignancy of T lymphocytes caused by human T-cell leukemia virus type 1 infection and remains incurable. Therefore, carotenoids could be potentially useful therapeutic agents for adult T-cell leukemia patients. A recent study from Japan demonstrates that anticancer activity of fucoxanthin goes way beyond its ability to induce apoptosis. Apoptosis inducing effect of fucoxanthin on human leukemia cells (HL-60) has been reported (Hosokawa *et al.*, 1999; Kotake Nara *et al.*, 2005b). The apoptosis induction was associated with activation of caspase-3, -8, and -9 which can be thought of as central executioner of the apoptotic pathway (Hengartner, 2000). Very recently, Ganesan *et al.* reported that siphonaxanthin derived from *Codium fragile* is a more potent growth inhibitor against HL-60 cells than fucoxanthin (Ganesan *et al.*, 2011). The structural differences between these two carotenoids are fucoxanthin contains epoxide and an allenic bond in its structure, whereas siphonaxanthin does not contain those functional groups; however, siponaxanthin has an additional hydroxyl group on the 19th carbon atom. Since esterified form of siphonaxanthin showed lower inhibitory effect, it is suggested that the presence of hydroxyl group is contributed to the strong inhibitory effect of siphonaxanthin (Ganesan *et al.*, 2011). Meanwhile, antiproliferative effect and apoptosis induction by fucoxanthin in human colon cancer cells (Caco-2, HT-29, and DLD-1) were observed by

Hosokawa *et al.* (2004). Fucoxanthin remarkably reduced the viability of human colon cancer cell lines and treatment with fucoxanthin induced DNA fragmentation. Exposure to fucoxanthin decreased the level of apoptosis-suppressing protein (Bcl-2), which suggest that anticancer activity of fucoxanthin were mainly caused by apoptosis. Apoptosis-inducing effect of fucoxanthin in human prostate cancer cells (PC-3, DU 145, and LNCaP) has also been observed (Kotake Nara *et al.*, 2001, 2005a). Although current knowledge of relationship between the structure and apoptosis activity of the fucoxanthin is limited, some researchers suggest that conjugated double bonds and 5,6-monoepoxide are thought to be highly susceptible to acids, alkali and oxygen lead to their prooxidant actions which might cause apoptosis induction in the several cancer cells.

Therefore, it might be suggested that these marine algae-derived NPs have potent capacities for new anticancer product developments in the pharmaceutical as well as the food industries as novel chemopreventing agents for cancer therapy.

C. Anti-inflammatory activity

The anti-inflammatory effect of fucoxanthin is mainly based on modulation of macrophages function. Macrophages are the residents of immune cells in the innate immune system which play an important role in the maintenance of homeostasis by changing their function according to the tissue. As the residence of the immune system, macrophages are a predominant source of proinflammatory mediators including nitric oxide (NO), prostaglandin E_2 (PGE_2), proinflammatory cytokines [tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β)], and ROS (Block *et al.*, 2007). It has been consistently demonstrated that the origin of cancer was at sites of chronic inflammation, in part based on the hypothesis that some classes of irritants, together with the tissue injury and ensuing inflammation they cause, enhance proliferation. Chronic inflammation may also play significant role in mediating neurodegenerative diseases such as Parkinson's disease (PD), AD, multiple sclerosis (MS), and acquired immune deficiency syndrome (AIDS) dementia complex (Kim and Joh, 2006).

Secondary metabolites derived from marine algae are known to have promising anti-inflammatory activities (Abad *et al.*, 2008). However, the scientific analysis of anti-inflammatory activity of fucoxanthin has been poorly carried out, and until now, only few studies were reported. Fucoxanthin is recently known to be a potent anti-inflammatory agent *in vitro* and *in vivo* in responses to bacterial lipopolysaccharides (LPS). Shiratori *et al.* reported that anti-inflammatory effect of fucoxanthin is comparable with predinisolone, a commercially available steroidal anti-inflammatory drug (Shiratori *et al.*, 2005). More recently, Heo *et al.* screened inhibitory

effect of NO production from nine species of brown algae and confirmed that inhibition of NO production correlates with fucoxanthin contents (Heo *et al.*, 2010). In addition, Heo *et al.* also demonstrated anti-inflammatory effect of fucoxanthin isolated from *Myagropsis myagroides* in LPS-stimulated RAW 264.7 cells. Fucoxanthin treatment attenuates the productions of NO and PGE_2 by inhibiting inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) expressions. The release and expression levels of inflammatory cytokines (TNF-α, IL-6, and IL-1β) were attenuated by fucoxanthin in a dose-dependent fashion. The anti-inflammatory activities of fucoxanthin were due to the suppression of nuclear factor-κB (NF-κB) and the phosphorylation of mitogen-activated protein kinases (MAPKs; Kim *et al.*, 2010). Production of proinflammatory mediators has been continuously reported in many inflammatory tissues, along with increased expression of their mRNAs and proteins. Therefore, inhibition of proinflammatory mediators by fucoxanthin suggests its potential for the treatment of inflammatory and other related diseases.

D. Antiobesity activity

Obesity may be defined as an excessive body weight in the form of fat (Kong *et al.*, 2009). It is one of the greatest public health challenges in the first half of this century (Inoue *et al.*, 2000). A number of studies indicated that obesity is associated with type 2 diabetes mellitus, cardiovascular disease, certain forms of cancer, and sleep-breathing disorder (Kopelman, 2000; Lee *et al.*, 2005; Mokdad *et al.*, 2003; Pi-Sunyer, 2002). Moreover, obesity (from teen to seniors) continues to increase in many industrialized and developing countries, which cause a worrying health trend (Kelishadi, 2007). Therefore, the necessity of discovering alternative sources of antiobesity has arisen with interesting demand for safer antiobesity agents.

A research group from Japan reported that oral treatment with fucoxanthin significantly reduced the abdominal white adipose tissue (WAT) weight of obese mice model, KKA^y female mice and normal mice fed with a high-fat diet (Maeda *et al.*, 2005, 2007a,b, 2008). Moreover, no reductions on normal mice fed with normal diet were found. Those results suggest that fucoxanthin specifically suppresses adiposity in the obese mice. WAT is the predominant type of adipose tissue and commonly called ''fat'' in mammals (Trayhurn and Wood, 2005). Besides its role in energy storage, WAT is now recognized as an endocrine and active secretory organ through its production of biologically active mediators termed, adipokines (Curat *et al.*, 2006). Most studies reported that antiobesity effect of fucoxanthin was mainly mediated by the expression of uncoupling protein-1 (*UCP-1*) gene in visceral adipose tissues which lead to the induction of thermogenesis in adipose tissue and dissipating excess energy intake as heat to resist body

weight gain (Mercader *et al.*, 2010; Woo *et al.*, 2009). Recent clinical study carried by Abidov *et al.* (2010) clearly showed antiobesity effect of xanthigen, an antiobesity supplement which consists of fucoxanthin and pomegranate seeds oil. In their study, they demonstrated that xanthigen promoted weight loss, reduced body and liver fat content, and improved liver function tests in obese nondiabetic women (Abidov *et al.*, 2010).

Since the excessive growth of adipose tissue in obesity has been suggested to result from adipocyte hypertrophy and the recruitment of new adipocytes from precursor cells, regulation of adipogenesis also appears to be a potential strategy for the treatment of obesity (Wang *et al.*, 2008). Fucoxanthin isolated from *U. pinnatifida* and its metabolite fucoxanthinol have been reported to inhibit the differentiation of 3T3-L1 preadipocytes into adipocytes (Hayato *et al.*, 2006). The inhibitory effect of fucoxanthin and fucoxanthinol on adipocyte differentiation might be mediated through the downregulation of adipogenic transcription factors, such as peroxisome proliferator-activated receptor-γ. Structure suppressive effect on adipocyte differentiation has been reported by Okada *et al.* (2008). In their study, they used 13 naturally occurring carotenoids found in human diet. Interestingly, carotenoids with keto group, epoxy group, hydroxyl carotenoid, epoxy-hydroxy carotenoid, and keto-hydroxy carotenoid did not show suppressive effect on adypocite differentiation. Meanwhile, treatment with fucoxanthin and neoxanthin showed significant suppressive effect suggesting that allenic bond is crucial factor for the antiobesity effect. Moreover, the result of those studies leads to the hypothesis that other carotenoid with an allenic group and an additional hydroxyl group in the end may also effective in suppressing adipocyte differentiation.

Taken together, fucoxanthin has a potential to be used in food and pharmaceuticals in the treatment or prevention of obesity as they may act as a regulator of lipid metabolism in fat tissues. There are numerous advantages of fucoxanthin derived from marine algae to be used in functional foods and pharmaceuticals, such as relatively low production costs, low cytotoxicity, safety, and wide acceptability. Further, fucoxanthin derived from marine algae may be considered as a promising food supplement, slimming supplement, and drug in the prevention and management of obesity.

E. Neuroprotective effect

Neuroprotection may be defined as a mechanism and strategy used in order to protect neuronal cells against injury, apoptosis, dysfunction, and degeneration in the central nervous system (CNS) by limiting neuronal dysfunction or death after CNS injury (Tucci and Bagetta, 2008; Zarros, 2009). Many categories of natural and synthetic compounds have been reported to possess neuroprotective activities. However, these synthetic

neuroprotective agents are believed to have certain side effects such as dry mouth, tiredness, drowsiness, anxiety or nervousness, difficulty to balance, etc. (Narang *et al*., 2008; Pangestuti and Kim, 2010). Hence, scientists have studied natural bioactive compounds, which can act as neuroprotective agents. Several scientific studies have provided insight into neuroprotective properties of marine algae-derived NPs (Pangestuti and Kim, 2011). Okuzumi *et al*. (1990) found that fucoxanthin isolated from *H. fusiformis* inhibited N-myc expression and cell cycle progression of GOT0 cells, a human neuroblastoma cell line. Fucoxanthin at a concentration of 10 μg/ml reduced the growth rate of GOT0 cells to 38%, but its exact mechanisms of action are not yet completely understood.

Ikeda *et al*. (2003) recently found that wakame was able to attenuate the development of hypertension and its related diseases in stroke-prone spontaneously hypertensive rats (SHRSP). Further, they isolated fucoxanthin from wakame and showed that fucoxanthin amazingly attenuated cell damage in cortical neurons during hypoxia and oxygen reperfusion (Khodosevich and Monyer, 2010). Since ROS generation is considered to occur after hypoxia and reoxygenation, whereby free radicals damage neurons, it may be assumed that neuroprotective activity of fucoxanthin is mainly based on their scavenging activity.

Neurite outgrowths are fundamental neuronal features which play an important role in neuronal development during embryogenesis and in the adult brain. Pheophytin *a* and its analog, vitamin B12 derived from *S. fulvellum*, have been reported to promote neurite outgrowth in phaeochromocytoma (PC12) cells (Ina and Kamei, 2006; Ina *et al*., 2007). Neurite outgrowth promoting activity of pheophytin *a* has been reported to be closely related to their low molecular weight. The rationale for this is that low molecular weight pheophytin *a* may incorporate into the cells more efficiently and therefore promote neurite outgrowth effectively.

Based on several findings, it may be concluded that NPs are a valuable source of neuroprotective agents and could be introduced for the preparation of novel functional ingredients in functional foods and pharmaceuticals as a good approach for the treatment and or prevention of neurodegenerative disease. Further, it can be suggested that NPs are an alternative source to synthetic ingredients that can contribute in neuroprotection. Until now, neuroprotective activities of NPs have been observed *in vitro*. Therefore, further researches are needed in order to investigate NPs neuroprotective activities *in vivo* and in human subject.

F. Antiangiogenic activity

Angiogenesis refers to the process of new blood vessel formation from a preexisting vasculature that occurs under, either physiological or pathological conditions (Carmeliet, 2003). It is observed at tightly regulated

condition in normal physiology during embryogenesis, ovary cycling, and wound healing. However, in pathological conditions such as inflammatory diseases, rheumatoid arthritis, and tumor metastasis, a chronic unregulated angiogenic state often helps spreading of the diseases (Kirk *et al.*, 2004). Hence, preventing angiogenesis under pathological conditions is a promising approach in the prevention of cancer and other angiogenic-related diseases.

Sugawara *et al.* showed that fucoxanthin significantly suppressed human umbilical vein endothelial cells (HUVEC) proliferation and tube formation at more than 10 μM. Fucoxanthin effectively suppressed the differentiation of endothelial progenitor cells into endothelial cells involving new blood vessel formation (Sugawara *et al.*, 2006). Fucoxanthin and fucoxanthinol suppressed microvessel outgrowth *in vivo* and *ex vivo* angiogenesis assay using a rat aortic ring. In a recent study, Ganesan *et al.* demonstrated antiangiogenic effect of siphonaxanthin derived from green algae, *C. fragile* (Ganesan *et al.*, 2010). The antiangiogenic effects of siponaxanthin were comparable with fucoxanthin. The structure similarity between fucoxanthin and siponaxanthin is the presence of hydroxy group on the 3 and 3′ position of both compounds. Therefore, the presence of those hydroxyl groups might conceivably be a part of their antiangiogenesis effect.

G. Skin protective effect

Fucoxanthin isolated from *L. japonica* has been reported to suppress tyrosinase activity in UVB-irradiated guinea pig and melanogenesis in UVB-irradiated mice. Oral treatment of fucoxanthin significantly suppressed skin mRNA expression related to melanogenesis, suggesting that fucoxanthin negatively regulated melanogenesis factor at transcriptional level (Shimoda *et al.*, 2010). Moreover, fucoxanthin has been demonstrated to possess photoprotective properties in human fibroblast cells via inhibition of DNA damage and enhance antioxidant activity (Heo and Jeon, 2009). These studies suggest that oral administration of fucoxanthin might prevent or minimize the negative effects of UV radiation such as melanin formation.

H. Other biological activities

Recently, Das *et al.* showed that the effects of fucoxanthin on osteoclastogenesis were investigated using cells from the macrophage cell line RAW264.7, which have the capacity to differentiate into osteoclast-like cells when stimulated by receptor activator of NF-κB ligand (Das *et al.*, 2010). Fucoxanthin significantly suppressed the differentiation of RAW264.7. Treatment with 2.5 μM fucoxanthin also induced apoptosis

accompanied by activation of caspase-3 in osteoclast-like cells. Those *in vitro* studies suggest that fucoxanthin suppresses osteoclastogenesis via the inhibition of osteoclast differentiation and the induction of apoptosis in osteoclasts. Hence, dietary fucoxanthin may be useful for the prevention of bone diseases such as osteoporosis and rheumatoid arthritis, which are known to be related to bone resorption. Moreover, dietary intake of fucoxanthin and fucoxanthinol has been demonstrated to enhance the amount of DHA and arachidonic acid (AA) content in the liver of C57BL6J/6J normal male mice (Tsukui *et al.*, 2007, 2009). However, further studies are needed to clarify the molecular mechanisms as to how fucoxanthin promotes DHA and AA synthesis in the mice liver.

IV. CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, fucoxanthin is a valuable source of bioactive compound and could be introduced for the preparation of novel functional ingredients in food and, also a good approach for the treatment or prevention of chronic diseases. Recently, much attention has been paid by the consumers toward natural bioactive compounds as functional ingredients in foods, and hence, it can be suggested that fucoxanthin is an alternative source for synthetic ingredients that can contribute to consumer's well-being, by being a part of new functional foods. Further, the wide ranges of biological activities associated with fucoxanthin derived from marine brown algae have potential to expand its health beneficial value in food and pharmaceutical industries.

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