1  Introduction

Obesity is recognized as a looming health menace worldwide, presenting ominous implications for public health and health-related costs\(^1\),\(^2\). Especially, the accumulation of fat around internal organs is a major risk factor for diseases of many kinds. When excess fat accumulates in adipocyte cells, the cells secrete various bioactive components: adipocytokines. Some of these adipocytokines induce health problems such as type-2 diabetes, hypertension, and dyslipidemia. Such comorbidities markedly increase the risk of cardiovascular disease. These problems have been designated as metabolic syndrome. The best way to resolve metabolic syndrome is by changing one’s lifestyle, with good exercise and consumption of food of appropriate quantity and quality. Nevertheless, many residents of industrialized countries have obesity problems because of their working style, with poor exercise habits and with high-fat, high-calorie diets. Fundamentally, obesity is a food-related problem. Therefore, it is possible to resolve this problem by addressing food itself. Effective anti-obesity components have been sought keenly in food materials.

Fucoxanthin (Fig. 1) is a specific carotenoid present in chloroplasts of brown algae, such as *Undaria pinnatifida* (Wakame), *Saccharina japonica* (Makonbu), and *Sargassum fulvellum* (Hondawara). It is the most abundant of all carotenoids, accounting for $>10\%$ of estimated total natural production of carotenoids\(^3\). Fucoxanthin has a unique structure including an unusual allenic bond and 5,6-monoepoxide in its molecule. Although it has no provitamin-A activity, it shows strong antioxidant properties, as do other carotenoids\(^4\). Furthermore, it shows anti-cancerous\(^5\), anti-angiogenic\(^8\), and anti-inflammation\(^9\) activities.

In addition, fucoxanthin reportedly has anti-obesity and anti-diabetic effects. It has attracted much attention from the food industry and from nutrition researchers because of the unique mechanism of these effects. These effects are specific for fucoxanthin: they have not been found for other carotenoids such as β-carotene and astaxanthin. Furthermore, fucoxanthin enhanced the amount of DHA in the liver of mice. This review describes unique bioactivity of fucoxanthin in brown algae.

2  Anti-obesity effect of fucoxanthin

Fucoxanthin up-regulates energy expenditures in abdominal WAT, and reduces excess lipid in WAT. This effect of fucoxanthin is partly attributable to the induction of uncoupling protein 1 (UCP1) expression in white adipose tissue (WAT). That inner membrane mitochondrial protein, UCP1, can dissipate energy through oxidation of fatty acids and heat production. Furthermore, fucoxanthin improves insulin resistance and ameliorates blood glucose levels through down-regulation of adipocytokines related to insulin resistance in WAT and up-regulation of glucose transporter 4 (GLUT4) in skeletal muscle. Algae fucoxanthin is a beneficial compound for the prevention of the metabolic syndrome.
coupling protein 1 (UCP1) in abdominal WAT. Reduction of WAT weight using fucoxanthin and lipid extract of algae containing fucoxanthin has been reported in an obesity model mouse, specifically with high-calorie-diet-induced obesity model mouse experiments. Wakame lipids contain about 10% fucoxanthin. Rats fed 0.5 and 2% Wakame-lipid-containing diets lost weight to a significant degree. In addition, Wakame lipid diets decreased WAT and body weight in obese model KK-AY mouse. There was no significant difference in food intake among experimental diets. The same effect was reported for another algae extracts containing fucoxanthin. Furthermore, UCP1 expression was found in WAT when KK-AY mice were fed Wakame lipid containing diets. To confirm the active components of UCP1 expression in WAT, fucoxanthin was purified from Wakame lipids. Then it was fed to KK-AY mice in...

Fig. 1 Chemical structure of fucoxanthin and metabolism.

Fig. 2 (A) Weight of white adipose tissue of KK-AY mice fed a fucoxanthin of algae and control diet. (B) UCP1 protein expression in WAT fed a fucoxanthin diet. UCP1 protein level normalized to the β-actin level, expressed as a value relative to the Control level. *p <0.05 vs. Control, **p <0.01 vs. Control.
0.1, 0.2% fucoxanthin diets for 4 weeks. Mice fed with fucoxanthin diets exhibited markedly suppressed body weight gain and WAT weights (Fig. 2(A)). In addition, UCP1 protein was expressed in WAT (Fig. 2(B)).

UCP1 is normally expressed only in brown adipose tissue (BAT), not in WAT. BAT is related to energy and heat production in tissues by the contribution of UCP1. UCP1 might reduce excess abdominal fat. Adaptive thermogenesis in BAT is mediated mainly by UCP1, an inner mitochondrial membrane protein that can catalyze the reentry of protons into the mitochondrial matrix, thereby bypassing ATP synthase, uncoupling oxidative phosphorylation, and releasing chemical energy as heat. UCP1 is expressed exclusively in BAT, where the gene expression is increased by cold, adrenergic stimulation, β3-agonists, retinoids, and thyroid hormone (Fig. 3). Thermogenetic activity of BAT is dependent on the UCP1 expression level, which is controlled by the sympathetic nervous system via noradrenaline. In contrast to the scarcity of BAT, almost all adipose tissue in humans is WAT. For that reason, UCP1 expression in WAT is expected to be an attractive target for the development of anti-obesity therapies. Recently, such a low basal expression of UCP1 in white adipocyte is defined as beige adipocyte. The activities of brown and beige fat cells have led to the proposal of a novel therapeutic treatment for obesity.

Results showed that fucoxanthin promoted mRNA expressions of β3-adrenergic receptor (Adrb3) in WAT. Adrb3 is regarded as responsible for lipolysis and adaptive thermogenesis through sympathetic nerve stimulation and UCP1 expression. The degree of obesity is correlated with the extent of loss of Adrb3 gene expression in WAT. This result might be related to the effects of fucoxanthin on UCP1 promotion and up-regulation of fat oxidation in WAT.

Some researchers have reported clinical experiments to assess fucoxanthin anti-obesity effects. Fucoxanthin (2.4 mg/day) was administered to obese women (average body weight 100 kg) for 16 weeks. The administered fucoxanthin showed significant reduction of body weight, waist circumference, body and liver fat content, and serum triacylglycerol content with a significant increase in resting energy expenditure. This result suggests the involvement of mitochondrial uncoupling UCP1 in the anti-obesity effect of fucoxanthin, which engenders increased resting energy expenditure by uncoupling a step during cellular metabolism in humans.

Numerous data have been collected to elucidate thermogenesis in BAT through UCP1 expression. Nevertheless, little information exists in relation to UCP1 expression in WAT induced by a dietary component, with the exception of fucoxanthin.

3 Anti-diabetic effects of fucoxanthin

Fucoxanthin shows anti-diabetic effects by changing of adipocyte cell properties. KK-A" mice not only developed obesity, but also developed hyperglycemia and hyper-insulinemia along with insulin resistance. The KK-A" mice fed the 0.1 or 0.2% purified fucoxanthin diets had signifi-

Fig. 3  Mechanism of energy expenditure in brown adipocyte cell by uncoupling protein 1 (UCP1).
cantly lower blood glucose concentrations (Fig. 4(A)) \(^1\). Furthermore, plasma insulin levels decreased dose-dependently after intake of purified fucoxanthin (Fig. 4(B)). Anti-obesity and anti-diabetic effects of fucoxanthin were also found in high-fat (HF) diet-induced obesity in mice \(^1\). Fucoxanthin intake significantly suppressed body weight and WAT weight gain induced by the HF diet. Dietary administration of the HF diet increased blood glucose and insulin level, although these levels were ameliorated in the fucoxanthin-containing diet group (Figs. 5(A), 5(B)).

Increasing the blood glucose level is related to adipocytes in WAT. In actuality, WAT plays an important role as an energy-storage organ and as an endocrine organ, producing adipokines such as monocyte chemoattractant...
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4 Promoting effects of DHA synthesis in liver

Polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have various physiological functions. Dietary DHA and EPA decrease cholesterol and triacylglycerol levels in the blood, thereby preventing cardiac infarction and vascular brain diseases. DHA and EPA are biosynthesized through desaturation and elongation reactions in the body. However, mammals have difficulty biosynthesizing these PUFAs in the body because Δ-6 desaturase is the rate-limiting enzyme in mammalian synthesis of PUFAs. Therefore, mammals must rely on a dietary supply of fish oil as a source of DHA or EPA. Dietary 0.2% fucoxanthin and fucoxanthinol have been shown to enhance the amount of DHA in the liver of KK-A^y mice. Few natural compounds have been shown to increase hepatic DHA levels, aside from direct consumption of fish oil. The novel effects of fucoxanthin and fucoxanthinol might contribute beneficial effects for the prevention of lifestyle-related diseases.
5 Fucoxanthin absorption and safety

Carotenoids are absorbed in the small intestine along with other lipid components of food. For example, α-carotene, β-carotene, lycopene, β-cryptoxanthin, and lutein are detected in high concentrations in human blood[17]. Carotenoid concentrations and species in blood are affected by food. Fucoxanthinol and amarouciaxanthin A have been detected in plasma and tissues of mice with different accumulation ratios[18, 31, 34]. Similarly, after daily intake for 1 week of cooked edible brown seaweed, Undaria pinnatifida (Wakame), of 6 g dry weight including 6.1 mg (9.26 mmol) of fucoxanthin, fucoxanthinol was detectable at 0.8 pmol/ml in human plasma[20]. In addition, the fucoxanthin absorption rate is affected by other food components, especially lipids. Promoting the rate of the increase in absorption remains unclear, but the combination of fucoxanthin and fish oil, medium-chain triacylglycerol, and scallop phospholipids exerts a beneficial anti-obesity effect[12, 35, 36].

Fucoxanthin toxicity has arisen as a concern from results of mice experiments[17, 38]. Fucoxanthin was orally administered at doses of 500 and 1,000 mg/kg to male and female ICR mice for 30 days. In this experiment, neither mortality nor histological abnormality was observed. In addition, the mutagenicity of fucoxanthinol was examined using an in vitro Ames test. Mutagenicity of fucoxanthinol was not found in Salmonella typhimurium or Escherichia coli with S9 mix. Moreover, the mutagenicity of fucoxanthin of the micronucleus test in bone marrow cells was examined in in vivo experiments with mice. The differences of micronucleus cells were examined in ICR mice that had been administered 500, 1000, or 2000 mg/kg fucoxanthin. The fucoxanthin-treated group showed no abnormalities of micronuclear cells. These results suggest that fucoxanthin is safe as a component of functional foods in common toxicity assay. Additionally, in eastern Asian countries, sea algae (Wakame, Laminaria) have been consumed as edible algae for centuries.

6 Conclusion

Fucoxanthin can be synthesized using chemical methods, but its reaction efficiency is extremely low. Consequently, dilution from natural algae is the most expedient and efficient means to industrialize fucoxanthin. Recently, some companies in Japan have begun to industrialize fucoxanthin as a functional food product. These products are diluted from natural algae such as Saccharina japonica, Nemacystus decipiens (Mozuku in Japanese), and Sargassum horneri (Turner) C. agardh. Additionally, fucoxanthin contents of algae differ among species. Algae containing high concentrations of fucoxanthin are sought as ingredients of commercial products.

Obesity-related diseases pose a severe hazard to public health worldwide. Fucoxanthin has a strong effect on resolving metabolic syndrome problems. That unique effect has not been reported for any other food component. Fucoxanthin in algae is useful as a new functional food from sea products.

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