Review

Impact of Seaweed-Derived Xanthophyll Carotenoid on Obesity Management: Overview of the Last Decade

Oyindamola Vivian Ojulari[1] Seul Gi Lee[1] Ju-Ock Nam[1, 2]

[1]Department of Food Science and Biotechnology, Kyungpook National University, 41566, Daegu, Republic of Korea

[2]Institute of Agricultural Science and Technology, Kyungpook National University, 41566, Daegu, Republic of Korea

Correspondence: namjo@knu.ac.kr; Tel.: +82-53-950-7760; Fax: +82-53-950-7762

Abstract: Present-day lifestyle associated with high calorie-fat intake and accumulation, as well as energy imbalance, has led to the development of obesity and its comorbidities, which have emerged as some of the major health issues globally. To combat the disease, many studies have reported the anti-obesity effects of natural compounds in foods, with some advantages over chemical treatments. Carotenoids, particularly xanthophyll derived from seaweeds, have attracted the attention of researchers due to their notable biological activities, which are associated mainly with their antioxidant properties. Their involvement in oxidative stress modulation, regulation of major transcription factors and enzymes as well as their antagonistic effects on various obesity parameters have been examined in both *in-vitro* and *in-vivo* studies. The present review is a collation of published research over the last decade on the anti-oxidant properties of seaweed xanthophyll carotenoids, with a focus on fucoxanthin and astaxanthin and their mechanisms of action in obesity prevention and treatment.

Keywords: carotenoids; seaweeds; antioxidants; astaxanthin; fucoxanthin; anti-obesity; oxidative stress

1. Introduction

Obesity, is defined as excessive or abnormal accumulation of body fat in the adipose tissue, energy imbalance, and lipogenesis resulting from modern lifestyles characterized by high intakes of fat, sugar and calorie intake, in addition to poor exercise and physical activity [1, 2]. Obesity is also associated with an increase in oxidative stress and low-grade inflammation whose intermediary molecules may include leptin, adiponectin and cytokines and leads to the development of metabolic diseases ranging from hyperglycemia, type 2 diabetes, high blood pressure, heart disease, liver disease, kidney disease, gallbladder disease, and certain types of cancer [2, 3] which pose major health risks globally [4]. Specifically, obesity and type 2 diabetes are associated with an increase in oxidative stress and inflammation in adipose tissues [2, 5, 6]. Consequently, researchers have been exploring functional materials of plant origin that contain antioxidants to combat obesity and its comorbidities as alternatives to conventional approaches that have been adopted previously including surgery and anti-obesity drugs, which do not often have enduring effects and have side effects ranging from headaches, excessive thirst, insomnia, constipation, and steatorrhea [7] or may have yo-yo effects [4, 8]. Therefore, the consideration of antioxidants as a therapeutic agent in the treatment and/or prevention of obesity and its comorbidities would be insightful.

Seaweed generally refers to plants and algae that grow in waterways such as   oceans, lakes, rivers and streams. They can be classified based on their pigmentation as brown algae, red algae,

and green algae [9, 10], and are natural sources of bioactive compounds such as polyphenols, lipids, and carotenoids, which exhibit antioxidant activity and other beneficial properties [11], with broad application in the food, feed, and pharmaceutical industries [12]. In some Asian countries such as Korea and Japan, seaweeds are widely consumed as functional foods for their health benefits, and are major traditional food items (e.g. Kimbap) [13, 14]. The prevalence of various metabolic syndromes in this region is reportedly lower than in western countries such as the USA and Australia [10] suggesting that dietary habits influences human health. Seaweeds contain carotenoids, which function as antioxidant, anti-viral, anti-cancer, anti-obesity, anti-inflammatory, anti-coagulant and anti-lipaemic agents[15]. Some bioactive compounds that have been isolated and identified from seaweeds include carotenoid pigments such as fucoxanthin (FXN) [16] astaxanthin (ASX), zeaxanthin, and β-carotene [17, 18].

Carotenoids are the largest group of lipid-soluble natural pigments, and they are responsible for the red, orange, and yellow colors in many fruits and vegetables [19, 20] Fruits and vegetables containing carotenoids have been reported to be antioxidant-rich and suitable for the formulation of functional foods to be consumed for their health benefits [21] In addition, they are associated with reduced risks of chronic diseases [22]. Dietary intake of carotenoid-containing vegetables such as seaweeds could reduce risks of development of cardiovascular disease, age- related macular degeneration, obesity, and certain cancer types [23-28] which is linked with longer life expectancy and lesser risk of metabolic diseases [29]. They have also been reported to exhibit many physiological and biological functions, including their antioxidant properties, such as quenching of singlet oxygen and radical scavenging [30]and coupled with other processes have positive impacts on human health [31]. Carotenoids are divided into carotenes and xanthophylls (e.g. FXN and ASX). Both xanthophylls and carotenes are potent antioxidants; however, xanthophylls have been reported to exhibit higher antioxidant activity, and various beneficial impacts on human physiology[32]. Xanthophylls have oxygen-containing functional group, long unsaturated aliphatic chain in their molecular structure, and are relatively abundant carotenoid in seaweeds [33]. In seaweeds, FXN and ASX are the major xanthophyll carotenoids that exhibit high antioxidant activity due to singlet oxygen quenching and free radical scavenging ability [13]. Numerous studies have investigated the antioxidant potential of the carotenoids and their metabolites with regard to their role in obesity management [26]. A recent study reported that xanthophyll intake could improve lipid metabolism and reduce abdominal fat and body Mass Index (BMI) in healthy overweight individuals [34]. Over the past decade,   a new perspective on the biological function of seaweed carotenoids and their potential applications in the treatment of obesity and obesity-related diseases has emerged [31, 35]. Some studies have reported the therapeutic effects of the compounds in adipose tissue biology to include adipogenesis (adipocyte differentiation), adipocyte metabolism, and oxidative stress regulation, in addition to the modulation of the expression of specific adopokines and pro-inflammatory factors [36-39]. The mechanism of action of carotenoids have been attributed to their ability to restrain adipogenesis and adipocyte hypertrophy while enhancing fat oxidation and energy dissipation in brown and white adipocytes, in turn, controlling obesity in animal models [26, 40].

The objective of the present review is to collate the findings of studies conducted over the past decade on the antioxidant properties of seaweed carotenoids, with a focus on xanthophylls (FXN and ASX), including findings on their relevance to obesity treatment and the mechanism of action by which they achieve the functions *in-vitro* (cells), *in-vivo* (animal models), and in clinical studies (human subjects).

2. Antioxidant properties of selected seaweed carotenoids

Obesity is characterized by chronic energy imbalance, excessive body weight, white adipose tissue (WAT) and lipogenesis [1, 2, 41] In addition, obesity is associated with increased oxidative

stress and inflammation. Therefore, the functions of antioxidants in the body cannot be over-emphasized. Dietary antioxidant serves as a defense system against oxidative stress and inflammation [2, 5, 42] and have received substantial attention in the potential roles in the prevention and treatment of obesity and obesity-related diseases [3, 4, 6]. One of the main biological properties of seaweed carotenoids is their antioxidant properties. When consumed in appreciable amount, edible seaweeds supply the body with potent antioxidants and enhances its ability to counteract excessive oxidative stress in the body [30]. Various seaweeds species have been demonstrated to exhibit good antioxidant effects and suppress oxidative stress *in-vitro* and *in-vivo* [43]. Studies have estimated the antioxidant properties of extract and isolates from various seaweed species using different in-vitro assays such as 2,2-Diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant capacity (FRAP) or oxygen radical absorbance capacity (ORAC) and 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) among others. [12, 33, 44-52]. In addition, the active compounds in seaweeds such as sulphated polysaccharides, phlorotannins, and particularly carotenoids, have been suggested to be the major antioxidant compounds responsible for the beneficial health effects and a lot of research has focused on the potential applications of the bioactive compounds in obesity management [53, 54]. As mentioned earlier, xanthophyll such as FXN and ASX exhibit greater antioxidant capacities than other seaweed carotenoids (e.g., B carotene) and, therefore, tends to have higher health benefits.

FXN, a xanthophyll carotenoid from seaweed, has been reported to exhibit high antioxidant capacity [55]. Seaweed (*F. vesiculosus*) extracts containing 0.0012% FXN, showed high antioxidant activity (DPPH, ABTS, and ABAP) and inactivated RAW 264.7 macrophages [16, 56]. Similarly, ASX, a red-pigmented xanthophyll, has been reported to be an antioxidant that is more effective than vitamins C and E or other carotenoids [57, 58]. The consumption of FXN and ASX carotenoids has been associated with reduced levels of oxidative stress-mediated inflammation in relation to obesity [36]. Over the past decade, accumulating evidence has demonstrated a link between the carotenoids and adipocyte/adipose tissue biology [35]. A recent study also revealed that the intake of xanthophylls improves lipid metabolism and reduces abdominal fat and BMI in healthy overweight individuals [34].
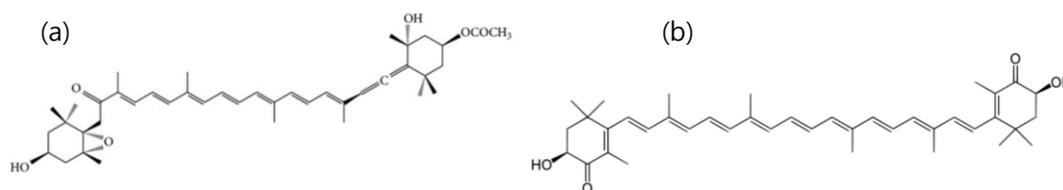
(a)   (b)

Figure 1. Chemical structure of (a) fucoxanthin and (b) astaxanthin.

3. Fucoxanthin and Obesity

FXN, a seaweed carotenoid has gained popularity recently due to its antioxidant properties, and is therefore considered a protective agent that could decrease the oxidative-inflammatory status associated with body weight gain and is being applied in the treatment of the various diseases triggered by obesity [59, 60]. FXN is present in the chloroplasts of brown seaweed such as *Hizikia fusiforme, Fucus serratus, Laminaria, Alaria crassifolia, japMiyatonica, Fucus vesiculosus, Sargassum horneri, and Undaria pinnatifida* and have been isolated for its bioactivity [56, 61-64]. The unique characteristics of FXN lies in its structure (contains allenic bond), which accounts for its distinctive therapeutic effects [37, 64, 65]. Health-related, dietary FXN has gained substantial awareness due to its beneficial effects in human. Also, fucoxanthin was reported to possess the most effective anticarcinogenic activity among other xanthophylls, thus, fucoxanthin as well as

other seaweed carotenoids have therapeutic potentials and could be used as nutraceuticals, functional foods ingredients and alternatives for synthetic antioxidants [66]

3.1. Therapeutic potential of fucoxanthin in obesity.

FXN isolated from *Pinnafida binghamiae* reportedly exerts anti-obesity effects in 3T3-L1 adipocytes by inhibiting the differentiation of adipocytes at both intermediate and late stages, in addition to inhibiting glucose uptake in mature adipocytes [67]. Various effects of FXN on obesity parameters have been observed with regard to body weight, visceral fat, and adipose tissues sizes, fasting blood glucose concentration, in addition to plasma insulin, lipid and cholesterol metabolism rates, among others. Reductions in bodyweight gain, WAT weight, visceral fat, hepatic total lipids, total cholesterols, and   plasma and liver triglyceride concentrations are usually accompanied with increased fecal lipid excretion, which has been observed and reported in various *in-vivo* studies of diet-induced obesity [37, 68-71]. Based on these studies, FXN supplementation have been effective in enhancing the expression of lipid metabolizing enzymes such as carnitine palmitoyltransferase-1 (CPT1) and Cholesterol 7α-hydroxylase1 (CYP7A1) [39], promoting fatty acid oxidation [38, 72], and suppressing the activity of cholesterol-regulating enzymes such as 3-hydroxy-3-methylglutaryl coenzyme A reductase and acyl-coenzyme A [37, 71] have been used to explain the aforementioned actions. Dietary fucoxanthin supplementation in KK-A^y mice increased serum cholesterol levels, attenuated fat accumulation and suppressed enlargement of visceral WAT during the development of obesity [59]. However, there are inconsistent reports with regard effective FXN dosages.

A low FXN concentration supplementation of 0.05 % (w/w) in mice diet was reported to lower plasma triglyceride and liver lipid concentration in HFD-fed C57BL/6N mice [37]. Surprisingly, similar effects were also observed in the same mice model, fed with a higher concentration of 0.2% fucoxanthin supplementation [37]. In another study, Sprague-Dawley rats fed with HFD and 0.2% FXN for four weeks both had significant decreases in hepatic total lipid, total cholesterol, and triglyceride concentrations compared to the HFD group [39]. Airaanthi et al., [16], reported FXN administration of about 60mg/kg/day to cause a decrease in abdominal WAT weight of obese animal model. Meanwhile, a lower dose of 2.4mg/day and 3mg/day FXN intake reduced abdominal WAT significantly in obese female individuals with an average weight of approximately100 kg [38], and also reduced body weight, BMI, and abdominal fat in male and female adults [70]. The effect of FXN on anti-obesity parameters seems similar at different concentration. However, the amount or dosage of FXN required to exert certain anti-obesity effects could vary depending on study models (human or animals), due to varying sensitivity [33] or different absorption rates [64]. Therefore, further clinical studies are necessary for a more unanimous report on its effective dosage. Furthermore, as a co-administered drug, the synergetic effects of FXN in combination with other compounds or materials in the treatment of obesity have been investigated [38, 71]. A combination of FXN and linoleic acid decreased body weight gain and improved lipid metabolism in HFD induced obese rats [71]. Similarly, combination with pomegranate seed oil reduced body weight, liver fat, and triglyceride concentrations significantly in obese premenopausal women [38]. Also, the direct consumption of wakame seaweed (*Undaria pinnatifida)* which is rich in carotenoids, particularly FXN has been reported to effectively reduce postprandial glucose and insulin response in healthy adults within 30 mins of consumption with rice [73]. In fact, cooked wakame has higher FXN concentration that fresh samples [74], validating its usefulness as a functional food. With regard to toxicity, most seaweeds are edible, and thus FXN isolated from seaweeds could be considered as a safe pharmaceutical ingredient [75]. Furthermore, a clinical trial reported no abnormalities and adverse effect was exhibited by individuals who ingested FXN [70].

3.2. Mechanisms of anti-obesity effect of fucoxanthin

Several studies in the literature have categorized the Anti-obesity mechanism of fucoxanthin to the modulation of key transcriptional factors related with obesity. Among these, the nuclear receptor PPARγ and C/EBPα are master regulator of adipogenesis [76, 77], playing a crucial role in differentiation and function of mature adipocytes [78] The activation of this nuclear receptor in adipocytes has been reported to enhance insulin resistance associated with obesity [77, 79]. PPARγ is highly expressed in adipose tissues and its expression is markedly induced during adipogenesis [76, 78]. Both PPARγ and C/EBPα, bind most induced genes linked to adipogenesis and metabolism [80], suggesting a synergistic upregulation of adipogenic gene expression by these two master regulators [81]. These nuclear receptors (PPARγ and C/EBPα) positively regulate each other's expression [82], and cooperate to promote their respective-stimulated adipogenesis (C/EBPα ↔PPARγ -stimulated adipogenesis)[77, 83].

A study by Kang et al.,[67], revealed FXN to present anti-obesogenic effects on 3T3-L1 adipocytes cells during the three differentiation (early, middle and late) stages. The promotion of adipocyte differentiation and increased protein expression of PPARγ, CCAAT/enhancer-binding protein α (C/EBPα), sterol regulatory element-binding protein 1c (SREBP1c) and adiponectin mRNA expression occurred at the early stage, while intercellular lipid accumulation was restrained by a reduction in the expressions of transcriptional factors (PPARγ, C/EBPα, and SREBP1c) during the intermediate and late differentiation stages of adipocyte cells. This study related the anti-obesity and anti-adipogenic effects of FXN to its structural characteristics, which promotes the down regulation of the expression of key regulatory proteins including PPARγ, C/EBPα and SREBP1c. Further investigation confirmed that FXN treatment increased the phosphorylation of AMPK and ACC as well as LKB1 phosphorylation, and decreased the expression of SREBP1c in mature 3T3-L1 adipocytes. SREBPs (including SREBP-1a, SREBP-1c, and SREBP-2) are other key transcriptional factors similarly involved in cholesterol homeostasis, and are induced during differentiation of preadipocytes [82]. SREBP-1c regulates fatty acid and cholesterol synthesis, and has been shown to promote adipogenesis by providing lipid ligands that mediate PPAR activation [76]. FXN enhanced cholesterol synthetic pathway in the liver, by increasing transcriptional factor SREBP2 and SREBP1, and the mRNA expression levels of HMGCR, HMGCS, FDPS, and CYP51 involved in cholesterol synthesis, which decreased hepatic cholesterol content in the FXN fed mice compared with the control mice [59]. Moreover, SR-B1 and LDLR proteins (which plays an important role circulating cholesterol levels in the liver) were also observed to be downregulated by FXN, and resulted in increased serum cholesterol levels and reduced hepatic clearance of serum cholesterol [59].

Conversely, the findings in in-vivo studies suggest that the administration of *Pinnafida binghamiae* extracts (containing FXN150 mg/kg/day) inhibited high-fat-diet (HFD)-induced obesity by increasing fatty acid β-oxidation and inhibiting de novo lipogenesis in adipose tissue of C57BL/6 obese mice [84]. The downregulation of stearoyl-coenzyme A desaturase-1 (SCD1), and the enhancement of insulin and leptin sensitivity have been suggested as a curative measure in HFD-induced obesity [73, 85, 86]. Leptin predominantly produced in adipose cells, regulates body and fat weights by regulating food intake and energy expenditure. A comparative in-vivo study using hyperleptinemia KK-Ay and leptin-deficiency ob/ob mice models revealed that FXN reduced body weight gain, visceral WAT mass and serum leptin levels by down-regulating hepatic SCD1

expression through the regulation of leptin signaling in KK-Ay mice with hyperleptinemia [86]. However, the effects were not remarkable in leptin-deficient ob/ob mice, suggesting the mechanism of action of FXN to be by the down-regulation of SCD1 expression through the regulation of leptin signaling.

Another study attributed the action of FXN on insulin resistance in HFD-induced KK-Ay diabetic obese and C57BL/6J lean mice to the regulation of mRNA expression of inflammatory adipocytokines (iNOS and COX-2) in WAT of diabetic/obese KK-Ay mice [60]. Cyclooxygenases (COX) are important regulators of metabolism [87]. At the mRNA level, cyclooxygenase-1 (COX-1) is constitutively expressed in adipocytes, whereas expression of cyclooxygenase-2 (COX-2) is induced in inguinal white adipose tissue (iWAT) in response to the induction of UCP 1 [87-89]. The overexpression of COX-2 was accompanied by decreased iWAT mass and adipocyte, improved insulin-stimulated glucose disposal and reduced markers involved in hepatic steatosis in HFD C57BL/6 mice [87]. Besides, UCP1 expression in WAT is modulated by the expressions and activities of PPARα, PPARγ [84], and COX-2 [84, 88, 89], which have been reported to be altered by fucoxanthin [1, 37, 84].

The anti-obesity mechanism of fucoxanthin has been linked to the upregulation of uncoupling protein 1(UCP1), which is a key molecule for metabolic thermogenesis to avoid an excess of fat accumulation, and act as a physiological defense against the onset of obesity [1, 53, 66, 90]. UCP1 is typically expressed in brown adipose tissue (BAT) and known as a significant component of whole-body energy expenditure [66], mediates the oxidation of fatty acids and promotes energy expenditure by thermogenesis. FXN induces (UCP1) in abdominal WAT, mediates the oxidation of fatty acids, heat production, promotes energy expenditure by thermogenesis [91]. Thus, the anti-obesity effects of fucoxanthin may be related to the browning of white adipocytes through the upregulation of UCP1, which results in increased energy expenditure in the body [90].

4. Astaxanthin and Obesity

ASX, a red-pigmented xanthophyll carotenoid, exhibits antioxidant activity that is approximately 10 times more potent than that of any other carotenoid including α-carotene and β-carotene [57, 92] and that is about 100 fold that of α-tocopherol [58, 93]. Its reactive oxygen scavenging ability and anti-inflammatory properties have been studied in both *in-vitro and in-vivo* [94, 95] and they exhibit protective effects against metabolic diseases including cardiovascular diseases and obesity [96, 97]. Studies have shown that the unique chemical structure (the presence of polar moieties on both ends of its polyene chain) of ASX greatly influences its antioxidant potency and ability to remove free radicals and excessive reactive oxygen species [98]. Besides possessing antioxidant activities, ASX was found to have antagonistic effects on adipocytes and agonistic effects on peritoneal macrophages, acting as a selective PPARg modulator, related to obesity [92].

ASX showed health-promoting potential such as considerable preventive and curative abilities against oxidative stress-related diseases including obesity, etc. [99]. It was suggested that ASX prevented HFD-induced obesity by lowering plasma triglyceride and total cholesterol and limiting the increase of body weight and adipose tissue. Another study showed that ASX can prevent mitochondrial damage and alleviate the oxidative stress that is associated with nonalcoholic fatty

liver disease [100]. Thus, AXN is regarded as a promising therapeutic agent, effective and safe for obesity management. [101].

4.1. Therapeutic potential of astaxanthin in obesity.

Oxidative stress is a major underlying cause for metabolic disorders and is characterized by insulin resistance, which is related to obesity. Insulin is an important hormone maintaining glucose homeostasis [102]. In obese mice, fat cells were observed to be more resistant to insulin, causing the accumulation of glucose in the blood [85]. Moreover, ASX exerts beneficial effects on glucose and lipid metabolism in diet-induced animal models, by lowering insulin resistance (according to the homeostasis index of insulin resistance) and decreasing fat accumulation [103]. ASX treatment was also reported to ameliorate insulin resistance and improve insulin signaling by activating the post-receptor insulin signaling [85, 104], reducing oxidative stress produced by various stimuli including TNF-α [103], and inhibit pro-inflammatory cytokines in obese mice [85, 102]. ASX improved blood lipid profile by reducing LDL-cholesterol(LDL-C)and triglycerides(TG), increasing high-density lipoprotein cholesterol (HDL-C), and decreasing markers of lipid peroxidation [94, 105], and equally exhibited anti-obesity activity and inhibitory effects on adipogenesis in mouse models [26, 92]. In-vivo studies showed the administration of ASX to significantly reduce body weight and adipose tissue weight gain induced by a high-fat diet, and also reduced the liver weight, liver triglyceride, plasma triglyceride, and total cholesterol by stimulating an increase in fatty acid utilization [102].

Choi et al., [106] reported that ASX (5 and 20mg/day) supplementation for three weeks improved oxidative stress biomarkers by suppressing lipid peroxidation and stimulating the antioxidant defense system in human. A dose-dependent decrease in plasma malondialdehyde and isoprostane levels accompanied with increases in plasma total antioxidant capacity and superoxide dismutase levels in overweight and obese young adults were observed in the study [106]. In addition, improved antioxidant defense mechanisms and lipid metabolism following ASX supplementation has been reported in mice models [81, 97]. ASX supplementation (0·03 %) in HFD-fed apoE knockout (apoE)−/− mice reduced plasma cholesterol and triglyceride levels, however, there was no significant change in body weight when compared with the control group [97]. The observed hypocholesterolemic effect was attributed to an increase in mRNA expression of low-density lipoprotein receptor and fatty acid β-oxidation in the livers of ASX-fed mice. In their further studies, the authors investigated the effect of ASX on lowering plasma triacylglycerol concentrations [81]. According to their results, feeding C57BL/6J mice with 0.03% ASX similarly exhibited significantly lower plasma triacylglycerol concentrations, with a significant increase in the fatty acid synthase and diglyceride acyltransferase2 mRNA abundance than in the control mice. They concluded that ASX could prevent obesity-associated metabolic disturbances and inflammation by increasing hepatic expression of endogenous antioxidant genes, and rendering splenocytes less sensitive to lipopolysaccharide stimulation.

A clinical study by Yoshida et al. [96] investigated the effects of ASX on the lipid profile in humans. ASX concentrations of 12–18-mg/day reduced triglyceride concentrations significantly, which were correlated with increases in serum adiponectin hormone concentration, while 6–12-mg/day dose increased high-density lipoprotein cholesterol significantly. However, BMI remained unaltered at all doses [96]. The increased adiponectin concentrations following ASX consumption were suggested to be due to its anti-inflammatory properties; however, it was not demonstrated in the study.

4.2. Mechanisms of anti-obesity effect of astaxanthin

Adiponectin, an abundantly expressed adipose-specific adipokine that produces insulin-sensitizing effects, and is directly involved in regulating glucose levels as well as fatty acid metabolism [107]. In obese subjects, the levels of adiponectin are usually low, which is associated with lower degrees of insulin sensitivity and glucose tolerance, and a higher adipose TNF-α expression [108-110]. Leptin is another important adipokine abundantly expressed in adipose tissue and is involved in the balancing of energy homeostasis [107]. Leptin helps to control food intake, energy expenditure, and, hence, body weight [108].

In this point of view, the anti-obesity mechanism of ASX might be mediated by improving adipokine levels (i.e. ↓ leptin level and ↑ adiponectin level). In fact, ASX-mediated adiponectin elevation has been observed in human trials [96]. Since adiponectin is regulated by the peroxisome proliferator-activated receptor-γ (PPARγ) pathway and is involved in close-inhibition relationships with inflammatory cytokines [96], the dysregulation of the nuclear receptor peroxisome proliferator-activated receptor δ/β (PPARδ/β) could be associated with obesity, because of its key role in lipid metabolism [111]. Arunkumar et al., [85] attributed the improvement in insulin resistance, reduced lipid levels and adipose tissue weight observed in obese mice to PPARγ agonist and modulation effects of ASX supplementation. Furthermore, ASX was reported to bind PPARγ selectively in a dose-dependent manner, and inhibited rosiglitazone (a PPARγ ligand) induced adipogenesis in 3T3-L1 cells by antagonizing PPARγ transcriptional activity, upon direct binding [40, 92]. Clearly, the integrated activation of PPARδ/β (connecting the muscle and adipose tissue) by ASX could have led to the induction of non-shivering thermogenesis, in turn reducing fat accumulation in adipocytes and controlling body fat reduction [111].

In obesity-induced insulin resistance, inflammatory cytokines and free fatty acids (FFAs) released from adipose tissue are involved in insulin sensitivity [112], and are reportedly caused by abnormal insulin signaling in obese models [113]. High glucose and fatty acid levels associated with obesity leads to increased ROS production which causes insulin resistance in metabolic tissues [114]. The beneficial effect of ASX on ROS induced- insulin resistance in obese mouse models has been linked to the modulation of signaling pathways primarily mitogen-activated protein kinases (MAPK) and JNK (c-Jun N-terminal kinases) pathways [85, 113]. Since collated evidence confirms the role of cytokines such as TNF-α in the promotion of insulin resistance by generation of ROS or the activation of JNK in inflammatory pathway signaling, the inhibition of JNK could be an important target for the treatment of inflammation-induced insulin resistance or abnormal glucose tolerance in obesity [113, 114]. As a potent antioxidant, ASX reportedly improved insulin resistance, through the JNK-IRS-1-Akt axis by suppressing insulin-induced JNK phosphorylation as well as IRS-1 serine phosphorylation in the liver of HFD mouse [104, 114]. Also, ASX significantly decreased ROS produced by oxidants including TNF-α and enhanced Akt phosphorylation related to the increase in GLUT4 translocation or glucose uptake [103].

The expression of nuclear factor erythroid 2-related factor 2 (NRF-2), a responsive antioxidant gene plays a critical role in cellular defense against oxidative stress by inducing the transcription of antioxidant genes, and decreasing the concentrations of oxidative stress marker such as glutathione disulfide (GSSG) in the liver of mice [81]. ASX has been able to enhance the antioxidant defense mechanisms as well as prevented non-alcoholic fatty liver disease (NAFLD) by improving lipid metabolism in HFD fed C57BL/6J and apoE 2/2 mice [81, 97]. The mechanism was further explained to be due to the induction of NRF-2 which caused a significant 2-fold increase in the mRNA expression of NRF-2 as well as an increased expression of its target endogenous antioxidant genes, including superoxide dismutase 1, glutamate–cysteine ligase regulatory subunit and glutathione peroxidase 1, in the liver of ASX-fed mice [81, 98]. Some recent studies have substantiated that

NRF-2 inducers improve insulin resistance in obesity models and increase glucose uptake by decreasing oxidative stress in the hypothalamus [115, 116].

Additionally, Yang et al., [81] reported the TAG lowering effects of ASX as observed in ASX supplemented mice and was attributed to the expression of genes involved in lipogenesis and fatty acid b-oxidation. The increase in the mRNA expression of acyl-CoA oxidase 1 (ACOX-1), increases in the hepatic expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) and LDL receptor and the rate-limiting enzyme in the peroxisomal fatty acid b-oxidation were observed in ASX- fed mice, however, no difference was observed in that of SREBP-2 [81, 97].

Overall, ASX has been proven by various studies as beneficial natural antioxidant that improves insulin resistance, lipid metabolism and ameliorates oxidative stress-induced obesity. Moreover, the ingestion of ASX is considered safe [32, 93, 94, 117].

5. Conclusion

The prevalence of obesity is of global concern, with accumulated evidence tending towards oxidative stress-induced maladies, making the supplementation of natural antioxidant a feasible intervention. This review presented the relationships between antioxidants, oxidative stress, inflammation, and obesity, with clear illustrating that seaweed carotenoids are antioxidant-packed bioactive compounds with potent oxidative defense mechanisms and anti-obesity properties. Xanthophyll carotenoids (FXN and ASX) as described in the reviewed studies positively modulated the expressions of various transcriptional factors, cytokines, and enzymes associated with obesity, substantiating their therapeutic potentials for obesity management. The molecular mechanisms of action on various obesity parameters have been highlighted in this review. Moreover, these xanthophyll carotenoids have proven to positively mediate the abnormalities caused by excess ROS and depletion of antioxidant system in obese subjects. Thus, a detailed understanding of their mechanisms could evolve new ideas in the treatment of obesity and peripheral metabolic diseases. Based on the safety and molecular mechanisms highlighted, FXN and ASX showed good pharmacological effects on obesity and could be potential materials for functional foods and drugs for human health benefits.
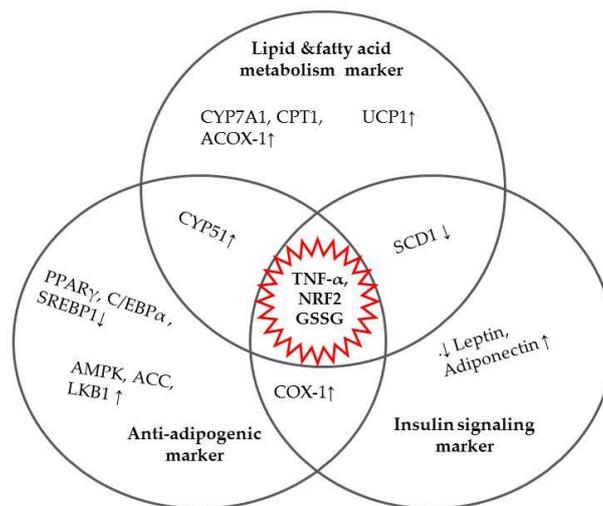
Figure. 2 Transcription factors, mRNA expressions and cytokines involved in the antiobesity mechanism of FXN, and ASX Xanthophyll Carotenoids

Table 1. Reported studies on the effect of selected xanthophylls and their anti-obesity effects.

s/n	Subject/Model	Effective dose	Seaweed Specie	Observed effect	References
1	Male Sprague Dawley Rat	0.083 and 0.167 mg/kg/bw FXN supplementation in HFD	not mentioned	Reduces plasmatic and hepatic triglyceride concentrations and positively influenced cholesterol-regulating enzymes such as 3-hydroxy-3-methylglutarylcoenzyme A reductase and acyl-coenzyme A	[71]
2	Obese KK-Ay mice	0.2% FXN diet	*Undaria pinnatifida*	Increased High-Density Lipoprotein (HDL)-cholesterol and non-HDL-cholesterol levels in KK-Ay mice, reduced cholesterol uptake in the liver, via down-regulation of Low-Density Lipoprotein (LDL)-receptor and (Scavenger Receptor class B member 1) SR-B1	[59]
3	KK-Ay mice and B6.V-Lepob/J (ob/ob) mice	0.1 or 0.2% FXN supplemented diet	*Undaria pinnatifida*	Suppressed body weight, visceral WAT mass, and lowered serum leptin levels	[86]
4	KK-Ay mice/ lean C57BL/6J mice			FXN regulated adipocytokine mRNA expression in WAT of diabetic/obese KK-Ay mice	[53]
5	Mice	150mg/kg/day	*Petalonia binghamiae*	PBE (or FXN) exert improving effects on HFD-induced obesity by promoting β-oxidation and reducing lipogenesis.	[84]
6	C57BL/6J and KK-Ay mice	0.2% fucoxanthin FXN	*Undaria pinnatifida*	FXN regulated mRNA expression of inflammatory adipocytokines, attenuated both body weight gain and WAT weight in diabetic/obese KK-Ay mice, but did not affect these parameters in lean C57BL/6J mice	[60]
7	obese female volunteers with 100 kg average weight	2.4 mg/kg/day	*Undaria pinnatifida*	Increased energy expenditure in the body and resulted in significant weight loss after 16 weeks	[38]
9	KK-Ay mice	60 mg FXN intake/kg body weight/day	*Undaria pinnatifida (Wakame), Sargassum horneri (Akamoku), and Cystoseira hakodatensis (Uganomoku)*	Significant decrease in liver lipid hydroperoxide levels and abdominal WAT weight of obese model	[16]
11	C57BL/6N mice	0.05% and 0.2% FXN in diet, w/w	*Undaria pinnatifida*	FXN supplementation improves plasma and hepatic lipid metabolism and blood glucose concentration	[37]
12	C57BL/6J mice	0.02% dose	*Undaria pinnatifida*	Ethanol extract on diet-induced-insulin resistance in C57BL/6J mice	[69]
13	C57BL/6J mice	0.05 or 0.2% FXN supplemented diet	*Undaria pinnatifida*	Regulated the plasma and hepatic lipids metabolism; increased fecal lipid excretion. Fecal weight, liver and triglycerides and cholesterol were not significantly different between 0.05 and 0.2% FX fed mice	[72]
14	30 male 4-week-old C57BL/6 mice	Oral; 150 mg/kg/day for 70days	*Petalonia binghamiae*	Extract (PBE) administration e reduced body weight gain, adipose tissue weight, adipose cell size, serum triglyceride level, and reduced lipid accumulation in the liver in HFD-induced obese mice.	[84]
15	3T3-L1 adipocyte	10uM treatment	*Petalonia binghamiae*	FXN activated the AMPK signaling pathway; increased the phosphorylation of LKB1, AMPK, and ACC and inhibited the expression of PPARγ, C/EBPα, and SREBP1c in mature 3T3-L1 adipocytes.	[67, 84]

16	Sprague-Dawley rats	0.2% FXN powder in feed	*Undaria pinnatifida*	The hepatic total lipids, total cholesterols, and triglycerides were significantly decreased while the fecal excretions of total lipids, cholesterol, and triglycerides were significantly increased in HFD+Fx group	[39]
17	Sprague-Dawley rats	5% seaweeds powder supplemented in HFD	*Eucheuma cottonii; aulerpa lentillifera, and Sargassum polycystum*	All seaweeds significantly reduced body weight gain, and plasma lipid peroxidation of HCF diet rats. However S. polycystum showed the best anti-obesity properties	[43]
18	KK-Ay mice and B6.V-Lepob/J (ob/ob) mice	0.1 or 0.2% FXN supplemented diet	*Undaria pinnatifida*	Suppressed body weight, visceral WAT mass, and lowered serum leptin levels	[86]
19	C57BL/6N mice	0.05 or 0.2% FXN supplemented diet	*Undaria pinnatifida*	Regulated the plasma and hepatic lipids metabolism; increased fecal lipid excretion. Fecal weight, liver and triglycerides and cholesterol were not significantly different between 0.05 and 0.2% FX fed mice	[72]
20	Human	6, 12, and 18 mg/day of ASX	*Haematococcus pluvialis*	12 and 18 mg/day improved the serum lipid profile in humans (decrease in TG levels observed), 6 and 12 mg/day increased HDL-cholesterol, however BMI values remained unchanged	[96]
21	Male C57BL/6J mice	HF diet supplemented 0·003, 0.01 and 0.03 %of ASTX (by weight)	*Hematococcus pluvialis*	0.03% ASX fed group showed significantly lowered triacylglycerol concentrations increased the hepatic expression of endogenous antioxidant genes	[81]
22	male apoE knockout (apoE)−/− mic	0.03 % ASX	*Haematococcus pluvialis*	ASX-rich H. pluvialis extract improves cholesterol and lipid metabolism as well as antioxidant defense mechanisms	[97]
23	male Swiss albino mice	6 mg kg^{-1} per day for 60days	*Haematococcus pluvialis*	ASX treatment reduced lipid accumulation and oxidative stress and adipose tissue weight. Also improved insulin sensitivity	[85]
24	Human; verweight and obese young adults	5mg and 20mg soft ASX capsule	not mentioned	Improved lipid metabolism and prevented oxidative stress by stimulating the activity of the antioxidant defense system	[106]

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Abbreviations

ABTS	2,2′-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid
DPPH	2,2-Diphenyl-1-picrylhydrazyl
ABAP	2,2'-azobis(2-amidopropane)
ACC	Acetyl-CoA carboxylase
AMPK	AMP-activated protein kinase
ASX	Astaxanthin
BMI	Body mass index
TNF-α	Tumor necrosis factor α
C/EBPα	CCAAT Enhancer Binding Protein Alpha
COX-2	Cyclooxygenase-2,
FRAP	Ferric reducing antioxidant capacity
FXN	Fucoxanthin
iNOS	Inducible nitric oxide synthase
mRNA	Messenger RNA
ORAC	Oxygen radical absorbance capacity
PPARγ	Peroxisome Proliferator-activated Receptor γ
SCD1	Stearoyl-coenzyme A desaturase-1
SREBP-1c	Sterol regulatory element-binding protein
WAT	White adipose tissue

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