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Fucoxanthin: A review of potential benefits relative to human health

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Fucoxanthin: A Review of Potential Benefits Relative to Human Health

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Abstract

Fucoxanthin is a carotenoid sourced and extracted mainly from dark orange and brown seaweeds found in the pacific ocean, such as the wakame algae. The allenic bonds and unique oxygen groups give fucoxanthin its unique structure and are thought to be part of the reason fucoxanthin has unique physiological functions. Fucoxanthin has potentially numerous effects on the physiology of human health, ranging from skin health to metabolic health, which have been demonstrated in animal model research. The goal of this review is to examine current literature to discuss fucoxanthin's potential application as a nutraceutical, treatment for obesity, type 2 diabetes, chronic inflammation, and dyslipidemia to provide an alternative, or additive treatment to pharmacoligcal interventions.

Chapter 1: Introduction

Fucoxanthin, a brown seaweed carotenoid, has the potential to be used to ameliorate a host of health issues, ranging from dermatitis[1] and skin wrinkling [2] to prevention and treatment of several types of cancer in mouse models[3–7]. Fucoxanthin further provides benefits through unique mechanisms of action with regards to some of the world's most far-reaching diseases, such as obesity, diabetes, and other inflammatory diseases as shown in several murine model projects[8–11]. The unique actions of fucoxanthin may prove to be a beneficial additive treatment, or even as a stand-alone treatment option for those who prefer a holistic approach to health.

Fucoxanthin's health benefits were first discussed in the late 1920s, as it was noted to be in high quantities in cod liver oil, a successful treatment for rickets[12]. In murine model research, the current literature now reveals fucoxanthin having benefits to health beyond treating rickets and directly benefitting diseases such as diabetes, heart disease, and obesity[8–11]. A small quantity of murine research emerged in the 2000s about fucoxanthin's health benefits, however, most of the research on fucoxanthin is related to plant biology and physiology, leaving much to be explored in the field of human health and physiology. Many of the research projects examining the health benefits of fucoxanthin have been conducted in murine models, leaving a large gap in the literature on the potential benefits to humans.

The objective of this paper is to review the current body of literature relative to fucoxanthin's potential benefits to human health and chronic disease management with specific regards to adiposity, blood glucose, inflammation, and blood lipids.

Chapter 2: Methods

Three online databases (PubMed, Scopus, and Alt HealthWatch) were reviewed using the following search terms: “fucoxanthin” combined with “diabetes”, “UCP1”, “Obesity”, “lipids”, and “inflammation”. Both animal and human research were included, as human experimental data on fucoxanthin is currently limited. Peer-reviewed articles reported in English from January 2000- March 2021 were included in the search review. All research included were full-text articles available through the James Madison University library databases at the time of authorship. (Figure 1)

Chapter 3: Manuscript

History

The earliest mention of fucoxanthin's potential health benefits was in 1928 from Knut Wejdling, a Swedish researcher from Stockholm University. Wejdling was investigating the antirachitic nature of cod liver oil and found that fucoxanthin may act as a link for unsaturated carbon linkages found within cod liver. Wejdling hypothesized that during the depigmentation of fucoxanthin within the livers of deep water cod, lipids were released, yielding cod liver to become antiarachtic[12].

The first true experimental trial showing fucoxanthin's promising benefit to human health was published in 1990 from Jyunichi Okuzumi's research group from the Kyoto Prefectural University of Medicine. Okuzumi's group found that treating in-vitro human malignant tumor cells with a 10 μg/ml fucoxanthin serum for three days reduced the rate of growth of neuroblastoma cells to 38% of their original growth rates[13]. It was revealed that fucoxanthin inhibited the G0-G1 phases of the cell cycle, being the initial replicative steps of cell growth[13]. The same fucoxanthin serum reduced the expression of N-myc proto-oncogene protein, a gene that is responsible for cell proliferation in cancer cells[13]. Fucoxanthin was largely left unstudied in human trials following Okuzumi's findings until the early 2000's when research groups found anti-cancer effects in human prostate cells[14,15], and inhibition of replicative DNA polymerase activity, lending fucoxanthin to being coined as an anti-neoplastic compound[16].

Between these first mentionings of fucoxanthin in cod liver oil and its later application in its anti-cancer potential, most research about fucoxanthin was describing its general contribution to plant biology. James Mann and Jack Myers from The

University of Texas, Austin, discussed the fact that fucoxanthin was much more efficient at energy transfer to chlorophyll during photosynthesis than other carotenoids[17]. Fucoxanthin was also found to have significantly higher absorption rates of light across various spectrums (450-700nm) compared to other carotenoids commonly found in algae and referred to as Mann and Myers to be one of the most important light-absorbing pigments for the photosynthetic process[17].

Biological Properties

Contrasting with the majority of other carotenoids, fucoxanthin contains an allenic bond as well as the oxygen functional groups: beta-gamma-epoxy ketone, hydroxyl, carbonyl, and carboxyl groups[18]. Using ozonolysis to chemically degrade fucoxanthin, two synthetic fucoxanthin metabolites, apo-9'-fucoxanthinone, and apo-13-fucoxanthinone can be created[19–21]. Ozonolysis will chemically split the fucoxanthins polyene chain into two groups, one being a group with an allenic bond, and the other being a beta-gamma-epoxy ketone group[21]. Current literature would indicate that the two synthetic metabolites seemingly function the same as their organic counterparts[22].

In nature, carotenoids are absorbed by the Caco-2 cells in the intestinal lining, the same pathway as dietary fat due to the fact that all carotenoids are hydrophobic similar to lipids[23]. Fucoxanthin is metabolized into two different bioactive compounds, fucoxanthinol and amarouciaxanthin, with fucoxanthin primarily metabolizing into fucoxanthinol in the human gastrointestinal tract[24]. It has been suggested that lipase and carboxylesterase are released for the enzymatic breakdown of fucoxanthin in the gastrointestinal tract, and the hydrolyzed form of fucoxanthin is then absorbed by Caco-2 cells, then circulated by the lymphatic system[23]. The atypical functional oxygen groups

are in part what gives fucoxanthin its molecular shape and unique biological function[18,25]. Among fucoxanthins numerous physiological functions, their effects on obesity, diabetes, inflammation, and dyslipidemia are extremely promising. It's known in the field of medicine and human health that obesity is associated with dyslipidemia, and will negatively impact inflammatory cytokines, which may cause type 2 diabetes[26,27].

Obesity

The prevalence of obesity is far-reaching, showing prevalence in all races, sexes, and ages within the United States, and has become the most prevalent metabolic disease in the modern world[28–32]. Screening for obesity in a clinical setting can be done by calculating an individual's body mass index (BMI) by using a person's height and weight, with the highest risk group for developing chronic disease being those with a BMI greater than 29.9kg/m^2[33]. While BMI may have limitations on describing body fatness for all individuals, it provides an effective estimation of body fatness for most patients within a clinical setting[33,34]. With rates of obesity in the United States being projected to continually increase[30,35], alternative routes to help individuals manage their obesity, such as pharmacological aids and bariatric surgery amongst other plans, are constantly being developed and implemented[36–38]. Adipose tissue is comprised of two different subtypes of adipose, referred to as white adipose tissue (WAT) and brown adipose tissue (BAT). The main difference between WAT and BAT, with concerns to this review, is that BAT contains uncoupling protein-1 (UCP1)[39]. While UCP1 mRNA is found both within BAT, as well as WAT, but largely lay unexpressed, and dormant in most WAT cells, unless exposed to certain environmental factors such as extreme cold. UCP1 expression upregulating within WAT cells is reffered to as "browning", as the

tissue now displays the metabolic characteristics of BAT[40] . UCP1 is found within the inner membrane of the mitochondria of BAT, and when UCP1 is upregulated, protons outside of the mitochondrial space are taken by the UCP1 to produce heat (thermogenesis) rather than being utilized for energy[41–45].

Murine rat models and limited human trials have revealed promising capabilities that fucoxanthin supplementation has the unique capability to induce UCP1 expression in WAT to stimulate whole-body adipose tissue loss[10,11,18,46]. A murine model study that was performed by Maeda et. al (2005) revealed that when KK-A(y) mice and Wister rats were fed either 0.32% or 1.3% fucoxanthin by weight of diet for four weeks, UCP1 expression was almost 5 times higher in WAT when compared to the control group. WAT tissue relative to total body weight was over 25% lower in the fucoxanthin-fed group, indicating the increased UCP1 expression within the WAT lead to overall weight loss [46]. The fucoxanthin-fed mice and rats also had significantly lower body weight when compared to the control group, which can be solely attributed to the loss of WAT as there was no significant difference in the mean daily feeding intake, or other lifestyle factors between the fucoxanthin group and the control group[46].

In a study by Gille et. al, researchers revealed that after 26 days, C57BL/6 mice gained less body fat when being fed a fucoxanthin-rich phaedoactylum triconutum extract (PTE) when compared to the placebo group. Gille et. al also found that the two groups of mice being fed either 2.4 mg/kg body weight or 7.1 mg/kg bodyweight of fucoxanthin had as high as 11x higher UCP1 expression compared to the placebo mice[47]. In the only human study of fucoxanthin's effects on body fat, Abidov et. al found that when obese women supplemented with 2.4 mg of fucoxanthin for 16 weeks, they lost an average of

7.94 lb of body fat and had an average of a 5cm decrease in waist circumference when compared to the placebo group[48]. While there is no current literature observing the expression of UCP1 in WAT of a human subject supplementing with fucoxanthin, the loss in body fat presented by Abidov et. al shows promise for the potential of UCP1 expression in WAT similar to those of Madea's research in rats.

Diabetes

Globally, type 2 diabetes mellitus (T2DM) has rapidly become one of the largest public health concerns[49]. T2DM is an extremely complex polygenic condition in which individuals have blunted insulin secretion or action (insensitivity), causing hyperglycemia and impaired carbohydrate metabolism[50–52]. Various medications, diets, exercise interventions, and even bariatric surgery have all been shown to be effective routes in treating T2DM[53–58], with the most popular non-insulin-based drug being metformin[59–64].

Research conducted in murine models revealed that fucoxanthin may decrease blood glucose through a myriad of actions stemming from fucoxanthin's ability to upregulate glucose transporter 4 (GLUT4) in muscle tissue[8]. Maeda et. al showed that after 4 weeks, out of the 24 obese C57BL/6 mice, the groups that were fed a high-fat diet enriched with either 1.06%, or 2.22% fucoxanthin, sourced from wakame lipids, had the same muscular GLUT4 activity, as well as plasma insulin and blood glucose levels as the non-obese mice[8]. Another murine model using C57BL/6 mice from Gille et. al, showed that after 26 days, the obese mice who received 2.4 mg/kg body weight, or 7.1 mg/kg bodyweight of fucuxanthin had lower plasma insulin levels (27.7 mU/L and 33.5 mU/L, respectively) when compared to the placebo group (42.1 mU/L)[47]. Interestingly, the group that received the 2.4 mg/kg treatment had significantly lower 6 hour fasted plasma

glucose (134 mg/dL) when compared to the group that was supplemented with 7.1 mg/kg (179 mg/dL), who had plasma glucose levels higher than the placebo group (161 mg/dL)[47]. Through it's utility in decreasing blood glucose using different pathways from pharmaceutical intervention, metformin, fucoxanthin may prove in the future to be a potential treatment option for those who cannot tolerate the GI discomfort from metformin, and may also serve as an additive prescriptive to an already metformin based intervention.

Inflammation

Both chronic and acute inflammation is induced by the production of inflammatory cytokines in response to a stressor, and when left unchecked, chronically high-stress levels can lead to increased risk of non-communicable chronic disease development[65,66]. Interleukin-6 (IL-6) is a cytokine heavily involved in acute and chronic inflammatory responses, as well as the regulation of various metabolic processes[67–70]. IL-6 has been demonstrated to play a critical role in the development and progression of pancreatic cancer tumor growth by stimulating cancerous neoplastic cells[71]. By blocking IL-6 activity via prescription Tocilizumab, researchers have been able to effectively treat the autoimmune disease rheumatoid arthirits[72]. Neutralizing IL-6 via IL-6 antibodies has beneficial effects in other autoimmune diseases such as Castleman's Disease, and juvenile idiopathic arthritis[68].

Tumor necrosis factor apha (TNF-α) is another inflammatory cytokine that is responsible for inducing cellular apoptosis, and activation of the proinflammatory nuclear factor-kB pathway(NF-kB)[73]. TNF-α directly impairs the signaling and responsiveness of

insulin by upregulating serine phosphorylation on insulin receptor substrate 1 (IRS-1), leading to the development of insulin resistance[74,75].

Fucoxanthin has the ability to attenuate tumor necrosis factor-alpha (TNF-α), and leptin levels, both of which contribute to insulin resistance[76,77]. The same study previously mentioned in this section from Maeda et. al revealed that the C57BL/6 mice had more than 60% lower TNF-α levels after being fed a high-fat diet enriched with fucoxanthin when compared to the control group, and the high-fat diet group who did not get the fucoxanthin[8]. Maeda et. al also showed that leptin mRNA levels expression was significantly lower in the groups being fed a high-fat diet, enriched with fucoxanthin when compared to the high-fat diet group that did not receive the fucoxanthin[8].

Fucoxanthin supplementation has exhibited decreases in IL-6 and TNF-α in another murine model study from Jiang et. al using ICR mice. Seven days before treatment with a lipopolysaccharide injection, the group of ICR mice that were treated with 200 mg/kg of fucoxanthin had up to 55% lower concentration of IL-6 and TNF-α in the hippocampus when compared to the group that received no fucoxanthin treatment. The same mice treated with 200 mg/kg of fucoxanthin showed up to a 59% lower concentration of IL-6 and TNF-α in the frontal cortex, and up to a 51.9% lower concentration of IL-6 and TNF-α in the hypothalamus when compared to the group of mice that did not receive the fucoxanthin treatment[78]. The group of mice treated with 200 mg/kg of fucoxanthin also showed lower significantly lower expressions of NF-kB in the hippocampus, hypothalamus, and frontal cortex, indicating that one of the fucoxanthins potential routes of inflammation attenuation is by inhibiting the NF-kB pathway[78]. The mechanisms in how fucoxanthin inhibits the NF-kB pathway are currently still unclear[79],

but these preliminary studies provide the groundwork for future research to explore fucoxanthin's mechanism(s) of action in inflammation.

Hyperlipidemia

Hyperlipidemia is a condition characterized by the elevation of serum triglycerides and/or low-density lipoprotein cholesterol (LDL-C) and is a strong risk factor for the development of cardiovascular disease (CVD)[80–82]. Hyperlipidemia impacts the function of vascular endothelial cells by damaging the vascular wall[83]. Pharmaceutical treatments such as statins work to reduce LDL-C[84,85], by inhibiting endogenous cholesterol production. While statins are successful at attenuating hyperlipidemia, they are also associated with negative side effects such as myopathy[86], development of T2DM[87], and potential hemorrhagic strokes in those who have high blood pressure[88,89]. The supplementation of fucoxanthin may be a unique treatment for those with hyperlipidemia that either prefer to not use statins, or who perhaps cannot tolerate statins as part of their treatment plan.

In murine model experiments, fucoxanthin demonstrates promise as a potential treatment for hyperlipidemia, by having multiple effects on lipid profiles. Beppu et. al found that in obese KK-A(y) mice, that after 4 weeks of being on a diet containing 0.2% fucoxanthin increased serum serum high-density lipoprotein cholesterol (HDL-C) by 50 mg/dL, and reduced the amount of total cholesterol found in the liver by 4.6 mg[90]. Maeda et. al explored the effect of fucoxanthin in mice during a high-fat diet and found that after feeding C57BL/6 mice a high-fat diet, the groups receiving 1.06% and 2.22% fucoxanthin had up to 53% lower LDL-C when compared to the high-fat non-fucoxanthin group[8]. Research from Ha et. al has revealed that rats who were on a high-fat diet made

up of 0.2% fucoxanthin for 4 weeks had 158% higher plasma HDL-C and 23% lower serum triglycerides, as well as 46% lower total liver cholesterol and 41% lower liver triglycerides, compared to the high-fat diet without fucoxanthin or a control diet groups[91].

These lipid-altering actions can be attributed to fucoxanthin downregulating the mRNA expression of SREBP-1c, a gene in which controls the lipogenic enzymes Acetyl-CoA carboxylase, fatty acid synthase, and glucose-6-phosphate dehydrogenase[91]. Fucoxanthin has also demonstrated the capability to upregulate CYP7A1 gene expression in the liver, causing more fecal excretion of cholesterol[91]. The aforementioned data collected insinuates that fucoxanthin supplementation, in addition to, or in replacement of a statin-based treatment regimen, may help decrease serum total cholesterol, LDL-C, and triglycerides, as well as increasing serum HDL-C.

Discussion

In conclusion, fucoxanthin has the potential mechanisms to postivitley impact many different aspects of human health. Not only obesity, but glucose management, inflammation, and dyslipidemia may all be aided by fucoxanthin's promising effects. Fucoxanthin has implications as a potential clinical intervention to help those who are overweight/obese, as these individuals can typically benefit from increased GLUT4 translocation, decreased adiposity, reduced inflammation, and lipid profile improvements. If fucoxanthin were to be used to attenuate any of the previously mentioned areas of health, there would be potential beneficial outcomes in other areas of health such as using fucoxanthin to reduce blood glucose, but also achieving a reduction in LDL-C for a patient with T2DM.

The current landscape of literature is limited by numerous factors. As it stands, the majority of fucoxanthin-based research has been done in mouse model research. More research needs to be done in various human populations to examine fucoxanthin's true effects on human health, as opposed to discussing its potential health effects for humans. In human studies, an established dose of fucoxanthin for supplementation should be investigated based on the desired health outcome. Hand in hand with an established dosage, researchers should elucidate any negative side effects, as well any interactions with other pharmaceutical or nutraceutical interventions, currently no human studies suggest harmful side effects. Long-term supplementation studies are another area of continued research that needs to be further established so that clinicians be aware of how long an individual can supplement with fucoxanthin. Further research is needed to elucidate more of fucoxanthin's mechanisms of action that haven't yet been discovered,

such as exactly how fucoxanthin affects the expression of the NF-kB pathway, as well as UCP1 genes, and the expression of mRNA signaling of Acetyl-CoA carboxylase, fatty acid synthase, and glucose-6-phosphate dehydrogenase via SREBP-1c. An investigation as to whether fucoxanthin will have a larger lipolytic effect on subcutaneous adipose tissue, or visceral adipose tissue may also prove to provide further insight into fucoxanthins use case. Fucoxanthin offers unique potential to be a nutraceutical treatment option for those who are obese, as fucoxanthin not only directly attenuates obesity, but also will attenuate the commonly associated co-morbidites of obesity, being T2DM, chronic inflammation, and hyperlipidemia.

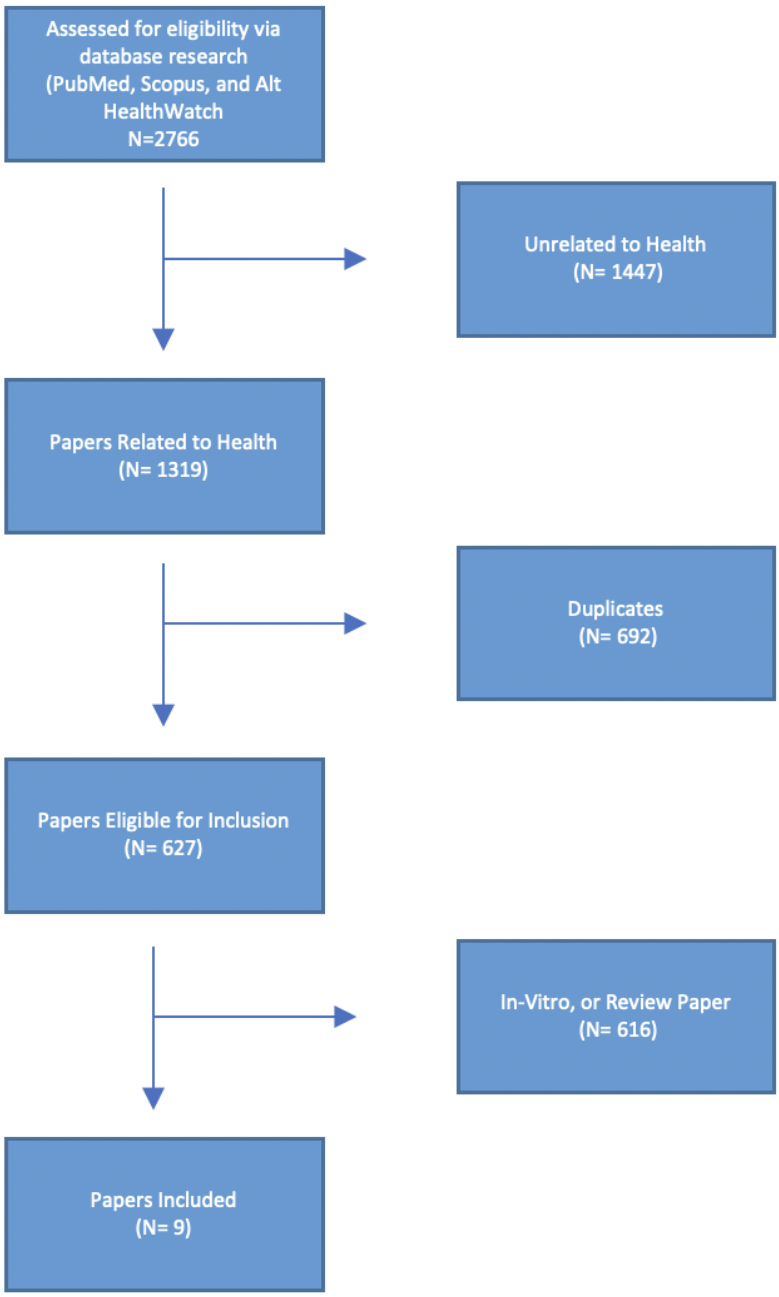

Figure 1. CONSORT Diagram

Table 1. In Vivo Fucoxanthin Research Effecting Obesity

Title	**Author**	**Subjects**	**Treatment**	**Results**
Anti-obesity and anti-diabetic effects of fucoxanthin on diet-induced obesity conditions in a murine model	Madea et. al	C57BL/J Mice	1.06% or 2.22% fucoxanthin by weight of diet	Higher weight loss in FX groups, WAT gain was suppressed in FX group. Leptin mRNA expression up to 89% lower in the FX group.
Dietary Combination of Fucoxanthin and Fish Oil Attenuates the Weight Gain of White dipose Tissue and Decreases Blood Glucose in Obese/Diabetic KK-Ay Mice	Madea et. al	KK-Ay Mice	0.2% Fucoxanthin, or 0.1% Fucoxanthin + 6.9% Fishoil by weight of diet	FX treated mice were 6.4g lighter on average compared to control group.
Fucoxanthin from edible seaweed, *Undaria pinnatifida*, shows antiobesity effect through UCP1 expression in white adipose tissues	Madea et. al	Male Wistar Rates, Female KK-Ay Mice	1.3% or 0.3% Fucoxanthin by weight of diet for four weeks	Over 25% lower WAT in Fx fed group. UCP1 expression ~5x higher in WAT of subjects treated with Fx.
A Lipophilic Fucoxanthin-Rich *Phaeodactylum tricornutum* Extract Ameliorates Effects of Diet-Induced Obesity in C57BL/6J Mice	Gille et. al	C57BL/J Mice	2.4mg fucoxanthin/kg bw or 7.1mg fucoxanthin kg/bw for 26 days	Fx fed groups had UCP1 as high as 11x higher expression in inguinal WAT.
The effects of Xanthigen™ in the weight management of obese premenopausal women with non-alcoholic fatty liver disease and normal liver fat	Abidov et. al	Obese premenopausal women	2.4mg fucoxanthin + 300mg pomegranate seed oil daily for 16 weeks	6.9kg +/1.9kg loss in body weight in the Fx group. Average of 5cm lost in waist circumference.

Table 2. In Vivo Fucoxanthin Research Effecting Diabetes, Hyperlipidemia, and Inflammation

Title	**Author**	**Subjects**	**Treatment**	**Effects on Diabetes**	**Effects on Hyperlipidemia**	**Effects on Inflammation**
Anti-obesity and anti-diabetic effects of fucoxanthin on diet-induced obesity conditions in a murine model	Madea et. al	C57BL/J Mice	1.06% or 2.22% fucoxanthin by weight of diet for 26 days	Fx group regained healthy GLUT4 levels in muscle tissue by the end of a high fat diet.		
Dietary Combination of Fucoxanthin and Fish Oil Attenuates the Weight Gain of White dipose Tissue and Decreases Blood Glucose in Obese/Diabetic KK-Ay Mice	Madea et. al	KK-Ay Mice	0.2% Fucoxanthin, or 0.1% Fucoxanthin + 6.9% Fish oil by weight of diet	Blood improved glucose and insulin in FX fed groups.	53% lower LDL-C in Fx group compared to control group.	
Effects of dietary fucoxanthin on cholesterol metabolism in diabetic/obese KK-Ay mice	Beppu et. al	KK-Ay Mice	0.2% Fucoxanthin by weight of diet for 4 weeks		Serum HDL 50 mg/dL higher, and 4.6g less liver cholesterol in Fx fed rats.	
A Lipophilic Fucoxanthin-Rich *Phaeodactylum tricornutum* Extract Ameliorates Effects of Diet-Induced Obesity in C57BL/6J Mice	Gille et. al	C57BL/J Mice	2.4mg fucoxanthin/kg bw or 7.1mg fucoxanthin kg/bw for 26 days	Fx treated mice had 45 mg/dL lower plasma insulin.		
The effect of fucoxanthin rich power on the lipid metabolism	Ha et. al	Sprague-Dawley rats	4% Fucoxanthin by weight of diet for 4 weeks	.	158% higher plasma HDL-C, 46% lower liver	

in rats with a high fat diet.					cholesterol, and 41% lower liver triglycerides in the Fx fed group when compared to control. Fx group also had lower expression of SREBP-1c mRNA. CYP7A1 gene expressed higher in Fx fed groups compared to control.	
Fucoxanthin prevents lipopolysaccharide-induced depressive-like behavior in mice via AMPK- NF-κB pathway.	Jiang et. al	ICR Mice	Control +200mg/kg FX Lipopolysaccharide + 50mg/kg FX, Lipopolysaccharide + 100mg/kg FX Lipopolysaccharide + 200mg/kg FX			LPS+200 mg/kg of Fx group had 55%, 59%, and 51.9% lower IL-6 and TNF-α in the hippocampus, frontal cortex, and hypothalamus, respectively. LPS+200 mg/kg Fx group also had lower NF-kB expression compared to control.

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