Potential Use of Fucoxanthin to Alleviate Hyperlipidemia: A review

.

ABSTRACT

|  |
| --- |
| Fucoxanthin from marine alga has beneficial used to alleviate hyperlipidemia due to high antioxidant capacity. The challenge to use this material due to unstable in harsh condition. Some previous studies showed extraction method was a crucial point to extract fucoxanthin. After extraction, fucoxanthin need to be encapsulated because it was not stable in the gastrointestinal tract. In this review article will be describe fucoxanthin, extraction method in fucoxanthin, encapsulation method for fucoxanthin and the ability of fucoxanthin to alleviate hyperlipidemia. The article was used in this review from 2015-2023 that has been published in journal portal. The results of this review showed advance extraction method in fucoxanthin to increase yield content done at low temperature. Encapsulation technique used to stabilized this active material and can be used as targeted release component in gastrointestinal tract. Due to high content of antioxidant, fucoxanthin can be used to alleviate hyperlipidemia through enhancement fat oxidation, regulation body weight, lipid metabolism management and regulation fat through AMPK regulation. From this review article showed that fucoxanthin can be used as treatments to alleviate hyperlipidemia. |

***Keywords:*** *Fucoxanthin, Encapsulation, Hyperlipidemia, antioxidant, fat oxidation, regulation body weight, lipid metabolism*

1. INTRODUCTION

People lifestyles greatly affects the metabolic events that occur in the human body. Some types of unhealthy lifestyles lead to the emergence of various kinds of metabolic disorders in the body, one of which is fat metabolism disorders. Fat metabolism is a stage of fat digestion in the body to produce a certain amount of energy. Fat metabolism also plays an important role in the process of hormone secretion (Bahesti et al., 2020). The process of fat metabolism that does not run properly in the body can cause disorders and have a fatal impact on the human body (Bae et al., 2020).

 So far, people still utilize synthetic compounds in the form of drugs as a compound that plays a role in overcoming several types of diseases caused by fat metabolism disorders. The use of synthetic compounds is considered more efficient in overcoming metabolic disorders in fat because it can react quickly in reducing the level of fat in the body (Packard et al., 2020). However, what needs to be realized is that the use of synthetic drugs over a long period of time can cause other health problems.

To overcome the health problems that may arise from some types of synthetic compounds, treatment with natural compounds is carried out. Some natural compounds can play a role in reducing fat levels in the body. The impact of treatment using natural compounds will be felt more slowly and takes a relatively longer time (Achour et al., 2023). However, treatment with natural compounds has a better health impact than treatment with drugs.

 One type of natural compound that is useful in the treatment of fat metabolism disorders is fucoxanthin. Fucoxanthin is a type of carotenoid pigment found in brown seaweed. Seaweed must be extracted first to obtain fucoxanthin compounds. Fucoxanthin also has a disadvantage due to its low stability (Gholami et al., 2021). This review will discuss the extraction methods that can be done, encapsulation methods and the use of fucoxanthin in regulating lipid metabolism disorders in the body.

2. FUCOXANTHIN

Fucoxanthin is a group of carotenoids derived from marine sources. It is a pigment produced through the process of photosynthesis (Khaw et al., 2022). Fucoxanthin is classified as a non-provitamin A carotenoid and comprises 40 organic carbon molecules, which are divided into two groups: xanthophylls (containing oxygen in their chemical structure) and carotenes (lacking oxygen in their chemical structure) (D’Orazio et al., 2012; Pereira et al., 2021). The chemical structure of fucoxanthin consists of an unusual allenic bond, a 5,6-monoepoxide, and nine conjugated double bonds. A distinctive feature of fucoxanthin is the presence of the allenic bond, which is not found in other carotenoid compounds (Bae et al., 2020). Fucoxanthin can form cis-isomeric structures through isomerization, a process influenced by conditions, medium, and the type of carotenoid. In its pure form, fucoxanthin exhibits three main peaks in the trans form along with two isomers (Sun et al., 2022). Naturally, fucoxanthin undergoes degradation at temperatures between 25°C and 60°C (Zhao et al., 2020).

4. SOURCE OF FUCOXANTHIN

Fucoxanthin is widely found in both microalgae and macroalgae, including Undaria pinnatifida, Laminaria japonica, Phaeodactylum tricornutum, Alaria crassifolia, Cladosiphon akamuranus, Cystoseira hakodatensis, Eisenia bicyclis, Fucus vesiculosus, Padina tetrastromatica, Petalonia binghamiae, Sargassum fulvellum, and Cylindrotheca closterium (Miyashita et al., 2020; Bayu et al., 2020; Mao et al., 2020). Several brown seaweeds with high fucoxanthin content that are utilized in the food industry include Saccharina spp., Fucus spp., Sargassum spp., Hijikia fusiformis, and Undaria pinnatifida (Bayu et al., 2020). Microalgae have been shown to contain fucoxanthin levels up to 100 times higher than macroalgae (Khaw et al., 2022). In industrial applications, the extraction of fucoxanthin from macroalgae is more challenging due to the lower concentration of fucoxanthin in macroalgal biomass. The fucoxanthin content in various plants varies widely, ranging from 17.2 mg to 72.0 mg per 100 g of dry weight (Miyashita et al., 2020).

Differences in fucoxanthin content across species are influenced by several factors, including species type, geographic location, season, temperature, salinity, and light intensity. One of the main factors affecting fucoxanthin levels is lipid content; higher lipid levels in seaweed are generally associated with higher fucoxanthin content. Fucoxanthin concentrations in seaweed tend to decrease during the summer but increase in the autumn, reaching peak levels in January (Heavisides et al., 2018; Marinho et al., 2019).

5. CHEMICAL COMPOSITION RELATED BENEFITS OF FUCOXANTHIN

Fucoxanthin is a carotenoid predominantly found in brown seaweeds, where it acts as a photosynthetic pigment along with chlorophyll a and c, and β-carotene (Zhang et al., 2015; Lourenço-Lopes et al., 2021). With a molecular weight of 658.9 g/mol, fucoxanthin (C₄₂H₅₈O₆) is located in the photosynthetic organs of brown seaweeds and microalgae and plays a key role in photochemical processes (Murase et al., 2021; Terasaki et al., 2021). Fucoxanthin possesses a unique structure, including an allenic bond, conjugated carbonyl, 5,6-monoepoxide, and an acetyl group, as well as hydroxyl, carbonyl, and carboxyl groups, which contribute to its strong antioxidant capacity (Guvatova et al., 2020).

An allenic bond refers to a structure in which a carbon atom forms two double bonds with two adjacent carbon atoms. This unique structural feature of fucoxanthin contributes to various therapeutic effects, including antioxidant, anti-obesity, anti-diabetic, anti-cancer, anti-inflammatory, hepatoprotective, skin-protective, antiangiogenic, cerebrovascular, bone-protective, eye-protective, and cardiovascular-protective properties (Oliyaei et al., 2020). Several non-allenic carotenoids, including β-carotene 5,6-epoxide, lutein, and lutein epoxide, are known to lack the ability to suppress fat accumulation in adipose tissues or the liver, suggesting that the allenic bond in fucoxanthin and its derivatives may play a role in inhibiting fat deposition.

Fucoxanthin exhibits a wide range of beneficial biological activities, including hypolipidemic, anti-obesity, anti-diabetic, and anti-carcinogenic effects (Wang et al., 2020). These diverse bioactivities are largely attributed to its unique chemical structure, especially its conjugated system, which facilitates antioxidant activity (Bae et al., 2020). Various biological activities of fucoxanthin have been confirmed, including anti-tumor effects (Long et al., 2020; Méresse et al., 2020), antibacterial activity (Karpiński et al., 2021; Karpiński & Adamczak, 2019), anti-obesity effects (Guo et al., 2019), neuroprotection (Wu et al., 2021), and anti-inflammatory properties (Liu et al., 2020).

In addition to its diverse biological activities, fucoxanthin has been shown to reduce hepatic lipid levels by increasing docosahexaenoic acid (DHA) concentrations. It also improves lipid metabolism and glycemic status under obese conditions. Fucoxanthin has been found to alleviate hyperlipidemia in diabetic mice by modulating insulin receptor substrate 1 (IRS-1) and activating the AMP-activated protein kinase (AMPK) signaling pathway (Zhang et al., 2018).

Fucoxanthin also shows positive effects on weight reduction and lipid lowering. For example, Gille et al. (2019) reported that fucoxanthin-rich Trichochromophore extract could reduce the expression of genes involved in fatty acid oxidation in white adipocytes. Similarly, Sharma & Baskaran (2021) confirmed that adipocyte differentiation was suppressed through inhibition of the PI3K/MAPK signaling pathway. In line with this, Koo et al. (2019) observed that fucoxanthin upregulated uncoupling protein 1 (UCP1) in the liver and downregulated peroxisome proliferator-activated receptor gamma (PPARγ), thus demonstrating anti-obesity potential.

Upon consumption, fucoxanthin is primarily absorbed in the gastrointestinal tract as fucoxanthinol, a hydrolyzed metabolite, which enters the bloodstream via the lymphatic system in mammals. Part of the fucoxanthinol is further metabolized into amarouciaxanthin A in the liver. Fucoxanthin is generally metabolized into fucoxanthinol and amarouciaxanthin A (Hao et al., 2023).

6. EXTRACTION METHOD OF FUCOXANTHIN

There is a challenge in obtaining pure fucoxanthin from marine sources due to the presence of salts in the fucoxanthin matrix (Khaw et al., 2022). Several extraction methods for fucoxanthin include:

1. Maceration Extraction

Maceration is a conventional extraction method involving the soaking of seaweeds for a specific period to obtain fucoxanthin. Key factors to consider in fucoxanthin extraction using maceration are temperature, duration, and type of solvent used. Extraction time ranges from 15 minutes to 96 hours, with temperatures between 4°C and 65°C. Various solvents used include methanol, ethanol, ethyl acetate, acetone, water, hexane, chloroform, dichloromethane, heptane, and diethyl ether (Renhoran et al., 2017; Savira et al., 2021; Noviendri et al., 2023). Savira et al. (2021) reported that methanol is an effective solvent for fucoxanthin extraction, yielding 145.86 μg/g. Noviendri et al. (2023) found that extraction of Padina sp. using ethanol resulted in the highest fucoxanthin content of 133.31 ppm. Renhoran et al. (2017) showed that extraction using 96% ethanol at 18°C yielded 0.54%.

1. Vortex Assisted Extraction (VAE)

Vortex Assisted Extraction utilizes a vortex mixer to enhance the interaction between solvent and sample by creating rotational movement (Gholami et al., 2021). Nunes et al. (2019) reported that vortex-assisted solid-liquid microextraction (VASLME) with ethanol produced yields ranging from 10 to 853 μg/g.

1. Soxhlet Assisted Extraction (SAE)

Soxhlet Assisted Extraction uses a soxhlet apparatus. Temperature is a critical factor; higher extraction temperatures improve solvent efficiency in breaking the matrix, thus enhancing extraction efficiency (Alara et al., 2019). Raji et al. (2020) showed that Soxhlet extraction with ethyl acetate resulted in high fucoxanthin yields.

1. Enzyme Assisted Extraction

This method uses enzymes for extraction (Gligor et al., 2019; Zhang et al., 2020). The principle involves cellulose hydrolysis in the algal cell wall. Enzymatic extraction is considered a "green technology" due to its non-toxic waste production. It is also cost-effective, as the expense of enzymes corresponds to high yields. Shannon and Ghannam (2018) reported that extraction of Fucus vesiculosus using β-glucanase yielded 0.657 mg/g after 3.05 hours of incubation.

1. Microwave Assisted Extraction (MAE)

MAE utilizes microwave radiation for extraction (Bagade and Patil, 2021; Figueroa et al., 2021). Solvents used include ethanol and acetone, capable of yielding high amounts (Xiao et al., 2012). The extraction temperature remains moderate (around 50°C), preserving the matrix integrity. Lopes et al. (2023) reported a yield of 58.83 mg Fx/g E using MAE.

1. Ultrasound Assisted Extraction (UAE)

UAE employs ultrasound to create microscopic bubbles in the solvent. Bubble formation disrupts the microalgal cell wall, facilitating fucoxanthin extraction (Cikoš et al., 2023). Padina tetrastromatica extracted with 80% ethanol at 50°C for 30 minutes yielded 750 μg fucoxanthin (Raguraman et al., 2018). Oliyaei and Nasab (2021) reported that UAE with methanol on Cystoseira indica yielded 0.77 ± 0.05 mg/g. Extraction from Sargassum angustifolium with methanol and acetone yielded 0.70 ± 0.02 mg/g. A combination of sonication pre-treatment followed by UAE gave the highest yield of 0.79 ± 0.01 mg/g. Lopes et al. (2023) noted that UAE resulted in a total yield of 124.39 mg Fx/g.

1. Pressurized Liquid Extraction (PLE)

PLE utilizes high temperature and pressure with low solvent volumes and short extraction times (Archour et al., 2023). Subcritical solvents are used to shorten extraction time by heating and pressurizing them to their critical point (Guler et al., 2020). Derwenskus et al. (2020) reported that PLE at 100°C with ethanol yielded 16.2 ± 0.5 mg/g.

1. Solid Phase Extraction (SPE)

SPE uses a sorbent to isolate target compounds from complex mixtures (Chisvert et al., 2019). Sun et al. (2018) demonstrated that fucoxanthin recovery using SPE reached up to 70%.

7. ENCAPSULATION METHOD OF FUCOXANTHIN

Encapsulation is a method that provides physical protection to a target analyte, thereby enhancing its stability (Rezvankhah et al., 2020; Jafari et al., 2023). Fucoxanthin requires encapsulation due to its very low stability. The encapsulating materials used for fucoxanthin must be food-grade and non-toxic. Various substances suitable for fucoxanthin encapsulation include hydroxypropyl-β-cyclodextrin, maltodextrin, gum Arabic, whey protein isolate, isolated pea protein, and gelatin.

A study conducted by Oliyaei et al. (2020) demonstrated that encapsulating fucoxanthin with porous starch combined with halloysite nanotubes effectively enhanced the stability of fucoxanthin. This encapsulation method achieved an encapsulation efficiency (EE) of 94.05 ± 0.29%, indicating that porous starch and halloysite nanotubes are effective encapsulating agents. The encapsulated fucoxanthin exhibited good thermal stability and a sustained release profile, with release over 6 hours targeting specific sites. Another study by Oliyaei et al. (2020) reported that encapsulation using maltodextrin and gum Arabic resulted in a high EE of 96%. Moreover, this method maintained the stability of fucoxanthin throughout the entire storage period (4 weeks).

Zhao et al. (2022) reported that fucoxanthin encapsulated using skim milk powder (SMP) with zein nanoparticles as intermediate vectors exhibited an EE of 91% and good stability under UV light exposure. In simulated drug release studies across different gastrointestinal organs, approximately 6% of fucoxanthin was released in the duodenum, 13% in the jejunum, 32% in the ileum, and 42% in the colon. Another study by Li et al. (2022) indicated that protein-based encapsulation, using bovine serum albumin (BSA), significantly improved fucoxanthin stability. Encapsulation with BSA enhanced fucoxanthin’s absorption, accumulation, and antioxidant activity.

8. Hyperlipidemia

Indicators of lipid metabolism disorders in the body are often associated with elevated levels of low density lipoprotein (LDL)

1. Hypercholesterolemia

There are two types of hypercholesterolemia: familial and non-familial hypercholesterolemia. Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated levels of LDL in the body. FH is caused by mutations in the **LDLR**, **APOB**, and **PCSK9** genes, which code for LDL receptors. This condition is incurable; however, the risk of LDL surges can be minimized. The global prevalence of FH is relatively high, with approximately 91% of cases reported from Europe, North America, East Asia, and Australia (Behesti et al., 2020). The prevalence of FH increases by 10-fold in patients with ischemic heart disease (IHD), 20-fold in patients with premature IHD, and 23-fold in those with hypercholesterolemia (Behesti et al., 2020). Diagnosis can be made in children aged 9–11 years with elevated LDL levels. If high LDL levels are detected in children under the age of 2, a family history of coronary artery disease (CAD) should be investigated among blood relatives (McGowan et al., 2019). Pharmacological treatment of FH includes the use of **statins**, **ezetimibe**, and **monoclonal antibodies** that inhibit PCSK9 circulation (Raal et al., 2020). Further research has explored lowering LDL levels through genetic intervention by inhibiting **ANGPTL3** (a gene involved in triglyceride metabolism), which has been proven effective in reducing LDL levels (Steg et al., 2019).

Non-familial hypercholesterolemia refers to a condition in which cholesterol levels in the body increase due to dietary patterns and lifestyle habits. Consumption of foods high in cholesterol and fat can elevate the risk of hypercholesterolemia. Currently, the primary treatment for hypercholesterolemia involves **statins** as a therapy to lower LDL levels. Recent research indicates that statin therapy may be replaced by **inclisiran**, a drug that inhibits the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) (Khan et al., 2020).

1. Hypertriglyceridemia

Hypertriglyceridemia is a condition marked by elevated levels of **very-low-density lipoprotein (VLDL)** and other lipolytic products (Packard et al., 2020). Under normal conditions, triglyceride levels in the blood are below 100 mg/dL, while in pathological conditions, levels exceed 100 mg/dL. Increased body weight is associated with elevated triglyceride levels (Simha, 2020).

1. Cardiovascular Disorders (CVD)

The risk of developing cardiovascular disorders increases in correlation with elevated LDL levels in the body (Raal et al., 2020).

9. MECHANISM OF FUCOXANTHIN ALLEVIATE HYPERLIPIDEMIA

Fucoxanthin is a natural carotenoid pigment found in brown algae. It exhibits hypolipidemic and anti-obesity activities (Wang et al., 2020). Fucoxanthin has various biological activities due to its unique chemical structure, which contains a conjugated system that enables its antioxidant properties (Bae et al., 2020). Studies have demonstrated that fucoxanthin has potential in regulating lipid metabolism through several mechanisms, including:

1. Enhancement of Fat Oxidation

Fucoxanthin has been shown to increase the activity of enzymes involved in fat burning within mitochondria, thereby enhancing fatty acid oxidation and energy production. Mitochondria play a critical role in maintaining energy homeostasis and metabolism, including the generation of energy necessary for human physiology (Ramanathan et al., 2022). Mitochondrial dysfunction and increased oxidative stress are observed in patients with fatty liver disease, indicated by reduced respiratory chain activity and impaired β-oxidation in mitochondria (Li et al., 2019).
Fucoxanthin exhibits anti-obesity effects, particularly via thermogenic mechanisms through the upregulation of uncoupling protein 1 (UCP1) in mitochondria (Koo et al., 2019). UCP1 is a mitochondrial membrane protein responsible for thermogenic respiration and heat production in brown adipose tissue (BAT). Fucoxanthin induces UCP1 expression in abdominal white adipose tissue (WAT), initiating a process known as browning, whereby WAT transforms into BAT-like tissue. BAT dissipates energy via heat production, unlike WAT, which stores excess energy as triglycerides. The browning process thus promotes energy expenditure, reducing WAT volume and subsequent fat accumulation (Spagolla Napoleão Tavares et al., 2020).

1. Body Weight Regulation

Studies report an inverse relationship between plasma leptin levels and fucoxanthin intake. Leptin, predominantly secreted by adipose tissue, regulates body weight via lipid metabolism. Fucoxanthin administration has been shown to reduce leptin concentrations in adipocytes. Fucoxanthin-rich lipids also activate monocyte chemoattractant protein-1 (MCP-1) expression in high-fat diet (HFD)-induced obese mice. Oliyaei et al. (2023) reported significant weight reduction and fat accumulation inhibition in HFD mice treated with fucoxanthin at doses of 10 mg/kg and 50 mg/kg over 7 weeks. After 7 weeks, HFD mice weighed 327.5g, while fucoxanthin-treated mice weighed only 263.33g, indicating significant weight loss facilitated by fucoxanthin.

Moreover, fucoxanthin's anti-obesity effects are associated with inhibition of intercellular lipid accumulation via UCP1 expression, suppression of excessive TNF-α expression in obese WAT, and downregulation of iNOS and COX-2 mRNA expression in obese subjects. Fucoxanthin also modulates the expression of genes critical for fatty acid synthesis and oxidation, such as peroxisome proliferator-activated receptor alpha (PPARα), phosphorylated acetyl-CoA carboxylase (p-ACC), and carnitine palmitoyltransferase 1 (CPT-1) (Zhang et al., 2018). The anti-obesity effects of fucoxanthin reported by Grasa-López et al. (2018) also showed that fucoxanthin administration at 1 mg/kg/day reduced TG, TC, and LDL levels in diet-induced obese mice. Sharma & Baskaran (2021) revealed that fucoxanthin and fucoidan prevent excessive weight gain by upregulating Akt, UCP1, and downregulating PPAR-γ, which are key mechanisms for combating obesity.

1. Regulation of Antioxidant Response

Fucoxanthin’s hepatoprotective effects are linked to upregulation of antioxidant responses mediated by Nrf2, increased antioxidant enzyme activity, and overexpression of PPARα and CPT-1, along with reduced MDA levels. Obesity elevates MDA (a lipid peroxidation marker) while decreasing antioxidant enzyme levels, PPARα, and CPT-1 expression. PPARα and CPT-1 are associated with enhanced fatty acid oxidation under high-fat dietary conditions. PPARα overexpression stimulates fatty acid oxidation via CPT-1 expression. Fucoxanthin prevents hepatic lipid accumulation through the PPARα pathway and lipid droplet deposition. Furthermore, it suppresses lipid production by activating AMPK, thereby inhibiting ACC, SREBP-1c, and FAS gene expression, which reduces hepatic TG and fatty acid accumulation (Ye et al., 2022). Study by Yılmaz et al., (2021) showed the use of chemical compound contain antioxidant activity can be used as neuroprotective.

1. Lipid Metabolism Management

In addition to inducing thermogenesis via UCP1 activation, fucoxanthin modulates lipid metabolism and absorption by inhibiting lipogenesis and promoting lipolysis. This mechanism counteracts lipid metabolism disorders associated with non-alcoholic fatty liver disease (NAFLD). Fucoxanthin upregulates enzymes associated with lipolysis while downregulating those related to lipogenesis. In HFD-fed mice, fucoxanthin reduces hepatic lipid and plasma triacylglycerol levels, evidenced by increased excretion of undigested fecal lipids. It also reduces hepatic lipogenesis activity and enhances β-oxidation of fatty acids. Fucoxanthin increases the expression of other key proteins in lipid metabolism, such as AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) in epididymal adipose tissue. Additionally, it induces β3-adrenergic receptors (β3Ad), thereby promoting lipolysis and thermogenesis (Winarto et al., 2023).

1. Regulation of AMPK Signaling Pathway

The AMPK signaling pathway regulates metabolic organs such as the liver, skeletal muscle, pancreas, and adipose tissue. AMPK modulates glucose transport and fatty acid oxidation in skeletal muscle, while enhancing fatty acid oxidation and suppressing cholesterol and triglyceride synthesis in the liver. Studies have shown that AMPK activation suppresses acetyl-CoA carboxylase, inhibiting fatty acid synthase and reducing hepatocellular lipid accumulation (Chang et al., 2018). Liver-specific AMPK activation has been reported to reduce hepatic steatosis, inflammation, and fibrosis in NAFLD patients. It also confers resistance to weight gain and reduces overall lipid accumulation in mice (Garcia et al., 2019). Fucoxanthin upregulates AMPK, thereby enhancing fatty acid oxidation and providing protection against NAFLD.

10. CONCLUSION

Based on findings from several studies conducted both **in vitro** and **in vivo**, fucoxanthin has demonstrated potential as a natural compound for managing lipid metabolism disorders. Fucoxanthin functions as an antioxidant, thereby reducing inflammatory responses in the body. Its administration as a treatment can improve lipid metabolism by regulating **lipogenesis** and **lipolysis** processes. Fucoxanthin is considered to have promising potential in the treatment of lipid metabolism disorders such as **obesity**, **hypertension**, **fatty liver disease**, and others, due to its effective mechanism of action. In the food industry, fucoxanthin can be applied through **microencapsulation processes**, allowing its incorporation as a supplement in various food products. Considering the characteristics of microencapsulated products and the physicochemical properties of fucoxanthin, suitable applications would be in food products that do not involve high-temperature processing, such as **ice cream**, **milk**, and other **dairy products**.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

All author declare that NO generative AI technologies such as ChatGPT etc, and text to image generate have been used during the writing or editing of this manuscript

References

Achour, H. Y., Llamero, C. B., Saadi, S. A., Bouras, N., Zitouni, A., & Señoráns, J. (2023). Pressurized Liquid Extraction for the Recovery of Carotenoids and Functional Compounds from Green and Orange Dunaliella salina Biomasses. *Periodica Polytechnica Chemical Engineering*, *67*(2), 278-286.

Alara, O. R., Abdurahman, N. H., Ukaegbu, C. I., & Kabbashi, N. A. (2019). Extraction and characterization of bioactive compounds in Vernonia amygdalina leaf ethanolic extract comparing Soxhlet and microwave-assisted extraction techniques. *Journal of Taibah University for Science*, *13*(1), 414-422.

Bae, M., Kim, M. B., Park, Y. K., & Lee, J. Y. (2020). Health benefits of fucoxanthin in the prevention of chronic diseases. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, *1865*(11), 158618.

Bae, M., Kim, M.-B., Park, Y.-K., & Lee, J.-Y. (2020). Health benefits of fucoxanthin in the prevention of chronic diseases. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, *1865*(11), 158618. https://doi.org/10.1016/j.bbalip.2020.158618

Bagade, S. B., & Patil, M. (2021). Recent advances in microwave assisted extraction of bioactive compounds from complex herbal samples: a review. *Critical reviews in analytical chemistry*, *51*(2), 138-149.

Bayu, A.; Rachman, A.; Noerdjito, D.R.; Putra, M.Y.; Widayatno, W.B. High-Value Chemicals from Marine Diatoms: A Biorefinery Approach. In IOP Conference Series: Earth and Environmental Science; IOP Publishing: West Java, Indonesia, 2020; Volume 460, p. 12012

Beheshti, S. O., Madsen, C. M., Varbo, A., & Nordestgaard, B. G. (2020). Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. *Journal of the American College of Cardiology*, *75*(20), 2553-2566.

Chang, Y.-H., Chen, Y.-L., Huang, W.-C., & Liou, C.-J. (2018). Fucoxanthin attenuates fatty acid-induced lipid accumulation in FL83B hepatocytes through regulated Sirt1/AMPK signaling pathway. *Biochemical and Biophysical Research Communications*, *495*(1), 197–203. https://doi.org/10.1016/j.bbrc.2017.11.022

Chisvert, A., Cárdenas, S., & Lucena, R. (2019). Dispersive micro-solid phase extraction. *TrAC Trends in Analytical Chemistry*, *112*, 226-233.

Cikoš, A. M., Aladić, K., Velić, D., Tomas, S., Lončarić, P., & Jerković, I. (2023). Evaluation of ultrasound-assisted extraction of fucoxanthin and total pigments from three croatian macroalgal species. *Chemical Papers*, *77*(3), 1545-1559.

D’Orazio, N., Gemello, E., Gammone, M. A., De Girolamo, M., Ficoneri, C., & Riccioni, G. (2012). Fucoxantin: A treasure from the sea. *Marine drugs*, *10*(3), 604-616.

Derwenskus, F., Schäfer, B., Müller, J., Frick, K., Gille, A., Briviba, K., ... & Hirth, T. (2020). Coproduction of EPA and fucoxanthin with P. tricornutum–A promising approach for up‐and downstream processing. *Chemie Ingenieur Technik*, *92*(11), 1780-1789.

Figueroa, J. G., Borrás-Linares, I., Del Pino-García, R., Curiel, J. A., Lozano-Sánchez, J., & Segura-Carretero, A. (2021). Functional ingredient from avocado peel: Microwave-assisted extraction, characterization and potential applications for the food industry. *Food Chemistry*, *352*, 129300.

Garcia, D., Hellberg, K., Chaix, A., Wallace, M., Herzig, S., Badur, M. G., Lin, T., Shokhirev, M. N., Pinto, A. F. M., Ross, D. S., Saghatelian, A., Panda, S., Dow, L. E., Metallo, C. M., & Shaw, R. J. (2019). Genetic Liver-Specific AMPK Activation Protects against Diet-Induced Obesity and NAFLD. *Cell Reports*, *26*(1), 192-208.e6. https://doi.org/10.1016/j.celrep.2018.12.036

Gholami, Z., Marhamatizadeh, M. H., Yousefinejad, S., Rashedinia, M., & Mazloomi, S. M. (2021). Vortex-assisted dispersive liquid-liquid microextraction based on hydrophobic deep eutectic solvent for the simultaneous identification of eight synthetic dyes in jellies and drinks using HPLC-PDA. *Microchemical Journal*, *170*, 106671.

Gille, A., Stojnic, B., Derwenskus, F., Trautmann, A., Schmid-Staiger, U., Posten, C., Briviba, K., Palou, A., Bonet, M., & Ribot, J. (2019). A Lipophilic Fucoxanthin-Rich Phaeodactylum tricornutum Extract Ameliorates Effects of Diet-Induced Obesity in C57BL/6J Mice. *Nutrients*, *11*(4), 796. https://doi.org/10.3390/nu11040796

Gligor, O., Mocan, A., Moldovan, C., Locatelli, M., Crișan, G., & Ferreira, I. C. (2019). Enzyme-assisted extractions of polyphenols–A comprehensive review. *Trends in Food Science & Technology*, *88*, 302-315.

Grasa-López, A., Miliar-García, Á., Quevedo-Corona, L., Paniagua-Castro, N., Escalona-Cardoso, G., Reyes-Maldonado, E., & Jaramillo-Flores, M.-E. (2018). Undaria pinnatifida and Fucoxanthin Ameliorate Lipogenesis and Markers of Both Inflammation and Cardiovascular Dysfunction in an Animal Model of Diet-Induced Obesity. *Marine Drugs*, *14*(8), 148. https://doi.org/10.3390/md14080148

Guler, B. A., Deniz, I., Demirel, Z., Yesil-Celiktas, O., & Imamoglu, E. (2020). A novel subcritical fucoxanthin extraction with a biorefinery approach. *Biochemical Engineering Journal*, *153*, 107403.

Guo, B., Yang, B., Pang, X., Chen, T., Chen, F., & Cheng, K.-W. (2019). Fucoxanthin modulates cecal and fecal microbiota differently based on diet. *Food & Function*, *10*(9), 5644–5655. <https://doi.org/10.1039/C9FO01018A>

Guvatova, Z., Dalina, A., Marusich, E., Pudova, E., Snezhkina, A., Krasnov, G., Kudryavtseva, A., Leonov, S., & Moskalev, A. (2020). Protective effects of carotenoid fucoxanthin in fibroblasts cellular senescence. *Mechanisms of Ageing and Development*, *189*, 111260. <https://doi.org/10.1016/j.mad.2020.111260>

Hao, J., Zhang, J., & Wu, T. (2023). Fucoxanthin extract ameliorates obesity associated with modulation of bile acid metabolism and gut microbiota in high-fat-diet fed mice. *European Journal of Nutrition*. https://doi.org/10.1007/s00394-023-03256-z

Heavisides, E., Rouger, C., Reichel, A. F., Ulrich, C., Wenzel-Storjohann, A., Sebens, S., & Tasdemir, D. (2018). Seasonal variations in the metabolome and bioactivity profile of Fucus vesiculosus extracted by an optimised, pressurised liquid extraction protocol. *Marine Drugs*, *16*(12), 503.

Jafari, S., Jafari, S. M., Ebrahimi, M., Kijpatanasilp, I., & Assatarakul, K. (2023). A decade overview and prospect of spray drying encapsulation of bioactives from fruit products: Characterization, food application and in vitro gastrointestinal digestion. *Food Hydrocolloids*, *134*, 108068.

Karpiński, T. M., & Adamczak, A. (2019). Fucoxanthin—An Antibacterial Carotenoid. *Antioxidants*, *8*(8), 239. <https://doi.org/10.3390/antiox8080239>

Karpiński, T. M., Ożarowski, M., Alam, R., Łochyńska, M., & Stasiewicz, M. (2021). What Do We Know about Antimicrobial Activity of Astaxanthin and Fucoxanthin? *Marine Drugs*, *20*(1), 36. https://doi.org/10.3390/md20010036

Khaw, Y. S., Yusoff, F. M., Tan, H. T., Noor Mazli, N. A. I., Nazarudin, M. F., Shaharuddin, N. A., ... & Takahashi, K. (2022). Fucoxanthin production of microalgae under different culture factors: a systematic review. *Marine Drugs*, *20*(10), 592.

Koo, S. Y., Hwang, J.-H., Yang, S.-H., Um, J.-I., Hong, K. W., Kang, K., Pan, C.-H., Hwang, K. T., & Kim, S. M. (2019). Anti-Obesity Effect of Standardized Extract of Microalga Phaeodactylum tricornutum Containing Fucoxanthin. *Marine Drugs*, *17*(5), 311. <https://doi.org/10.3390/md17050311>

Li, Z., Li, Y., Zhang, H., Guo, J., Lam, C. W. K., Wang, C., & Zhang, W. (2019). Mitochondria‐Mediated Pathogenesis and Therapeutics for Non‐Alcoholic Fatty Liver Disease. *Molecular Nutrition & Food Research*, *63*(16). <https://doi.org/10.1002/mnfr.201900043>

Liu, M., Li, W., Chen, Y., Wan, X., & Wang, J. (2020). Fucoxanthin: A promising compound for human inflammation-related diseases. *Life Sciences*, *255*, 117850. <https://doi.org/10.1016/j.lfs.2020.117850>

Long, Y., Cao, X., Zhao, R., Gong, S., Jin, L., & Feng, C. (2020). Fucoxanthin treatment inhibits nasopharyngeal carcinoma cell proliferation through induction of autophagy mechanism. *Environmental Toxicology*, *35*(10), 1082–1090. <https://doi.org/10.1002/tox.22944>

Lourenço-Lopes, C., Fraga-Corral, M., Jimenez-Lopez, C., Carpena, M., Pereira, A. G., Garcia-Oliveira, P., Prieto, M. A., & Simal-Gandara, J. (2021). Biological action mechanisms of fucoxanthin extracted from algae for application in food and cosmetic industries. *Trends in Food Science & Technology*, *117*, 163–181. https://doi.org/10.1016/j.tifs.2021.03.012

Marinho, G. S., Sørensen, A. D. M., Safafar, H., Pedersen, A. H., & Holdt, S. L. (2019). Antioxidant content and activity of the seaweed Saccharina latissima: A seasonal perspective. *Journal of Applied Phycology*, *31*, 1343-1354.

McGowan, M. P., Hosseini Dehkordi, S. H., Moriarty, P. M., & Duell, P. B. (2019). Diagnosis and treatment of heterozygous familial hypercholesterolemia. *Journal of the American Heart Association*, *8*(24), e013225.

Méresse, S., Fodil, M., Fleury, F., & Chénais, B. (2020). Fucoxanthin, a Marine-Derived Carotenoid from Brown Seaweeds and Microalgae: A Promising Bioactive Compound for Cancer Therapy. *International Journal of Molecular Sciences*, *21*(23), 9273. https://doi.org/10.3390/ijms21239273

Miyashita, K., Beppu, F., Hosokawa, M., Liu, X., & Wang, S. (2020). Bioactive significance of fucoxanthin and its effective extraction. *Biocatalysis and Agricultural Biotechnology*, *26*, 101639.

Murase, W., Kamakura, Y., Kawakami, S., Yasuda, A., Wagatsuma, M., Kubota, A., Kojima, H., Ohta, T., Takahashi, M., Mutoh, M., Tanaka, T., Maeda, H., Miyashita, K., & Terasaki, M. (2021). Fucoxanthin Prevents Pancreatic Tumorigenesis in C57BL/6J Mice That Received Allogenic and Orthotopic Transplants of Cancer Cells. *International Journal of Molecular Sciences*, *22*(24), 13620. https://doi.org/10.3390/ijms222413620

Noviendri, D., Qurrotu’ain, N., Nurbayti, S., & Hasrini, R. F. (2023, August). The Carotenoid Contents (Fucoxanthin and β-Carotene), Total Phenolic Content, and Antioxidant Activity of Ethanolic Extracts from Selected Indonesian Seaweeds. In *IOP Conference Series: Earth and Environmental Science* (Vol. 1221, No. 1, p. 012034). IOP Publishing.

Nunes, N., Leça, J. M., Pereira, A. C., Pereira, V., Ferraz, S., Barreto, M. C., ... & de Carvalho, M. P. (2019). Evaluation of fucoxanthin contents in seaweed biomass by vortex-assisted solid-liquid microextraction using high-performance liquid chromatography with photodiode array detection. *Algal Research*, *42*, 101603.

Oliyaei, N., & Moosavi‐Nasab, M. (2021). Ultrasound‐assisted extraction of fucoxanthin from Sargassum angustifolium and Cystoseira indica brown algae. *Journal of Food Processing and Preservation*, *45*(11), e15929.

Oliyaei, N., Moosavi-Nasab, M., Tamaddon, A. M., & Fazaeli, M. (2020). Encapsulation of fucoxanthin in binary matrices of porous starch and halloysite. *Food Hydrocolloids*, *100*, 105458. https://doi.org/10.1016/j.foodhyd.2019.105458

Oliyaei, N., Moosavi‐Nasab, M., Tamaddon, A. M., & Fazaeli, M. (2020). Double encapsulation of fucoxanthin using porous starch through sequential coating modification with maltodextrin and gum Arabic. *Food Science & Nutrition*, *8*(2), 1226-1236.

Oliyaei, N., Tanideh, N., Moosavi-Nasab, M., Dehghanian, A. R., & Iraji, A. (2023). Development and characterization of a fucoidan-based nanoemulsion using Nigella sativa oil for improvement of anti-obesity activity of fucoxanthin in an obese rat model. *International Journal of Biological Macromolecules*, *235*, 123867. https://doi.org/10.1016/j.ijbiomac.2023.123867

Packard, C. J., Boren, J., & Taskinen, M. R. (2020). Causes and consequences of hypertriglyceridemia. *Frontiers in endocrinology*, *11*, 252.

Pereira, A. G., Otero, P., Echave, J., Carreira-Casais, A., Chamorro, F., Collazo, N., ... & Prieto, M. A. (2021). Xanthophylls from the sea: algae as source of bioactive carotenoids. *Marine drugs*, *19*(4), 188.

Raal, F. J., Rosenson, R. S., Reeskamp, L. F., Hovingh, G. K., Kastelein, J. J., Rubba, P., ... & Gaudet, D. (2020). Evinacumab for homozygous familial hypercholesterolemia. *New England Journal of Medicine*, *383*(8), 711-720.

Raguraman, V.; MubarakAli, D.; Narendrakumar, G.; Thirugnanasambandam, R.; Kirubagaran, R.; Thajuddin, N. Unraveling rapid extraction of fucoxanthin from *Padina tetrastromatica*: Purification, characterization and biomedical application. *Process Biochem.* 2018, *73*, 211–219.

Raji, V., Loganathan, C., Sadhasivam, G., Kandasamy, S., Poomani, K., & Thayumanavan, P. (2020). Purification of fucoxanthin from Sargassum wightii Greville and understanding the inhibition of angiotensin 1-converting enzyme: An in vitro and in silico studies. *International journal of biological macromolecules*, *148*, 696-703.

Ramanathan, R., Ali, A. H., & Ibdah, J. A. (2022). Mitochondrial Dysfunction Plays Central Role in Nonalcoholic Fatty Liver Disease. *International Journal of Molecular Sciences*, *23*(13), 7280. https://doi.org/10.3390/ijms23137280

Rezvankhah, A., Emam-Djomeh, Z., & Askari, G. (2020). Encapsulation and delivery of bioactive compounds using spray and freeze-drying techniques: A review. *Drying Technology*, *38*(1-2), 235-258.

Savira, A. D. R., Amin, M. N. G., & Alamsjah, M. A. (2021, March). The effect of different type of solvents on the antioxidant activity of fucoxanthin extract from brown seaweed Sargassum duplicatum. In *IOP Conference Series: Earth and Environmental Science* (Vol. 718, No. 1, p. 012010). IOP Publishing.

Shannon, E., & Abu‐Ghannam, N. (2018). Enzymatic extraction of fucoxanthin from brown seaweeds. *International Journal of Food Science & Technology*, *53*(9), 2195-2204.

Sharma, P. P., & Baskaran, V. (2021). Polysaccharide (laminaran and fucoidan), fucoxanthin and lipids as functional components from brown algae (Padina tetrastromatica) modulates adipogenesis and thermogenesis in diet-induced obesity in C57BL6 mice. *Algal Research*, *54*, 102187. https://doi.org/10.1016/j.algal.2021.102187

Simha, V. (2020). Management of hypertriglyceridemia. *Bmj*, *371*.

Spagolla Napoleão Tavares, R., Stuchi Maria-Engler, S., Colepicolo, P., Debonsi, H. M., Schäfer-Korting, M., Marx, U., Rigo Gaspar, L., & Zoschke, C. (2020). Skin Irritation Testing beyond Tissue Viability: Fucoxanthin Effects on Inflammation, Homeostasis, and Metabolism. *Pharmaceutics*, *12*(2), 136. https://doi.org/10.3390/pharmaceutics12020136

Steg PG, Szarek M, Bhatt DL, et al. Effect of alirocumab on mortality after acute coronary syndromes. Circulation 2019;140:103-112.

Sun, J., Zhou, C., Cheng, P., Zhu, J., Hou, Y., Li, Y., ... & Yan, X. (2022). A simple and efficient strategy for fucoxanthin extraction from the microalga Phaeodactylum tricornutum. *Algal Research*, *61*, 102610.

Sun, P., Wong, C. C., Li, Y., He, Y., Mao, X., Wu, T., ... & Chen, F. (2019). A novel strategy for isolation and purification of fucoxanthinol and fucoxanthin from the diatom Nitzschia laevis. *Food chemistry*, *277*, 566-572.

Terasaki, M., Kubota, A., Kojima, H., Maeda, H., Miyashita, K., Kawagoe, C., Mutoh, M., & Tanaka, T. (2021). Fucoxanthin and Colorectal Cancer Prevention. *Cancers*, *13*(10), 2379. <https://doi.org/10.3390/cancers13102379>

Wang, C., Chen, X., Nakamura, Y., Yu, C., & Qi, H. (2020). Fucoxanthin activities motivate its nano/micro-encapsulation for food or nutraceutical application: a review. *Food & Function*, *11*(11), 9338–9358. <https://doi.org/10.1039/D0FO02176H>

Winarto, J., Song, D.-G., & Pan, C.-H. (2023). The Role of Fucoxanthin in Non-Alcoholic Fatty Liver Disease. *International Journal of Molecular Sciences*, *24*(9), 8203. <https://doi.org/10.3390/ijms24098203>

Wu, W., Han, H., Liu, J., Tang, M., Wu, X., Cao, X., Zhao, T., Lu, Y., Niu, T., Chen, J., & Chen, H. (2021). Fucoxanthin Prevents 6-OHDA-Induced Neurotoxicity by Targeting Keap1. *Oxidative Medicine and Cellular Longevity*, *2021*, 1–14. https://doi.org/10.1155/2021/6688708

Xiao, X.; Si, X.; Yuan, Z.; Xu, X.; Li, G. Isolation of fucoxanthin from edible brown algae by microwave-assisted extraction coupled with high-speed countercurrent chromatography. *J. Sep. Sci.* **2012.**

Ye, J., Zheng, J., Tian, X., Xu, B., Yuan, F., Wang, B., Yang, Z., & Huang, F. (2022). Fucoxanthin Attenuates Free Fatty Acid-Induced Nonalcoholic Fatty Liver Disease by Regulating Lipid Metabolism/Oxidative Stress/Inflammation via the AMPK/Nrf2/TLR4 Signaling Pathway. *Marine Drugs*, *20*(4), 225. https://doi.org/10.3390/md20040225

Yılmaz, A., Taghizadehghalehjoughi, A., Hacimuftuoglu, A., & Türkmen, A. (2021). Investigation of Aloe vera barbadensis Miller leaf extract effects on glutamate and glyphosate induced toxicity: in vitro study. *Journal of Anatolian Environmental and Animal Sciences*, *6*(3), 376-381.

Zhang, H., Tang, Y., Zhang, Y., Zhang, S., Qu, J., Wang, X., ... & Liu, Z. (2015). Fucoxanthin: A promising medicinal and nutritional ingredient. *Evidence‐Based Complementary and Alternative Medicine*, *2015*(1), 723515.

Zhang, Y. G., Kan, H., Chen, S. X., Thakur, K., Wang, S., Zhang, J. G., ... & Wei, Z. J. (2020). Comparison of phenolic compounds extracted from Diaphragma juglandis fructus, walnut pellicle, and flowers of Juglans regia using methanol, ultrasonic wave, and enzyme assisted-extraction. *Food chemistry*, *321*, 126672.

Zhang, Y., Xu, W., Huang, X., Zhao, Y., Ren, Q., Hong, Z., Huang, M., & Xing, X. (2018). Fucoxanthin ameliorates hyperglycemia, hyperlipidemia and insulin resistance in diabetic mice partially through IRS-1/PI3K/Akt and AMPK pathways. *Journal of Functional Foods*, *48*, 515–524. https://doi.org/10.1016/j.jff.2018.07.048

Zhao, D., Yu, D., Kim, M., Gu, M. Y., Kim, S. M., Pan, C. H., ... & Chung, D. (2019). Effects of temperature, light, and pH on the stability of fucoxanthin in an oil-in-water emulsion. *Food chemistry*, *291*, 87-93.

Zhao, Y., Zhi, J., Huang, S., Zhang, X., Kim, Y. R., Xu, Y., ... & Luo, K. (2022). Fabrication of starch/zein-based microcapsules for encapsulation and delivery of fucoxanthin. *Food Chemistry*, *392*, 133282.