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Progress on the biological characteristics and physiological activities of fucoxanthin produced by marine microalgae

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Background: Fucoxanthin is a carotenoid found in seaweed. Its unique chemical structure gives it a variety of properties. Thus fucoxanthin have attracted the attention of companies and researchers.

Methods: Scientific papers were collected from the database. Duplicates and unavailable literature were excluded first. Then the remaining literature was categorized for referencing in the review.

Results: This article contains a summary of the microalgae species producing fucoxanthin and their progress in breeding and cultivation modes. Additionally, the review summarized the progress of research on physiological activities and organized the experimental models used in these studies.

Conclusions: These present findings may provide information for the upstream production of fucoxanthin from algal species selection to process optimization. The analysis of the physiological activity results will help advance subsequent physiological and biochemical experiments. Furthermore, it intends to pique researchers' enthusiasm for fucoxanthin and enrich related research data to accelerate the development of this natural product.

KEYWORDS

microalage, carotenoid, fucoxanthin, biological properties, physiological activities

1 Introduction

Fucoxanthin, a carotenoid, is a significant component of carotenoids found in nature, accounting for more than 10% (Matsuno, 2001). This natural product contains multiple functional groups, as depicted in Figure 1, enabling it to bind to a wider range of disease targets. It has shown biological activity and has good nutritional and health care value. Fucoxanthin nutraceuticals have gained approved from the Food Standards Agency of

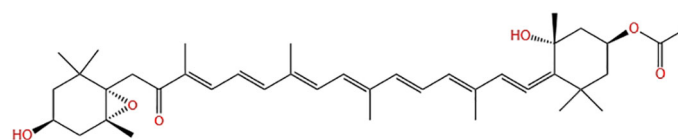


FIGURE 1
Chemical structure diagram of fucoxanthin.

Australia and New Zealand (Abu-Ghosh et al., 2021), resulting in a high demand for this compound. However, its supply remains limited. A Flow chart illustrating the culture and product application of microalgae producing fucoxanthin is presented in Figure 2.

As of 2021, the price of high-purified fucoxanthin ranges from 40,000 to 80,000 USD/kg (Market Watch, 2020). This elevated price significantly hinders the commercialization, progress of fucoxanthin, necessitating the exploration of new approaches for industrializing the production of fucoxanthin raw materials. Fucoxanthin products are primarily extracted from macroalgae such as kelp and sea mustard. However, macroalgae have several drawbacks, including a lengthy growth cycle, low fucoxanthin content (0.02~0.58 mg/g fresh weight) (Mori et al., 2004), and other shortcomings, such as thick algal cell walls, high content of polysaccharides, and difficulties in crushing, which contribute to high production costs (Kim et al., 2011; Joel, 2016). On the other hand, marine microalgae have been found to be rich in fucoxanthin and easy to obtain. These

microalgae have a fucoxanthin content about 100 times higher than that of macroalgae. For example, the fucoxanthin content in *Synurophyceae* is as high as 26.6 mg/g dry weight (Petrushkina et al., 2017). Diatoms have a fucoxanthin content of up to 25.5 mg/g dry weight (Wang et al., 2018), and *Prymnesiophyceae* have a fucoxanthin content of 18.23 mg/g dry weight (Petrushkina et al., 2017).

This marine natural substance has gained increased attention in recent years for its potential in various diseases related to inflammation and oxidative stress reactions. These include skin inflammation (Rodríguez-Luna et al., 2018; Spagolla Napoleão Tavares et al., 2020), ulcerative colitis (Yang et al., 2020), and contact hypersensitivity (Sakai et al., 2011). It has also been a research hotspot for its anti-diabetic (Maeda et al., 2007; Sakai et al., 2011; Kong et al., 2019) and anti-obesity (Abidov et al., 2010; Hu et al., 2012; Hitoie and Shimoda, 2017; Gille et al., 2019; Koo et al., 2019) efficacy. Non-alcoholic steatohepatitis (Takatani et al., 2020; Shih et al., 2021; Ye et al., 2022), Alzheimer's disease (Lin et al.,

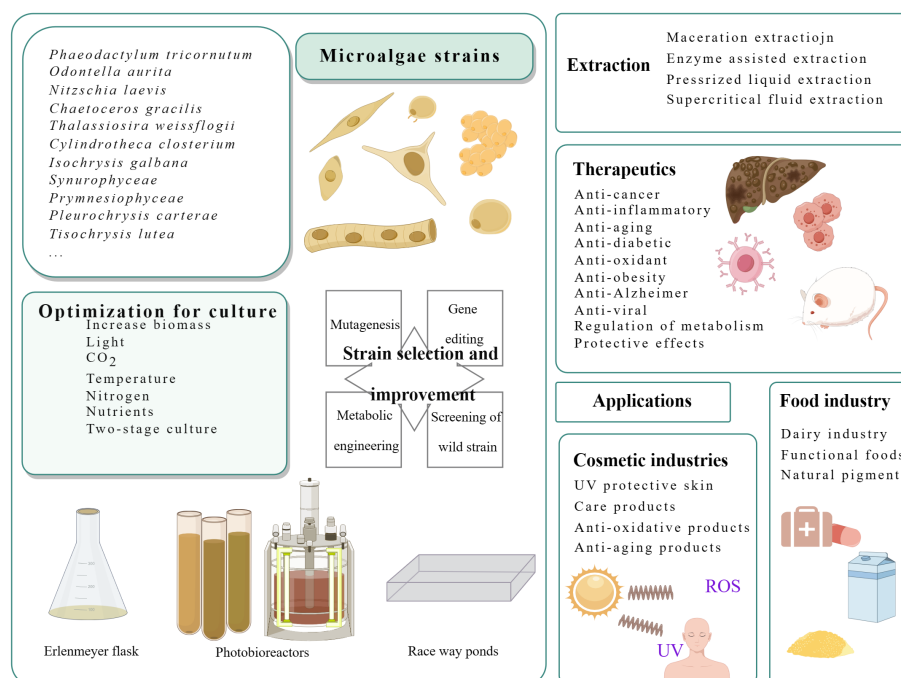


FIGURE 2
Flow chart of culture and product application of microalgae producing fucoxanthin.

2017; Xiang et al., 2017; Alghazwi et al., 2019; Shih et al., 2021; Yang et al., 2021; Zhu et al., 2021), and other biological activities [e.g., antiviral (Tsushima et al., 1995; Tamama, 2021)] have also been proven.

Microalgae-produced fucoxanthin is green and environmentally friendly, which is in line with the development trend. However, the current production of fucoxanthin from microalgae is constrained by traditional technologies. The precise pharmacological targets and signaling mechanisms of fucoxanthin remain unclear. Therefore, there is a need to further develop research on the upstream and downstream of fucoxanthin.

This review focuses on the production of fucoxanthin by microalgae and its pharmacological activity. It provides a summary of fucoxanthin-rich microalgae and their culture modes. The review also discusses the recent developments in investigating the pharmaceutical properties of fucoxanthin.

2 Results

2.1 Microalgae producing fucoxanthin and its biological properties

2.1.1 Microalgae producing fucoxanthin

Fucoxanthin in microalgae often binds to chlorophyll to form a fucoxanthin chlorophyll a/c protein complex (FCP), which can respond quickly to changes in the light environment (Xia et al., 2013). While fucoxanthin can be chemically synthesized, it is more efficient to extract it from microalgae. Compared with plants, microalgae grow quickly, often doubling their number per hour. Their productivity is measured in days, whereas plants often take months or years to produce. Microalgae isolated from nature are small and easily viable, making them suitable for cultivation in closed systems in laboratories or factories. There do not require arable land and are unaffected by seasonal climate and the marine environment. Moreover, the high fucoxanthin content of microalgae, the relative ease of the extraction and preparation process compared to macroalgae, and the variety of strain sources make microalgae an ideal cellular factory for the sustainable, large-scale production of fucoxanthin.

2.1.2 Synthesis pathway of fucoxanthin in microalgae

The biosynthesis of fucoxanthin was studied using *Phaeodactylum tricornutum* as a common model species, with high photosynthetic efficiency (Figure 3). The process begins with the generation of isopentenyl pyrophosphate (IPP) through the mevalonate pathway, which is the rate-limiting step in the synthesis of β -carotene. Geranylgeranyl diphosphate (GGPP) is produced by IPP under the action of geranyl pyrophosphate synthase (GGPS) (Xia et al., 2013). Subsequently, octahedron lycopene synthase (PSY) enzyme converts GGPP to produce the first carotenoid, phytoene (Kadono et al., 2015). Phytoene undergoes continuous dehydrogenation by octahedron lycopene desaturase (PDS), ζ -carotene desaturase (ZDS), carotenoid isomerase (CRTISO),

resulting in the formation of lycopene (Kadono et al., 2015). Lycopene can produce α -carotene or further forms β -carotene from γ -carotene. Under the action of β -carotene hydroxylase (BCH), β -carotene generates zeaxanthin. Zeaxanthin epoxidase (ZEP) cyclizes zeaxanthin to form violaxanthin through two-step catalysis (Coesel et al., 2008). Ultimately, fucoxanthin can be synthesized from Diadinoxanthin (Lohr and Wilhelm, 1999) or also from Neoxanthin (Kadono et al., 2015). There are two hypothetical pathways for fucoxanthin synthesis, Figure 3. These are the currently known pathway for fucoxanthin synthesis.

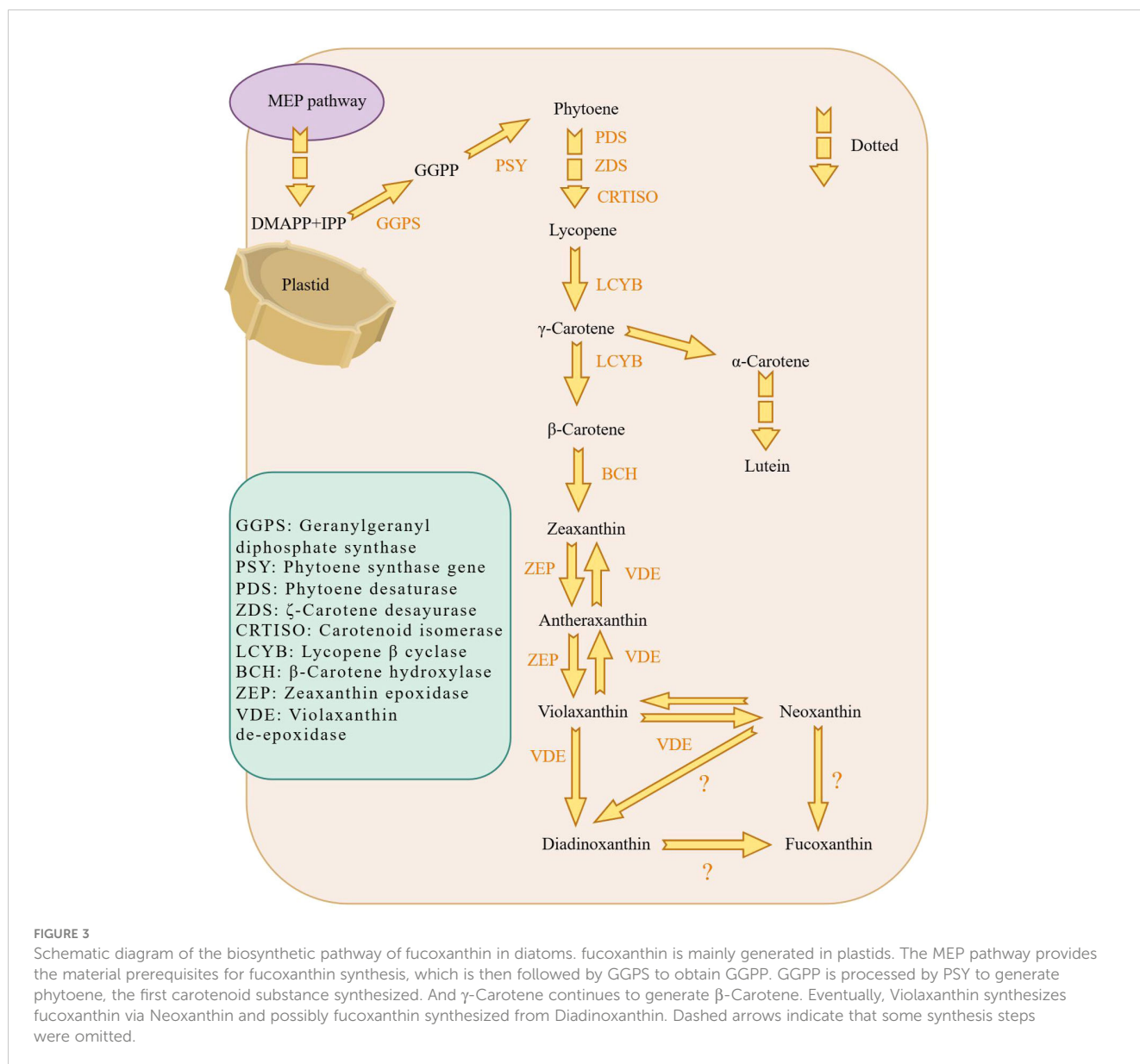
Clarifying of the pathway of fucoxanthin synthesis is also important for biomolecular experiments and molecular level studies. It is evident that the enzymes involved in key synthetic pathways are not yet known and further research is needed to investigate potential branching pathways for synthesis.

2.1.3 Selection and breeding of fucoxanthin-producing microalgae

In the field of research and development of microalgae resources, one of the key problems that must be solved is the screening and breeding of excellent algal strains. Most of the microalgae cultured in current times are isolated directly from the natural environment. They are wild-type algae, which have single traits and poor adaptability to the environment. As a result, they are prone to trait degradation and are not suitable for industrial production and conditions (Benemann, 2013). Natural selection, is time-consuming and laborious. Hence, there is a need for effective breeding methods. Mutagenic breeding, an ideal method for microalgal breeding, is outstanding and easy to operate. Researchers screened a mutant of *Phaeodactylum tricornutum* using a fluorescence-based high-throughput method (Yi et al., 2018). The mutant showed a 69.3% increase in fucoxanthin compared to wild type, making it an industrially useful fucoxanthin-producing algal strain. UV mutagenesis is also an effective breeding strategy. Yi et al. used stress mutagenesis induced by UV light to enhance the accumulation of fucoxanthin in *Phaeodactylum tricornutum* and produced mutant strains with improved growth rates (Yi et al., 2015). Furthermore, mutagenesis has the advantage of not being classified as a method producing genetically modified organisms, which exempts it from regulatory issues in many places such as the EU (Tillich et al., 2012). However, there are currently challenges in microalgae mutation breeding. Such as obtaining ideal mutant strains, optimizing mutation conditions, and screening efficiency. It is necessary to adopt appropriate mutation methods for different algal strains. A combination of different mutation methods can also be used by applying higher mutation pressures in order to obtain the desired mutant strain.

2.1.4 Culture of fucoxanthin producing microalgae

Culture parameters for microalgae are typically species-specific, requiring individualized culture processes for each microalgal strain to achieve high-quality algal cultures. While most microalgal cultures adopt a one-stage culture mode. The culture



conditions have no change during the whole process from microalgae growth to fucoxanthin accumulation (Heo et al., 2010; Petrushkina et al., 2017; Lu et al., 2018; Wang et al., 2018; Li et al., 2019; Marella and Tiwari, 2020; Mc et al., 2020; Kanamoto et al., 2021; Zhu et al., 2021; Jin et al., 2022), as shown in Supplementary Table 1.

However, the one-stage mode cannot solve the contradiction between biomass and metabolite production accumulation. It cannot fulfill the demands of industrial production. Microalgae metabolites are often produced under extreme conditions that may inhibit their growth. If the conditions for metabolite accumulation are met, it can lead to the death of the algal cells, while the conditions for microalgal growth are not satisfied for pigment accumulation.

In contrast, the two-stage culture mode separates periods of microalgal growth and product accumulation. In Stage I, provided sufficient cell factories are provided, while and Stage II optimizes

growth conditions (e.g. autotrophic, heterotrophic, batch sequential, nutrient conditions) to enhance metabolite production (Wan et al., 2015), as shown in (Chang et al., 2018; Chiang et al., 2020; Dambek et al., 2012; Erdogan et al., 2021; Fierli et al., 2022; Gao et al., 2020; Kim et al., 2010b; Lakey-Beitia et al., 2019; Li et al., 2000; Li et al., 2021; Masse et al., 2004; Okcu et al., 2021; Qin et al., 2013; Tachihana et al., 2020; Wei et al., 2022; Wu et al., 2011; Yang and Wei, 2020; Zhu et al., 2021) Table 1. Compared to separate cultivation, the two-stage mode offers advantages such as high product yield, energy saving, environmental protection and a wide range of applications (Liyanaarachchi et al., 2021). Researchers have successfully improved the fucoxanthin contents and blue light amplification yield using two-stage photofermentation techniques. Yang et al. (Yang et al., 2023). raised the fucoxanthin content and yield by 45.98% and 48.3% reperceiving a two-stage culture technique. The highest recorded fucoxanthin yield among available results was obtained by Yang

TABLE 1 Two-stage culture of microalgae for the production of fucoxanthin and its yield.

Strain		Medium	Light condition	Photobioreactors	Trophic modes and Strategies	Fucoxanthin	Reference
Diatom	<i>Phaeodactylum tricornerutum</i>	Modified F/2, nitrogen supplementation (stage 1 and 2)	Red-blue light (stage 1), red- blue light with blue light enhancement (stage 2)	Light fermenter	Two-stage culture, heterotrophy	19.62 mg g ⁻¹	(Yang et al., 2023)
	<i>Phaeodactylum tricornerutum</i>	Modified F/2,nitrogen supplementation (stage 2)	Red-blue light (stage 1), red- blue light with blue light enhancement (stage 2)	Light fermenter	Two-stage culture, heterotrophy	13.26 mg g ⁻¹	(Yang et al., 2020)
	<i>Nitzschia laevis</i>	Modified LDM, nitrogen supplementation (exponential growth stage)	Dark (stage 1), blue-white light (stage 2)	Light fermenter	Two-stage culture, heterotrophy	16.5 mg L ⁻¹ day ⁻¹	(Lu et al., 2018)

et al., measuring 8.22 mg/d-L (Yang et al., 2020). Li et al. achieved a fucoxanthin yield of 16.5 mg/d-L by employing a two-stage culture technique involves in high-density fermentation in the dark and blue-white light as a light source (Lu et al., 2018). The two stages of cultivation are detailed in Table 1. In conclusion, the two-stage culture method is considered to be a viable approach.

2.2 Physiological activity of fucoxanthin

2.2.1 Anti-inflammatory activity

Similar to other anti-inflammatory drugs, fucoxanthin has been found to play an anti-inflammatory role through the down-regulation of the release of relevant inflammatory mediators. It's inhibition of the enzymatic activities, which are associated with inflammation induction in macrophages RAW264.7 (Heo et al., 2010; Kim et al., 2010a). Fucoxanthin has demonstrated beneficial effects in various conditions, such as ulcerative colitis (Yang et al., 2020), uveitis (Shiratori et al., 2005), and contact hypersensitivity (Sakai et al., 2011; Namkoong et al., 2012). In a colitis model using mice, fucoxanthin inhibited NF- κ B and COX-2 expression, resulting in significant improvement of histological damage in the colon (Yang et al., 2020). Fucoxanthin has also been shown efficacy in treating uveitis in an LPS-induced inflammation rat model (Li et al., 2020). Moreover, fucoxanthin has been shown effectively alleviate dinitrofluorobenzene-induced contact hypersensitivity in BALB/c mice (Sakai et al., 2011). And prevent allergic diseases by inhibiting IgE-antigen complex-stimulated RBL-2H3 cells (Namkoong et al., 2012).

In previous studies, mechanistic studies of fucoxanthin have focused on the classical NF- κ B and MAPK-related pathways. Fucoxanthin treatment has been shown to dose-dependently reduce the inflammatory factor expression levels of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) by inhibiting the MAPK and NF- κ B pathways (Heo et al., 2010; Kim et al., 2010a). There are other related signaling pathways, such as the inflammasome, which is composed of NOD-like receptor thermal protein domain associated protein (NLRP), apoptosis-associated

speck-like protein (ASC), and cysteinyl aspartate specific protein (caspase). Li et al (Li et al., 2020). found that fucoxanthin attenuated palmitate-induced transcriptional of NLRP3 inflammasomes for anti-inflammatory efficacy. Similarly, the union of fucoxanthin and rosmarinic acid has been shown to reduce the inflammatory response by downregulating inflammasome components including NLRP3, ASC, and caspase-1, as well as interleukin IL-1 β production, according to Rodriguez-Luna et al., (Rodríguez-Luna et al., 2019). According to these studies, the product may have a protective impact by downregulating the inflammasome and inflammatory factors.

In this line, due to its anti-inflammatory activity, this carotenoid has been proposed as a protective compound. Given its promising anti-inflammatory effect, fucoxanthin holds potential as an independent anti-inflammatory drug or as a synergizedstic agent with other therapeutic drugs for other diseases to exert anti-inflammatory effect treatment of various diseases.

2.2.2 Antioxidant activity

Fucoxanthin is a very powerful antioxidant. Its six-oxygen-atom propylene structure makes fucoxanthin extremely reactive to free radicals. Oxidative stress is brought on by an increase in reactive oxygen species (ROS). Heo et al., (Heo et al., 2008). induced oxidative stress in Vero cells using H₂O₂, and the addition of fucoxanthin significantly reduced intracellular ROS production while also dose-dependently inhibiting oxidative-induced cellular damage. Fucoxanthin may scavenge ROS and free radicals by means of a three-step process that involves electron transfer, dehydrogenation, and addition (Rao and Rao, 2007). Additionally, fucoxanthin has demonstrated its efficacy in modifiedying skin inflammation and skin damage caused by UV-induced photo-oxidative stress (Ichihashi et al., 2003; D'Orazio et al., 2013). When fucoxanthin isolated from algae was incorporated into sunscreen at 0.5% (w/v), it inhibited the formation of ROS significantly in reconstructed skin cells and HaCaT cells (Tavares et al., 2020). Furthermore, intracellular ROS and oxidative stress were lower in cells exposed to UV-B radiation than in cells without different concentrations of fucoxanthin

(Heo and Jeon, 2009). Its powerful anti-oxidant qualities protect the skin from oxidative stress-related skin damage and aging.

Other than directly interacting with free radicals, fucoxanthin enhances the synthesis of related proteins and antioxidant enzymes. Resulting in increased plasma antioxidant enzyme activity, total antioxidant capacity, and mRNA levels of Nrf2 (Liu et al., 2011; Ha et al., 2013). It also promotes the synthesis of antioxidant proteins such as heme oxygenase-1 (HO-1) and (NAD(P)H): quinone oxidoreductase 1 (NQO-1) through activation of the Nrf2/ARE system, thereby exerting its antioxidant activity in BNL CL2 cells from murine hepatic (Liu et al., 2011). Similarly, fucoxanthin activates the Nrf2 pathway and the gene NQO1, which reduced oxidative stress under high-fat diet feeding (Ha et al., 2013). Moreover, fucoxanthin has been found to alleviate oxidative stress by retinol deficiency in rats by modifying the $\text{Na}^{(+)}\text{-K}^{(+)}\text{-ATPase}$, catalase (CAT) and glutathione S-transferase (GST) activities (Ravi Kumar et al., 2008).

Collectively, these findings highlight the potent antioxidant activity of fucoxanthin. Specifically, fucoxanthin, a microalgal product, is a natural green substance. It is expected to become a valuable antioxidant in the food, pharmaceutical, and cosmetics industries in the future.

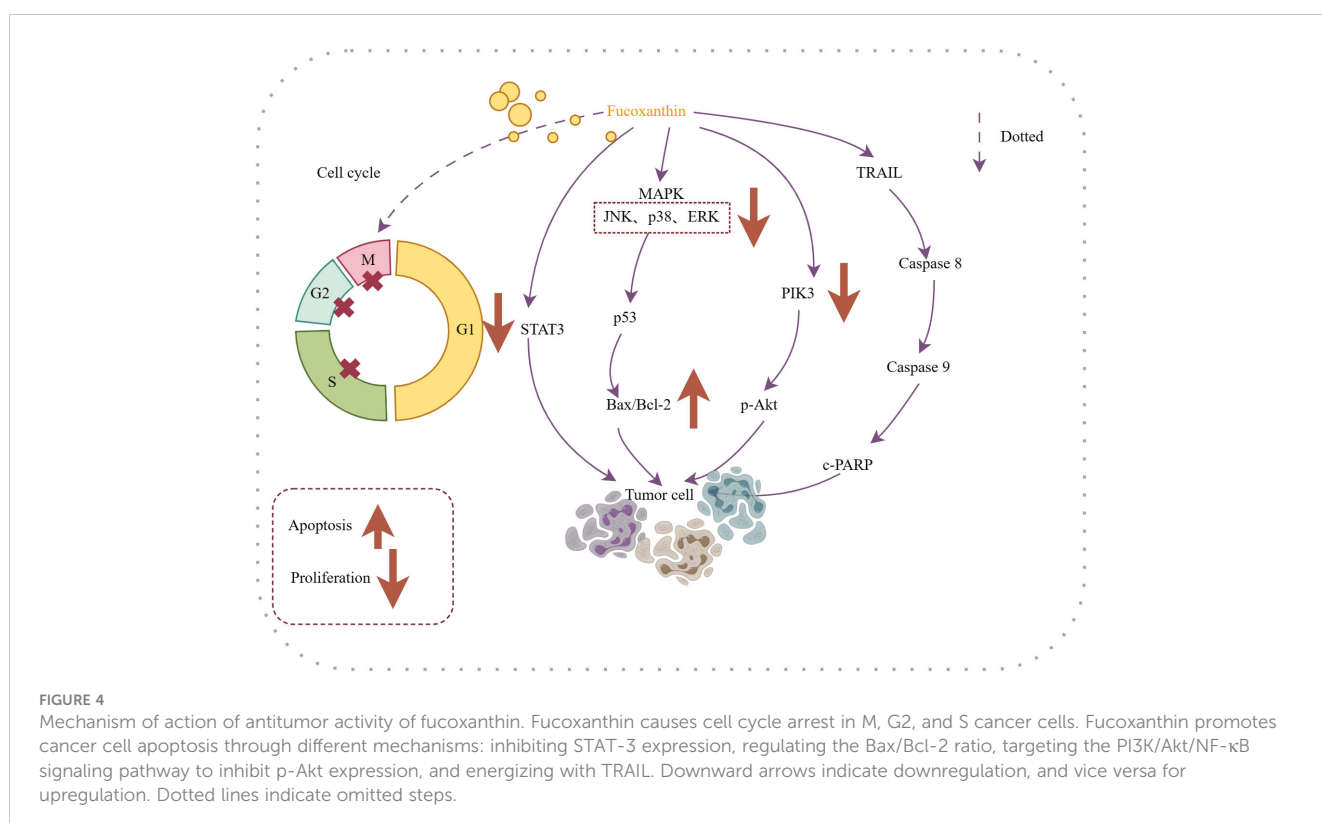
2.3 Pharmacological activity of fucoxanthin

2.3.1 Antitumor activity

Fucoxanthin can exhibit direct antitumor effects or work in conjunction with antitumor drugs to enhance their efficacy. Experimental studies have demonstrated that fucoxanthin impacts

various types of cancer by promoting apoptosis (Jin et al., 2018; Yu et al., 2018). Yu et al., (Yu et al., 2018). suggested that fucoxanthin may decrease proliferation and induce apoptosis through the JAK/STAT signaling pathway, leading to cell arrest at the S phase in gastric cancer cells (SGC-7901) and at the G2/M phase in gastric cells (BGC-823). It also inhibits proliferation of cancer cells and blocking the cell cycle (Das et al., 2008) (Das et al., 2008; Hou et al., 2013; Liu et al., 2013; Long et al., 2020). Liu et al (Liu et al., 2013). found that fucoxanthin pretreatment increased the chemotherapeutic efficacy of cisplatin on human hepatoma HepG2 cells by potentially altering the DNA repair system associated with ERK, p38, and PI3K/AKT pathways, which subsequently increased cisplatin-induced apoptosis in cancer cells. Das conducted surveys showing that fucoxanthin-rich methanolic extract reduced the viability of HepG2 cells and induced G0/G1 cell cycle arrest through proteasomal degradation and inhibition of cell cycle protein D synthesis (Das et al., 2008). The effects of fucoxanthin on antitumor activity are illustrated in Figure 4.

Therefore, it has a therapeutic effect on cancers. Fucoxanthin has shown potential in treating nasopharyngeal cancer (Long et al., 2020), cervical cancer, cervical cancer (Hou et al., 2013; Jin et al., 2018), lung cancer (Moreau et al., 2006), breast cancer (Wang et al., 2019) and other cancers to promote apoptosis and inhibit of tumor cells proliferation. In addition to its direct pharmacological effects, the anti-inflammatory and antioxidant properties of fucoxanthin contribute to its anti-tumor activity. Shin et al., (Shin et al., 2020). revealed that fucoxanthin may improve the efficacy of targeted anticancer drug therapy by reduce oxidative stress on tumor cells, while increasing oxidative stress on tumor cells.



Therefore, fucoxanthin can be used in anti-cancer treatment and in combination with anti-cancer drugs to assist anti-cancer treatment. At the same time, it can be used in combination with some anti-cancer drugs to improve the targeting of tumor cells and prevent damage to healthy cells.

2.3.2 Antimetabolic syndrome

2.3.2.1 Anti-obesity

Studies on the anti-metabolic disease activity of fucoxanthin have focused on the anti-obesity direction. Fucoxanthin exerts its anti-obesity effect by affecting white adipose mitochondrial uncoupling protein1 (UCP1) (Maeda et al., 2007; Kang et al., 2011; Gammon and D'Orazio, 2015), suppressed lipid accumulation (Marchesini et al., 2003; Woo et al., 2010; Takatani et al., 2020) and adipocyte differentiation (Kang et al., 2011).

In the clinical experimental group, overweight male and female Japanese adults were administered capsules containing fucoxanthin or placebo capsules for 4 weeks (Hitoe and Shimoda, 2017). The study showed a significant reduction in relative body weight and BMI with no observed abnormalities (Hitoe and Shimoda, 2017). Another clinical trial revealed an increase in resting energy expenditure (REE), in obese patients who were supplemented with 4 mg of fucoxanthin per day (Abidov et al., 2010). It was observed that 8 mg fucoxanthin demonstrated an even higher REE expenditure, suggesting that its efficacy may be dose-dependent (Abidov et al., 2010).

Being overweight has become a general problem for the world's citizens and can lead to other diseases. The current results of clinical trials show that the administration of fucoxanthin can help mildly obese adults regain their normal weight. These facts highlight the potential of fucoxanthin as a valuable natural product with health-promoting and anti-obesity properties.

2.3.2.2 Anti-nonalcoholic steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) is a significant cause of chronic liver disease, and fucoxanthin has been proven to be effective in alleviating NAFLD and preventing its progression to hepatic fibrosis.

Firstly, NAFLD is closely associated with obesity (Marchesini et al., 2003). Thus, fucoxanthin may exert anti-NAFLD effects by preventing hepatic lipid accumulation. Fucoxanthin has dual roles in preventing hepatic lipid accumulation: maintaining mitochondrial homeostasis, reducing lipid synthesis, and accelerating lipid degradation. Ye et al. (Ye et al., 2022) demonstrated that upregulation of Sirt1/AMPK expression by fucoxanthin accelerated fatty acid β -oxidation. Fucoxanthin supplementation decreases the activities of lipid synthesis-related enzymes [e.g., hydroxymethylglutaryl-coenzyme A reductase (HMG-CoA)] and modulates hepatic antioxidant activity and insulin sensitivity to achieve hepatic lipid metabolism in mice (Kang et al., 2010). Additionally, the anti-inflammatory and antioxidant activity of fucoxanthin can help alleviate free fatty acid-induced liver inflammation, stopping the progression of NAFLD. Activation of the Nrf2 antioxidant signaling pathway by fucoxanthin inhibited the TLR4-mediated inflammatory pathway and the production of inflammatory factors IL-6, IL-8, and TNF- α (Ye et al., 2022).

Furthermore, fucoxanthin prevents the progression of hepatitis to liver fibrosis. Takatani et al. (Takatani et al., 2020) revealed that dietary fucoxanthin also prevents the early phase of fibrosis in NAFLD model. Hepatic Stellate Cells (HSC) are considered as the primary effector cells of liver fibrosis and are susceptible to activation by inflammation or oxidative stress. Fucoxanthin downregulates the activation markers of HSC, including α -smooth muscle actin (α -SMA). Transforming growth factor β 1 (TGF β 1), fibrillar collagen 1 (Col1a1), matrix metalloproteinases-1 (Timp1) expression, and other fibrogenic factors, thus inhibiting hepatic fibrosis in mice (Takatani et al., 2020). Kim et al. (Kim et al., 2019) suggested that fucoxanthin exerts an anti-fibrogenic effect in HSCs. It primarily prevents pro-fibrogenic gene expression by inhibiting the activation of SMAD3 and quiescent HSCs (Kim et al., 2019).

In this context, fucoxanthin could serve as a natural product to protect liver health and shows great potential for the treatment of liver fibrosis and NAFLD treatments. It is important to know that there is no drug for NAFLD at the moment. This activity of fucoxanthin definitely brings a viable approach to the treatment of fatty liver and subsequent liver fibrosis. The effects of fucoxanthin on anti-nonalcoholic steatohepatitis are illustrated in Figure 5.

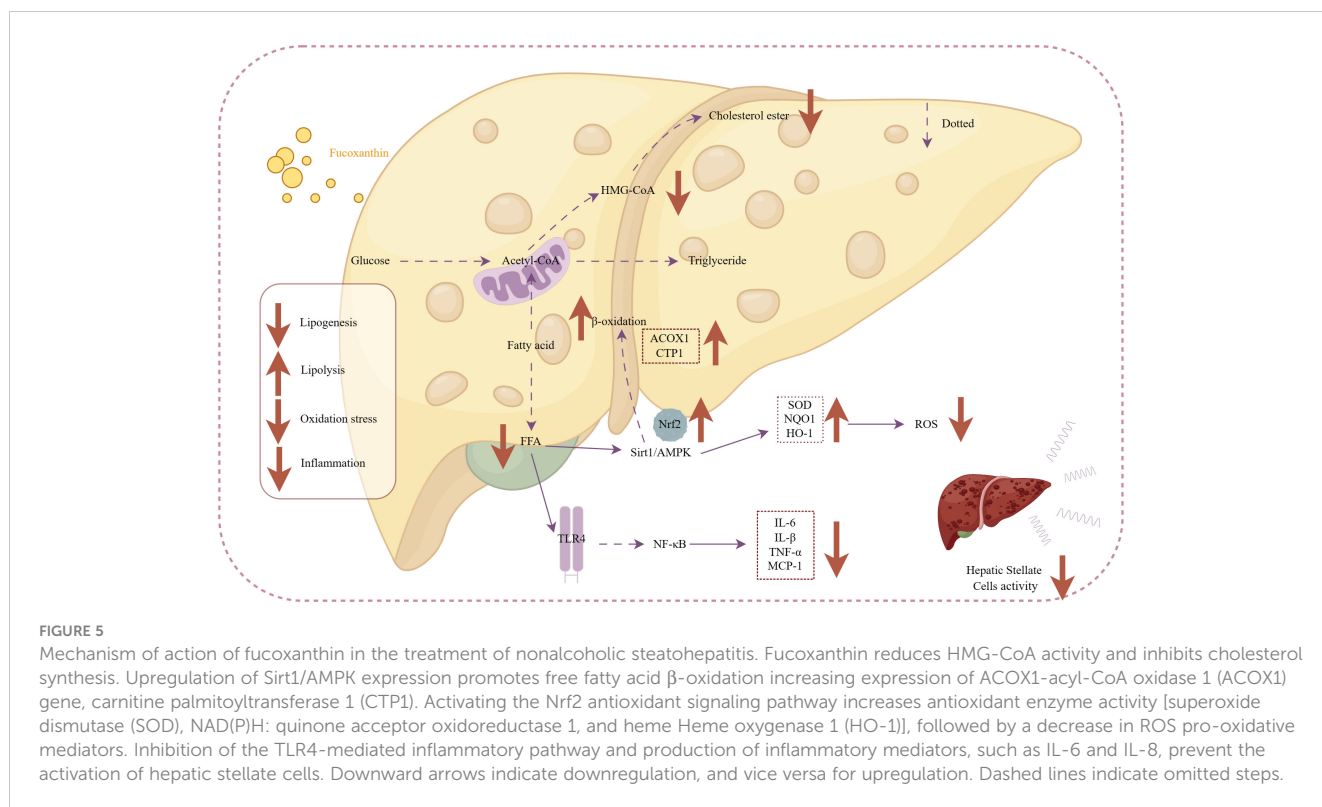
2.3.2.3 Antidiabetic

Studies have shown that fucoxanthin has excellent pharmacological effects on diabetes treatment, as it is able to lower blood glucose levels through multiple pathways.

Firstly, fucoxanthin has been found to have a strong effect on suppressor of cytokine signaling (SOCS-3) (Sakai et al., 2011), Monocyte Chemoattractant Protein-1 (MCP-1) (Maeda et al., 2009) plasminogen activator inhibitor-1 (PAI-1) (Hosokawa et al., 2010) to alleviate insulin resistance in an in diabetes experiment models. While inflammation also affects the level of insulin release in adipocytes and hepatocytes (Ye, 2013). Due to the anti-inflammatory activity of fucoxanthin, it is possible to alleviate inflammation-induced insulin resistance and thus restore glucose consumption.

Other factors, leptin also affects insulin sensitivity. In an *in vivo* experiment, hyperglycemia and low plasma insulin concentrations were alleviated by fucoxanthin in KK-Ay mice, and TNF- α and leptin mRNA were also down-regulated (Maeda et al., 2007).

In addition, fucoxanthin also lowers blood glucose by affecting glucose uptake in normal tissues. Maeda et al. (Maeda et al., 2009) found that fucoxanthin promoted mRNA expression of β 3-adrenergic receptor (Adrb3) and glucose transporter 4 (GLUT4) mRNA in skeletal muscle tissues to promote muscle glucose uptake in mice. Diets that contain fucoxanthin may help treat insulin resistance as well as alterations in lipid metabolism. Kang et al. (Kang et al., 2011) found that fucoxanthin differing effects on 3T3-L1 cells according to differentiation stage and inhibits glucose uptake in mature adipocytes by reducing the phosphorylation of insulin receptor substrate 1 (IRS-1). In diabetic/obese KK-A^y mice, fucoxanthin induced GLUT4 expression in flounder and toe extensor muscles and ameliorated symptoms of hyperglycemia by activating insulin expression for lowering blood sugar (Nishikawa et al., 2012).



Aside from antidiabetic, fucoxanthin also acts on the complications of diabetes. Chiang et al., (Kong et al., 2019), demonstrated that fucoxanthin was effective in improving diabetic retinopathy. While fucoxanthin has also shown promise in treating therapeutic effects on diabetes-induced male dysfunction (Sakai et al., 2011).

The most well-known pharmacological action of fucoxanthin is its antidiabetic efficacy, which has been demonstrated in numerous research. Fucoxanthin may provide therapeutic help to diabetics as well as treatment for the symptoms of diabetic complications.

2.3.3 Anti-Alzheimer's

Alzheimer disease (AD) is a devastating neurodegenerative disorder (Shih et al., 2021). Fucoxanthin has shown potential neuroprotective effects against these diseases.

There is often associated with the binding of amyloidogenic fibers (e.g., A β , tau proteins) in Alzheimer's disease. Drug design analysis and molecular docking simulations conducted by Lakey-Beitia et al., (Shih et al., 2021), revealed the action of carotenoids on A β amyloidogenic fibers. They found that carotenoids can bind to A β through hydrogen bonding and van der Waals interactions. These findings are consistent with the findings of studies by Xiang et al., (Xiang et al., 2017), and Yang et al., (Yang et al., 2021), which also showed that fucoxanthin inhibits A β assembly.

Additionally, A β deposition furthermore results in many issues that induce oxidative stress and neuronal cell death. In the mouse hippocampal regions, fucoxanthin has been shown to reduce oxidative stress in neuronal cells, increase brain-derived neurotrophic factor expression, and expand ChAT-positive areas (Xiang et al., 2017). This helps to maintain neuronal cell viability

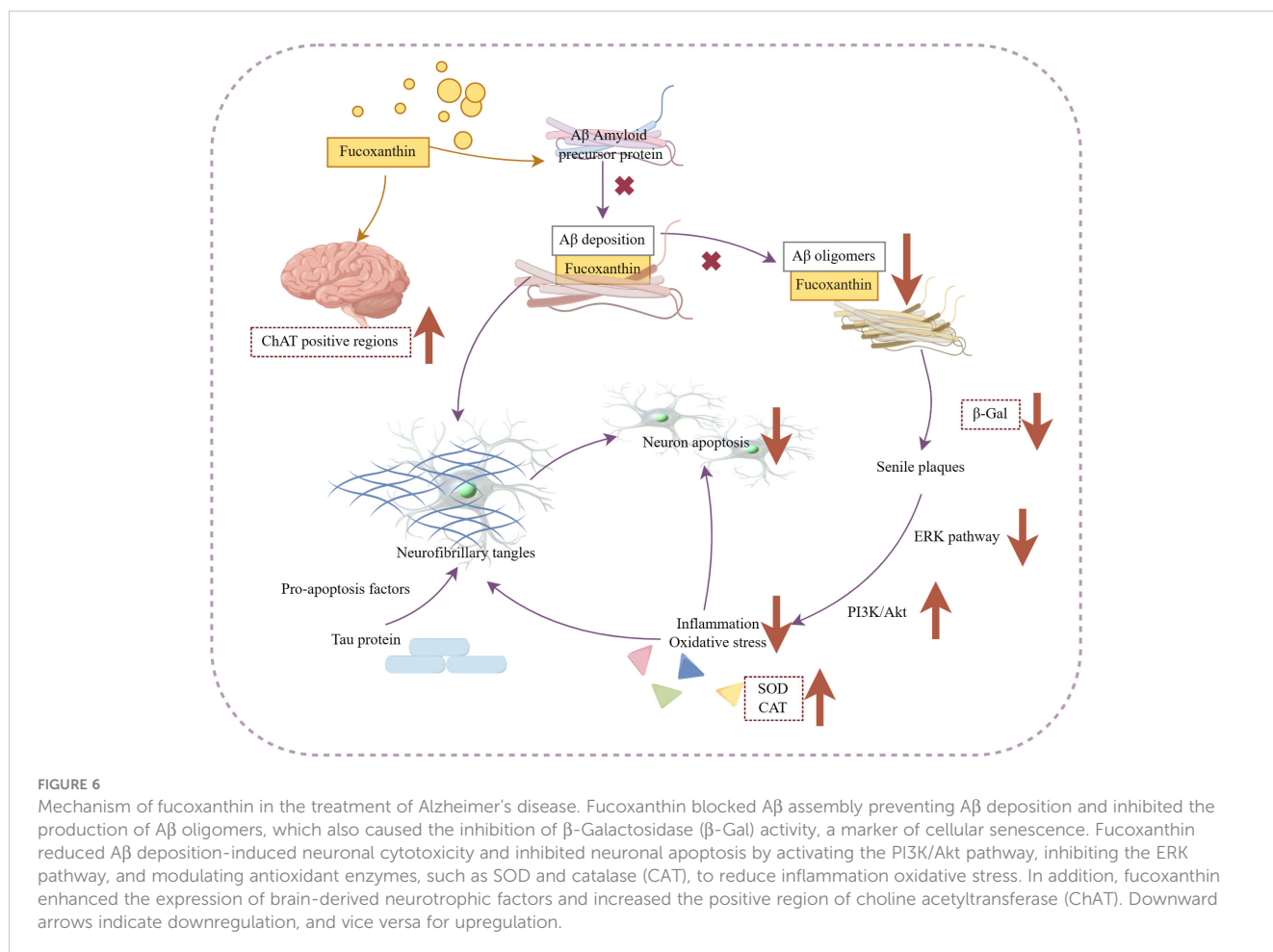
(Xiang et al., 2017). Fucoxanthin also prevented neuronal apoptosis and intracellular reactive oxygen stress by A β oligomer through activating the PI3K/Akt cascade and inhibiting the ERK pathway in SH-SY5Y cells (Lin et al., 2017). Zhu et al., (Zhu et al., 2021), *in vitro* research showed that 5-10 μ M fucoxanthin reduced the activity of the senescence marker SA- β -galactosidase. Another *in vitro* study demonstrated that fucoxanthin modulated antioxidant enzymes such as superoxide dismutase (SOD) to exert antioxidant effects on neuronal cells, inhibited A β ₁₋₄₂ induced apoptosis (Zhu et al., 2021).

The available evidence supports the neuroprotective effects of fucoxanthin and highlights the potential marine-derived carotenoids as novel strategies for preventing or treating dementia. Figure 6 illustrates the mechanism of its anti-Alzheimer activity.

2.4 Other active

2.4.1 Antimicrobial

Fucoxanthin can be a natural antimicrobial agent. Although it has antibacterial activity against both Gram-positive and negative bacteria, it does not show activity against strict anaerobic bacteria (Karpinski and Adamczak, 2019). Liu Z et al., (Liu et al., 2019), reported the antimicrobial properties of fucoxanthin against human pathogens (*Streptococcus agalactiae*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*), indicating that fucoxanthin effectively inhibits their growth. Peraman M et al (Peraman and Nachimuthu, 2019), screened methanolic extracts of marine microalgae fucoxanthin for antimicrobial activity. Among them, both the extract of *Dunaliella salina* and *Thalassiosira* extract showed better antibacterial activity against bacteria and fungi (minimum



inhibitory concentration MIC: 40 mg/mL), whereas the bacterial species acted were different. Transmission electron microscopy was applied for determining the morphological changes in bacterial after fucoxanthin treatment (El Shafay et al., 2016). Perforation of cell wall, leakage of cytoplasmic contents, severe distortion of outer cell shape, inner chromatin mild scattered cytoplasmic vacuolation, rupture of cell wall, and decreased cell size for bacteria treated with fucoxanthin-containing seaweed extracts (El Shafay et al., 2016). And carotenoids induce the accumulation of a lysozyme that can digest bacterial cell walls. The antimicrobial mechanism of fucoxanthin may be associated with it (Abu-Ghannam and Rajauria, 2013).

Based on these findings, fucoxanthin is expected to contribute to addressing the issue of bacterial drug resistance.

2.4.2 Antiviral

In terms of antiviral activity, fucoxanthin has been found to inhibit the activation of Epstein-Barr Virus at lower concentrations (Tsushima et al., 1995). Additionally, there is a hypothesis that the consumption of fucoxanthin-containing dietary seaweeds may provide resistance against COVID-19 damage through various mechanisms, but further investigation is needed to understand its pharmacological activity and mechanism (Tamama, 2021).

2.4.3 Anti-angiogenic

During the process of angiogenesis, the vascular endothelium releases proteases and migrates through the extracellular matrix in order to proliferate and differentiate into new blood vessels. Ponesakki G et al (Ganesan et al., 2013). conducted a study using human umbilical vein endothelial cells (HUVEC) to clarify the molecular mechanisms of fucoxanthin, an antivascular compound. Their findings revealed that fucoxanthin inhibits FGF-2-mediated intracellular signaling proteins, thereby suppressing the migration of endothelial cells. Their differentiation into tubular structures was also inhibited. In *in vitro* angiogenesis assays, fucoxanthin in doses more than 10 μM demonstrated significant suppression of HUVEC tube formation and proliferation (Sugawara et al., 2006). Moreover, in an *ex vivo* angiogenesis assay, fucoxanthin exhibited a dose-dependent suppression of microvessel outgrowth (Sugawara et al., 2006).

Angiogenesis is crucial for both the healing of wounds and the advancement of illnesses like rheumatoid arthritis and cancer. Many pathological conditions, such as tumors, atherosclerosis, and SARS-CoV-2, are known to be associated with angiogenesis (Viillard and Larrivé, 2017). Studies indicate that fucoxanthin is a potentially useful product that can be used to treat angiogenesis-related illnesses in a secure and efficient manner.

2.4.4 Osteoprotective

Osteoclasts and osteoblasts work in tandem to regulate the process of bone development and formation. Treatment with 2.5 μ M fucoxanthin inhibited osteoclast RAW264.7 differentiation and induced osteoclast apoptosis to inhibit osteoclast formation. Notably, fucoxanthin induced apoptosis effect on osteoclasts was stronger compared to osteoblasts (Das et al., 2010). You-Jung et al (Ha et al., 2021). investigated the effects of fucoxanthin on osteoblast differentiation and its regulatory pathways. Their results demonstrated that fucoxanthin altered the expression of mitogen-activated protein kinase and Nrf2, leading to a significant inhibition of osteoclast differentiation and bone resorption.

Therefore, fucoxanthin potentially holds promise as a therapeutic agent for skeletal diseases, for example, rheumatoid arthritis and osteoporosis.

3 Methods

The scientific literature was primarily searched from two databases: Web of Science and PubMed. The search words are not limited to “fucoxanthin” AND “fucoxanthin anti-” OR “microalgae”. If the article contains relevant citations of interest, the paper will also be included in the section to be searched. The obtained material was then screened. Articles that were inaccessible, irrelevant to the review’s direction, or duplicates.

To determine whether to include a review, the abstract and discussion sections of the article were read. Additionally, the full text was examined to extract information about microalgae species, culture process parameters, and models used in cellular experiments for subsequent tabulation.

4 Summary and outlook

Fucoxanthin has demonstrated its value in various applications due to its ability to bind to a wider range of targets, thanks to the presence of multiple functional groups. Its anti-inflammatory activity and antioxidant properties make it effective in alleviating diseases associated with inflammation and oxidative stress, such as skin inflammation, ulcerative colitis, and contact hypersensitivity. Additionally, fucoxanthin has been a subject of research interest for its potential anti-diabetic and anti-obesity effects, as well as its proven biological activities in non-alcoholic steatohepatitis and Alzheimer’s disease. The discovery of fucoxanthin-rich microalgae has opened up possibilities for industrial production. Furthermore, natural products are generally more preferable to chemically synthesized drugs.

However, the industrial production of fucoxanthin is still a distant goal, primarily due to the challenge of obtaining superior algal strains. Gene editing can be used for breeding, but the synthetic pathway needs to be clarified first. Currently, new physical and chemical mutagenesis technologies provide a convenient method for breeding without molecular alteration, although issues related to excessive unpredictability and poorly directed mutation must be considered. In terms of culture techniques, microalgae culture still relies on traditional cultivation

methods. The optimization of cultivation processes can accelerate the commercial development of fucoxanthin, but researchers also need to address the challenges of transitioning from small trials to factory production.

Considerable advancements have been achieved in the study of the biological properties and activity of fucoxanthin. Notably, fucoxanthin extracts have shown no indications of drug toxicity in both *in vivo* and *ex vivo* experiments. However, the specific pharmacological targets and signaling mechanisms of fucoxanthin are still not fully understood and require further investigation. Additionally, it is crucial to ensure the safety and effectiveness of high-purity fucoxanthin obtained through biorefining methods for its incorporation in pharmaceuticals, food, and cosmetics.

Author contributions

BG: Writing – original draft, Writing – review & editing. SM: Project administration, Writing – review & editing. YY: Project administration, Writing – review & editing. ZW: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmars.2024.1357425/full#supplementary-material>

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