Fucoxanthin

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Fucoxanthin is a well-known carotenoid of the xanthophyll family, mainly produced by marine organisms such as the macroalgae of the fucus genus or microalgae such as *Phaeodactylum tricornutum*. Fucoxanthin has antioxidant and anti-inflammatory properties but also several anticancer effects. Fucoxanthin induces cell growth arrest, apoptosis, and/or autophagy in several cancer cell lines as well as in animal models of cancer. Fucoxanthin treatment leads to the inhibition of metastasis-related migration, invasion, epithelial–mesenchymal transition, and angiogenesis. Fucoxanthin also affects the DNA repair pathways, which could be involved in the resistance phenotype of tumor cells. Moreover, combined treatments of fucoxanthin, or its metabolite fucoxanthinol, with usual anticancer treatments can support conventional therapeutic strategies by reducing drug resistance.

Keywords: angiogenesis ; apoptosis ; cancer ; cell growth arrest ; DNA repair ; EMT ; fucoxanthin ; inflammation ; invasion ; migration

1. Introduction

Carotenoids are colored and natural pigments widely distributed in nature. They include more than 1100 molecules [1], divided into two classes: xanthophylls, which contain oxygen, and carotenes, which are pure hydrocarbons. In photosynthetic organisms such as plants and algae, carotenoids have two major roles: they absorb energy for photosynthesis and also protect chlorophyll from photodamage [2]. At a structural level, xanthophyll pigments are close to each other, they share a long carbon chain containing one or more oxygen atoms, which differentiates them from carotenes. These carotenoids pigments are well-known for their antioxidant and anti-inflammatory properties [3][4][5], but they also display some potential anticancer effects [6].

First isolated in 1914 by Willstätter and Page, fucoxanthin (Figure 1) is an orange-colored xanthophyll pigment derived from brown algae and microalgae [7][8][9]. It is found in high content in taxons such as Phaeophyceae, Haptophyta, Bacillariophyceae, and Chrysophyceae, and to a lesser extent in Rhodophyta, Raphidophyceae, and Dinophyta [10][6]. Fucoxanthin is one of the most abundant carotenoid pigments, which contributes to more than 10% of the estimated total carotenoid production in nature, particularly in the marine environment [11].

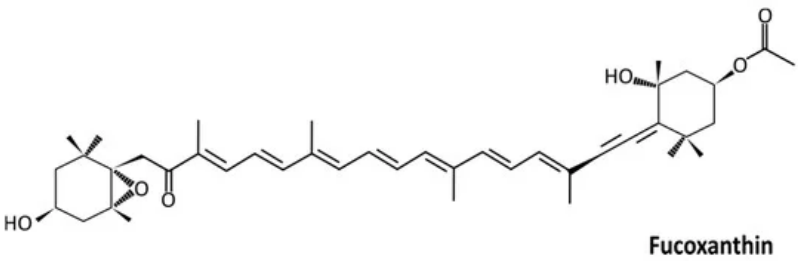

Figure 1. Structure of fucoxanthin (3′-acetoxy-5,6-epoxy-3,5′-dihydroxy-6′,7′-didehyro-5,6,7,8,5′,6′-hexahydro-β,β-carotene-8-one; $C_{42}H_{58}O_6$; 658.91 g/mol).

Popular sources of fucoxanthin include macroalgae such as *Laminaria japonica*, *Eisenia bicyclis*, and the well-known brown seaweed Wakame (*Undaria pinnatifida*), as well as diatoms microalgae such as *Phaeodactylum tricornutum* [12]. Fucoxanthin exhibit several biological activities that are beneficial to human health including antioxidant, anti-inflammatory, anti-obesity, anti-diabetic, anti-angiogenic, and anticancer properties [6][13][14][15][16][17][18][19].

2. Antiproliferative Effects of Fucoxanthin

Antiproliferative effect of fucoxanthin has been reported for numerous cancer cell lines and the inhibition of cell proliferation by fucoxanthin is due to cell growth arrest at G0/G1 or G1 phase of the cell cycle [6]. The molecular mechanism of the G0/G1 phase arrest mainly involves the downregulation of cyclin D1 and/or D2 and cyclin-dependent kinase-4 (CDK4). However, cyclin E and CDK2 or CDK6 could also be involved in some cell types. Furthermore, studies showing tumor growth arrest in the presence of fucoxanthin with several types of cancer has confirmed the antiproliferative effect of fucoxanthin *in vivo* [20][21]. Fucoxanthin also induces cancer cell death through the induction of apoptosis and/or autophagy in various cellular cancer cell lines, including HeLa, SGC-7901 and human cervical cancer [22][23][24]. In addition, it appears that fucoxanthin-induced autophagy occurs prior to apoptosis and may be a promoter of apoptosis [23]. Molecular mechanisms that sustain the cell death induction by fucoxanthin include, but are not limited to, inhibition of Akt/mTOR signaling pathway [22], downregulation of NF-κB pathway, increase of Bax and decrease of Bcl2 and/or BclXL through the MAP kinase pathway (reviewed in [6]). The effects of fucoxanthin on cell death of cancer cell lines *in vitro* have been confirmed by *in vivo* studies in mice bearing xenografted sarcoma 180, where fucoxanthin, at 50 and 100 mg/kg, significantly inhibited the growth of sarcoma and induced apoptosis as demonstrated by the decrease of Bcl-2 expression and a clear increase of cleaved caspase-3 [25].

3. Anti-Metastatic Effect of Fucoxanthin

Fucoxanthin was found to possess strong anticancer and anti-metastatic activities that work irrespective of the p53 status of cancer cells and cause a decrease in hallmark proteins associated with the metastatic spread of cancer cells at doses that were relatively safe to the normal cells [26]. Fucoxanthin inhibited the expression and secretion of MMP-9, which plays a critical role in tumor invasion and migration, and suppressed invasion of highly metastatic B16-F10 melanoma cells [27] as well as the human glioblastoma cell line U87 [28]. This effect, in glioblastoma cell line U87, is dependent on the p38 MAPK signalling [28]. Furthermore, fucoxanthin decreased the expression of the cell surface glycoprotein CD44 and C-X-C motif chemokine receptor-4 (CXCR4), which are involved in migration, invasion and adhesion of cancer cells to endothelial cells. Indeed, the adhesion of B16-F10 melanoma cells to the endothelial cells was significantly inhibited by fucoxanthin [27]. Moreover, the development of osteosarcoma in mice inoculated with osteosarcoma cells was inhibited by a treatment with fucoxanthin [29] and *in vivo* metastasis was reduced by fucoxanthin as shown by a significant reduction of tumor nodules in an experimental lung metastasis *in vivo* assay [27] and glioblastoma xenografts [28].

4. Anti-Angiogenic Effect of Fucoxanthin

Angiogenesis could be defined as the process of remodeling the primitive network of blood vessels and its growth into a complex network that is regulated by the balance between pro- and anti-angiogenic molecules. During this process, vascular endothelial cells secrete proteases and then migrate through the extracellular matrix, proliferate, and differentiate into new blood vessels [30]. Pathological angiogenesis is involved in many diseases, including rheumatoid arthritis, atherosclerosis, diabetic retinopathy, and cancer [31]. Angiogenesis is mandatory for tumor progression because newly formed blood vessels are needed to supply oxygen and nutrients, which are essential to the growing tumor, and to remove waste products. Also, the metastasis process depends on angiogenesis, as tumor cells migrate from the primary tumor and grow in distant target organs. Few studies highlighted the anti-angiogenic potential of fucoxanthin [15][32][33]. First, fucoxanthin was shown to inhibit human umbilical vein endothelial cells' (HUVEC) proliferation and tube formation, but without a significant effect on HUVEC chemotaxis [32]. Fucoxanthin (10–20 µM) also suppressed the development of blood vessel-like structures from CD31-positive cells, and then may suppress the differentiation of endothelial progenitor cells into endothelial cells involving new blood vessel formation. The molecular mechanism of this anti-angiogenic effect of fucoxanthin involves the downregulation of the mRNA level of FGF-2 and its receptor (FGFR-1) as well as their trans-activation factor, EGR-1, as shown in HUVEC treated by fucoxanthin [15]. Moreover, fucoxanthin downregulates the FGF-2-mediated phosphorylation of signaling proteins such as ERK1/2 and Akt, which leads to the repression of endothelial cells' migration as well as their differentiation into tube-like structures on Matrigel® [15]. Fucoxanthin also inhibited the formation of tube-like structures from human lymphatic endothelial cells as well as it suppressed the malignant phenotype of human breast cancer MDA-MB-231 cells and decreased tumor-induced lymphangiogenesis when used in combination with a conditional medium culture system [33]. *In vivo*, using a MDA-MB-231 nude mouse model of breast cancer, high doses of fucoxanthin (100–500 µM) decreased micro-lymphatic vascular density, suggesting that fucoxanthin inhibits tumor-induced lymphangiogenesis *in vitro* and *in vivo*. At the cellular level, the mechanism of action of fucoxanthin involves decreased levels of VEGF-C, VEGF receptor-3, NF-κB, p-Akt, and p-PI3K in HLEC [33].

5. Anti-Inflammatory Effects of Fucoxanthin

Pro-inflammatory mediators including interleukins, tumor necrosis factor α (TNFα), prostaglandin E2, and nitric oxide contribute to the development of a variety of inflammatory diseases. Natural products such as carotenoids have been used in the prevention of oxidative stress due to their antioxidant activities [34]. Despite the fact that the oxidative or anti-oxidative properties of fucoxanthin are discussed and seem to depend on the cellular context, this compound has been studied in an anti-inflammatory context in vivo and in vitro [35][36].

Fucoxanthin inhibited cell viability of adult T-cell leukemia, which is a fatal malignancy of T lymphocytes caused by human T-cell leukemia virus type 1 (HTLV-1) [37]. Interestingly, uninfected cell lines and normal peripheral blood mononuclear cells were resistant to fucoxanthin [37]. The combination of fucoxanthin and rosmarinic acid (a bioactive compound from Lamiaceae plants) improved anti-inflammatory effects from each [16]. Indeed, the inflammatory response is modulated through downregulation of inflammasome components such as “NOD-like receptor family, pyrin domain containing 3” (NLRP3), “apoptosis-associated speck-like protein” (ASC), caspase-1, and interleukins. These results suggest that fucoxanthin, in combination with rosmarinic acid, exerts anti-inflammatory effects by downregulating NRLP3-inflammasome and increasing the NFE2L2/Nrf2 signaling pathway in UVB-exposed HaCaT keratinocytes [16].

6. Fucoxanthin Effect on DNA damage and DNA repair

The antioxidant properties of fucoxantin can limit ROS-induced DNA damage, such as UVB-induced DNA-damage in human fibroblast [38] or in rat glioma cells [39]. In addition, a protective effect of fucoxanthin toward bleomycin-induced DNA damage has been observed in MCF-7 breast cancer cells [40]. By contrast, fucoxanthin can also lead to DNA damages in cancer cells [41][42], and this can be used for anticancer therapy by increasing the cytotoxic effect of common drugs such as 5-fluoro-uracile in colon cancer cells [42]. This induction of DNA damage is mediated by the production of reactive oxygen species and the subsequent activation of ATM/ATR/p53 pathways and the phosphorylation of Ser139 of histone H2AX [43]. Fucoxanthin decreases the mRNA expression of the DNA repair gene ERCC1, which is induced by cisplatin and this leads to the improvement of chemotherapeutic efficacy of cisplatin [44].

7. Conclusions

Cellular and animal studies have shown that fucoxanthin has anticancer effects. However, investigation of this role in humans is lacking. Clinical trials are required to assess the effect of fucoxanthin in close connection with the study of the mechanisms involved in the antitumoral action of fucoxanthin. Moreover, anticancer effects of fucoxanthin are regulated by several mechanisms leading to cell cycle arrest, induction of cell death and DNA damages, inhibition of metastasis-related migration, invasion and epithelial–mesenchymal transition, anti-angiogenic, and anti-inflammatory effects. Furthermore, combined treatments of fucoxanthin or fucoxanthinol with usual anticancer treatments can support conventional therapeutic strategies by reducing drug resistance. Indeed, as an anticancer molecule, fucoxanthinol appears to be a more effective bioactive compound than fucoxanthin. Therefore, the potential use of fucoxanthinol and other fucoxanthin derivatives (such as apo-9′-fucoxanthinone and apo-13-fucoxanthinone) as co-adjuvant agents in the treatment of cancer should be further investigated. However, further studies are necessary for precise and complete inhibitory effects of fucoxanthin and its derivatives, but regarding these hallmarks, fucoxanthin appears to be a promising compound for cancer therapy.

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