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Review

Antitumor and Cancer-preventative Function of Fucoxanthin: A Marine Carotenoid

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Abstract. *Fucoxanthin is a marine carotenoid mainly found in brown seaweeds. Its antitumor and cancer-preventative function has been extensively investigated. Investigations have indicated that fucoxanthin and its metabolite fucoxanthinol induce G_1 cell-cycle arrest and apoptosis in various cell lines and can inhibit cancer development in animal models. It is imperative that the underlying mechanism of action of fucoxanthin be elucidated in order to facilitate the development of cancer-prevention strategies in humans. Key molecules that require consideration include mitogen-activated protein kinase, growth arrest and DNA damage-inducible 45, AP-1 transcription factor, nuclear factor-kappa B and several others, including cell cycle-related molecules for G_1 cell-cycle arrest and the B cell lymphoma-2 family, X-linked inhibitor of apoptosis, cellular inhibitor of apoptosis protein and AKT serine/threonine kinase/phosphatidylinositol-3-kinase for apoptosis. In this review, the mechanisms by which fucoxanthin exerts its antitumor and cancer-preventative action in cell lines and mouse models is discussed, in addition to the potential use of fucoxanthin as a promising compound for cancer prevention.*

Fucoxanthin is a red- or orange-colored carotenoid pigment that is produced in brown seaweeds and some microalgae (1-3). In humans, dietary fucoxanthin is mainly metabolized to fucoxanthinol, the deacetylated form of fucoxanthin (4, 5), and which is considered to be an active form of fucoxanthin. The chemical structure of fucoxanthin and fucoxanthinol is shown in Figure 1. Fucoxanthin possesses a unique chemical structure that includes an allene bond, 5,6-monoepoxide and acetylated group. Fucoxanthin is one of the most abundant carotenoids and fucoxanthin-containing brown algae, such as wakame (*Undaria pinnatifida*) and kombu (*Laminaria japonica*), are commonly consumed in Asia. Recent studies have revealed several health benefits of fucoxanthin, including anti-inflammatory, anti-obesity, anti-diabetes, hepato-protective and cardiovascular-protective activities, in addition to anticancer activity (2, 6). With regard to the anticarcinogenic effect of fucoxanthin, it is well-known that fucoxanthin exerts tumor-inhibitory effects in various cancer cells and mouse models. In order to clarify the anticancer effect of fucoxanthin, it is crucial to understand the underlying mechanism of action. In this review, the effects of fucoxanthin on cancer are summarized and the proposed mechanisms suggested by many researchers accounting for these are detailed.

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Fucoxanthin Inhibits Tumor Cell Growth by Inducing G_1 Cell-cycle Arrest With/Without Apoptosis in Various Tumor Cells

The antitumor effects of fucoxanthin are summarized in Figure 2.

G_1 cell-cycle arrest with/without apoptosis. Fucoxanthin has been mainly observed to induce G_1 cell-cycle arrest in many tumor cell lines. Okuzumi *et al.* found that 5-10 μg/ml (7.6–15.2 μM) of fucoxanthin caused arrest during the G_0/G_1 phase of the cell cycle, and was accompanied with a decrease in *MYCN* proto-oncogene expression in human neuroblastoma GOTO cells (7).

Das *et al.* observed that fucoxanthin induced cell-cycle arrest during the G_0/G_1 phase in a dose- (25 and 50 μM) and time- (24 and 48 h) dependent manner, and that apoptosis was induced at a high concentration (50 μM) and at a later time (48 h) in human colon carcinoma WiDr cells (8). They also found that the increase in $p21^{WAF1/CIP1}$, a cyclin-dependent kinase (CDK)-inhibitory protein, and decreased phosphorylation levels of RB

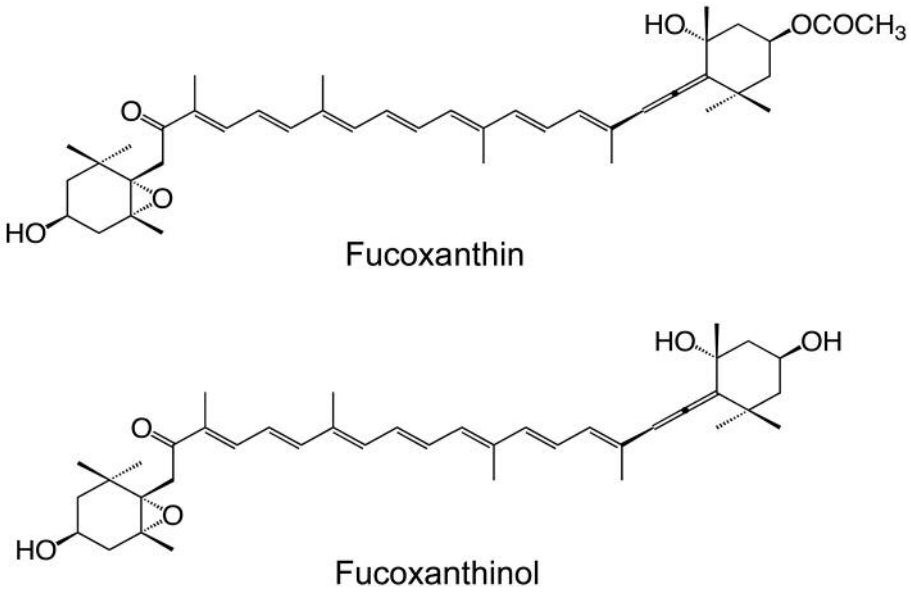

Figure 1. *Chemical structures of fucoxanthin and fucoxanthinol.*

transcriptional corepressor (RB), were dose-dependent. Furthermore, the increase in another CDK inhibitory protein $p27^{KIP1}$ and decrease in CDK4 and cyclin D, which phosphorylate the RB protein, were observed at high concentrations of fucoxanthin (50 and 75 μM). They speculated that $p21^{WAF1/CIP1}$ plays a key role in G_0/G_1 arrest and that $p27^{KIP1}$ may be important for apoptosis by fucoxanthin. Another of their studies showed that 25 μM of fucoxanthin induced cell-cycle arrest during the G_0/G_1 phase in $HepG_2$ human hepatocarcinoma cells (9). The induction of cell-cycle arrest was accompanied by a decrease in phosphorylated forms of RB without reducing the RB protein level, although $p21^{WAF1/CIP1}$ and $p27^{KIP1}$ levels remained unchanged. The kinase activity of the cyclin D/CDK4 complex and protein level of cyclin D were also reduced by fucoxanthin. They suggested that down-regulation of cyclin D may be an important factor in the action of fucoxanthin. Yu *et al*. found that G_2/M arrest and apoptosis were induced by fucoxanthin (50 and 75 μM) in human gastric adenocarcinoma MGC-803 cells (10). Their study showed that fucoxanthin reduced the expression of cyclin B1 and survivin, and they suggested that these factors might contribute to the action of fucoxanthin. Since fucoxanthin usually induces G_0/G_1 arrest, the mechanism by which fucoxanthin induced G_2/M arrest but not G_1 arrest in MGC-803 cells should be clarified.

Ishikawa *et al*. showed that fucoxanthin (10 μM) and fucoxanthinol (5 μM), a metabolite of fucoxanthin, induced cell-cycle arrest during the G_1 phase and caspase-dependent apoptosis in adult T-cell leukemia cells (11). The reduction in cell cycle-related proteins such as cyclin D1, cyclin D2, CDK4 and CDK6, and the induction of DNA damage-inducible 45α (GADD45α), were observed concomitantly. A reduction in apoptosis-related proteins such as B-cell lymphoma-2 (BCL2), X-linked inhibitor of apoptosis (XIAP), cellular inhibitor of apoptosis protein 2 (CIAP2) and survivin was also observed. Additionally, they speculated that the effects of fucoxanthin and fucoxanthinol might be mediated through the inactivation of transcription factor nuclear-factor kappa B (NF-κB) or AP-1 transcription factor (AP1). Another study by the same group revealed that fucoxanthin (2.5 and 5 μM) and fucoxanthinol (1.25 and 2.5 μM) induced cell-cycle arrest during the G_1 phase at low concentration and caspase-dependent apoptosis at high concentration in Burkitt's and Hodgkin's lymphoma cells (12). The decrease in cyclin D1, cyclin D2, BCL2, XIAP and CIAP2 protein levels was associated with suppression of NF-κB activity. They supposed that major roles were played by the down-regulation of NF-κB-dependent cell survival proteins in apoptosis, and down-regulation of cyclin D in cell-cycle arrest, as induced by fucoxanthin and fucoxanthinol. They also observed that fucoxanthin (5 and 10 μM) and fucoxanthinol (2.5 and 5 μM) induced G_1 cell-cycle arrest and caspase-dependent apoptosis in primary effusion lymphoma cells (13). Concomitantly, the expression of BCL-xL, XIAP, survivin, cyclin D2, CDK4, CDK6 and c-MYC proto-oncogene protein were reduced, and inactivation of NF-κB, AP1 and AKT serine/threonine kinase (AKT) was found in the cells, some of which are heat-shock protein 90 (HSP90) client proteins the expression of which was restored by treatment with a proteasome inhibitor. They speculated that the effects of fucoxanthin and fucoxanthinol might be related to inhibition of HSP90 chaperon function.

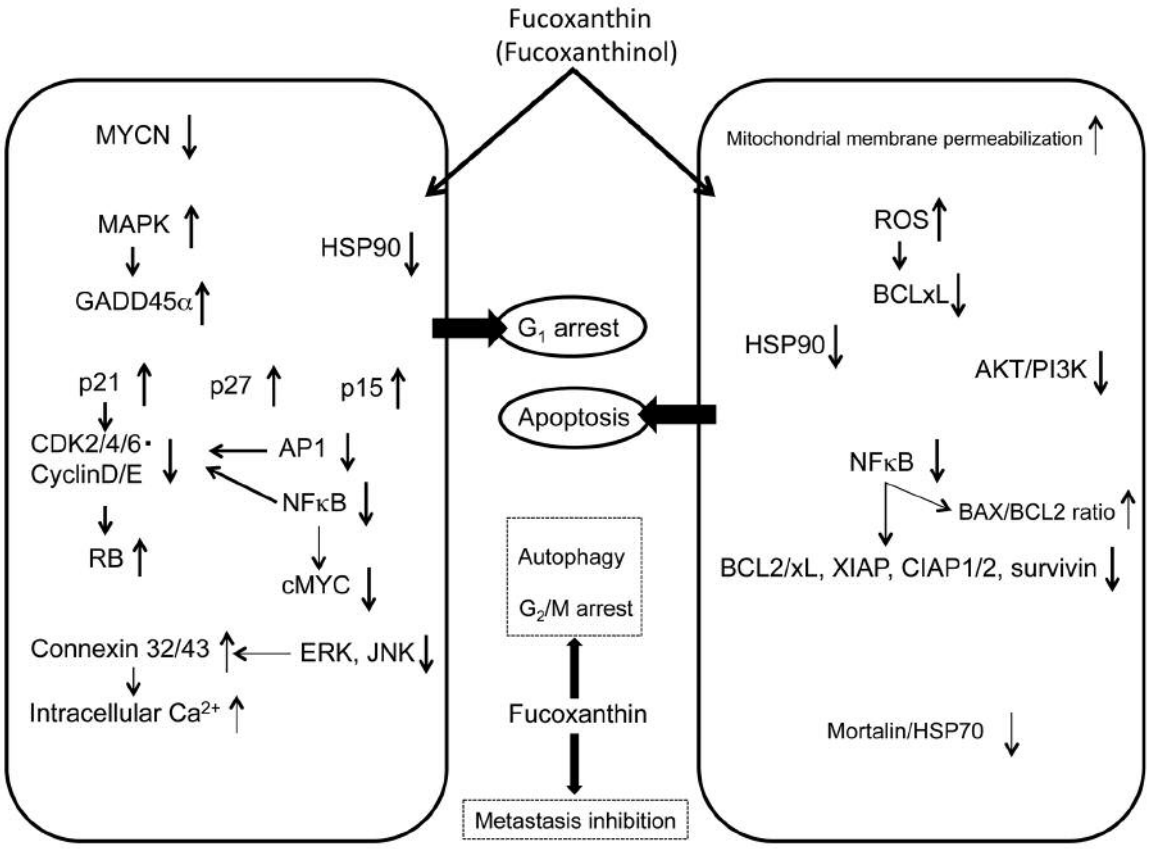

Figure 2. *Antitumor effects of fucoxanthin and associated factors. ↑ Indicates induction or activation. ↓ Indicates reduction or inactivation. Arrows between factors indicate former factors affect latter factors. Thick arrows indicate that several research groups have observed these effects.*

Kim *et al*. revealed that fucoxanthin (50, 100 and 200 μM) caused caspase-dependent apoptosis following G_0/G_1 arrest in mouse melanoma B16F10 cells (14). Observations of cells showed a decrease in phosphorylated RB, cyclin D1, cyclin D2 and CDK4, and an increase in $p15^{INK4B}$ and $p27^{KIP1}$ in addition to a decrease in BCL-xL, CIAP1, CIAP2 and XIAP. Wang *et al*. reported that 5 and 10 μM of fucoxanthin induced cell-cycle arrest during the G_0/G_1 phase by up-regulation of $p21^{WAF1/CIP1}$ and down-regulation of CDK2, CDK4, cyclin D1 and cyclin E in human bladder cancer T24 cells (15). Additionally, treatment of cells with 20 and 40 μM of fucoxanthin induced caspase-dependent apoptosis accompanied by a decrease in mortalin (a member of the HSP70 family inhibiting p53 function) and its decrease resulted in reactivation of p53. Liu *et al*. reported that fucoxanthin (1-20 μM) caused cell-cycle arrest during the G_0/G_1 phase and apoptosis in SK-Hep-1 human hepatoma cells (16). These effects were associated with enhancement of gap junctional intercellular communication (GJIC) and an increase in connexin 43 and connexin 32 expression, as well as intracellular calcium level. A decrease in the phosphorylated forms of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) was observed in the cells. They supposed that fucoxanthin increased intracellular calcium levels by GJIC enhancement and then caused cell-cycle arrest and apoptosis. Hou *et al*. found that fucoxanthin (10, 20 and 40 μM) caused G_0/G_1 arrest accompanied by an increase in $p21^{WAF1/CIP1}$ and decrease in cyclin D1 and CDK2 protein levels in human epithelial cervical cancer HeLa cells (17). They simultaneously observed that fucoxanthin induced autophagy associated with a reduction in phosphorylated AKT and its downstream proteins p53, phosphorylated forms of p70S6K and mechanistic target of rapamycin, and recorded an increase in phosphatase and tensin homolog PTEN.

Fucoxanthin (3.8-5.5 μM) induced G1 cell-cycle arrest accompanied by induction of the *GADD45A* gene and activation of mitogen activated protein kinase (MAPK) pathways in $HepG_2$, human prostate cancer DU145 and LNCap cells (18-20). MAPKs responsible for these effects were dependent on cell type. p38 MAPK was negatively associated with the fucoxanthin-mediated induction of

Table I. *Anticarcinogenic effects of fucoxanthin.*

	Cancer type	Method of administration	Effect
Carcinogenesis models	Duodenal	Oral	Inhibition
	Skin	Topical application	
	Colon	Oral	
	Liver	Oral	
Xenograft models	Lung metastasis of melanoma cells	Intraperitoneal injection	Inhibition
	Sarcoma, osteosarcoma	Oral	Apoptosis
	Melanoma	Oral	Growth inhibition
	Lymphoma	Oral	
	Cervical cancer	Oral	

GADD45A followed by G_1 arrest in $HepG_2$ cells, and JNK was positively associated with that in DU145 cells. On the other hand, p38 and ERK1/2 were negatively and JNK positively implicated in the induction of *GADD45A* and G_1 arrest by fucoxanthin in LNCap cells.

Apoptosis. Kotake-Nara *et al*. reported that fucoxanthin (20 μM) induced DNA fragmentation as indicated by a TdT-mediated dUTP nick end labeling method using human prostate cancer cells PC-3, DU145 and LNCap cells (21). Furthermore, they observed that fucoxanthin (10 μM) induced caspase-dependent apoptosis in human promyelocytic leukemia HL-60 cells *via* loss of mitochondrial membrane potential (22). Another study of theirs showed that fucoxanthin (20 μM) induced caspase-dependent apoptosis accompanied by a decrease in BCL2-associated X (BAX) and BCL2 protein levels in PC-3 cells (23). They suggested that fucoxanthin might induce apoptosis by modulating the ratio of BAX/BCL2. Hosokawa *et al*. reported that fucoxanthin (at least 7.6 μM for 48 h) caused DNA fragmentation indicating apoptosis, which was partially inhibited by a caspase inhibitor, and that it reduced the BCL2 protein level in Caco-2 human colon cancer cells, all of which led them to conclude that BCL2 may contribute to apoptosis induced by fucoxanthin (24). In another report by the same group, fucoxanthin (25 μM) was shown to induce apoptosis in MCF-7 human breast cancer cells (25). Apoptosis was induced by 5-40 μg/ml of fucoxanthin (7.6-60.7 μM), as indicated by DNA ladder and morphological changes in lung cancer cells NSCLC-N6 and A549 cells (26).

Zhang *et al*. observed that 20 μM of fucoxanthin significantly induced apoptosis accompanied by caspase-3 activation at 72 h in EJ-1 human bladder cancer cells (27). Kim *et al*. reported that fucoxanthin induced caspase-dependent apoptosis following reactive oxygen species (ROS) generation and BCL-XL reduction in HL-60 cells (28). They indicated that ROS generation by fucoxanthin played a crucial role. Ganesan *et al*. showed that 10 μM of fucoxanthin caused apoptosis and caspase-3 activation in HL-60 cells (29). Fucoxanthin (0.5 μM) was shown to induce caspase-dependent apoptosis with an increase in BAX and reduction in BCL2, phosphatidylinositol-3-kinase (PI3K) and a phosphorylated form of AKT in HeLa cells (30). The authors also found NF-κB inactivation and a decrease in its translocation to the nucleus from the cytoplasm in cells treated with fucoxanthin. Rwigemera *et al*. reported that both fucoxanthin and fucoxanthinol (10-40 μM) induced caspase-dependent apoptosis in human breast cancer cell lines MCF-7 and MDA-MB-231 (31, 32). Fucoxanthinol, but not fucoxanthin, reduced the expression of members of the NF-κB pathway such as p65, p52 and RELB proto-oncogene in MDA-MB-231 cells alone, which are estrogen-resistant.

Liu *et al*. observed that fucoxanthin (1-10 μM) enhanced cisplatin-induced apoptosis and attenuated cisplatin-induced NF-κB activation, resulting in an increase in the BAX/BCL2 ratio in $HepG_2$ cells (33). Fucoxanthin combined with cisplatin attenuated the expression of DNA repair genes such as ERCC excision repair 1 and thymidine phosphorylase, which led to an improvement in the action of cisplatin.

Other effects. Chung *et al*. found that fucoxanthin at a concentration that did not have a cytotoxic effect on cells (30 μM) suppressed the invasion of mouse B16-F10 melanoma cells as measured by a Transwell invasion assay, as well as cell migration in a wound-healing assay, and the adhesion of B16-F10 cells to human umbilical vein endothelial cells stimulated with tumor necrosis factor-α (34). These events were accompanied by a decrease in matrix metallopeptidase 9, CD44 and C-X-C motif chemokine receptor 4, which are known to play crucial roles in cancer migration and invasion, as well as a reduction in actin fiber formation in the cells.

Fucoxanthin Prevents Cancer Development In Mouse Models

The cancer-preventative actions of fucoxanthin are summarized in Table I.

Okuzumi *et al*. found that oral administration of fucoxanthin (0.005% in drinking water) significantly

inhibited *N*-ethyl-*N*'-nitro-*N*-nitrosoguanidine-induced mouse duodenal carcinogenesis (35). Nishino reported that topical application of fucoxanthin with 12-*O*-tetradecanoylphorbol 13-acetate completely suppressed skin tumor formation in mouse 2-stage skin carcinogenesis (36). Kim *et al*. reported that the development of aberrant crypt foci in the colons of mice initiated by 1,2-dimethylhydrazine was significantly suppressed by oral administration of fucoxanthin (0.01% in drinking water) (37). Additionally, Nishino *et al*. reported that fucoxanthin (0.001% in drinking water) suppressed spontaneous liver carcinogenesis (38). Das *et al*. found that oral administration of fucoxanthin (0.005 and 0.01% in drinking water) significantly reduced the number of aberrant crypt foci in azoxymethane-treated mice (39).

Yamamoto *et al*. reported that fucoxanthin (150 mg/kg given by gavage) reduced tumor weight in severe combined immunodeficiency mice inoculated with BCBL-1 cells (primary effusion lymphoma) (13). In a study by Wang *et al*., fucoxanthin (50 and 100 mg/kg given by gavage) appeared to inhibit the growth of sarcomas in sarcoma 180 xenograft-bearing mice (40). In the sarcoma tissues, caspase-dependent apoptosis was observed, which was accompanied with a decrease in the BCL2 protein. Additionally, a decrease in survivin, vascular endothelial growth factor, epidermal growth factor receptor (EGFR), signal transducer and activator of transcription 3 (STAT3) and phosphorylated STAT3 was observed. The authors supposed that fucoxanthin-induced apoptosis was associated with down-regulation of STAT3/EGFR signaling. Kim *et al*. observed that intraperitoneal injection of fucoxanthin (0.3 mg/mouse) inhibited the increase in tumor volume in B16F10 melanoma cell-implanted mice (14). Ye *et al*. found that fucoxanthin (10 and 20 mg/kg given by gavage) inhibited the growth of tumors in nude mice implanted with HeLa cells (30). Rokkaku *et al*. reported that fucoxanthin (200 mg/kg given by gavage) significantly reduced tumor volume in association with increased apoptotic cells in osteosarcoma-inoculated mice (41). Furthermore, they observed that lung metastasis decreased in these mice compared to the control.

Chung *et al*. revealed that intraperitoneal injection of fucoxanthin (0.1 mg/mouse) inhibited lung metastasis as indicated by a reduction in metastatic foci on the lung surface and reduced metastatic nodule numbers in lung tissues of mice injected with B16-F10 melanoma cells through their tail veins (34).

Conclusion

Fucoxanthin causes antitumor and anticarcinogenic effects by modulating expression of various cellular molecules and cellular signal transduction pathways. These findings suggest that fucoxanthin could be utilized as a possible cancer-preventative agent in strategies designed to combat human cancer.

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