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A Systematic Review on Fucoxanthin's Potential in Cancer Research over the Last Two Decades

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Abstract

Plants have always been considered strengthening specialists in conventional medicine. Several studies are being conducted on phytocompounds to confirm their medicinal effects. These compounds have been found to be able to combat mutagenicity, malignancy, and bacterial and viral infections in mild or severe degrees. Carotenoids are found in plants, microorganisms and green plants, as well as in various food sources, including organic products and vegetables. Carotenoids share several natural properties, including antioxidants, the ability to prevent harmful tumor formation, and the ability to stimulate apoptosis in cancer cells. Carotenoids can influence cell growth, gene expression and immune response through dietary supplementation. Carotenoids such as capsanthin, astaxanthin, canthaxanthin, crocetin, lycopene, fucoxanthin, lutein, zeaxanthin, carotene, carotene, cryptoxanthin, etc. are used as human nutrition and are found in soil-grown foods. Fucoxanthin, an orange color pigment from edible brown seaweed, prevents the formation of cancer cells caused by oxidative stress and obesity. It causes loss of mitochondrial membrane potential, which further leads to apoptosis. Permeabilization of the mitochondrial membrane is an important step in the early stage of the apoptosis pathway via mitochondria. The aim of this systematic review is to investigate the anticancer potential of fucoxanthin in various types of cancer. We conducted a comprehensive systematic review of publications in last 22 years using database search from PubMed, PubMed Central, Google Scholar, Embase, and Web of Science by retrieving 57 eligible publications including in-vitro and in-vivo studies.

Keywords: apoptosis, cancer, carotenoids, fucoxanthin, phytocomponds

Introduction and Background

Numerous studies are underway to analyze and confirm the medicinal properties of various phytocompounds extracted from plants. Carotenoids are such phytocompounds, which can also be found in microorganisms, vegetables, and fishes. These are brightly colored lipid-soluble compounds [1]. Out of the 600 carotenoids classified as carotenes, xanthophylls, and lycopene, only 40 are taken into the diet by humans and only 20 of these have been reported in human blood and tissue samples [2,3]. In human diet carotenoids such as fucoxanthin (Fx), capsanthin, astaxanthin (AST), canthaxanthin (CXN), crocetin, lycopene, lutein, zeaxanthin (ZXN), α-carotene, β-carotene, β-cryptoxanthin, and others are found in various fruits and vegetables [4,5]. Studies confirm that carotenoids possess antioxidant, anti-tumor, and apoptosis-inducing properties impacting cell development, gene expression, and immunity when supplemented in the diet. High carotenoid intake correlates with reduced cancer risk for tissues like breast, cervix, ovary, colon, rectum, and heart,

attributed to mechanisms like intracellular gap junctional communication, growth factor signaling, progression of cell cycle, and inflammatory pathways [6].

The in-vitro study where the extract of Paradicsompaprika containing capsanthin (TOMA-P) was tested on three cancer cell lines: Colo201, A549, and HeLa suggested its potential as an anti-tumor agent against certain malignancies [7]. Treatment of human colorectal cancer cells (LS-180) with AST upregulated Bax and Caspase-3 genes, downregulated Bcl-2, inducing apoptosis and inhibiting cancer cell growth. Moreover, it enhanced the activities of antioxidant enzymes, reducing malondialdehyde levels [8]. Astaxanthin has been found to enhance tumor immunity by inhibiting the growth of Meth-A tumor cells in mice through increased cytotoxic T lymphocyte activity and Interferon-γ synthesis in response to tumor antigens expressed by the cancer cells [9].
Crocetin induces apoptosis in various cancer cells by inhibiting DNA synthesis and RNA polymerase II activity, while also elevating the Bax/Bcl-2 ratio [10,11]. Crocin and crocetin were observed to inhibit triple-negative metastatic breast cancer cells (TNBC) through interference in the Wnt/β catenin pathway [12]. Consuming lycopene significantly decreased the severity of pancreatic cancer in men and inhibited the proliferation of human oral cancer cells [13, 14]. Study indicates that incorporating a diverse range of carotenoid-rich foods, such as those containing lycopene and beta-carotene, could potentially lower the risk of ovarian cancer [15]. Treatment of human colon cancer cell lines Caco-2, HT-29, and DLD-1 with Fx led to a decreased count of viable cells [16]. In various malignancies, including brain carcinoma, overexpression of PDGF receptors was detected, and lutein exhibited significant inhibition of PDGF-induced signaling [17].

Fucoxanthin (Fx), a prominent marine carotenoid characterized by its allenic bond and a 5,6-monoepoxide structure, is found in seaweeds like "Hijikia fusiformis, Undaria pinnatifida, and Sargassum fulvellum," and it demonstrates anticancer and anti-inflammatory properties through the induction of apoptosis and reduction of free radicals [18]. The carotenoid Fx has a molecular formula of C42H58O6. While possessing a distinctive molecular structure (Figure 1) [19]. it is inherently unstable and susceptible to degradation when exposed to factors such as light, heat, enzymes, oxygen, unsaturated

lipids, and other pro-oxidant substances throughout the phases of extraction, purification, and storage. Studies emphasized that the bioavailability of Fx is closely linked to its absorption and metabolic processes [20].

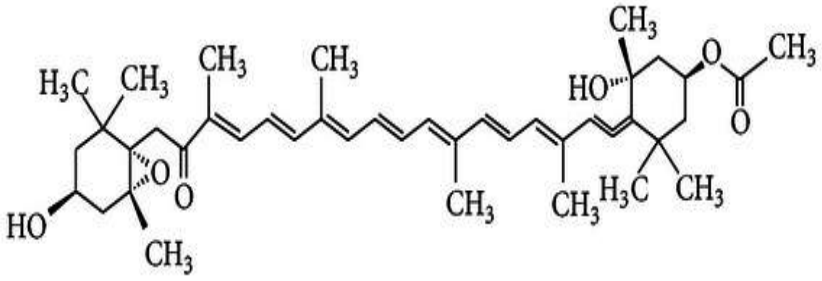


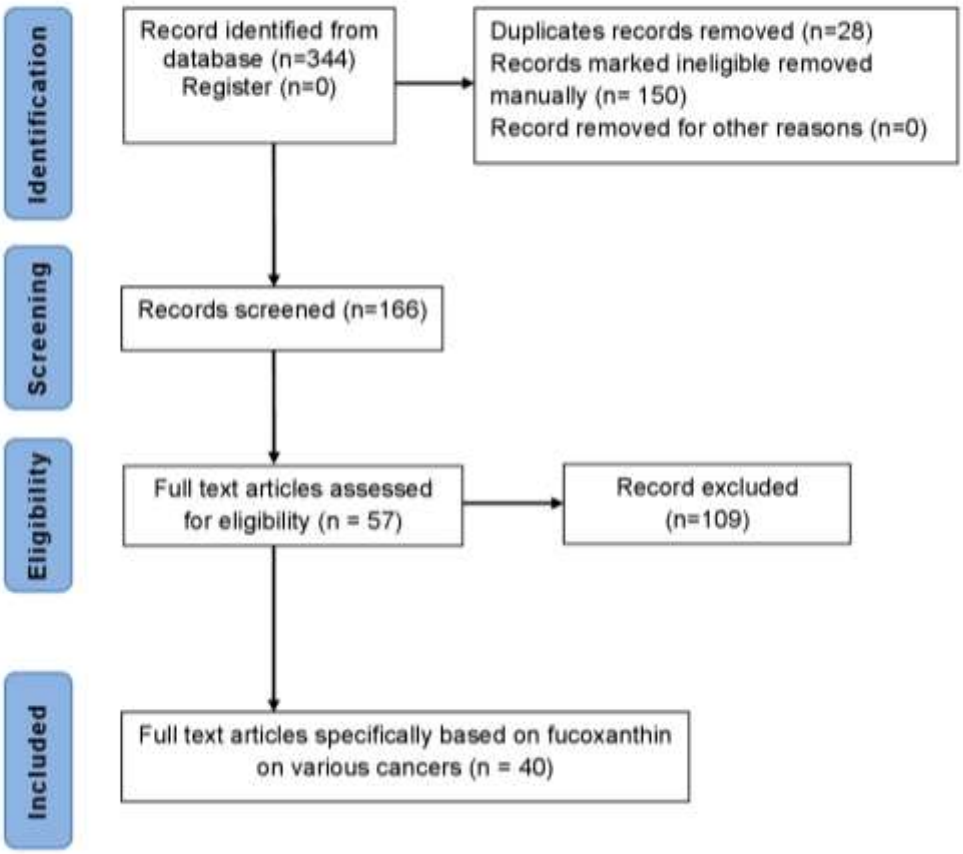
Figure 1: Chemical structure of fucoxanthin

Materials and Methods

Review studies were systematically found, screened, and eventually included in accordance with the "Recommended Reporting Units for Systematic Reviews" and Meta-analysis (PRISMA) methodology [21]. We conducted a thorough search of the literature in the databases PubMed, PubMed Central, Google Scholar, Embase, and Web of Science using a combination of the keywords Fucoxanthin, capsanthin, astaxanthin (AST), canthaxanthin, crocetin, lycopene, lutein, zeaxanthin, α-carotene, β-carotene, β-cryptoxanthin from 2000 to 2023. We extracted all pertinent publications discussing the anticancer effects of carotenoids on various cancers. Individual records from the initial search were checked for appropriate selection criteria (fucoxanthin's anticancer properties), and then those records were checked again using English titles and abstracts. To make sure that all pertinent materials were included, we meticulously combed through the reference lists of pertinent publications and cited the sources.

In selecting relevant articles, we went through a three-step approach. Initially, we reviewed the titles and summaries of the articles. The next step involved eliminating those that were not relevant. Finally, we examined the full content of the remaining articles to ensure their relevance. This process was carried out by four independent reviewers, who worked together to resolve disagreements. From the eligible articles, we took relevant information and used it for this systematic review. The names of the authors, the study year, and the publication year were among the general study attributes. 344 article records were obtained from the first database search. Following screening, 150 articles, deemed ineligible were manually removed, and 28 duplicates were eliminated.166 articles were screened and for a various reasons, not aligning with our study objectives, another 109 records were excluded. Studies and dissertations that were published in journals without peer review were also omitted. After screening, 57 articles were found eligible for the systematic review. (Figure 2)

Figure 2: Flowchart of identification of database and search criteria



Anti-cancer properties of Fucoxanthin in various cancers

Extensive research has been conducted to investigate the impact of Fx on various types of cancer tissues.

The effect of Fx in breast cancer

In a study by Rwigemera et al [22], two breast cancer cell lines, MCF-7 and MDA-MB-231, were exposed to low doses (10 and 20 μM) of Fx and fucoxanthinol (Fxol) to assess their anticancer effects. Both Fx and Fxol at 10 μM demonstrated antiproliferative properties by inducing apoptosis. Fucoxanthinol exhibited more rapid and effective

inhibition of cell growth compared to Fx. Specifically, at 20 μM, Fxol reduced MCF-7 cell viability by 58% after 48 hours of incubation, while MDA-MB-231 cell viability decreased to 13% and 47% at doses of 10 μM and 20 μM, respectively. Additionally, only MDA-MB-231 cells showed growth suppression with 10 μM Fxol after 48 hours.

Previous studies have consistently demonstrated that Fxol exhibits greater potency compared to Fx. Fucoxanthinol induced cell death in both estrogen-resistant MDA-MB-231 and estrogen-sensitive MCF-7 breast cancer cell lines. In particular, Fxol was observed to inhibit the expression of NF-κB pathway members (p65, p50, RelB, and p52) in MDA-MB-231 cells [23]. It is worth noting that women with estrogen receptor-positive tumors generally show a more favorable response to therapy; however, approximately 25% of cases did not respond due to acquired resistance. This resistance may be attributed to the presence of constitutive NF-κB activity, which helps estrogen-independent growth [24,25]. In estrogen receptor-positive cancers, there is substantial evidence of the continuous nuclear presence of key transcription factors such as asp50, p52, c-Rel, and the overexpression of p100/p52 [26]. The mammary gland cancer perspective presents an observation of heightened expression and activation of the p65 and p50 dimer, leading to an augmented transcriptional activity of anti-apoptotic genes [27].

Tumor lymphangiogenesis, characterized by the release of lymphangiogenic factors like vascular endothelial growth factor-C (VEGF-C) from inflammatory and tumor cells, plays a pivotal role in shaping endothelial cells into tubular structures within lymphatic vessels and facilitating their infiltration into tumors. To assess the impact of Fx, cancer cells were exposed to varying concentrations (25, 50, and 100 μMol/l) of Fx for different time intervals (12, 24, and 48 hours). Cell viability was evaluated using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Furthermore, the anti-migration effects of Fx on these cells were measured through transwell assays. To examine the influence of Fx on the formation of tube-like structures in lymphatic endothelial cells, a matrigel-based assay was employed. Protein expression levels in endothelial cells were assessed through western blot analysis after treating the cells with Fx for 24 hours. The findings indicated that Fx effectively inhibited the process of tumor lymphangiogenesis,

thereby preventing endothelial cell proliferation, migration, and the formation of tube-like structures [28].

Fucoxanthin interrupts MCF-7 cell adhesion to endothelium and transendothelial migration led to inhibition of CTCs-based pulmonary metastasis in vivo. Fx inhibits transendothelial migration by inhibiting EMT, PI3K/AKT, and FAK/Paxillin signaling pathways.The hetero-adhesion assay revealed that carotenoid significantly inhibited the expression of inflammatory factor induced cell adhesion molecules (CAMs) and the resulting adhesion between MCF-7 cells and endothelial cells. Mechanistically,it was mediated by inhibition of NF-kB pathway by down-regulating the phosphorylation level of IKK-α/β, IkB-α, and NF-kB p65. The wound-healing and transwell assays showed that Fx (25 μM) significantly inhibited the motility and invasion MCF-7 cells. Fucoxanthin also inhibited transendothelial migration abilities of cells when treated with 5, 10, 25 μM concentration. Moreover, Fx significantly inhibited the formation of lung micrometastatic foci in immune competent syngeneic mouse breast cancer metastasis models. Fucoxanthin increased the antitumor immune responses by substantially increasing the subsets of cytotoxic T lymphocytes in the peripheral immune system [29].

The effect of Fx in hepatic cell cancer

The Fx exhibits a robust inhibitory effect on the growth of SK-Hep-1 cells (human hepatoma cells) within a 24-hour timeframe. This inhibitory influence persisted for Fx concentrations exceeding 1 μM after 48 hours of exposure. Conversely, about BNL CL2 cells (murine embryonic liver cells), Fx initially appeared to facilitate cell growth up to the 24-hour mark, but a slight reduction in proliferation was noted after 48 hours. These findings led to the inference that the cell proliferation arrest and apoptosis induced by Fx were likely mediated through mechanisms involving increased cell gap junction communication and elevated intracellular calcium ion (Ca2+) levels [30]. Additionally, when human hepatoma HepG2 cells were subjected to a 10 μM dose of Fx, a notable 28% reduction in cell proliferation was observed 48 hours post-incubation [31].

The evaluation of proteasome activity in HepG2 cells revealed a considerable increase in its function when these cells were treated with Fx in comparison to cells treated with a control vehicle. Further investigation using Western blot analysis showed that Fx led to the suppression of cyclin D, and this inhibitory effect was found to be synchronized with the administration of the proteasome inhibitor MG132. Additionally, RT-PCR analysis indicated that Fx repressed the mRNA expression of cyclin D in HepG2 cells. Fucoxanthin functions as a suppressor of cyclin D by promoting its proteasomal degradation and concurrently decreasing its transcriptional activity, resulting in cell cycle arrest. Especially the expression of the cyclin-dependent kinase inhibitor p21waf1/Cip1 remained largely unaffected by the presence of Fx [32].

The HepG2 cells underwent apoptosis when exposed to both the crude methanolic extract and the Fx-rich fraction extracted from Chaetoceroscalcitrans. The antiproliferative activity against cancer cells was significantly more potent in the cells treated with the Fx-rich fraction (IC50: 18.89 mg/ml) compared to those treated with the crude methanolic extract (IC50: 87.5 mg/ml) ($p < 0.05$), depending on the dosage and duration of treatment. Cells treated with the Fx-rich fraction displayed a higher accumulation of G0/G1 phase cells, leading to a cessation of the cell cycle at the G2/M phase. The gene expression analysis revealed that treatment with the extract resulted in the modulation of signaling patterns in cancer cells, affecting various genes responsible for cell signaling (such as AKT1, ERK1/2, JNK), oxidative stress (including CAT, SOD1, SOD2), and cell death (such as Bax, Bcl-2, BID, CYCS, APAF) [33].

Effect of Fx in prostate cancer

When Fx was administered to prostate cancer cells (DU145), it was found to arrest the cell cycle at the G1 phase and exhibited a dose and time-dependent inhibition of cancer cell growth. This cell cycle arrest induced by Fx was associated with the up-regulation of GADD45A. Particularly, Fx did not induce apoptosis but functioned as a cytostatic agent in these cancer cells [34]. A succeeding study was carried out to clarify the functions of GADD45A and MAPK in the context of Fx action on an androgen-dependent prostate cancer cell line. The results showed that Fx stimulated the expression of the GADD45A

gene, leading to cell cycle arrest in the G1 phase. This process was primarily driven by the strong activation of SAPK/JNK signaling. Furthermore, Fx demonstrated the ability to inhibit the growth of cancer cells, although there was no observed evidence of cell death occurring [35].

In another investigation involving prostate cancer cells (PC-3), a decrease in the number of viable cells following treatment with Fx was observed. Additionally, they detected the presence of an apoptotic DNA ladder, indicating programmed cell death. When Fx at a concentration of 20 μmol/L derived from U. Pinnatifida was administered, it resulted in a substantial reduction in cell viability: 5.0% for DU145, 9.8% for lutein CaP, and 14.9% for PC-3, after 72 hours of treatment. The TUNEL assay confirmed the occurrence of DNA fragmentation, providing further evidence of Fx-induced cell death [36].

Effect of Fx in cancer of the urinary bladder

In one of the studies experiments on EJ-1 urinary bladder cancer cell lines to investigate the potential chemopreventive effects of Fx (a substance of interest) was conducted. To assess the impact of Fx on cell growth, the researchers exposed the cells to various concentrations of Fx for different durations, using the WST-8 assay to measure cell viability. The assay relied on the production of formazan, which is directly linked to the number of viable cells in the culture. They also examined changes in the appearance of EJ-1 cells by staining them with Hoechst 33258. In the control group, the cells displayed round nuclei with evenly distributed chromatin. However, when exposed to 20 μMFx for 72 hours, apoptotic cells exhibited densely packed chromatin, nuclear degradation, and the characteristic DNA fragmentation pattern known as a DNA ladder. Furthermore, the researchers assessed caspase-3 activity at various time points (12, 24, 48, and 72 hours). Caspase-3 is an enzyme involved in the apoptosis process. They found that caspase-3 activity increased significantly over time. Specifically, it was 2.6 times higher than the control after 12 hours of incubation, reached its peak at 6.1 times the control level after 24 hours, and then gradually decreased to 3.9 times the control level during the late stages of apoptosis [37]. Fx halted the growth of human T24 bladder cancer cells in a manner that depended on both the dosage and duration of treatment. This inhibition occurred by causing cell cycle arrest in the G0/G1 phase. This process was characterized by an increase in the

levels of p21, a protein that inhibits cyclin-dependent kinases (CDKs), and a decrease in the expression of cyclin D1, cyclin E, CDK-2, and CDK-4 [38].

Effect of Fx in colorectal cancer

Colorectal cancer stem cells can intermittently emerge within colorectal tissue and serve as potential markers for tumor development. These cells possess several remarkable characteristics, including the ability to resist drugs, exhibit multi-potentiality, undergo self-renewal, form spherical structures, and promote tumorigenesis when studied in xenograft models. Identifying their presence can be achieved by observing specific surface markers such as CD44, CD166, LGR5, and EpCAM [39,40].

In a study involving CD44high/EpCAM high cells isolated from human colorectal cancer cells (HT-29), researchers explored the antiproliferative effects of Fxol in severe combined immunodeficiency mice. Fxol, an intestinal metabolite derived from Fx, is known for its various health benefits, including cancer prevention in humans. Fxol demonstrated significant inhibition of the growth of CD44high/EpCAMhigh cells and the disruption of colon spheres (Csps) produced by tumor cells. Additionally, it induced the formation of numerous condensed chromatin bodies in the cells in a manner dependent on the dosage. The IC50 value for Fxol regarding these changes in Csps was determined to be 1.8 μM. Furthermore, Fxol down-regulated proteins such as pAkt (Ser473), PPARβ/δ, and PPARγ in Csps, play pivotal roles in processes like cell proliferation, cell cycle, metastasis, and extracellular adhesion. When Fxol was administered post-treatment at a dose of 5 mg/kg body weight for 10 days in mice, it significantly suppressed the formation of Csps tumors compared to control mice. These findings indicate that Fxol holds promise as a chemo-preventive agent against human colorectal cancer cells [41].

Six colorectal cancer cell lines and 20 cancerous tissue samples were subjected to treatment with Fx and Fxol to assess their potential anticancer effects using CD-DST (cell viability assay). The evaluation of in-vitro sensitivity to Fx and Fxol was based on the T/C ratio, which served as a marker. Upon treatment with 20 μM concentrations of Fx and Fxol, three colon cancer cell lines, namely HCT116, Caco 2, and WiDr, exhibited a notable decrease in

the T/C ratio, indicating reduced cell viability. Interestingly, Fxol significantly reduced the T/C ratio in DLD 1 and SSW620 cells, while Fx treatment did not yield significant results in these particular cells. On the contrary, none of the carotenoid treatments led to a reduced T/C ratio in Colo205 cells. Additionally, cancerous tissue specimens, when treated with 20 and 10 μM concentrations of Fxol as compared to Fx, displayed a higher T/C ratio (>50%), suggesting that Fxol might exert a more pronounced cytotoxic effect on specific colorectal cancers when compared to Fx. The study's findings indicated that both Fx and Fxol have the potential to act as cytotoxic agents against particular colorectal cancer cell lines and tissue samples, as evidenced by their impact on the T/C ratio [42].

Effect of Fx in human erythrocyte cancer

A separate research investigation aimed to establish eryptosis, a phenomenon analogous to apoptosis but occurring in erythrocytes, induced by Fx. In this study, erythrocytes were subjected to a 48-hour incubation period in a Ringer solution, both with and without varying concentrations of Fx (ranging from 25 μM to 75 μM), before measurements were taken. Results revealed that the presence of Fx at a concentration of 50 μM led to a statistically significant decrease in the average forward scatter of erythrocytes. Additionally, when erythrocytes were treated with Fx, a putative effect on hemolysis was observed, with a significant increase in the percentage of hemolytic erythrocytes noted after 24 hours of incubation with a 25 μM Fx concentration. To further investigate the impact of Fx, the concentration of hemoglobin in the supernatant was determined through photometry. The study found that Fx induced a significant increase in hemoglobin release. The investigation also involved the quantification of Fluo3-fluorescence to estimate cytosolic calcium (Ca++) activity. After a 48-hour exposure to Fx, Fluo3-fluorescence levels were found to increase, with statistical significance reached at the 50 μM Fx concentration. To assess whether Fx induced phosphatidylserine translocation or erythrocyte shrinkage, which are necessary for the entry of extracellular calcium, erythrocytes were incubated for 48 hours in the presence or absence of 75 μM Fx, in both the presence and nominal absence of extracellular calcium. The findings suggested that Fx partially induced the scrambling of cell membranes, which was attributed to the influx of extracellular calcium. Particularly, Fx did not induce noticeable oxidative stress, and the

study concluded that Fx triggered eryptosis characterized by cell shrinkage and cell membrane scrambling, an effect that was linked, at least in part, to the increased cytosolic calcium [43].

Effect of Fx in cancer of human leukemia cells

Fx was found to induce the generation of reactive oxygen species (ROS), leading to apoptosis in HL-60 leukemic cell lines. The cells treated with Fx exhibited an excess of H2O2 and $O2^{-}$, along with a decrease in the sub-G1 DNA content, indicating cell cycle arrest in the G1 phase. When exposed to commercial antioxidants like NAC, there was a reduction in the number of apoptotic bodies and DNA fragmentation in the cells. Consequently, the study highlighted that the cytotoxic effects of Fx were attributed to ROS generation, which in turn initiated apoptosis in HL-60 cells [44]. Fx and Fxol were found to induce apoptosis in human leukemia cancer cells (HL-60) by cleaving procaspase-3, -7, and poly (ADP-ribose) polymerase (PARP), and by regulating the expression of Bcl proteins (Bcl-xLand Bcl-2) [45]. In contrast, treatment of similar cells with Fx led to increased cleavage of PARP and procaspase-3, while the protein levels of pro-apoptotic Bax and anti-apoptotic Bcl-xLand Bcl-2 remained undisturbed [46].

Effect of Fx in cancer of human neural tissues

Fucoxanthin was evaluated for its protective effects against H2O2-induced neurotoxicity in two types of neuronal cells: human neuroblastoma SH-SY5Y cells and primary cerebellar granule neurons (CGNs). To assess cell viability in CGNs, FDA/PI double staining was employed to visualize viable cells. Remarkably, the application of 3μMFx led to a significant reduction in neuronal cell death induced by H2O2. In the H2O2-treated group, cell viability was only 48.8%, whereas in the group treated with 3 μMFx + H2O2, it increased to 73.4%. Notably, no significant change in CGN viability was observed when treated with 3 μMFx alone for 26 hours. Furthermore, there was a substantial increase in intracellular reactive oxygen species (ROS) in SH-SY5Y cells when exposed to H2O2. Interestingly, Fx effectively reversed the alterations induced by H2O2. As a result, Fx was identified as a potential compound capable of counteracting H2O2-induced toxicity in

neuronal cells. It achieved this by activating the PI3-K/Akt pathway while inhibiting the ERK pathway, ultimately leading to a reduction in neuronal cell damage [47].

Effect of Fx in skin cancer

A research study was conducted to investigate how Fx could protect human HaCaT keratinocytes from oxidative stress induced by H2O2. The study employed the comet assay to assess the extent of oxidative DNA damage. It was observed that Fx effectively prevented H2O2-induced cellular DNA damage by inhibiting the formation of comet tails and the expression of phospho-histone H2AX. Furthermore, Fx exhibited a protective role in shielding keratinocytes from oxidative stress and cellular apoptosis. This protection against cellular apoptosis was achieved by Fx through the suppression of apoptosis-promoting factors such as Bcl-2-associated x protein, caspase-3, and caspase-9, while simultaneously promoting the presence of an apoptosis inhibitor [48].

Metastasis plays a crucial role in determining the fatality of malignant cancers. Fx demonstrated its ability to inhibit the expression and release of MMP-9, which is associated with the invasion and movement of tumors. Moreover, Fx suppressed the direct growth and infiltration of highly metastatic melanoma cells. Additionally, it reduced the expression of cell surface glycoprotein CD44 and CXC chemokine receptor-4 (CXCR4), both of which are responsible for the migration, invasion, and attachment of malignant endothelial cells to melanoma cells. These findings underscore the anti-metastatic properties of Fx [49].

Effect of Fx in cancerous cells of the cervix

Research conducted on HeLa cells revealed that Fx triggered autophagy, a process of cellular self-cleansing, but did not induce apoptosis, even when pretreated with 3-MA (methyl adenine). This autophagic response was achieved by inhibiting the Akt/mTOR signaling pathway specifically in cervical cancer cells. Consequently, Fx was regarded as a potential agent with anti-carcinogenic properties [50]. In another investigation, it was observed that Fx effectively inhibited Akt phosphorylation in a manner dependent on its concentration. Fx also induced cell death in HeLa cell lines through a caspase-dependent

mechanism. Furthermore, Fx reduced the extent of NF-κB activation, with only a negligible impact on AP-1 activation. As a result, the study's author concluded that Fx exhibited antitumor activity in HeLa cell lines [51].

The impact of Fx on the PI3K/Akt signaling pathway in HeLa cells was investigated. Cells were subjected to various concentrations of Fx for 24 hours, followed by western blot analysis to assess its effect on proteins associated with the PI3K/Akt signaling pathway. The western blot results indicated that Fx deactivated the Akt pathway, reduced the levels of the Bcl-2 protein, promoted Bax formation, and triggered caspase-3 cleavage. These findings suggested that Fx inhibited the growth of HeLa cells by suppressing the PI3K/Akt signaling pathway. To further understand the relationship between Fx and nuclear transcription factor activity, the activities of NF-κB and AP-1 were evaluated using the luciferase reporter gene method. Fx was found to decrease the activation level of NF-κB, while no significant effect was observed on AP-1. Western blot analysis confirmed that Fx halted the migration of NF-κB from the nucleus to the cytoplasm and increased the nuclear NF-κB (P65) protein levels. These results suggested that NF-κB might play a role in inducing cell death in HeLa cells by Fx [52]. A study focused on human cervical cancer cell lines SiHa, HeLa, and CaSki to investigate the mechanism of Fx and Tumor Necrosis Factor-Related apoptosis-induced ligand (TRAIL). TRAIL, belonging to the Tumor Necrosis Factor (TNF) family, can induce apoptosis in cancer cells without affecting normal cell functions. The study employed the XTT method to assess cell viability and used flow cytometry to quantify apoptosis. Specifically, human SiHa cells were treated with Fx (0.5 µMol/L), TRAIL (100ng/ml), and a combination of Fx and TRAIL (0.5 µMol/L + 100ng/ml) for 48 hours. Protein expression levels of PI3K/AKT, phosphorylated AKT (P-AKT), PIkBa, and NF-kB (p65) were analyzed using a Western blot assay. The study findings demonstrated that cervical cancer cells treated with TRAIL and Fx in combination exhibited more effective apoptosis compared to cells treated with Fx alone or TRAIL alone. Additionally, the study highlighted the essential role of the PI3K/AKT/NF-κB signaling pathway in mediating apoptosis induction by Fx and TRAIL, as well as their ability to inhibit cancer cell viability [53].

In a research investigation carried out by our research team, HeLa cells were exposed to a range of Fx concentrations (20, 10, 5, 2.5, 1.25, 0.625, 0.3125, and 0.078 μM) over 24 and 48 hours to assess its impact on cell viability. The MTT assay was employed to measure the viability of the cells, and IC50 values were calculated to gauge the anti-cancer potential of Fx.The findings of the study revealed that Fx exhibited its most significant anti-cancer effects at a concentration of 20 μM within the first 24 hours of exposure. Notably, at 24 hours, Fx resulted in a more substantial decrease in cell viability compared to the 48-hour timeframe. This suggests that Fx has a more pronounced effect on cell viability in the shorter time frame. Intriguingly, when comparing the effects of Fx to tamoxifen, a known anti-cancer drug, it was observed that Fx's impact at 24 hours exceeded that of tamoxifen at the same timeframe. This observation underscores the potential of Fx as a promising candidate for further exploration in the context of cervical cancer treatment [54].

Effect of Fx in human ovarian cancer cells

The ability of Fx to kill cancer cells was measured through an MTT assay. It was found that Fx causes cancer cells to die at different concentrations (5–100 μM), with cells exposed to Fx seeing a decline in their ability to survive to 80% compared to those not treated with Fx. The main reason for this was the splitting of cell nuclei into smaller pieces, suggesting the creation of apoptotic bodies in the Fx-treated cells. Treatment with Fx (20 μM) also led to larger numbers of cells in the late stages of apoptosis (orange-red colored), indicating damage to the cell membrane. It's possible that Fx increased the production of reactive oxygen species (ROS) in the A2780 cells. To assess how Fx affects the reduction of MMP, the A2780 cells were marked with Rhodamine 123 dye. Untreated cells showed a rise in green fluorescence, indicating an increased number of polarized mitochondria. On the other hand, cells treated with Fx (20 μM) displayed a significant decrease in MMP activity, which was characterized by a continuous decline in the green fluorescence signal. The treatment also significantly boosted the activity of caspase-9 compared to the control group. Furthermore, there was a notable increase in the expression of caspase-8 in the A2780 cells. The PI3K/AKT/mTOR pathway plays a crucial role in controlling cell growth and survival, and it was found to be involved in the inhibition of A2780 cell growth by Fx. Treatment with Fx led to a significant reduction in PI3K phosphorylation and an even

greater decrease in pAKT expression in A2780 cancer cells. Moreover, it's believed that Fx could lower the expression of mTOR in A2780 cancer cells. The data suggests that the activity of ribosomal protein S6K is increased in various cancer cell lines or tumors. These proteins have been linked to drug resistance and chemotherapy treatment, and their function in carcinogenesis is understood. In this research, it was demonstrated that Fx significantly reduced the expression of S6K in A2780 cancer cells. This clearly indicates that ribosomal protein S6K is upregulated in many cancer cell lines or tumors. These proteins have also been associated with resistance to drugs and chemotherapy treatments, and their role in the development of cancer is known. In this study, the ability of Fx to decrease the expression of S6K in A2780 cancer cells was demonstrated [55].

A subsequent study sought to explore the possible roles and mechanisms through which fucoxanthin could impact ovarian cancer metastasis and the process of glycolysis. Ovarian cancer cells, namely OVCAR-3 and A2780, were exposed to varying doses of fucoxanthin over a period of 48 hours. The outcomes of the CCK8 assays indicated that fucoxanthin treatment significantly reduced the viability of ovarian cancer cells, with the effect decreasing with higher concentrations. The study also examined how fucoxanthin affected the ability of ovarian cancer cells to migrate and invade. Results from a wound healing assay indicated that fucoxanthin concentrations of 50, 75, or 100 μM were sufficient to significantly impede the movement of OVCAR-3 and A2780 cells. Furthermore, the data from a transwell invasion assay clearly demonstrated a dose-dependent decrease in the number of cells able to invade. Additionally, a decrease in the expression of MMP2 and MMP9 following fucoxanthin treatment indicated that it inhibited the migration and invasion process of ovarian cancer cells. The uptake of FDG in OVCAR-3 and A2780 cells significantly decreased as the fucoxanthin concentrations increased. Additionally, fucoxanthin treatment led to a decrease in ATP levels in these cells, and ATP levels varied with the concentration of fucoxanthin used. The impact of fucoxanthin on the enzyme ECAR in ovarian cancer cells treated with glucose, oligomycin, or 2-DG was observed. The findings revealed that fucoxanthin treatment curtailed glycolysis. Moreover, the expression of enzymes and proteins involved in glycolysis, such as LDHA, HK2, and PDK1, was considerably reduced in fucoxanthin-treated OVCAR-3 and A2780 cells. By inhibiting

STAT3/c-Myc signaling, fucoxanthin was found to slow down the proliferation, metastasis, and glycolysis of ovarian cancer cells [56].

Discussion

Carotenoids like Fx has several biological properties, including antioxidant properties, the ability to inhibit malignant tumour formation, and the ability to induce apoptosis. While the anti-cancer properties of Fx have been proven on various cancers by previous researchers, few studies are based on the cellular model. Fucoxanthin may inhibit the growth of HeLa cells by inhibiting the PI3/Akt pathway. It also reduces the activation level of NF-kappa B. NF-kappa B is activated in many cancers, including inflammation, proliferation, and angiogenesis. It mediates the inhibition of apoptosis by biological signals and promotes the growth of tumor cells [52]. The involvement of the PI3/AKT signaling pathway was suggested in cervical cancer cell proliferation, cell cycle regulation, and apoptosis. It serves a key role in the occurrence and development of a tumor [57]. FX may suppress the growth of cells, mainly cancer cells, by blocking the Akt/mTOR/S6K signaling pathway in ovarian cancer cells. Decreasing the activity of S6K leads to the stoppage of Akt signaling pathways, indicating a positive effect of Akt pathway regulation through S6K. FX enhances cell death; decreases cell growth, spread, and invasion; and suggests a possible way in which Fx acts to suppress Akt/mTOR pathways in human ovarian cancer cells [55]. Further, Fx protects defends keratinocytes from oxidative damage by scavenging ROS and cell death [48].

Fucoxanthin has powerful antioxidant properties, which can help neutralize free radicals that can contribute to cancer development. By reducing oxidative stress, it may slow the growth of cancer cells and reduce the risk of developing cancer. Chronic inflammation plays an important role in the progression of cancer. Fucoxanthin has been shown to have anti-inflammatory properties that may help inhibit the growth and spread of cancer cells. By blocking inflammatory signaling pathways, Fx may help alleviate the inflammatory microenvironment that supports cancer. Apoptosis is a natural process that prevents the accumulation of abnormal cells. Studies show that Fx can induce apoptosis in various cancer cells. This effect is important to prevent uncontrolled growth of cancer cells. Fucoxanthin has been reported to block the cell cycle at various checkpoints, thereby

preventing cancer cells from dividing and multiplying. This mechanism may be particularly effective in controlling cancer progression.

Conclusion

Fucoxanthin has shown promising effects on various cancer cells. Its anti-proliferative, anti-angiogenic, anti-inflammatory and apoptosis-inducing properties make it a compound of interest. In addition, its anti- cancer effects and ability to enhance the effects of conventional cancer treatments have opened new avenues for cancer research and treatment strategies. However, it should be noted that most studies have been conducted in-vitro or in animal models and additional clinical research is needed to confirm these findings and determine dosage and administration. Fucoxanthin represents a promising area of discovery in the ongoing fight against cancer. The natural origin of Fx and its diverse mechanisms of action make it an intriguing candidate for further exploration in cancer research and potential development as an adjuvant treatment or prevention. Integrating it into a healthy and balanced diet may also be beneficial in reducing cancer risk.

References

1. El-Agamey A, Lowe G, McGarvey D, Mortensen A, Phillip D, Truscott T, Young A: Carotenoid radical chemistry and antioxidant/pro-oxidant properties. Archive of Biochemistry and Biophysics. 2004, 430:37–48. 10.1016/j.abb.2004.03.007
2. Rutz JK, Borges CD, Zambiazi RC, da Rosa CG, da Silva MM: Elaboration of microparticles of carotenoids from natural and synthetic sources for applications in food. Food Chem. 2016, 1;202:324-33. 10.1016/j.foodchem.2016.01.140
3. Rao AV, Rao LG: Carotenoids and human health. Pharmacol Res. 2007,55(3):207-16. 10.1016/j.phrs.2007.01.012
4. Saini RK, Prasad P, Lokesh V, Shang X, Shin J, Keum YS, Lee JH: Carotenoids: Dietary Sources, Extraction, Encapsulation, Bioavailability, and Health Benefits-A Review of Recent Advancements. Antioxidants (Basel). 2022,11:795. 10.3390/antiox11040795
5. Tanaka T, Shnimizu M, Moriwaki H: Cancer chemoprevention by carotenoids. Molecules. 2012, 14;17:3202-42. 10.3390/molecules17033202
6. Milani A, Basirnejad M, Shahbazi S, Bolhassani A: Carotenoids: biochemistry, pharmacology and treatment. Br J Pharmacol. 2017,174:1290-1324. 10.1111/bph.13625
7. Mori T, Ohnishi M, Komiyama M, Tsutsui A, Yabushita H, Okada H: Growth inhibitory effect of paradicsompaprika in cancer cell lines. Oncol Rep. 2002, 9:807-10. 10.3892/or.9.4.807
8. Hormozi M, Ghoreishi S, Baharvand P: Astaxanthin induces apoptosis and increases activity of antioxidant enzymes in LS-180 cells. Artif Cells Nanomed Biotechnol. 2019, 47:891-895. 10.1080/21691401.2019.1580286
9. Jyonouchi H, Sun S, Iijima K, Gross MD: Antitumor activity of astaxanthin and its mode of action. Nutr Cancer. 2000,36:59-65. 10.1207/S15327914NC3601_9
10. Bathaie SZ, Hoshyar R, Miri H, Sadeghizadeh M: Anticancer effects of crocetin in both human adenocarcinoma gastric cancer cells and rat model of gastric cancer. Biochem Cell Biol. 2013,91(6):397-403. 10.1139/bcb-2013-0014
11. Li S, Jiang S, Jiang W etal: Anticancer effects of crocetin in human esophageal squamous cell carcinoma KYSE-150 cells. Oncol Lett. 2015, 9:1254-1260. 10.3892/ol.2015.2869

12. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA: Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011, 121:2750-67. 10.1172/JCI45014
13. Nkondjock A, Ghadirian P, Johnson KC, Krewski D: Canadian Cancer Registries Epidemiology Research Group. Dietary intake of lycopene is associated with reduced pancreatic cancer risk. J Nutr. 2005, 135:592-7. 10.1093/jn/135.3.592
14. Livny O, Kaplan I, Reifen R, Polak-Charcon S, Madar Z, Schwartz B: Lycopene inhibits proliferation and enhances gap-junction communication of KB-1 human oral tumor cells. J Nutr. 2002,132:3754-9. 10.1093/jn/132.12.3754
15. Cramer DW, Kuper H, Harlow BL, Titus-Ernstoff L: Carotenoids, antioxidants and ovarian cancer risk in pre- and postmenopausal women. Int J Cancer. 2001, 94:128-34. 10.1002/ijc.1435. PMID: 11668487.
16. Hosokawa M, Kudo M, Maeda H, Kohno H, Tanaka T, Miyashita K: Fucoxanthin induces apoptosis and enhances the antiproliferative effect of the PPARgamma ligand, troglitazone, on colon cancer cells. Biochim Biophys Acta. 2004,1675:113-9. 10.1016/j.bbagen.2004.08.012
17. Pietras K, Sjöblom T, Rubin K, Heldin CH, Ostman A: PDGF receptors as cancer drug targets. Cancer Cell. 2003, 3:439-43. 10.1016/s1535-6108(03)00089-8
18. D'Orazio N, Gemello E, Gammone MA, De Girolamo M, Ficoneri C, Riccioni G: Fucoxantin: a treasure from the sea. Mar Drugs. 2012, 10:604-616. 10.3390/md10030604
19. Zhang H, Tang Y, Zhang Y et al: Fucoxanthin: A promising medicinal and nutritional ingredient. Evid Based Complement Alternat Med. 2015, 2015:723515. 10.1155/2015/723515
20. Aman R, Schieber A, Carle R: Effects of heating and illumination on trans-cis isomerization and degradation of beta-carotene and lutein in isolated spinach chloroplasts. J Agric Food Chem. 2005, 30;53:9512-8. 10.1021/jf050926w
21. Page MJ, McKenzie JE, Bossuyt PM et al: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021, 29;372:n71. 10.1136/bmj.n71
22. Rwigemera A, Mamelona J, Martin LJ: Comparative effects between fucoxanthinol and its precursor fucoxanthin on viability and apoptosis of breast cancer cell lines MCF-7 and MDA-MB-231. Anticancer Res. 2015, 35:207-19

23. Rwigemera A, Mamelona J, Martin LJ: Inhibitory effects of fucoxanthinol on the viability of human breast cancer cell lines MCF-7 and MDA-MB-231 are correlated with modulation of the NF-kappaB pathway. Cell Biol Toxicol. 2014,30:157-67. 10.1007/s10565-014-9277-2
24. Frasor J, Weaver A, Pradhan M, Dai Y, Miller LD, Lin CY, Stanculescu A: Positive cross-talk between estrogen receptor and NF-kappaB in breast cancer. Cancer Res. 2009, 69:8918-25.10.1158/0008-5472.CAN-09-2608 Erratum in: Cancer Res. 2010 Jan 15;70(2):854. Erratum in: Cancer Res. 2010 Mar 1;70:2140
25. Zubair A, Frieri M: Role of nuclear factor-κB in breast and colorectal cancer. Curr Allergy Asthma Rep. 2013, 13:44-9. 10.1007/s11882-012-0300-5
26. Cogswell PC, Guttridge DC, Funkhouser WK, Baldwin AS Jr: Selective activation of NF-kappa B subunits in human breast cancer: potential roles for NF-kappa B2/p52 and for Bcl-3. Oncogene. 2000, 19(9):1123-31. 10.1038/sj.onc.1203412
27. Fan Y, Dutta J, Gupta N, Fan G, Gélinas C: Regulation of programmed cell death by NF-kappaB and its role in tumorigenesis and therapy. Adv Exp Med Biol. 2008, 615:223-50. 10.1007/978-1-4020-6554-5_11
28. Wang J, Ma Y, Yang J et al: Fucoxanthin inhibits tumour-related lymphangiogenesis and growth of breast cancer. J Cell Mol Med. 2019, 23:2219-2229. 10.1111/jcmm.14151
29. Wang W, Fu C, Lin M: Fucoxanthin prevents breast cancer metastasis by interrupting circulating tumor cells adhesion and transendothelial migration. Front Pharmacol. 2022,9;13:960375. 10.3389/fphar.2022.960375
30. Liu CL, Huang YS, Hosokawa M, Miyashita K, Hu ML: Inhibition of proliferation of a hepatoma cell line by fucoxanthin in relation to cell cycle arrest and enhanced gap junctional intercellular communication. Chem Biol Interact. 2009, 10;182:165-72. 10.1016/j.cbi.2009.08.017
31. Liu CL, Lim YP, Hu ML: Fucoxanthin enhances cisplatin-induced cytotoxicity via NFκB-mediated pathway and downregulates DNA repair gene expression in human hepatoma HepG2 cells. Mar Drugs. 2013, 8;11:50-66.10.3390/md11010050
32. Das SK, Hashimoto T, Kanazawa K: Growth inhibition of human hepatic carcinoma HepG2 cells by fucoxanthin is associated with down-regulation of cyclin D. Biochim Biophys Acta. 2008, 1780:743-9. 10.1016/j.bbagen.2008.01.003.

33. Foo SC, Yusoff FM, Imam MU et al: Increased fucoxanthin in Chaetoceros calcitrans extract exacerbates apoptosis in liver cancer cells via multiple targeted cellular pathways. Biotechnol Rep (Amst). 2018, 6;21:e00296. 10.1016/j.btre.2018.e00296.
34. Yoshiko S, Hoyoku N: Fucoxanthin, a natural carotenoid, induces G1 arrest and GADD45 gene expression in human cancer cells. In Vivo. 2007, 21:305-9.
35. Satomi Y: Fucoxanthin induces GADD45A expression and G1 arrest with SAPK/JNK activation in LNCap human prostate cancer cells. Anticancer Res. 2012,32:807-13.
36. Kotake-Nara E, Kushiro M, Zhang H, Sugawara T, Miyashita K, Nagao A: Carotenoids affect proliferation of human prostate cancer cells. J Nutr. 2001,131:3303-6. 10.1093/jn/131.12.3303
37. Zhang Z, Zhang P, Hamada M, Takahashi S, Xing G, Liu J, Sugiura N: Potential chemoprevention effect of dietary fucoxanthin on urinary bladder cancer EJ-1 cell line. Oncol Rep. 2008, 20:1099-103
38. Wang L, Zeng Y, Liu Y et al: Fucoxanthin induces growth arrest and apoptosis in human bladder cancer T24 cells by up-regulation of p21 and down-regulation of mortalin. Acta Biochim Biophys Sin (Shanghai). 2014, 46:877-84. 10.1093/abbs/gmu080
39. Dalerba P, Dylla SJ, Park IK et al: Phenotypic characterization of human colorectal cancer stem cells. Proc Natl Acad Sci USA. 2007,12;104:10158-63. 10.1073/pnas.0703478104
40. Vermeulen L, Todaro M, de Sousa Mello F et al: Single-cell cloning of colon cancer stem cells reveals a multi-lineage differentiation capacity. Proc Natl Acad Sci U S A. 2008, 9;105:13427-32. 10.1073/pnas.0805706105.
41. Terasaki M, Maeda H, Miyashita K, Tanaka T, Miyamoto S, Mutoh M: A marine bio-functional lipid, fucoxanthinol, attenuates human colorectal cancer stem-like cell tumorigenicity and sphere formation. J Clin Biochem Nutr. 2017, 61:25-32. 10.3164/jcbn.16-112
42. Takahashi K, Hosokawa M, Kasajima H, Hatanaka K, Kudo K, Shimoyama N, Miyashita K: Anticancer effects of fucoxanthin and fucoxanthinol on colorectal cancer cell lines and colorectal cancer tissues. Oncol Lett. 2015, 10:1463-1467. 10.3892/ol.2015.3380

43. Briglia M, Calabró S, Signoretto E, Alzoubi K, Laufer S, Faggio C, Lang F: Fucoxanthin Induced Suicidal Death of Human Erythrocytes. Cell Physiol Biochem. 2015,37:2464-75. 10.1159/000438599
44. Kim KN, Heo SJ, Kang SM, Ahn G, Jeon YJ. Fucoxanthin induces apoptosis in human leukemia HL-60 cells through a ROS-mediated Bcl-xL pathway. Toxicol In Vitro. 2010,24:1648-54. 10.1016/j.tiv.2010.05.023
45. Konishi I, Hosokawa M, Sashima T, Kobayashi H, Miyashita K: Halocynthiaxanthin and fucoxanthinol isolated from Halocynthia roretzi induce apoptosis in human leukemia, breast and colon cancer cells. Comp Biochem Physiol C Toxicol Pharmacol. 2006, 142:53-9. 10.1016/j.cbpc.2005.10.005
46. Kotake-Nara E, Asai A, Nagao A: Neoxanthin and fucoxanthin induce apoptosis in PC-3 human prostate cancer cells. Cancer Lett. 2005,220:75-84. 10.1016/j.canlet.2004.07.048
47. Yu J, Lin JJ, Yu R, He S, Wang QW, Cui W, Zhang JR: Fucoxanthin prevents H_2O_2-induced neuronal apoptosis via concurrently activating the PI3-K/Akt cascade and inhibiting the ERK pathway. Food Nutr Res. 2017, 61:1304678. 10.1080/16546628.2017.1304678
48. Zheng J, Piao MJ, Keum YS, Kim HS, Hyun JW: Fucoxanthin protects cultured human keratinocytes against oxidative stress by blocking free radicals and inhibiting apoptosis. Biomol Ther (Seoul). 2013,21:270-6.10.4062/biomolther.2013.030
49. Chung TW, Choi HJ, Lee JY, et al: Marine algal fucoxanthin inhibits the metastatic potential of cancer cells. Biochem Biophys Res Commun. 2013, 439:580-5. 10.1016/j.bbrc.2013.09.019
50. Hou LL, Gao C, Chen L, Hu GQ, Xie SQ: Essential role of autophagy in fucoxanthin-induced cytotoxicity to human epithelial cervical cancer HeLa cells. Acta Pharmacol Sin. 2013, 34:1403-10. 10.1038/aps.2013.90.
51. Ye G, Lu Q, Zhao W, Du D, Jin L, Liu Y: Fucoxanthin induces apoptosis in human cervical cancer cell line HeLa via PI3K/Akt pathway. Tumour Biol. 2014, 35:11261-7. 10.1007/s13277-014-2337-7.

52. Ye, G.L., Jin. L.J., Wang L.L., Dan Du.D.L., 2018. Effect of fucoxanthin on pi3k/akt signaling pathway in human cervical cancer HeLa cells. Biomedical Journal of Scientific & Technical Research, 9(3):pp7218-7223.
53. Jin Y, Qiu S, Shao N, Zheng J: Fucoxanthin and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) Synergistically Promotes Apoptosis of Human Cervical Cancer Cells by Targeting PI3K/Akt/NF-κB Signaling Pathway. Med Sci Monit. 2018, 24:11-18.10.12659/msm.905360
54. Saxena A, Mahajan A, Nagtilak S, Bahuguna SN. In vitro anti-proliferative activity of fucoxanthin on HeLa cells. J Anat Sci. 2020;28(2): pp01-12
55. Li Y, Tao L, Bao L, Chinnathambi A, Alharbi SA, Cui J. Fucoxanthin inhibits cell proliferation and stimulates apoptosis through downregulation of PI3K/AKT/mTOR signaling pathway in human ovarian cancer cells. Phcog Mag 2020;16:pp311-6. 10.4103/pm.pm_330_19
56. Zhang Z, Wang Y, Li J: Fucoxanthin suppresses the malignant progression of ovarian cancer by inactivating STAT3/c-Myc signaling. Am J Transl Res. 2023, 15:2528-2540.
57. Shi X, Wang J, Lei Y, Cong C, Tan D, Zhou X: Research progress on the PI3K/AKT signaling pathway in gynecological cancer (Review). Mol Med Rep. 2019,19:4529-4535. 10.3892/mmr.2019.10121