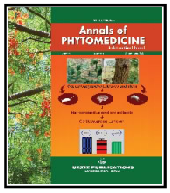
Annals of Phytomedicine 11(1): 164-174, 2022

DOI: http://dx.doi.org/10.54085/ap.2022.11.1.16

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Review Article : Open Access

Dietary carotenoid fucoxanthin as a promising biomarker to target the cancer cells: A focused review

A. Vijayalakshmi*, T. Prabha◆, V. Lalitha, S. Hemalatha, M. Jagadeeswaran, M.V.N.L Chaitanya, P. Selvamani***, and S. Latha*****

Department of Pharmaceutical Chemistry, Nandha College of Pharmacy, Erode-638052, Tamilnadu, India

**Department of Pharmacognosy, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Chennai-600117, Tamilnadu, India*

*** Department of Pharmacognosy, College of Pharmacy, Chitkara University, Punjab-140401, India*

****Department of Pharmaceutical Technology, Centre for Excellence in Nanobio Translational Research, Anna University, Bharathidasan Institute of Technology Campus, Tiruchirappalli-620024, Tamilnadu, India*

Article Info

Article history
Received 10 April 2022
Revised 26 May 2022
Accepted 27 May 2022
Published Online 30 June 2022

Keywords
Fucoxanthin
Apoptosis
Cytotoxicity
Cancer cell line
Marine seaweed
Diet-derived compounds

Abstract

Cancer, which ranks among the topmost prevalent diseases in the world, can obtain a good outcome with appropriate surgery and/or chemotherapy. Chemotherapy is an effective treatment for many types of cancer, however, its toxicity in normal cells and acquired tumor resistance to the drug users are considered the main barriers. New strategies have been proposed to increase the success of anticancer drugs; namely, combination with natural dietary compounds, decreasing the drug dose administered, and thereby reducing its toxicity to normal cells. Diet-induced lifestyle modification is suggested to be effective in reducing the risk of human cancer; therefore, experimental studies using diet-derived compounds have been conducted in modern days to explore the prevention of cancer. Seaweeds are rich in bioactive compounds,*viz*., phloroglucinol, fucoxanthin, fucoidan, *etc*., with attractive biological effects such as chemopreventive and chemotherapeutic effects against cancer. Seaweed fucoxanthin is one of the dietary carotenoids of the xanthophyl family and is predominantly present in edible brown algae, such as *Undaria pinnatifida* (Family: Alariaceae), *Phaeodactylum tricornutum* (Family: Phaeodactylaceae), and *Himanthalia elongate* (Family: Himanthaliaceae) that are consumed frequently in Asian countries. Several mechanisms, namely; antioxidants, cell cycle arrest, induction of cell death, inhibition of metastasis, and angiogenesis have been mentioned as responsible for its anticancer activity. This review focuses on the potential cytotoxic effect of the bioactive compound fucoxanthin on diverse cell lines. Also, this report focuses on the current knowledge of fucoxanthin could be a promising compound for cancer therapy by acting on most of the classical hallmarks of tumor cells and further research opportunities are discussed.

1. Introduction

Diet and lifestyle play a significant effect in cancer progression. Mankind now uses natural ingredients with a variety of medical characteristics. People were encouraged to adopt a Western eating pattern, which is constituted of high fat, protein content, low carbohydrate, and low grain, as a result of excessive socio-economic development and increasing urbanization, and this imbalanced diet is regarded to be a major risk factor for increased cancer rates. Diets rich in seaweeds are becoming increasingly important for lowering cancer risk since they contain a variety of phytochemicals with distinct biological characteristics (Tamanna *et al*., 2020; Donaldson, 2004).

Chemotherapy with anticancer drugs is usually associated with several issues, including serious side effects and the development of drug resistance, which may necessitate the discontinuation of therapies, despite the fact that it has been shown to play an important role in medical treatment for cancer. Natural marine food components are used to attain this goal. Because of their efficient potency on cancer cells with little or insignificant adverse effects, seaweed new chemicals are substitutes for traditional medicine and recently gained a lot of attention. Natural chemicals are being investigated in the hunt for novel medications because of their tremendous structural and chemical variety, as well as their therapeutic potential (Kaul *et al*., 2019; Afroz and Adnan, 2020; Mohd Hafizur and Sayeed, 2019). Many natural chemicals are being used in medication development because they have anticancer or antioxidant characteristics (Sri Bhuvaneswari *et al*., 2021; Duraisami *et al*., 2021).

Hippocrates has suggested, “Let food be thy medicine and medicine be thy food”. Numerous studies have suggested that a diet rich in fruits and vegetables is linked to a decreased cancer risk. Different dietary habits in various nationalities have been linked to lower or higher rates of cancer advancement in ethnicities, indicating a possible link between food products and tumor growth (Rodrguez-Garca *et al*., 2019).

Corresponding author: Dr. T. Prabha
Department of Pharmaceutical Chemistry, Nandha College of Pharmacy, Erode-638052, Tamilnadu, India
E-mail: drtpappa@yahoo.com
Tel.: +91-9965557346

2. Marine algae carotenoid dissemination

Marine algae are a rich source of biologically active substances because they contain a wide spectrum of pharmacological activities, including oxidative, antibacterial, anti-inflammation, and anticancer properties (Prabha and Sivakumar, 2018; Takaichi, 2011). Among the available seaweed secondary metabolites, fucoxanthin has been investigated in recent years for applications in foods, nutraceutical pharmaceuticals, and cosmeceutical industries. Carotenoids are among the dietary molecules being studied for their potential function in preventing cancer. Furthermore, they have been shown to have a role in halting or rectifying cellular signaling (*e.g.*, the NF-B and AP1 pathways) *via* influencing intracellular signaling network components associated with cell initiation and proliferation. Fucoxanthin has the ability to control malignancies by inducing antiproliferative activity and apoptosis.The diverse cancer-targeting mechanisms of fucoxanthin are illustrated in Figure 1.

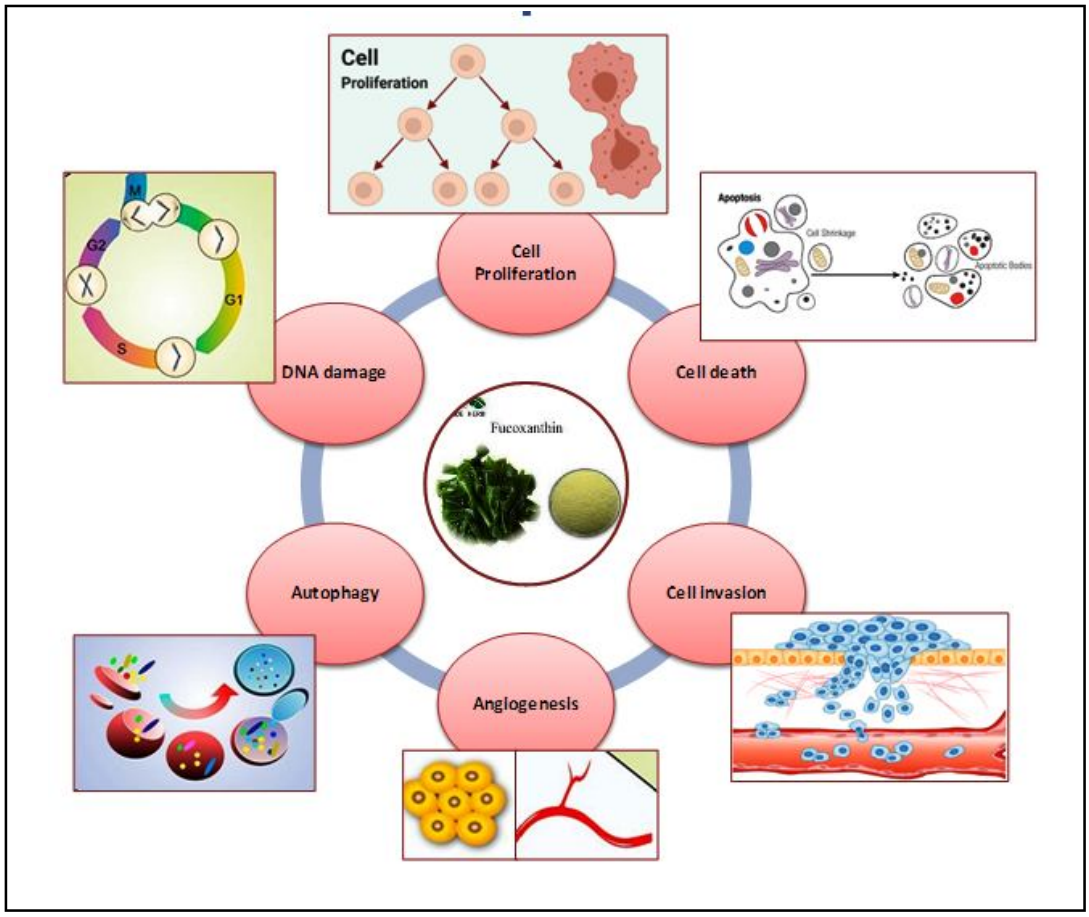


Figure 1: Diverse cancer targeting mechanism of fucoxanthin.

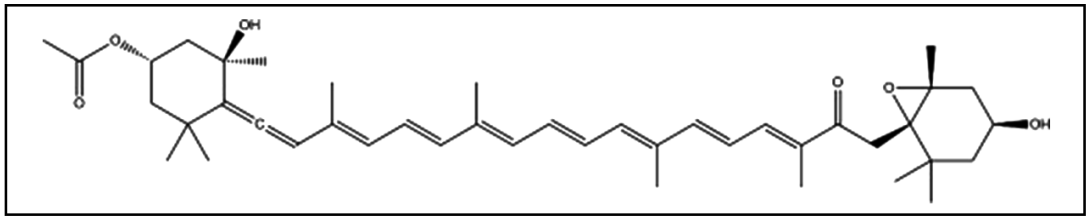


Figure 2: Chemical structure of fucoxanthin.

3. Chemistry of fucoxanthin

Fucoxanthin (FX) is a natural marine carotenoid (also known as xanthophyll) and it is isolated from brown seaweed. It is categorized in the class of Phaeophyceae. The chemical formula of FX is $C_{42}H_{58}O_6$ and the molecular weight is 658.9 g/mol. Chemically, it has 10.5%-20.8% of the δ13C group. Being hydrophobic, carotenoids are absorbed in the intestine following the same path as dietary fats. Fucoxanthin has an allenic bond, a polyene chain, an acetyl, and a β,λ-epoxy ketone group. There is no symmetry between the two six-membered ring derivatives bound by the polyene chain: one has an allenic bond, the second has a β,λ-epoxy ketone group (Figure 2).

In vivo, the bioactive forms of fucoxanthin are fucoxanthinol and/or amarouciaxanthin. When ingested, fucoxanthin is mainly metabolized to fucoxanthinol in the gastrointestinal tract by digestive enzymes such as lipase and cholesterol esterase by hydrolysis (Asai *et al*., 2004), and it is further converted to amarouciaxanthin A in the liver (Figure 3).

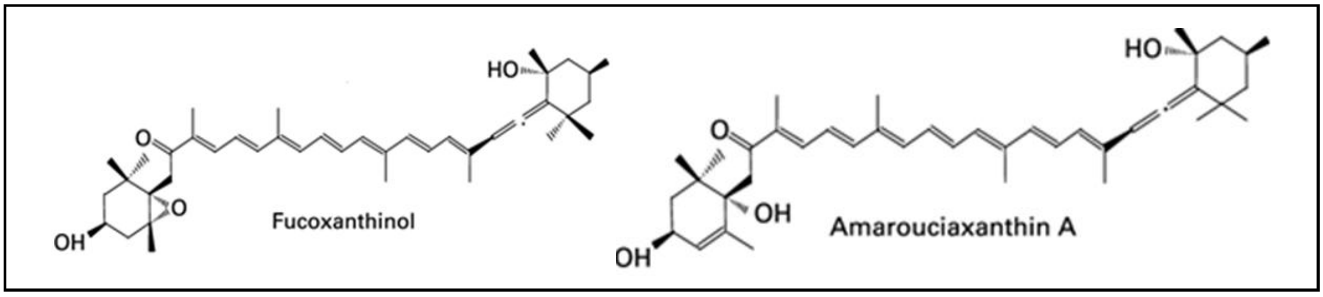


Figure 3: Chemical structure of fucoxanthin derived compounds.

4. Clinical study report on fucoxanthin

One study conducted in human suggested the effects of fucoxanthin on weight loss. The combination of 300 mg pomegranate seed oil and 300 mg brown seaweed extract containing 2.4 mg fucoxanthin significantly resulted in the reduction of body weight and liver fat content in obese women who were treated for 16 days (Abidov *et al*., 2010). Shoketsu and Hiroshi (2017), conducted a clinical trial of fucoxanthin supplementation in Japanese obese subjects and their results demonstrated that a 4 week treatment with fucoxanthin (3 mg/day) reduced body weight, BMI and abdominal fats.

5. Collection of source materials

Publications related to the fucoxanthin metabolite used as cytotoxicity on various cancer cell lines were collected from diverse databases such as PubMed, Scopus, Science Direct, Wiley, Springer, *etc*.We herein review the most recent studies on fucoxanthin as a potential candidate drug for cancer prevention.

6. Cytotoxicity profile of fucoxanthin on diverse cancer cell lines

Table 1: Effect of fucoxanthin on diverse cancer cell lines model

Activity	Cell lines	Dose	References
Showed most potent anticancer activity on the breast cancer cells lines at 24 h treatment with 50 µg/ml	Breast cancerous and normal human skin fibroblast cells	10, 25, and 50 g/ml	Karkhane *et al*., 2018
Showed that the number of positive cells in the fucoxanthin treated group was higher than that of the control group. Moreover, it reduced the expression of BCL-2 and increased the expression of cleaved caspase-3 and epidermal growth factor receptors, STAT3, and phosphorylated STAT3 proteins.	Xenografted sarcoma 180 (S180) in mice	50 to 100 mg/kg	Wang *et al*., 2012
It triggered the growth inhibition at G0-G1 phase and improved the transcription of N-myc genes at 4 h treatment.	Neuroblastoma cell line (GOTO)	10 µg/ml	Okuzumi *et al*., 1990
Fucoxanthin (1-10 µM) pretreatment for 24 h inhibited cell proliferation. They also increased the activity in the NFκB-regulated Bax/Bcl-2 mRNA ratio and reduced the cisplatin-induced NFκB expression.	Human hepatoma cell line (HepG2)	1-10 µM	Liu *et al*., 2013
Anti-proliferative activity	Human liver cancer cell line (HepG2)	IC_{50} value 18.89µg/ml	Foo *et al*., 2019
It markedly decreased the *in vitro* sensitivity (T/C%) of Caco-2, and WiDr by 1.4 ± 0.2 and 12.0 ± 0.3%, respectively, and showed the anti-tumor activity	Colorectal cancer cell lines (Caco-2, WiDr, HCT116, SW620, Colo205) and DLD-1 cell lines	20 µM	Takahashi *et al*., 2015
It showed antitumoral activity *via* inhibition of cancer growth	Human cancer cell line (SK-MEL-28)	104 and 114 µM	Imbs *et al*., 2013

Cytotoxicity effect	Human prostate cancer cell line (PC-3)	3.0, 2.0, and 4.6 ìM	Asai *et al*., 2004
Fx against KB cells exhibited structural changes and reduced tumor survival and significantly increased apoptosis and reduced MMP (Rh-123) concentrations.	Oral squamous cell line (KB)	50 µM/ml	Iyappan *et al*., 2021
It decreased inflammation and protected the stability of the blood-retinal barrier by lowering apoptosis and cell adherence factor protein expression. It showed a significant antioxidant effect.	Human retinal epithelial cell line (ARPE-19)	1 mg/ml	Chiang *et al*., 2020
It reduced HL-60 cell viability, and cell cycle, and caused DNA fragmentation.	Human leukemic HL-60 cells	-	Hosokawa *et al*., 1999
It reduced the survival of HepG2 cells with the activation of cell cycle arrest during the G0/G1 phase. It also down-regulated the cyclin D and cdk4 complex kinase activity, which is linked to antitumorigenic activity.	Human hepatocarcinoma cell line (HepG2)	25 µM	Das *et al*., 2008
Fucoxanthin rich portion isolated from algae, *viz*., *Ulva fasciata, Uivalactuca, Amphiroa anceps, Corallina mediterranea,* and *Sargassum filipendula* showed cytotoxicity activity.	Human breast adenocarcinoma cell line (MCF-7) and Colorectal carcinoma cell line (HCT-116)	3.54 ± 1.2 to 21.2 ± 1.1 µg/ml	Mofeed *et al*., 2021
Anticancer activity is associated with cell cycle arrest, induction of apoptosis *via* decreasing the expression of stress regulator protein mortalinand up-regulation of cleaved caspase-3.	Human bladder cancer cell line (T24)	5 and 10 µM	Wang *et al*., 2014
At 50 µM or 75 µM promoted the cell ratio in the G2/M phase and apoptotic MGC-803 cell line in a dose-dependent manner and significantly reduced CyclinB1, survivin, and STAT3 expressions at 24 h and 48 h, respectively.	Human gastric adenocarcinoma cell line (MGC-803)	25 µM, 50 µM or 75 µM	Yu *et al*., 2011
The viability of human colon cancer cell lines was decreased and apoptosis caused DNA fragmentation was 10-fold higher in Caco-2 cells treated with fucoxanthin for 24h than in control cells.	Human colon cancer cell lines (Caco-2, HT-29, and DLD-1)	22.6 µM	Hosokawa *et al*., 2004
Apoptosis in PC-3 cells was characterized by morphological alterations, DNA fragmentation, and an increased percentage of hypodiploid cells, caspase-3, and PARP cleavages at 48h of treatment.	Human prostate cancer cell line (PC-3)	20 µM	Kotake-Nara *et al*., 2005
By triggering the ROS-mediated damage and dysfunction of MAPKs and PI3-AKT pathways, fucoxanthin induced apoptosis in U251 human glioma cells.	Human glioma cell line (U251)	64.4 ± 4.8 µg/ml	Wu *et al*., 2019
Apoptosis was categorized in EJ-1 cells by morphological alterations, a DNA ladder, and increased hypodiploid cells, which are responsible for caspase-3 activity after 72h treatment.	Human bladder tumours (EJ-1)	20 µM	Zhang *et al*., 2008
At 24 h of incubation, fucoxanthin substantially reduced the proliferation of SK-Hep-1 cells (IC_{50} = 9.4 µM), however, it enhanced the growth of murine embryonic hepatic (BNL CL.2) cells.	Murine normal liver *cell* line (BNL CL.2) and Human hepatoma cell lines (SK-Hep-1)	1-20 µM	Liu *et al*., 2009
Fx and TRAIL (a cytokine) showed apoptosis by upstream signaling of PI3K/Akt and NF-κB pathways.	Human cervical cancer cell lines (HeLa, SiHa, and CaSki)	0, 5, 10, 50, or 100 ng/ml	Jin *et al*., 2018

It increased apoptosis and inhibited cell proliferation, migration, and invasion, revealing a putative mechanism of fucoxanthin-mediated Akt/mTOR and p38 suppression.	Glioma cell lines (U87 and U251)	25, 50, 75, and 100 µM	Liu *et al*. 2016
Cells cycle arrest in the S phase and G2/M phase. It reduced the proliferation and induced cell death *via* the JAK/STAT signaling pathway.	Gastric adenocarcinoma cell lines (SGC-7901 and BGC-823)	50 or 75 µM	Yu *et al*., 2018
Fx enhanced the cytotoxicity against K562 cells and reduced cell expansion in both K562 and TK6 cells.	Human tumor cell lines, K562 and TK6	-	Almeida *et al*., 2018
Fucoxanthin lowered WiDr cell viability in a dose -dependent manner, followed by cell cycle arrest during the G0/G1 phase.	Human colon adenocarcinoma cell lines (WiDr)	25 and 50 µM	Das *et al*., 2005
The fucoxanthin synergistically increased the cytotoxicity of doxorubicin-resistant cell lines. The combination of fucoxanthin and doxorubicin enhanced the levels and activity of caspases and p53 while decreasing the levels and activity of CYP3A4, GST, and PXR.	Breast (MCF-7/ADR), hepatic (HepG-2/ADR), and ovarian (SKOV-3/ADR)	20 µM	Eid *et al*., 2020
The stimulation of autophagy by fucoxanthin in C666-1 cells in the presence of autophagy inhibitors was well established. It inhibited the expression of autophagy-linked proteins during stressful conditions, causing apoptosis.	Nasopharyngeal carcinoma cell- C666-1	0-25 µM/ml	Long *et al*., 2020
Cytotoxic effects on the antibrowning activity of B16F10 murine cells and suppression of lipo genesis in SW872.	B16F10 murine cells and SW872 liposarcoma cells	50 µg/ml	Conde *et al*., 2015
The inhibition of the Akt/mTOR signaling pathway by fucoxanthin causes autophagy-dependent cytotoxicity in HeLa cells.	HeLa cells	10-80 µm/l	Hou *et al*., 2013
By up-regulating the levels of beclin-1, LC3, and cleaved caspase-3, and down-regulating Bcl-2, fucoxanthin decreases the viability of SGC-7901 cells, effectively promoting both autophagy and apoptosis.	Gastric cancer SGC7901 cells	12.5, 25, and 50 µM	Zhu *et al*., 2018
It reduced the malignant phenotype, lowered tumor-induced lymphangiogenesis, and also reduced the levels of vascular endothelial growth factor, nuclear factor kappa B, phospho-Akt, and phospho-PI3K substantially.	Human breast cancer MDA-MB-231 cells	-	Wang *et al*., 2019

The molecular mechanism of fucoxanthin on melanoma B16F10 cell lines was investigated by Kim *et al*. (2013). Fucoxanthin suppressed the B16F10 cell proliferation by promoting cell cycle arrest at the G0/G1 phase in a dose-dependent manner. The protein expressions of phosphorylated-Rb (retinoblastoma protein), cyclin D (1 and 2), and cyclin-dependent kinase (CDK) 4 were down-regulated in Fucoxanthin-induced G0/G1 arrest, while protein levels of p15INK4B and p27Kip1 were up-regulated. Moreover, the *in vivo* antitumor activity of fucoxanthin on B16F10 cells showed reduced growth of cancer mass.

Mise *et al*. (2011), studied the effect of fucoxanthin (Fx) and a deacetylated product fucoxanthinol (Fxol), in cultured cancer cell lines such as Caco-2, Hep G2, and Neuro2a. Both Fx and Fxol reduced proliferation in a dose-dependent manner. Their study revealed that consuming Fx may help to prevent cancer without interacting with anticancer drug cisplatin actions during chemotherapy.

Chung *et al*. (2013), reported that the fucoxanthin isolated from the brown algae of *Saccharina japonica* (Family: Laminariaceae) displayed the *in vitro* antimetastatic effect. Fucoxanthin reduced the invasion of highly metastatic B16-F10 cancer cells by preventing the production of MMP-9, which is important for cancer invasion and migration. Moreover, it inhibited the binding of B16-F10 carcinoma cells into endothelial cells.

Jaswir *et al*. (2011), isolated the fucoxanthin from the species of Malaysian brown seaweed called *Padina australis* (Family: Dictyotaceae). The cytotoxicity MTT assays showed that fucoxanthin affects the viability of H1299 cell lines, with an IC_{50} value of 2.45 mM.

Neumann *et al*. (2019), studied the *in vitro* anti-inflammatory, antioxidative, and antiproliferative properties of fucoxanthin from *Phaeodactylum tricornutum* (Family: Phaeodactylaceae). The author studied the effects on metabolic activity in blood

polymorphonuclear leukocytes and other cell lines and followed by the activity of caspase 3/7. It had anti-inflammatory effects with no cytotoxic effects on polymorphonuclear leukocytes. The cell line metabolic activity was reduced by up to 58%, while fucoxanthin enhanced the caspase 3/7 activity by up to 4.6 times.

Maeda *et al.* (2006), examined the effect of fucoxanthin from edible seaweed such as *Undaria pinnatifida* (Family: Alariaceae) and *Hijikia fusiformis* (Family: Sargassaceae). They revealed that fucoxanthin and its metabolite, fucoxanthinol, inhibited the division of 3T3-L1 pre-adipocytes into adipocytes. The 3T3-L1 cells transformed the fucoxanthin into fucoxanthinol, whose inhibiting effect was stronger than fucoxanthin. Their findings also indicate that fucoxanthin and fucoxanthinol prevented the 3T3-L1 cell adipocyte formation *via* down regulation of PPARα.

The therapeutic effects of fucoxanthin *via* various mechanistic pathways are illustrated below in Figure 4.

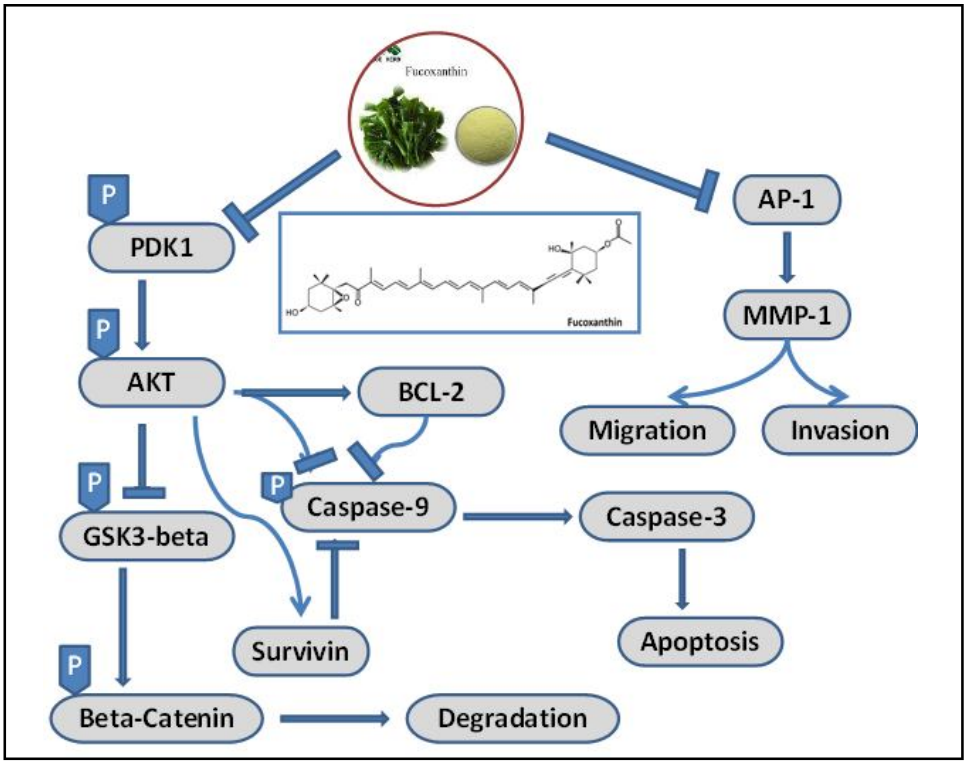


Figure 4: Therapeutic effect of fucoxanthin *via* various mechanistic pathways.

The effect of fucoxanthin induction on the development of reactive oxygen species (ROS) and the stimulation of the Bcl-xL signal transduction pathway in HL-60 cells showed cytotoxicity and apoptosis *via* ROS production, while a ROS scavenger, N-acetylcysteine inhibited these effects. The cleavage of caspases -3 and -7, poly-ADP-ribose polymerase, and a reduction in Bcl-xL levels were enhanced by fucoxanthin.However, those were inhibited and reduced by N-acetylcysteine pretreatment. The accumulation of ROS played a critical role in the fucoxanthin-induced Bcl-xL signaling pathway (Kim *et al.*, 2010).

The cytotoxic effects of Fx alone and in combination with anticancer drugs, *viz.*, doxorubicin and cisplatin on cancerous breast caner cell lines, *viz.*, MCF7, SKBR3, and MDA-MB-231 and a noncancerous cell line, MCF12A enhanced the cytotoxicity, while Dox treatment increased the cytotoxicity in only SKBR3 and MDA-MB-231 cells. When compared to control, the combination protocol, *i.e.*, Fx 10 µM + Dox 1 µM on MDA-MB-231, showed the highest cytotoxicity, induced apoptosis, and genotoxic effects than that of a single drug administration (Malhão *et al.*, 2021).

Chen *et al.* (2021), investigated the effect of fucoidan and fucoxanthin extracted from *Laminaria japonica* (Family: Laminariaceae), and L-carnitine on chronic kidney disease (CKD) in animal models. In CKD mice, both compounds prevented renal fibrosis and lowered serum creatine levels significantly when compared to any other treatment alone. Whereas, L-carnitine had no effect on renal fibrosis but did promote the preventive effect of oligo-fucoidan and fucoxanthin on renal function. The combination therapy further enhanced the kidney function and did not raise serum aspartate aminotransferase and alanine aminotransferase levels in CKD mice, further they inhibited the H_2O_2-induced apoptosis and activated AKT.

Yoshiko and Hoyoku (2007), studied the anticancer properties of fucoxanthin against HepG2 and DU145 cell linesand significantly increased GADD45A, a cell cycle-related gene. Following treatment with fucoxanthin, both cell types experienced G1 arrest, but not apoptosis. They used DNA microarray, RT-PCR, and RNA interference experiments for gene expression.

The antitumor activity off ucoxanthin and phloroglucinol (Ph), alone are in combination with the anticancer drug Temozolomide (TMZ) on glioblastoma cell lines, *viz.*, U251 and T98G had cytotoxic and antiproliferative. However, in U251 cells, the combination therapy (10 µM TMZ + 10 µM Fx) showed a more cytotoxicity effect than the combination therapy of TMZ and Ph (Ferreira, 2016).

Fucoxanthin reduced the amount of intracellular reactive oxygen species on cultured human HaCa tkeratinocytes. It also prevented the development of comet tails and the expression of phospho-histone H2A.X, indicating that it protects cells from hydrogen peroxide-induced DNA damage. The decrease in mitochondrial membrane potential was also reduced by fucoxanthin (Zheng *et al*., 2013).

Ye *et al.* (2014), conducted a study on fucoxanthin for the treatment of cancer and it caused significant apoptosis against HeLa cell lines. The level of phosphorylation was suppressed in a dose-dependent manner and the proteins of apoptotic markers were altered in HeLa cells after 24 h treatment with fucoxanthin. Besides, the mitochondrial signal transduction pathway has played a role in its mechanism, and as well the NF-κ B activation was reduced following fucoxanthin treatment.

According to Wang *et al.* (2014), the anticancer efficacy of extracts from the seaweed *Undaria pinnatifida* (Family: Alariaceae) containing fucoxanthin along with pure fucoxanthin was compared in nine human tumor cell lines, *viz*., Hep G2, A549, WiDr, NCI-H522, SK-N-SH, Lovo, MCF-7, SiHa, and Malme-3M. *Undaria pinnatifida* extracts inhibited the growth of cancer cells in a dose- and the time-dependent way in all types of cancer cell lines. They also studied the fucoxanthin's cytotoxicity in three human non-cancer cell lines, *viz*., HDFB, HUVEC, and HEK293. The results revealed that the low level of fucoxanthin extracts was found to be more effective than pure fucoxanthin in preventing the growth of lung carcinoma, colon adenocarcinoma, and neuroblastoma.

The *in vitro* antitumorigenic activity of the fxlowered cell viability in GBM1, A172, and C6 cell lines in a concentration-dependent manner (40-100 μM), but it was not cytotoxic to murine astrocytes. Fx additionally suppressed GBM1 cell proliferation and clonogenic potential, as well as reduced migration and proliferation. The vascularity of the quail yolk membrane was decreased by Fx-treated GBM1 cells-conditioned media (Lopes *et al*., 2020).

The lung cancer activity of fucoxanthin from *Laminaria japonica* (Family: Laminariaceae) was performed by Mei *et al.* (2017). The apoptosis effectof fucoxanthin showed by altering the caspase expression in A549 cells was noticed as 26.4%, 38.6%, and 40.6% for 12.5, 25, and 50 μM concentrations, respectively. Whereas, H1299 cell line apoptosis rates were found as 18.1%, 23.8%, and 27.9%, respectively when compared to the control group, which showed 0.93%.

Zakaria *et al*. (2018), determined the fucoxanthin content from brown seaweed algae, *Turbinaria deccurrens* (Family: Sargassaceae) and evaluated the cytotoxic activity of various fractions,*viz*., ethanol, n-hexane, ethyl acetate, respectively on colon cancer cell lines (HCT-116). The ethyl acetate fraction of *T. decurrens* contains rich in fucoxanthin along with other extracts reducing the growth of HCT-116 cells, which is evaluated *via* CCK-8 assay.

The apoptosis induced by fucoxanthin in the HL-60 cell line was undertaken by the author Kotake-Nara *et al.* (2005). The induction of apoptosis was characterized by a loss of mitochondrial function at a preliminary phase, but not with an increase in ROS. Fucoxanthin treatment induced the procaspase-3 and poly (ADP-ribose) polymerase cleavages and still had no effect on Bcl-2, Bcl-XL, or Bax protein levels. Fucoxanthin produced an apoptotic effect by permeabilization of mitochondrial membrane and activation of the caspase-3 enzyme.

At 2.5 μM, fucoxanthin reduced RAW 264.7 cell development but was not harmful to RAW 264.7 cells. In osteoclast-like cells, treatment with 2.5 μM fucoxanthin triggered apoptosis by activating caspase-3. In addition to this, in cells of the osteoblast-like cell line MC3T3-E1, 2.5 μM fucoxanthin had no effect on cell viability, showing that fucoxanthin's apoptosis-inducing activity in osteoclasts is stronger than that in osteoblasts. The authors concluded that the treatment with fucoxanthin reduced osteoclastogenesis by inhibiting osteoclast development (Das *et al*., 2010).

Satomi (2012), studied the antitumor effect of fucoxanthin on prostate cancer cells. In a dose-dependent manner, fucoxanthin reduced the development of LNCap prostate cancer cells with an IC_{50} value of approximately 2.5 μM. Fucoxanthin stimulated c-Jun N-terminal kinase (SAPK/JNK), whereas SAPK/JNK inhibition reduced fucoxanthin-induced G1 arrest and GADD45A expression. The author's findings further imply that fucoxanthin causes G1 cell cycle arrest in prostate cancer cells.

Zhuang *et al.* (2021), investigated the anti-carcinogenic efficacy of Fx on 7,12-dimethylbenz [a] anthracene (DMBA)-induced oral cancer in hamsters. Squamous cell malignancy was promoted in hamsters by injecting 0.5% DMBA into the left oral mucosa for ten weeks. Fx (50 mg/kg) treatment of DMBA-induced animals resulted in mild-to-moderate premalignant lesions such as hyperplasia and dysplasia, but control animals developed oral cancer. In the DMBA-induced hamster cheek pouch carcinogenesis, FX showed chemoprotective potential owing to antiproliferative, antiapoptotic, and antioxidant actions, as well as anti-LPO effects.

Rokkaku *et al*. (2013), used osteosarcoma cell lines, to test the anticancer potency of fucoxanthin and its metabolite fucoxanthinol. Fucoxanthinol caused G1 cell cycle arrest by inhibiting CDK 4, CDK 6, and cyclin E and apoptosis by inhibiting survivin, XIAP, Bcl-2, and Bcl-xL expression. The immunostaining assay on Apo 2.7 showed the proportion of 7A6-positive cells incubated for 9h without fucoxanthinol was 0.3%, whereas, the 20 μM fucoxanthinol treatment increased to 34.9%. Fucoxanthin suppressed the osteosarcoma proliferation, relocation, and invasion, as well as promoted apoptosis.

Jang *et al.* (2021), examined the effects of fucoxanthin on cell survival, mobility, tube formation, and angiopoietin 2 expressions in CMT-U27 and HUVEC cell lines. The different concentrations, *viz*., 0, 5, 10, and 20 μM of fucoxan thin for 24 h in CMT-U27 cells, triggered the apoptosis by activating caspases, whereas, in HUVEC cells, it reduced the tube formation and migration. The Authors concluded that by boosting Ang2 expression, fucoxanthin had an anti-angiogenic effect on HUVEC and CMT-U27 cells.

Fucoxanthin showed obvious cytotoxicity against A2780 human ovarian cancer cells, the study was undertaken by Li *et al.* (2020). Their results suggested that fucoxanthin at (5-100 μM) induces apoptosis in A2780 cells, as seen by decreased cell viability (80%), increased ROS generation, and altered the mitochondrial membrane potential when compared to control cells. Moreover, fucoxanthin (20 μM) treatment results in an increased mass of late apoptotic cells as a consequence of a damaged cell membrane. The authors

concluded that in a human ovarian cancer cell line, fucoxanthin enhanced apoptosis, decreased cell proliferation, migration, and invasion, and suggested a putative mechanism of fucoxanthin-mediated Akt/mTOR suppression.

Sargassum oligocystum, seaweed containing the secondary metabolites of fucoxanthin, fucoidan, vitamins, *etc*., was studied for its anti-proliferative activity against human lung cancer cell line (GLC4/ADR) (Praiboon *et al*., 2018). The ethanolic, lipophilic, acidic, and alkali extracts of the seaweed showed a noteworthy cytotoxicity effect on the lung cancer cell line. Moreover, the lipophilic extracts showed a significant IC_{50} value of 2.52 ± 0.54 µg/ml when compared to other extracts owing to the presence of vitamin E (-tocopherol).

The purpose of Molina *et al*. (2014) study was to assess the cytotoxicity effects of Fx alone and in combination with vitamin C on lymphocytes related to reactive oxygen/nitrogen species production. The T- and B-lymphocytes cell proliferation capacity, production of superoxide anion radicals, hydrogen peroxide, nitric oxide, antioxidant enzyme activities, and oxidative damage proteins was stimulated with increasing concentration of the treatment. Moreover, in the *in vitro* study, the healthy human lymphocyte cells were administered with Fx (2 µM) with or without vitamin C (100 µM) and the results revealed that the Fx alone treatment did not exhibit any changes in T- and B-lymphocyte proliferation. Besides, Vitamin C increased T-lymphocyte proliferation, whereas vitamin C with Fx promoted a reduction in the proliferation rate of these cells.

Neumann *et al*. (2019), investigated the antiproliferative property of fucoxanthin on HeLa cells and metabolic activity on blood mononuclear cells along with caspase 3/7 activity. Their result showed that the fucoxanthin did not exert the cytotoxicity activity; however, it decreased the metabolic activity (up to 58%) and increased the caspase 3/7 activity (4.6-fold). There were dose-dependent antioxidant effects in blood neutrophils, with a 63% reduction in chemiluminescence and a 3.3-fold rise in the ratio of reduced to oxidized glutathione.

Alghazwi *et al*. (2019), compared the neuroprotective properties of two marine-derived carotenoids, astaxanthin and fucoxanthin against Aα1-42-mediated toxicity in pheochromocytoma (PC-12) neuronal cells. Both astaxanthin and fucoxanthin had multi-neuroprotective effects; however, fucoxanthin favors more effects.

Wang *et al*. (2021), prepared the whey protein isolate (WPI)-based nano complexes using Ca^{2+} crosslinked flaxseed gum (FG) and marine carotenoid-fucoxanthin (Fx). The FX-WPI-FG-Ca nano complex with a nano-size (~350 nm) was found to have the best encapsulation efficiency (96.19 ± 0.33%) and loading capacity (2.47 ± 0.04%). Furthermore, the nano complex was demonstrated to successfully transport Fx into pheochromocytoma (PC12) cells, with increased cytotoxicity with an increased concentration of Fx. The encapsulated-Fx disrupted lipid metabolism, resulting in an increase in ROS, mitochondrial damage, and apoptotic regulation.

Manmua and Manmuan (2019), conducted to evaluate the anticancer activity and the mechanism of fucoxanthin on cell growth inhibition, cell attachment, and cell incursion in colorectal cancer cells (SW-620). Moreover, to test the synergistic potential, SW-620 cells were cultured with fucoxanthin for 24, 48, 72, and 96 h with 5-fluorouracil (5-FU) treatment. After treating the cells with fucoxanthin with 5-FU at various doses, the inhibition effect of cellular uptake and adherence was determined to regulate the MMP-9 gene and protein expression, which could suppress significantly cellular proliferation in SW-620 cells. Thus, fucoxanthin has been shown to kill cancerous cells, suggesting that it could be a promising anticancer agent.

Rwigemera *et al*. (2015), found that the low concentrations of the fucoxanthin and its metabolite fucoxanthinol to be effective against MCF-7 and MDA-MB-231 breast cancer cell lines. These cell lines were stimulated with 10 to 20 µM fucoxanthin and/or fucoxanthinol, and decreased viability and increased apoptosis were found in a time-dependent and dose-dependent way. However, fucoxanthinol modulatory effects on members of the NF-κB pathway were more significant in both cell lines than fucoxanthin.

7. Conclusion

According to our review study, fucoxanthin has a great potential application in understanding and managing diseases such as cancer and other chronic conditions. The focus has switched in recent years to developing novel targeted cancer medicines that can modify particular pathways that are frequently mutated in carcinoma. Fucoxanthin might be employed as a pharmaceutical to target certain pathways that lead to the activation of apoptosis and cell death. In different experimental cancer models, Fx and its deacetylated form "fucoxanthinol" have been found to reduce numerous cancer-related signal pathways and the cancer microenvironment. Fucoxanthin caused cell growth arrest, apoptosis, cytotoxicity, and/or autophagy in a variety of cancer cell lines and *in vivo* animal cancer studies. It might also be employed as a neutraceutical to boost the anticancer effects of already available chemotherapeutics. Despite the fact that research into the signaling molecules and pathways affected by fucoxanthin is restricted, the present research demonstrates the use of this substance alone and in conjunction with other cancer treatments. Consequently, more thorough animal investigations are necessary prior to human trials may begin. With this assessment report, we believe that fucoxanthin will be simpler to develop into effective marine pharmaceuticals for the treatment of lifestyle-related disorders such as cancer, infectious disease, and other illnesses.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abidov, M.; Ramazanov, Z.; Seifulla, R.; Grachev, S. (2010). The effects of Xanthigen in the weight management of obese premenopausal women with non-alcoholic fatty liver disease and normal liver fat. Diabetes, Obesity and Metabolism. **12**(1):72-81.

Afroz, A. and Adnan A.K. (2020). Argemone mexicana L: A weed with versatile medicinal and pharmacological applications. Ann. Phytomed., **9**(1):218-223.

Alghazwi, M.; Smid, S.; Musgrave, I. and Zhang, W. (2019). *In vitro* studies of the neuroprotective activities of astaxanthin and fucoxanthin against amyloid beta (Aα1-42) toxicity and aggregation. Neurochemistry International, **124**:215-224.

Almeida, T.P.; Ferreira, J.; Vettorazzi, A.; Azqueta, A.; Rocha, E. and Ramos, A.A. (2018). Cytotoxic activity of fucoxanthin, alone and in combination

with the cancer drugs imatinib and doxorubicin, in CML cell lines. Environmental Toxicology. and Pharmacology. **59**:24-33.

Asai, A.; Sugawara, T.; Ono, H. and Nagao, A. (2004). Biotrans-formation of fucoxanthinol into amarouciaxanthin A in mice and HepG2 cells: Formation and cytotoxicity of fucoxanthin metabolites. Drug Metabolism and Disposition, **32**(2):205-211.

Chen, Y.C.; Cheng, C.Y.; Liu, C.T.; Sue, Y.M.; Chen, T.H.; Hsu, Y.H. and Chen, C.H. (2020). Combined protective effects of oligo-fucoidan, fucoxanthin, and L-carnitine on the kidneys of chronic kidney disease mice. EuropeanJournalof Pharmacology, **892**:173-708.

Chiang, Y.F.; Chen, H.Y.; Chang, Y.J.; Shih, Y.H.; Shieh, T.M.; Wang, K.L. and Hsia, S.M. (2020). Protective effects of fucoxanthin on high glucose-and 4-hydroxynonenal (4-HNE)-induced injury in human retinal pigment epithelial cells. Antioxidants, **9**(12):11-76.

Chung, T.W.; Choi, H.J.; Lee, J.Y.; Jeong, H.S.; Kim, C.H.; Joo, M. and Ha, K.T. (2013). Marine algal fucoxanthin inhibits the metastatic potential of cancer cells. Biochemical and Biophysical Research Communications, **439**(4):580-585.

Conde, E.; Moure, A. and Domínguez, H. (2015). Supercritical CO_2 extraction of fatty acids, phenolics and fucoxanthin from freeze-dried *Sargassum muticum*. Journal of Applied Phycology, **27**(2):957-964.

Das, S. K.; Ren, R.; Hashimoto, T. and Kanazawa, K. (2010). Fucoxanthin induces apoptosis in osteoclast-like cells differentiated from RAW264. 7 cells. Journal of Agricultural and Food Chemistry, **58**(10):6090-6095.

Das, S.K.; Hashimoto, T. and Kanazawa, K. (2008). Growth inhibition of human hepatic carcinoma HepG2 cells by fucoxanthin is associated with down-regulation of cyclin D. Biochimica et Biophysica Acta (BBA)-General Subjects, **1780**(4):743-749.

Das, S.K.; Hashimoto, T.; Shimizu, K.; Yoshida, T.; Sakai, T.; Sowa, Y. and Kanazawa, K. (2005). Fucoxanthin induces cell cycle arrest at G0/G1 phase in human colon carcinoma cells through up-regulation of p21WAF1/ Cip1. Biochimica et Biophysica Acta (BBA)-General Subjects, **1726**(3):328-335.

Donaldson, M.S. (2004). Nutrition and cancer: A review of the evidence for an anticancer diet. Nutrition Journal, **3**:19.

Duraisami, R.; Sengottuvelu, S.; Prabha, T.; Sabbani, S.; Divya Presenna, S. and Muralitharan, C.K. (2021). Evaluation of antidiabetic efficacy potency of polyherbal formulations in experimentally induced hyperglycemic rats. Ann. Phytomed., **10**(2):286-291.

Eid, S. Y.; Althubiti, M. A.; Abdallah, M. E.; Wink, M. and El-Readi, M. Z. (2020). The carotenoid fucoxanthin can sensitize multidrug resistant cancer cells to doxorubicin *via* induction of apoptosis, inhibition of multidrug resistance proteins and metabolic enzymes. Phytomedicine, **77**:153-280.

Ferreira, J.R.N. (2016). Anticancer activity against glioblastoma cell lines by compounds present in algae, alone and in combination with anticancer drugs. Dissertation for the degree of Master in Environmental Contamination and Toxicology, Presented to Institute of Biomedical Sciences Abel Salazar of the University of Porto.

Foo, S.C.; Yusoff, F.M.; Imam, M.U.; Foo, J.B.; Ismail, N.; Azmi, N.H. and Ismail, M. (2019). Increased fucoxanthin in *Chaetoceros calcitrans* extract exacerbates apoptosis in liver cancer cells *via* multiple targeted cellularpathways. Biotechnology Reports, **21**:e00296.

Hosokawa, M.; Kudo, M.; Maeda, H.; Kohno, H.; Tanaka, T. and Miyashita, K. (2004). Fucoxanthin induces apoptosis and enhances the antiproliferative effect of the PPARα ligand, troglitazone, on colon cancer cells. Biochimica et Biophysica Acta (BBA)-General Subjects, **675**(1-3):113-119.

Hosokawa, M.; Wanezaki, S.; Miyauchi, K.; Kurihara, H.; Kohno, H.; Kawabata, J. and Takahashi, K. (1999). Apoptosis-inducing effect of fucoxanthin on human leukemia cell line HL-60. Food Science and Technology Research, **5**(3):243-246.

Hou, L. L.; Gao, C.; Chen, L.; Hu, G. Q. and Xie, S. Q. (2013). Essential role of autophagy in fucoxanthin-induced cytotoxicity to human epithelial cervical cancer HeLa cells. Acta Pharmacologica Sinica, **34**(11):1403-1410.

Imbs, T.I.; Ermakova, S.P.; Fedoreyev, S.A.; Anastyuk, S.D. and Zvyagintseva, T.N. (2013). Isolation of fucoxanthin and highly unsaturated monogalactosyldiacylglycerol from brown alga *Fucus evanescens* C Agardh and *in vitro* investigation of their antitumor activity. Marine Biotechnology, **15**(5):606-612.

Iyappan, P.; Bala, M.D.; Sureshkumar, M.; Veeraraghavan, V.P. and Palanisamy, A. (2021). Fucoxanthin induced apoptotic cell death in oral squamous carcinoma (KB) cells. Bioinformation, **17**(1):181.

Jang, H.; Choi, J.; Park, J. K.; Won, G. and Seol, J. W. (2021). Fucoxanthin exerts antitumor activity on canine mammary tumor cells *via* tumor Cell apoptosis induction and angiogenesis inhibition. Animals, **11**(6):15-12.

Jaswir, I.; Noviendri, D.; Salleh, H.M.; Taher, M. and Miyashita, K. (2011). Isolation of fucoxanthin and fatty acids analysis of *Padina australis* and cytotoxic effect of fucoxanthin on human lung cancer (H1299) cell lines. African Journal of Biotechnology, **10**(81):18855-18862.

Jin, Y.; Qiu, S.; Shao, N. and Zheng, J. (2018). 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. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, **24**:11.

Karkhane, Y.M.; Seyed, H.M.; Mashinchian, M.A. and Ghasempour, A.R. (2018). *In vitro* investigating of anticancer activity of focuxanthin from marine brown seaweed species. Global Journal of Environmental Science and Management, **4**(1):81-90.

Kaul, R.; Risinger, A.L. and Mooberry, S.L. (2019). Microtubule-targeting drugs: More than antimitotics. Journal of Natural Products, **82**:680-685.

Kim, K.N.; Ahn, G.; Heo, S.J.; Kang, S.M.; Kang, M.C.; Yang, H.M. and Jeon, Y.J. (2013). Inhibition of tumor growth *in vitro* and *in vivo* by fucoxanthin against melanoma B16F10 cells. Environmental Toxicology and Pharmacology, **35**(1):39-46.

Kim, K.N.; Heo, S.J.; Kang, S.M.; Ahn, G. and Jeon, Y.J. (2010). Fucoxanthin induces apoptosis in human leukemia HL-60 cells through a ROS-mediated Bcl-xL pathway. Toxicology *in vitro*. **24**(6):1648-1654.

Kotake-Nara, E.; Asai, A. and Nagao, A. (2005). Neoxanthin and fucoxanthin induce apoptosis in PC-3 human prostate cancer cells. Cancer Letters, **220**(1):75-84.

Kotake-Nara, E.; Terasaki, M. and Nagao, A. (2005). Characterization of apoptosis induced by fucoxanthin in human promyelocytic leukemia cells. Bioscience, Biotechnology, and Biochemistry, **69**(1):224-227.

Li, Y.; Tao, L.; Bao, L.; Chinnathambi, A.; Alharbi, S. A. and Cui, J. (2020). Fucoxanthin inhibits cell proliferation and stimulates apoptosis through downregulation of PI3K/AKT/mTOR signaling pathway in human ovarian cancer cells. Pharmacognosy Magazine, **16**(69): 311.

Liu, C.L.; Huang, Y.S.; Hosokawa, M.; Miyashita, K. and Hu, M.L. (2009). Inhibition of proliferation of a hepatoma cell line by fucoxanthin in relation to cell cycle arrest and enhanced gap junctional intercellular communication. Chemico-Biological Interactions, **182**(2-3):165-172.

Liu, C.L.; Lim, Y.P. and Hu, M.L. (2013). Fucoxanthin enhances cisplatin-induced cytotoxicity *via* NFκB-mediated pathway and down regulates DNA repair gene expression in human hepatoma HepG2 cells. Marine Drugs, **11**(1): 50-66.

Liu, Y.; Zheng, J.; Zhang, Y.; Wang, Z.; Yang, Y.; Bai, M. and Dai, Y. (2016). Fucoxanthin activates apoptosis *via* inhibition of PI3K/Akt/mTOR pathway and suppresses invasion and migration by restriction of p38-MMP-2/9 pathway in human glioblastoma cells. Neurochemical Research, **41**(10):2728-2751.

Long, Y.; Cao, X.; Zhao, R.; Gong, S.; Jin, L. and Feng, C. (2020). Fucoxanthin treatment inhibits nasopharyngeal carcinoma cell proliferation through induction of autophagy mechanism. Environmental Toxicology, **35**(10):1082-1090.

Lopes, F.G.; Oliveira, K.A.; Lopes, R.G.; Poluceno, G.G.; Simioni, C.; Gabriel, D.S.P.; Bauer, C.M.; Maraschin, M.; Derner, R.B.; Garcez, R.C.; Tasca, C.I. and Nedel, C.B. (2020). Anticancer effects of fucoxanthin on human glioblastoma cell line. Anticancer Res., **40**(12):6799-6815.

Maeda, H.; Hosokawa, M.; Sashima, T.; Takahashi, N.; Kawada, T. and Miyashita, K. (2006). Fucoxanthin and its metabolite, fucoxanthinol, suppress adipocyte differentiation in 3T3-L1 cells. International Journal of Molecular Medicine, **18**(1):147-152.

Malhão, F.; Macedo, A.C.; Costa, C.; Rocha, E. and Ramos, A.A. (2021). Fucoxanthin holds potential to become a drug adjuvant in breast cancer treatment: Evidence from 2D and 3D Cell Cultures. Molecules, **26**(14):4288.

Manmuan, S., and Manmuan, P. (2019). Fucoxanthin enhances 5-FU chemotherapeutic efficacy in colorectal cancercells by affecting MMP-9 invasive proteins. Journal of Applied Pharmaceutical Science, **9**:007-014.

Mei, C.; Zhou, S.; Zhu, L.; Ming, J.; Zeng, F. and Xu, R. (2017). Antitumor effects of Laminaria extract fucoxanthin on lung cancer. Marine Drugs, **15**(2):39.

Mise, T. and Yasumoto, T. (2011). Simultaneous treatment of cancer cells lines with the anticancer drug cisplatin and the antioxidant fucoxanthin. British Journal of Pharmacology and Toxicology, **2**(3):127-131.

Mofeed, J.; Deyab, M.; Sabry, A.E.N. and Ward, F. (2021). *In vitro* anticancer activity of five marine seaweeds extract from Egypt against human breast and colon cancer cell lines. Research Square, Preprint. doi: https://doi.org/10.21203/rs.3.rs-462221/v1

Mohd Hafizur, R.A. and Sayeed, A. (2019). Herbs that heal: Natural remedies for health promotion and longevity. Ann. Phytomed., **8**(1):7-18.

Molina, N.; Morandi, A. C.; Bolin, A.P. and Otton, R. (2014). Comparative effect of fucoxanthin and vitamin C on oxidative and functional parameters of human lymphocytes. International Immuno Pharmacology. **22**(1):41-50.

Neumann, U.; Derwenskus, F.; FlaizFlister, V.; Schmid-Staiger, U.; Hirth, T. and Bischoff, S.C. (2019). Fucoxanthin, a carotenoid derived from *Phaeodactylum tricornutum* exerts antiproliferative and antioxidant activities *in vitro*. Antioxidants, **8**(6):183.

Okuzumi, J.; Nishino, H.; Murakoshi, M.; Iwashima, A.; Tanaka, Y.; Yamane, T. and Takahashi, T. (1990). Inhibitory effects of fucoxanthin, a natural carotenoid, on N-myc expression and cell cycle progression in human malignant tumor cells. Cancer Letters, **55**(1):75-81.

Prabha, T. and Sivakumar, T. (2018). Design, synthesis, and docking of sulfadiazine schiff base scaffold for their potential claim as INHA enoyl-(Acyl-carrier-protein) reductase inhibitors. Asian Journal of Pharmaceutical and Clinical Research, **11**:233.

Praiboon, J.; Palakas, S.; Noiraksa, T. and Miyashita, K. (2018). Seasonal variation in nutritional composition and anti-proliferative activity of brown seaweed, *Sargassum oligocystum*. Journal of Applied Phycology. **30**(1):101-111.

Rodríguez-García, C.; Sánchez-Quesada, C. and Gaforio, J.J. (2019). Dietary flavonoids as cancer chemopreventive agents: An updated review of human studies. Antioxidants (Basel), **8**(5):137.

Rokkaku, T.; Kimura, R.; Ishikawa, C.; Yasumoto, T.; Senba, M.; Kanaya, F. and Mori, N. (2013). Anticancer effects of marine carotenoids, fucoxanthin and its deacetylated product, fucoxanthinol, on osteosarcoma. International Journal of Oncology, **43**(4):1176-1186.

Rwigemera, A.; Mamelona, J. and Martin, L.J. (2015). Comparative effects between fucoxanthinol and its precursor fucoxanthin on viability and apoptosis of breast cancer cell lines MCF-7 and MDA-MB-231. Anticancer Research, **35**(1):207-219.

Satomi, Y. (2012). Fucoxanthin induces GADD45A expression and G1 arrest with SAPK/JNK activation in LN Cap human prostate cancer cells. Anticancer Research, **32**(3):807-813.

Shoketsu, H. and Hiroshi, S. (2017). Seaweed fucoxanthin supplementation improves obesity parameters in mildly obese Japanese subjects, Functional Foods in Health and Disease, **7**(4):246-262.

Sri Bhuvaneswari, S.; Prabha, T.; Sameema Begum, S.; Sivakumar, T.; Saranraj, P.; Manivannan, V. and Ashok Kumar, B. (2021). Formulation and evaluation, comparison of herbal hair dye with marketed formulation. Ann. Phytomed., **10**(2):175-181.

Takahashi, K.; Hosokawa, M.; Kasajima, H.; Hatanaka, K.; Kudo, K.; Shimoyama, N. and Miyashita, K. (2015). Anticancer effects of fucoxanthin and fucoxanthinol on colorectal cancer cell lines and colorectal cancer tissues. Oncology Letters, **10**(3):1463-1467.

Takaichi, S. (2011). Carotenoids in algae: Distributions, biosyntheses and functions. Marine Drugs, **9**(6):1101-1118.

Tamanna, M.; Madan, V.K.; and Ram, P. (2020). Herbs that heal: Floristic boon to the natural healthcare system. Ann. Phytomed., **9**(2):6-14.

Wang, C.; Ren, J.; Song, H.; Chen, X. and Qi, H. (2021). Characterization of whey protein-based nanocomplex to load fucoxanthin and the mechanism of action on glial cells PC12. LWT-Food Science and Technology, **151**:112-208.

Wang, J.; Chen, S.; Xu, S.; Yu, X.; Ma, D.; Hu, X. and Cao, X. (2012). *In vivo* induction of apoptosis by fucoxanthin, a marine carotenoid, associated with down-regulating STAT3/EGFR signaling in sarcoma 180 (S180) xenografts-bearing mice. Marine Drugs, **10**(9):2055-2068.

Wang, J.; Ma, Y.; Yang, J.; Jin, L.; Gao, Z.; Xue, L. and Zou, X. (2019). Fucoxanthin inhibits tumour related lymphangiogenesis and growth of breast cancer. Journal of Cellular and Molecular Medicine, **23**(3):2219-2229.

Wang, L.; Zeng, Y.; Liu, Y.; Hu, X.; Li, S.; Wang, Y.; Li, L.; Lei, Z. and Zhang, Z. (2014). Fucoxanthin inducesgrowth arrest and apoptosis in human bladder cancer T24 cells by up-regulation of p21 and down-regulation of mortalin. Acta. Biochim. Biophys. Sin. (Shanghai), **46**(10):877-884.

Wang, S. K.; Li, Y.; White, W. L. and Lu, J. (2014). Extracts from New Zealand Undaria pinnatifida containing fucoxanthin as potential functional biomaterials against cancer *in vitro*. Journal of Functional Biomaterials, **5**(2):29-42.

Wu, H.L.; Fu, X.Y.; Cao, W.Q.; Xiang, W.Z.; Hou, Y. J.; Ma, J. K. and Fan, C.D. (2019). Induction of apoptosis in human glioma cells by fucoxanthin *via* triggering of ROS-Mediated oxidative damage and regulation of MAPKs and PI3K–AKT pathways. Journal of Agricultural and Food Chemistry, **67**(8):2212-2219.

Ye, G.; Lu, Q.; Zhao, W.; Du, D.; Jin, L. and Liu, Y. (2014). Fucoxanthin induces apoptosis in human cervical cancercell line HeLa via PI3K/Akt pathway. Tumor Biology, **35**(11):11261-11267.

Yoshiko, S. and Hoyoku, N. (2007). Fucoxanthin, a natural carotenoid, induces G1 arrest and GADD45 gene expression in human cancer cells. *In vivo*, **21**(2):305-309.

Yu, R. X.; Hu, X. M.; Xu, S. Q.; Jiang, Z. J. and Yang, W. (2011). Effects of fucoxanthin on proliferation and apoptosis in human gastric adenocarcinoma MGC-803 cells via JAK/STAT signal pathway. European Journal of Pharmacology, **657**(1-3):10-19.

Yu, R. X.; Yu, R. T. and Liu, Z. (2018). Inhibition of two gastric cancer cell lines induced by fucoxanthin involves downregulation of Mcl-1 and STAT3. Human Cell, **31**(1):50-63.

Zakaria, A. D.; Basah, K.; Bahtiar, A.; Deviyani, Z.; Basah, K. and Bahtiar, A. (2018). Cytotoxic activity of extract and active fraction of *Turbinaria decurrensbory* on colon cancer cell line HCT-116. The International Journal of Morphology, **36**(3):979-983.

Zhang, Z.; Zhang, P.; Hamada, M.; Takahashi, S.; Xing, G.; Liu, J. and Sugiura, N. (2008). Potential chemoprevention effect of dietary fucoxanthin on urinary bladder cancer EJ-1 cell line. Oncology Reports, **20**(5):1099-1103.

Zheng, J.; Piao, M.J.; Keum, Y.S.; Kim, H.S. and Hyun, J.W. (2013). Fucoxanthin protects cultured human keratinocytes against oxidative stress by blocking free radicals and inhibiting Apoptosis. Biomolecules and Therapeutics, **21**(4):270-276.

Zhu, Y.; Cheng, J.; Min, Z.; Yin, T.; Zhang, R.; Zhang, W. and Hu, X. (2018). Effects of fucoxanthin on autophagy and apoptosis in SGC 7901cells and the mechanism. Journal of Cellular Biochemistry, **119**(9):7274-7284.

Zhuang, Z.; Wang, J.; Yang, Y.; Hou, Y.; Li, S.; Wang, Y. and Wu, F. (2021). Antioral cancer effect of fucoxanthin on 7, 12-dimethylbenz [a] anthracene-induced experimental cancer model hamster through changes of apoptosis and cell proliferation. Pharmacognosy Magazine, **17**(75): 578.

Citation **A. Vijayalakshmi, T. Prabha, V. Lalitha, S. Hemalatha, M. Jagadeeswaran, M.V.N.L Chaitanya, P. Selvamani and S. Latha (2022). Dietary carotenoid fucoxanthin as a promising biomarker to target the cancer cells: A focused review. Ann. Phytomed., 11(1):164-174. http://dx.doi.org/10.54085/ap.2022.11.1.16.**