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REVIEW – CANCER RESEARCH

The anticancer effects and mechanisms of fucoxanthin combined with other drugs

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Abstract

Purpose Fucoxanthin (Fx) is a characteristic carotenoid present in brown seaweed that has been shown to have various benefits, including anticancer effects. In vitro studies demonstrated these various effects, including the suppression of cell viability, the promotion of apoptosis, and antiangiogenic, antiproliferative, and antimetastatic activity. Interestingly, combinations of Fx with other drugs have better effects than either Fx or other drugs alone. Although the antiproliferative and cancer prevention activities of the combination of Fx and other drugs are still unclear, several effects have been discovered, including the induction of apoptosis, cell cycle arrest at G1/G0, enhanced gap junctional intercellular communication, and the induction of autophagy via various mechanisms, such as decreasing P-gp, activating the CYP3A4 promoter, increasing reactive oxygen species and cellular uptake and suppressing the PI3K/Akt/NFκB pathway. In this review, we address the anticancer effects and mechanisms of the combination of Fx and other drugs in different types of cancer.

Methods The relevant literature from PubMed and Web of Science databases is reviewed in this article.

Results Fx combined with other drugs could enhance the effect of both Fx and the other drug or reduce the dose without reducing the effect, which may create more effective and less harmful therapeutic strategies.

Conclusion Fx combined with other drugs has significant anticancer effects by various mechanisms and could be a potential therapeutic strategy for different types of cancer.

Keywords Fucoxanthin · Troglitazone · 5-Fluorouracil · Pregnane X receptor · Imatinib

Abbreviations

Fx	Fucoxanthin
Akt	Protein kinase B
mTOR	Mammalian target of rapamycin
Bcl-2	B-cell lymphoma 2
SAPK/JNK	c-Jun N-terminal kinases
JAK	Janus kinases
STAT	Signal transducer and activator of transcription protein family
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
MAPK	Mitogen-activated protein kinase
5-FU	5-Fluorouracil
PXR	Pregnane X receptor
WAF/Cip1	Cyclin-dependent kinase inhibitor 1
PPARγ	Peroxisome proliferator-activated receptor γ
ABC transporters	ATP-binding cassette transporters
MDR	Multidrug resistance protein
P-gp	P-glycoprotein
CS	Chitosan
GL	Glycolipid
NGs	Nanogels
ROS	Reactive oxygen species
Bax	Bcl-2-associated X protein

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GADD45	Growth arrest and DNA-damage-inducible protein
CDK	Cyclin-dependent kinase
Cx	Connexin
CYP3A4	Cytochrome P450 3A4
SRC-1	Steroid receptor coactivator-1
ERCC1	Excision repair cross complementation 1
TP	Thymidine phosphorylase
ERK	Extracellular signal-regulated kinase
PI3K	Phosphoinositide 3-kinase
ALT	Adult T-cell leukemia
XIAP	X-linked inhibitor of apoptosis protein
cIAP2	Cellular inhibitor of apoptosis protein 2
IκBα	Nuclear factor of kappa light polypeptide gene enhancer in B-cell inhibitorα
Bcl-xL	B-cell lymphoma-extra large
CML	Chronic myelogenous leukemia
BCR	Breakpoint cluster region protein
ABL	Abelson murine leukemia viral oncogene homolog
Fxol	Fucoxanthinol
PTEN	Phosphatase and tensin homolog
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
TNF	Tumor necrosis factor

Introduction

Fucoxanthin (Fx) is a characteristic carotenoid present in edible brown seaweed with a distinct structure consisting of an allenic bond, epoxide group, and conjugated carbonyl group in a polyene chain. Studies have demonstrated the distinct benefits of Fx, including antimutagenic (Nishino et al. 2009), antidiabetic (Nishikawa et al. 2012), antiobesity (Maeda et al. 2005), anti-inflammatory (Kim et al. 2010b), neuroprotective (Zhang et al. 2017), and antitumor activity (Martin 2015). The anticancer behavior is especially of interest; such activity has been found in glioblastoma (Liu et al. 2016), colon cancer, bladder cancer, prostate cancer, liver cancer, leukemia, gastric cancer, cervical cancer, melanoma, osteosarcoma, breast cancer, and lung cancer (Martin 2015). Fx suppresses tumor formation through various mechanisms, including inducing autophagy (Hou et al. 2013), inducing apoptosis, arresting the cell cycle at G1/G0, and enhancing gap junctional intercellular communication, and involving different regulatory events in pathways such as the Akt/mTOR, Bcl-2, SAPK/JNK, JAK/STAT, NFκB and MAPK pathways (Martin 2015).

Recently, an increasing number of studies have focused on the combination of Fx and other drugs, including traditional anticancer drugs (e.g., cisplatin and 5-FU), new drugs still under exploration (e.g., TXR antagonists), and nanocarriers. The anticancer effects of Fx combined with other drugs have been evaluated in colon cancer (Eid et al. 2012; Hosokawa et al. 2004; Ravi et al. 2018), liver cancer (Liu et al. 2012, 2013), leukemia (Almeida et al. 2018), breast cancer (Vijay et al. 2018), and cervical cancer (Jin et al. 2018; Ye et al. 2017). However, combinations of Fx with other drugs have different mechanisms than Fx alone, which will be further discussed in the next section.

In animal experiments, oral administration of Fx showed no toxicity and mutagenicity (Beppu et al. 2009a, b; Iio et al. 2011). Though there are no human experiments of Fx yet, animal experiments have exhibited great anticancer effects Fx either alone or combined with other drugs and indicated the great clinical potential of Fx, which will be further discussed too.

In this review, the anticancer effects, possible underlying mechanisms, and the safety and efficacy, of Fx combined with other drugs in different types of cancer, will be discussed.

Anticancer effects of Fx combined with other drugs

Colon cancer (Fig. 1)

Colon cancer is the third and second most commonly diagnosed cancer in males and females, respectively (Torre et al. 2015). Epidemiologic studies have demonstrated that higher consumption of fruits and vegetables, which are abundant in carotenoids, has been linked to a lower risk of colon cancer (Mayne 1996; Slattery et al. 2000). In vitro experiments have

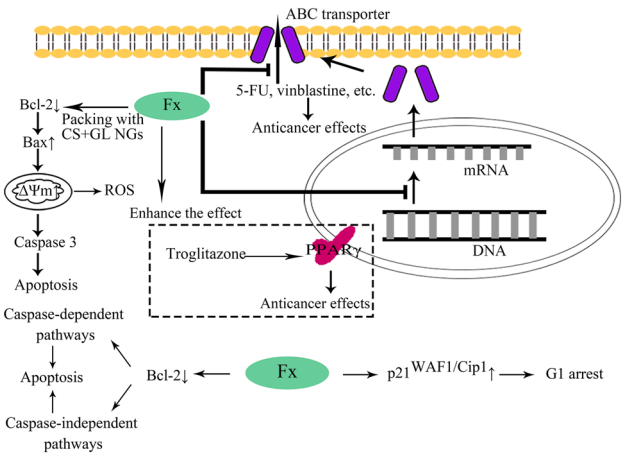

Fig. 1 The anticancer effects of Fx alone and combined with troglitazone, 5-FU, vinblastine, etc. and packing with CS + GL NGs in colon cancer

proven that Fx has anticancer effects in six colorectal cancer cell lines, including Caco-2, WiDr, SW620, HCT116, DLD-1, and Colo205 cells (Takahashi et al. 2015). Hosokawa et al. showed that Fx effectively decreased the viability of Caco-2 cells by suppressing Bcl-2 protein levels and inducing DNA fragmentation via both caspase-dependent and caspase-independent pathways (Hosokawa et al. 2004). Another study demonstrated that Fx could upregulate $p21^{WAF1/Cip1}$ to induce cell cycle arrest at G0/G1 phase in WiDr cells (Das et al. 2005).

Troglitazone has been shown to inhibit cell growth and induce apoptosis through the activation of peroxisome proliferator-activated receptor γ (PPARγ) (Brockman et al. 1998; Shimada et al. 2002). Hosokawa et al. (2004) demonstrated that Caco-2 cell viability was not affected by troglitazone at concentrations lower than 10 μM or by 3.8 μM Fx but was dramatically reduced by the combination of 10 μM troglitazone and 3.8 μM Fx. The results indicated the potential of a chemotherapeutic effect of Fx in combination with troglitazone (Hosokawa et al. 2004). However, the underlying mechanisms have not been uncovered.

ATP-binding cassette (ABC) transporters are associated with multidrug resistance (MDR) by preventing the buildup of a toxic concentration of chemotherapeutic drugs in cancer cells, and combinations of cytotoxic drugs with nontoxic ABC transporter inhibitors represent a new approach to overcome drug resistance (Gottesman et al. 2002). Eia et al. found that Fx is effective at reversing MDR; it significantly and synergistically enhanced the cytotoxicity of eight drugs, including doxorubicin, vinblastine, amphotericin-B, paclitaxel, 5-fluorouracil (5-FU), cycloheximide, etoposide, and cisplatin, in Caco-2 cells (Eid et al. 2012). Furthermore, Fx was found to be a substrate of ABC transporters, especially of P-glycoprotein (P-gp), and to significantly decrease P-gp mRNA levels after 48 h of treatment in Caco-2 cells (Eid et al. 2012). These authors concluded that Fx could reverse MDR and enhance the effects of chemotherapeutic drugs by interfering with ABC transporters, which indicated the synergistic effects of Fx in combination with other traditional antitumor drugs (Eid et al. 2012).

A recent study by Ravi et al. (2018) demonstrated that 10 μM Fx loaded in chitosan (CS) + glycolipid (GL) nanogels (NGs) had greater anticancer activity than control treatments in Caco-2 cells. These authors found that cell viability was significantly lower in the GL NG group (50.5%) than in the micellar group (72.5%) over a 48 h exposure (Ravi et al. 2018). Furthermore, cellular Fx uptake showed a positive correlation in the CS + GL NG groups with enhanced caspase-3 activity (Ravi et al. 2018). Enhanced reactive oxygen species (ROS) generation, increased chromatin condensation and DNA fragmentation, Bcl-2 downregulation, Bax upregulation, and increased mitochondrial membrane polarization were all detected in this experimental group (Ravi et al. 2018). This study proved that CS + GL NGs are effective nanocarriers for Fx delivery to induce the apoptosis of Caco-2 cells and suggested the therapeutic potential of Fx with this nanocarrier (Ravi et al. 2018).

Liver cancer (Fig. 2)

Liver cancer is the second leading cause of cancer death in men in the world (Torre et al. 2015). Fx has been shown to significantly induce G1 arrest and the expression of GADD45, a cell cycle-related gene in human hepatocellular carcinoma HepG2 cells, via different patterns of MAPK signaling and the inhibition of cyclin D/CDK4 (Das et al. 2008; Satomi and Nishino 2009; Yoshiko and Hoyoku 2007). In human hepatocellular carcinoma SK-Hep-1 cells, Fx effectively induced G1 arrest and apoptosis by upregulating Cx32 and Cx43, resulting in enhanced gap junctional intercellular communication, which could increase intracellular calcium levels and cause cell cycle

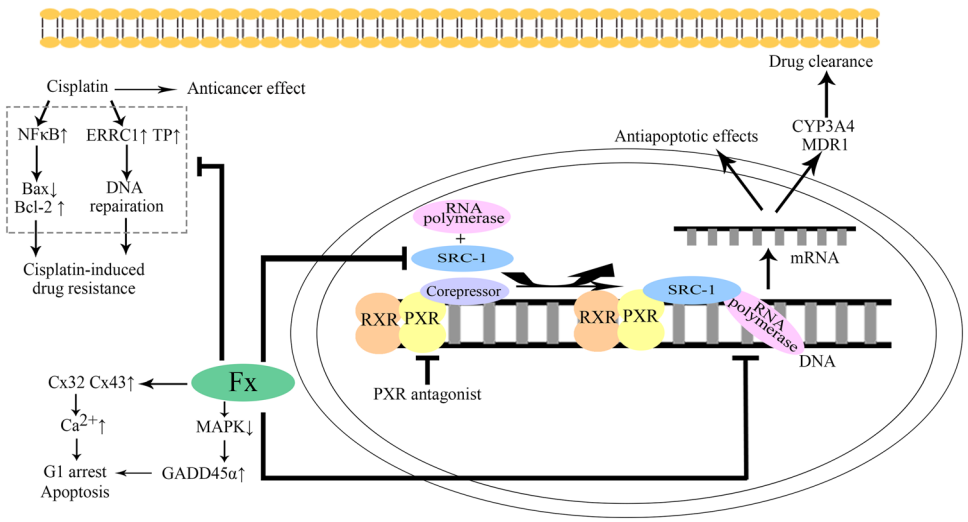

Fig. 2 The anticancer effects of Fx alone and combined with PXR antagonist and cisplatin in liver cancer

arrest and apoptosis (Liu et al. 2009). Pregnane X receptor (PXR) regulates drug clearance in the liver and intestine via the transcriptional regulation of xenobiotic-detoxifying enzymes and transporters, such as cytochrome P450 (CYP) and MDR1 (Dussault and Forman 2002). PXR activation was reported to have antiapoptotic effects in cancer cells (Gollamudi et al. 2008), and PXR antagonists can decrease cell proliferation (Miki et al. 2006). Liu et al. (2012) demonstrated that Fx markedly decreased PXR-mediated activation of the CYP3A4 promoter and rifampin-induced MDR1 expression in HepG2 cells. Furthermore, the interaction between PXR and its coactivator SRC-1 in HepG2 cells was significantly decreased after treatment with Fx for 24 h (Liu et al. 2012). These results illustrated that Fx decreases rifampin-induced CYP3A4 and MDR1 gene expression by attenuating PXR-mediated CYP3A4 promoter activation and the interaction between PXR and its coactivator, suggesting the potential of Fx as an adjuvant to prevent drug resistance in patients receiving chronic therapy with PXR antagonists (Liu et al. 2012).

Cisplatin is a traditional and widely used anticancer drug that enhances DNA repair and inhibits cell apoptosis (Cepeda et al. 2007; Go and Adjei 1999; Zorbas and Keppler 2005). However, its anticancer effect is limited by acquired or intrinsic resistance (Kartalou and Essigmann 2001). Liu et al. (2013) found that pretreatment with Fx followed by cisplatin treatment significantly decreased HepG2 cell proliferation compared to cisplatin treatment alone. Furthermore, this study demonstrated that Fx could improve the chemotherapeutic efficacy of cisplatin in HepG2 cells via two pathways: one, suppressing cisplatin-induced NFκB expression and increasing the NFκB-related Bax/Bcl-2 mRNA ratio; and two, attenuating the cisplatin-induced mRNA expression of excision repair cross complementation 1 (ERCC1) and thymidine phosphorylase (TP) regulated by ERK, p38, and PI3K/Akt. Thus, these data suggested the therapeutic potential of the combination of Fx and cisplatin in human hepatocellular cancer to decrease cisplatin-induced drug resistance (Liu et al. 2013).

Leukemia (Fig. 3)

Leukemia refers to a group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells. In adult T-cell leukemia (ATL), Fx induced G1 cell cycle arrest by decreasing the expression of cyclin D1, cyclin D2, CDK4, and CDK6 and inducing the expression of GADD45α (Ishikawa et al. 2008). Fx also induced ALT cell apoptosis by decreasing the expression of Bcl-2, XIAP, cIAP2, and other molecules in the survival and caspase-dependent pathways (Ishikawa et al. 2008). Moreover, Fx inhibited the activation of NFκB and activator protein-1 by suppressing IκBα phosphorylation and JunD expression (Ishikawa et al. 2008). In the human promyelocytic leukemia cell line HL-60, Fx was found to induce apoptosis by reducing the mitochondrial membrane potential and the cleavage of procaspase-3 and poly (ADP-ribose) polymerase without any effect on the protein levels of Bcl-2, Bcl-xL, or Bax (Kotake-Nara et al. 2005). However, others showed that Fx induced apoptosis via ROS mediated by the Bcl-xL pathway (Kim et al. 2010a).

Chronic myelogenous leukemia (CML) accounts for 15–20% of adult leukemia cases (Gu et al. 2012; Yin et al. 2004). As a BCR-ABL tyrosine kinase inhibitor, imatinib mesylate is the first-line therapy for most CML patients. It exerts a pronounced effect on CML by interacting with BCR-ABL ATP-binding sites and consequently inhibiting the phosphorylation of proteins linked to BCR-ABL signaling pathways (Gibson et al. 2013; Mahon et al. 2000). Doxorubicin, a type of anthracycline, is an clinical anticancer agent that inhibits DNA and RNA synthesis, inhibits topoisomerase II to create DNA double-strand breaks, and leads to free radical synthesis (Laroche-Clary et al. 2000; Lebrecht et al. 2004; Park et al. 2005; Thorn et al. 2011). Almeida et al. (2018) investigated the effect of Fx combined

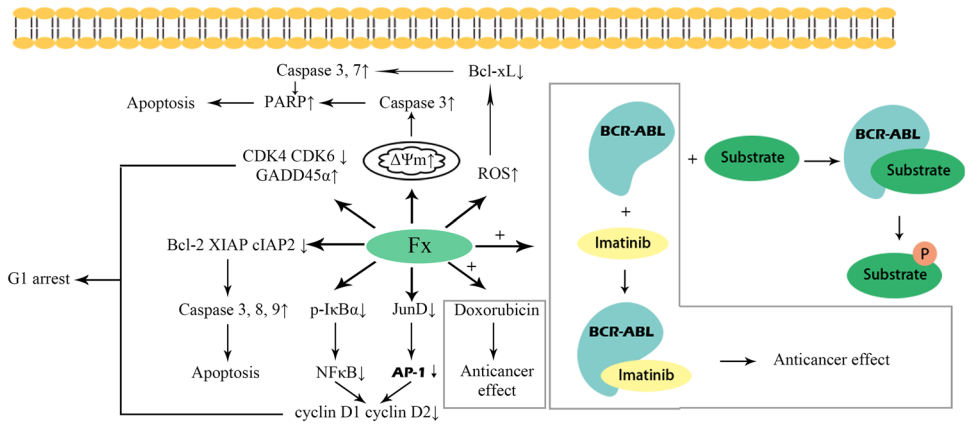

Fig. 3 The anticancer effects of Fx alone and combined with imatinib and doxorubicin in leukemia

with imatinib and doxorubicin on two different CML cell lines, K562 and TK6. Coincubation with 10 μM Fx and the two anticancer drugs caused a 30% increase in cytotoxicity in K562 cells and 56% and 51% inhibition of K562 and TK6 cell proliferation, respectively (Almeida et al. 2018). However, DNA damage did not significantly increase, and apoptosis was not detected, which means that the induction of apoptosis does not seem to be the main mechanism of the antiproliferative effect (Almeida et al. 2018). Although Fx combined with either imatinib or doxorubicin showed therapeutic potential in CML, the underlying mechanisms still need to be further studied.

Breast cancer (Fig. 4)

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide (Torre et al. 2015). Fx and its metabolite fucoxanthinol (Fxol) increased the apoptosis of the estrogen-sensitive cell line MCF-7 and the estrogen-resistant cell line MDA-MB-231 (Rwigemera et al. 2014). Fxol was found to inhibit p65, p50, RelB, and p52 in the NFκB pathway in MDA-MB-231 cells. SOX9 expression was highly correlated with cancer cell proliferation (Rwigemera et al. 2014). The decrease in nuclear SOX9 regulated by NFκB was also found in MDA-MB-231 cells upon treatment with both Fx and Fxol (Matheu et al. 2012; Saegusa et al. 2012; Sun et al. 2013).

Vijay et al. (2018) evaluated the cytotoxicity of four carotenoids, including Fx, β-carotene, lutein, and astaxanthin, in the presence and absence of the minimal cytotoxic dose of doxorubicin in both MCF-7 and MDA-MB-231 cells and discovered that these combinations of carotenoids and doxorubicin significantly reduced cell viability compared to carotenoid or doxorubicin alone at the same concentration. β-Carotene and lutein were used for further mechanistic studies, which revealed that cotreatment with these two carotenoids and low-dose doxorubicin could increase lipid peroxides and ROS levels (Vijay et al. 2018). Furthermore, mitochondrial dysfunction; G1 arrest; caspase signaling; increases in p53, p21, p27, and Bax; and decreases in Bcl-2 and cyclin D1 were detected (Vijay et al. 2018). Meanwhile, the combination of carotenoids and doxorubicin did not show marked cytotoxicity in normal breast epithelial cells (Vijay et al. 2018). These results demonstrated that doxorubicin combined with carotenoids could obviously enhance oxidative stress-mediated apoptosis in breast cancer compared with either carotenoid or doxorubicin alone, and the synergistic effect of this combination could be a new therapeutic strategy for breast cancer (Vijay et al. 2018). Although the mechanisms of the Fx and doxorubicin combination were not elucidated in this previous study, the similar results for β-carotene or lutein combined with doxorubicin suggest that Fx combined with doxorubicin might function via a similar mechanism because Fx is also a member of the carotenoid family. The combination of Fx and doxorubicin was clearly cytotoxic to breast cancer cell lines in the experiments. Therefore, the therapeutic potential of Fx combined with doxorubicin in breast cancer should not be ignored.

Cervical cancer (Fig. 5)

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death among females in less developed countries (Torre et al. 2015). Hou et al. (2013) discovered that Fx could induce G1 arrest and autophagy. The inhibition of phosphorylated Akt and its downstream target, mTOR, was demonstrated to contribute to the initiation of autophagy (Aoki et al. 2007). Fx was found to attenuate the phosphorylation of Akt and its downstream proteins p53, p70S6K, and mTOR and to enhance the expression of PTEN (Hou et al. 2013). These results demonstrated that Fx induces autophagy-dependent cytotoxicity in HeLa cells through inhibition of the Akt/mTOR signaling pathway (Hou et al. 2013).

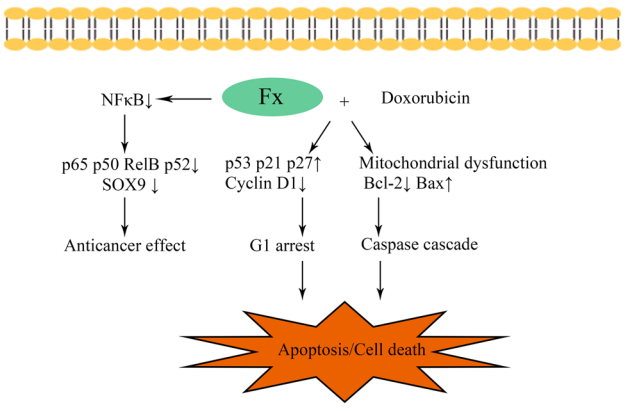

Fig. 4 The anticancer effects of Fx alone and combined with doxorubicin in breast cancer

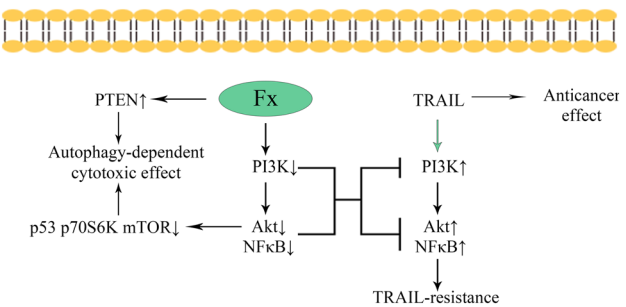

Fig. 5 The anticancer effects of Fx alone and combined with TRAIL in cervical cancer

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a member of the tumor necrosis factor (TNF) family, can selectively induce cancer cell death (Lemke et al. 2014). However, some cancers gradually become resistant to TRAIL, which limits its anticancer application (Trivedi and Mishra 2015; Wang et al. 2014). Ye et al. (2017) demonstrated that the TRAIL-resistant CaSki subline showed an increase in the PI3K/Akt pathway and was more sensitive to TRAIL combined with either Fx or an Akt inhibitor than to Fx or TRAIL alone, suggesting that the combination of TRAIL with Fx could sensitize TRAIL-resistant cervical cancer cells by inhibiting the PI3K/Akt pathway. Consistent with the above study, Jin et al. (2018) found that PI3K/Akt/NFκB pathway activation was enhanced by TRAIL alone but significantly suppressed by Fx in SiHa cells. Moreover, PI3K and NFκB inhibitors significantly downregulated apoptosis induced by Fx, TRAIL or Fx plus TRAIL (Jin et al. 2018). These two studies jointly demonstrated that the combination of Fx and TRAIL could enhance the apoptosis of cervical cancer cells, especially of TRAIL-resistant cervical cancer cells, via the PI3K/Akt/NFκB pathway and suggested the therapeutic potential of this combination (Jin et al. 2018; Ye et al. 2017).

Studies in vivo

Single and repeated oral dose toxicity study of Fx has conducted in mice (Beppu et al. 2009b). Both single dose study (1000 and 2000 mg/kg) and repeated dose study for 30 days (500 and 1000 mg/kg daily) exhibited no mortality and no abnormalities in gross appearance (Beppu et al. 2009b). Mutagenicity of orally administered Fx (500, 1000 and 2000 mg/kg) was also conducted in mice and the mutagenicity was negative at all doses (Beppu et al. 2009a). Another study conducted single oral and 13-week toxicity studies of Fx in rats which exhibited no mortality and abnormalities in fucoxanthin-administered groups either (Iio et al. 2011). As a result, Fx was proved to have no toxicity to bodies.

An in vivo experiment was conducted on mice using Fxol (the metabolite of Fx) (Terasaki et al. 2017) to test its effects on colon cancer. The suspension of single cells that were dissociated from sphere-forming colorectal cancer cells was injected onto the backbone of NOD-SCID mice (Terasaki et al. 2017). After 2 weeks, there was little difference in body weight between the Fxol and control groups (Terasaki et al. 2017); however, the tumors in the Fxol group were smaller after 8 days of treatment and was significantly smaller after 10 days of treatment than those in the control group (Terasaki et al. 2017). To test the effects of Fxol on leukemia, SCID mice were inoculated with HUT-102 and administered Fxol (Ishikawa et al. 2008). During the 4-week treatment, both the Fxol and control groups showed no adverse effects in general appearance, body weight, and food intake. The tumors in the Fxol group were significantly smaller after 14 days of treatment and weighed significantly less when excised than those in the control group (Ishikawa et al. 2008). The level of the surrogate marker (sIL-2Rα) in serum was significantly lower, and TUNEL assays showed more apoptotic cells of the tumor, in the Fxol group (Ishikawa et al. 2008) than in the control group. To test its effect on cervical cancer, Fx alone, TRAIL alone, and Fx plus TRAIL were administered to nude mice, which had been injected CaSKi cells into posterior flanks (Ye et al. 2017). Although both TRAIL alone and Fx alone groups suppressed tumor growth, the comparison of the volume of the tumors in the Fx plus TRAIL group with that in the TRAIL alone, Fx alone, and control groups demonstrated that the combination of Fx and TRAIL exhibited stronger anticancer effects (Ye et al. 2017). Other experiments in vivo of Fx or Fxol conducted in lymphoma (Yamamoto et al. 2011), melanoma (Kim et al. 2013), lung cancer (Mei et al. 2017), glioblastoma (Liu et al. 2016), and sarcoma (Wang et al. 2012), exhibit similar results. These animal experiments indicated the anticancer efficacy of Fx or Fxol alone or combined with other drugs and its great clinical potential.

Conclusion

A previous review discussed the anticancer effect of Fx and Fxol in different types of cancer and mentioned that combination treatments of Fx and Fxol with anticancer drugs may lead to important new therapeutic strategies with limited risk of MDR in many types of cancer (Martin 2015). In this review, we mainly focused on the effect of Fx in combination with other drugs in both drug-resistant and nondrug-resistant cancers. As summarized in Table 1, the anticancer effects and mechanisms of Fx combined with other drugs are diverse. Although Fx alone has a significant anticancer effect, combinations with other drugs could enhance the effect of both Fx and the other drug or reduce the dose without reducing the effect (e.g., as mentioned above for troglitazone and doxorubicin), which may create more effective and less harmful therapeutic strategies. And Fx has showed no toxicity and great anticancer efficacy in animal experiments, there is great clinical potential of Fx to become a novel adjuvant drug in cancer therapy.

This is the first review focusing on the effects of Fx in combination with other drugs, which broadens the application of Fx as an anticancer drug and provides guiding significance for future studies.

This review has limitations. There have been few studies on Fx combined with other drugs, and these studies have been conducted in only five types of cancer. However, the studies mentioned above reveal significant effects of

Table 1 Anticancer effects of Fx combined with various drugs in different types of cancer

Cancer type	Combination drugs	Effects of Fx	Mechanisms
Colon cancer	Troglitazone	Enhancing the reduction in cell viability	Unknown
	5-FU, vinblastine, etc.	Reversing multidrug resistance	Interfering with ATP-binding cassette transporters to decrease P-gp mRNA levels
	Packing with CS + GL NGs	Inducing apoptosis	Increasing the drug concentration in cells
Liver cancer	PXR antagonists	Attenuating CYP3A4 and MDR1 gene expression	Attenuating PXR-mediated CYP3A4 promoter activation and the interaction between PXR and a coactivator
	Cisplatin	Decreasing cisplatin-induced drug resistance	Inhibiting NFκB expression and attenuating DNA repair systems
Leukemia	Imatinib and doxorubicin	Enhancing the antiproliferative effect	Unknown but might not be through inducing apoptosis
Breast cancer	Doxorubicin	Enhancing G1 arrest and apoptosis	Increasing lipid peroxides and ROS levels to enhance oxidative stress-mediated apoptosis
Cervical cancer	TRAIL	Reversing TRAIL resistance	Suppressing the PI3K/Akt/NFκB pathway

The discovered mechanisms are also present

Fx in combination with other drugs, which could attract more attention to this combination and its potential for application in other types of cancer. In addition, it seems difficult to obtain consensus on the anticancer mechanisms of Fx combined with other drugs from the results of previous studies. This might be because the structure of Fx is complex, and structure–activity relationship studies have revealed various potential targeting molecules. This hypothesis can also explain the various health benefits of Fx, such as the anti-inflammatory and antiobesity activity, as mentioned in the introduction. Moreover, most of these experiments were performed in vitro, and more animal experiments should be conducted to explore the anticancer effect of Fx in vivo. Studies have shown that most dietary Fx may be converted to Fxol in rats (Sangeetha et al. 2010; Sugawara et al. 2002), indicating that the anticancer effects of Fxol combined with other drugs should also be considered.

Taken together, these current findings suggest that Fx combined with other drugs has significant anticancer effects by various mechanisms and could be a potential therapeutic strategy for different types of cancer.

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Compliance with ethical standards

Conflict of interest Authors declare that he/she have no conflict of interest.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

References

Almeida TP, Ferreira J, Vettorazzi A, Azqueta A, Rocha E, Ramos AA (2018) Cytotoxic activity of fucoxanthin, alone and in combination with the cancer drugs imatinib and doxorubicin, in CML cell lines. Environ Toxicol Pharmacol 59:24–33. https://doi.org/10.1016/j.etap.2018.02.006

Aoki H, Takada Y, Kondo S, Sawaya R, Aggarwal BB, Kondo Y (2007) Evidence that curcumin suppresses the growth of malignant gliomas in vitro and in vivo through induction of autophagy: role of Akt and extracellular signal-regulated kinase signaling pathways. Mol Pharmacol 72:29–39. https://doi.org/10.1124/mol.106.033167

Beppu F, Niwano Y, Sato E, Kohno M, Tsukui T, Hosokawa M, Miyashita K (2009a) In vitro and in vivo evaluation of mutagenicity of fucoxanthin (FX) and its metabolite fucoxanthinol (FXOH). J Toxicol Sci 34:693–698

Beppu F, Niwano Y, Tsukui T, Hosokawa M, Miyashita K (2009b) Single and repeated oral dose toxicity study of fucoxanthin (FX), a marine carotenoid, in mice. J Toxicol Sci 34:501–510

Brockman JA, Gupta RA, Dubois RN (1998) Activation of PPAR-gamma leads to inhibition of anchorage-independent growth of human colorectal cancer cells. Gastroenterology 115:1049–1055

Cepeda V, Fuertes MA, Castilla J, Alonso C, Quevedo C, Perez JM (2007) Biochemical mechanisms of cisplatin cytotoxicity. Anticancer Agents Med Chem 7:3–18

Das SK et al (2005) Fucoxanthin induces cell cycle arrest at G0/G1 phase in human colon carcinoma cells through up-regulation of p21WAF1/Cip1. Biochim Biophys Acta 1726:328–335. https://doi.org/10.1016/j.bbagen.2005.09.007

Das SK, Hashimoto T, Kanazawa K (2008) Growth inhibition of human hepatic carcinoma HepG2 cells by fucoxanthin is associated with down-regulation of cyclin D. Biochim Biophys Acta 1780:743–749. https://doi.org/10.1016/j.bbagen.2008.01.003

Dussault I, Forman BM (2002) The nuclear receptor PXR: a master regulator of "homeland" defense. Crit Rev Eukaryot Gene Expr 12:53–64

Eid SY, El-Readi MZ, Wink M (2012) Carotenoids reverse multidrug resistance in cancer cells by interfering with ABC-transporters. Phytomedicine 19:977–987. https://doi.org/10.1016/j.phymed.2012.05.010

Gibson J, Iland HJ, Larsen SR, Brown CM, Joshua DE (2013) Leukaemias into the 21st century. Part 2: the chronic leukaemias. Intern Med J 43:484–494. https://doi.org/10.1111/imj.12135

Go RS, Adjei AA (1999) Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 17:409–422. https://doi.org/10.1200/jco.1999.17.1.409

Gollamudi R, Gupta D, Goel S, Mani S (2008) Novel orphan nuclear receptors-coregulator interactions controlling anti-cancer drug metabolism. Curr Drug Metab 9:611–613

Gottesman MM, Fojo T, Bates SE (2002) Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer 2:48–58. https://doi.org/10.1038/nrc706

Gu Y et al (2012) CaMKII gamma, a critical regulator of CML stem/progenitor cells, is a target of the natural product berbamine. Blood 120:4829–4839. https://doi.org/10.1182/blood-2012-06-434894

Hosokawa M, Kudo M, Maeda H, Kohno H, Tanaka T, Miyashita K (2004) Fucoxanthin induces apoptosis and enhances the antiproliferative effect of the PPARgamma ligand, troglitazone, on colon cancer cells. Biochim Biophys Acta 1675:113–119. https://doi.org/10.1016/j.bbagen.2004.08.012

Hou L-l, Gao C, Chen L, Hu G-q, Xie S-q (2013) Essential role of autophagy in fucoxanthin-induced cytotoxicity to human epithelial cervical cancer HeLa cells. Acta Pharmacol Sin 34:1403–1410. https://doi.org/10.1038/aps.2013.90

Iio K, Okada Y, Ishikura M (2011) Single and 13-week oral toxicity study of fucoxanthin oil from microalgae in rats. Shokuhin eiseigaku zasshi J Food Hyg Soc Jpn 52:183–189

Ishikawa C et al (2008) Antiadult T-cell leukemia effects of brown algae fucoxanthin and its deacetylated product, fucoxanthinol. Int J Cancer 123:2702–2712. https://doi.org/10.1002/ijc.23860

Jin Y, Qiu S, Shao N, 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. Med Sci Monit 24:11–18. https://doi.org/10.12659/msm.905360

Kartalou M, Essigmann JM (2001) Mechanisms of resistance to cisplatin. Mutat Res 478:23–43

Kim K-N, Heo S-J, Kang S-M, Ahn G, Jeon Y-J (2010a) Fucoxanthin induces apoptosis in human leukemia HL-60 cells through a ROS-mediated Bcl-xL pathway. Toxicol In Vitro 24:1648–1654. https://doi.org/10.1016/j.tiv.2010.05.023

Kim KN, Heo SJ, Yoon WJ, Kang SM, Ahn G, Yi TH, Jeon YJ (2010b) Fucoxanthin inhibits the inflammatory response by suppressing the activation of NF-kappaB and MAPKs in lipopolysaccharide-induced RAW 264.7 macrophages. Eur J Pharmacol 649:369–375. https://doi.org/10.1016/j.ejphar.2010.09.032

Kim K-N et al (2013) Inhibition of tumor growth in vitro and in vivo by fucoxanthin against melanoma B16F10 cells. Environ Toxicol Pharmacol 35:39–46. https://doi.org/10.1016/j.etap.2012.10.002

Kotake-Nara E, Terasaki M, Nagao A (2005) Characterization of apoptosis induced by fucoxanthin in human promyelocytic leukemia cells. Biosci Biotechnol Biochem 69:224–227. https://doi.org/10.1271/bbb.69.224

Laroche-Clary A, Larrue A, Robert J (2000) Down-regulation of bcr-abl and bcl-x(L) expression in a leukemia cell line and its doxorubicin-resistant variant by topoisomerase II inhibitors. Biochem Pharmacol 60:1823–1828

Lebrecht D, Setzer B, Rohrbach R, Walker UA (2004) Mitochondrial DNA and its respiratory chain products are defective in doxorubicin nephrosis. Nephrol Dial Transplant 19:329–336

Lemke J, von Karstedt S, Zinngrebe J, Walczak H (2014) Getting TRAIL back on track for cancer therapy. Cell Death Differ 21:1350–1364. https://doi.org/10.1038/cdd.2014.81

Liu C-L, Huang Y-S, Hosokawa M, Miyashita K, 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. Chem Biol Interact 182:165–172. https://doi.org/10.1016/j.cbi.2009.08.017

Liu C-L, Lim Y-P, Hu M-L (2012) Fucoxanthin attenuates rifampin-induced cytochrome P450 3A4 (CYP3A4) and multiple drug resistance 1 (MDR1) gene expression through pregnane X receptor (PXR)-mediated pathways in human hepatoma HepG2 and colon adenocarcinoma LS174T cells. Mar Drugs 10:242–257. https://doi.org/10.3390/md10010242

Liu C-L, Lim Y-P, Hu M-L (2013) Fucoxanthin enhances cisplatin-induced cytotoxicity via NFκB-mediated pathway and downregulates DNA repair gene expression in human hepatoma HepG2 cells. Mar Drugs 11:50–66. https://doi.org/10.3390/md11010050

Liu Y, Zheng J, Zhang Y, Wang Z, Yang Y, Bai M, 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. Neurochem Res 41:2728–2751. https://doi.org/10.1007/s11064-016-1989-7

Maeda H, Hosokawa M, Sashima T, Funayama K, Miyashita K (2005) Fucoxanthin from edible seaweed, Undaria pinnatifida, shows antiobesity effect through UCP1 expression in white adipose tissues. Biochem Biophys Res Commun 332:392–397. https://doi.org/10.1016/j.bbrc.2005.05.002

Mahon FX, Deininger MW, Schultheis B, Chabrol J, Reiffers J, Goldman JM, Melo JV (2000) Selection and characterization of BCR-ABL positive cell lines with differential sensitivity to the tyrosine kinase inhibitor STI571: diverse mechanisms of resistance. Blood 96:1070–1079

Martin L (2015) Fucoxanthin and its metabolite fucoxanthinol in cancer prevention and treatment. Mar Drugs 13:4784–4798. https://doi.org/10.3390/md13084784

Matheu A et al (2012) Oncogenicity of the developmental transcription factor Sox9. Cancer Res 72:1301–1315. https://doi.org/10.1158/0008-5472.can-11-3660

Mayne ST (1996) Beta-carotene, carotenoids, and disease prevention in humans. FASEB J 10:690–701

Mei C, Zhou S, Zhu L, Ming J, Zeng F, Xu R (2017) Antitumor effects of laminaria extract fucoxanthin on lung cancer. Mar drugs. https://doi.org/10.3390/md15020039

Miki Y et al (2006) Expression of the steroid and xenobiotic receptor and its possible target gene, organic anion transporting polypeptide-A, in human breast carcinoma. Cancer Res 66:535–542. https://doi.org/10.1158/0008-5472.can-05-1070

Nishikawa S, Hosokawa M, Miyashita K (2012) Fucoxanthin promotes translocation and induction of glucose transporter 4 in skeletal muscles of diabetic/obese KK-A(y) mice. Phytomedicine 19:389–394. https://doi.org/10.1016/j.phymed.2011.11.001

Nishino H, Murakoshi M, Tokuda H, Satomi Y (2009) Cancer prevention by carotenoids. Arch Biochem Biophys 483:165–168. https://doi.org/10.1016/j.abb.2008.09.011

Park SS, Eom YW, Choi KS (2005) Cdc2 and Cdk2 play critical roles in low dose doxorubicin-induced cell death through mitotic catastrophe but not in high dose doxorubicin-induced apoptosis. Biochem Biophys Res Commun 334:1014–1021. https://doi.org/10.1016/j.bbrc.2005.06.192

Ravi H, Kurrey N, Manabe Y, Sugawara T, Baskaran V (2018) Polymeric chitosan-glycolipid nanocarriers for an effective delivery of marine carotenoid fucoxanthin for induction of apoptosis in human

colon cancer cells (Caco-2 cells). Mater Sci Eng C Mater Biol Appl 91:785–795. https://doi.org/10.1016/j.msec.2018.06.018

Rwigemera A, Mamelona J, Martin LJ (2014) 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 30:157–167. https://doi.org/10.1007/s10565-014-9277-2

Saegusa M, Hashimura M, Suzuki E, Yoshida T, Kuwata T (2012) Transcriptional up-regulation of Sox9 by NF-kappaB in endometrial carcinoma cells, modulating cell proliferation through alteration in the p14(ARF)/p53/p21(WAF1) pathway. Am J Pathol 181:684–692. https://doi.org/10.1016/j.ajpath.2012.05.008

Sangeetha RK, Bhaskar N, Divakar S, Baskaran V (2010) Bioavailability and metabolism of fucoxanthin in rats: structural characterization of metabolites by LC-MS (APCI). Mol Cell Biochem 333:299–310. https://doi.org/10.1007/s11010-009-0231-1

Satomi Y, Nishino H (2009) Implication of mitogen-activated protein kinase in the induction of G1 cell cycle arrest and gadd45 expression by the carotenoid fucoxanthin in human cancer cells. Biochim Biophys Acta 1790:260–266. https://doi.org/10.1016/j.bbagen.2009.01.003

Shimada T, Kojima K, Yoshiura K, Hiraishi H, Terano A (2002) Characteristics of the peroxisome proliferator activated receptor gamma (PPARgamma) ligand induced apoptosis in colon cancer cells. Gut 50:658–664

Slattery ML, Benson J, Curtin K, Ma KN, Schaeffer D, Potter JD (2000) Carotenoids and colon cancer. Am J Clin Nutr 71:575–582. https://doi.org/10.1093/ajcn/71.2.575

Sugawara T, Baskaran V, Tsuzuki W, Nagao A (2002) Brown algae fucoxanthin is hydrolyzed to fucoxanthinol during absorption by Caco-2 human intestinal cells and mice. J Nutr 132:946–951. https://doi.org/10.1093/jn/132.5.946

Sun L et al (2013) Epigenetic regulation of SOX9 by the NF-kappaB signaling pathway in pancreatic cancer stem cells. Stem Cells (Dayton Ohio) 31:1454–1466. https://doi.org/10.1002/stem.1394

Takahashi K, Hosokawa M, Kasajima H, Hatanaka K, Kudo K, Shimoyama N, Miyashita K (2015) Anticancer effects of fucoxanthin and fucoxanthinol on colorectal cancer cell lines and colorectal cancer tissues. Oncol Lett 10:1463–1467. https://doi.org/10.3892/ol.2015.3380

Terasaki M, Maeda H, Miyashita K, Tanaka T, Miyamoto S, Mutoh M (2017) A marine bio-functional lipid, fucoxanthinol, attenuates human colorectal cancer stem-like cell tumorigenicity and sphere formation. J Clin Biochem Nutr 61:25–32. https://doi.org/10.3164/jcbn.16-112

Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE, Altman RB (2011) Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenet Genom 21:440–446. https://doi.org/10.1097/FPC.0b013e32833ffb56

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108. https://doi.org/10.3322/caac.21262

Trivedi R, Mishra DP (2015) Trailing TRAIL resistance: novel targets for TRAIL sensitization in cancer cells. Front Oncol 5:69. https://doi.org/10.3389/fonc.2015.00069

Vijay K et al (2018) Low-dose doxorubicin with carotenoids selectively alters redox status and upregulates oxidative stress-mediated apoptosis in breast cancer cells. Food Chem Toxicol 118:675–690. https://doi.org/10.1016/j.fct.2018.06.027

Wang J, Chen S, Xu S, Yu X, Ma D, Hu X, 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. Mar Drugs 10:2055–2068. https://doi.org/10.3390/md10092055

Wang F, Lin J, Xu R (2014) The molecular mechanisms of TRAIL resistance in cancer cells: help in designing new drugs. Curr Pharm Des 20:6714–6722

Yamamoto K, Ishikawa C, Katano H, Yasumoto T, Mori N (2011) Fucoxanthin and its deacetylated product, fucoxanthinol, induce apoptosis of primary effusion lymphomas. Cancer Lett 300:225–234. https://doi.org/10.1016/j.canlet.2010.10.016

Ye GL, Du DL, Jin LJ, Wang LL (2017) Sensitization of TRAIL-resistant cervical cancer cells through combination of TRAIL and fucoxanthin treatments. Eur Rev Med Pharmacol Sci 21:5594–5601

Yin T et al (2004) Combined effects of As4S4 and imatinib on chronic myeloid leukemia cells and BCR-ABL oncoprotein. Blood 104:4219–4225. https://doi.org/10.1182/blood-2004-04-1433

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

Zhang L et al (2017) Fucoxanthin provides neuroprotection in models of traumatic brain injury via the Nrf2-ARE and Nrf2-autophagy pathways. Sci Rep 7:46763. https://doi.org/10.1038/srep46763

Zorbas H, Keppler BK (2005) Cisplatin damage: are DNA repair proteins saviors or traitors to the cell? Chembiochem Eur J Chem Biol 6:1157–1166. https://doi.org/10.1002/cbic.200400427