MINI-REVIEW

Anti-Cancer Mechanism and Possibility of Nano-Suspension Formulation for a Marine Algae Product Fucoxanthin

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Abstract

Recently, use of natural products available from marine sources, and especially algae products, are receiving more attention. Scientific evidence for claimed nutraceutical and therapeutical effects of one such marine algae product, fucoxanthin, is discussed in this paper with a summary of the currently available literature regarding its antioxidant, anti-obesity and anticancer activities. It is safe for use in humans, but as it has poor solubility a nano-suspension mode of delivery may be adopted to improve efficacy of supplments. We conclude from ourliterature review that the marine algae product fucoxanthin has significant antioxidant, anti-obesity and anticancer activity with established mechanisms of action.

Keywords: Anti-cancer mechanism - antioxidant activity - anti-obesity - fucoxanthin - marine algae

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Introduction

The marine carotenoid fucoxanthin (FX) can be found in marine brown seaweeds, macro algae, microalgae, diatoms and has significant biological properties. Numerous studies have shown that fucoxanthin has considerable potential and promising applications in human health (Peng et al., 2011). FX is a xanthophyll present in brown algae, it is an orange-colored pigment of edible brown algae consumed in Eastern Asia suppress carcinogenesis and obesity in rodents (Yonekura et al., 2010).

FX has been attributed with extraordinary potential for protecting the organism against a wide range of diseases (Kim and Pangestuti, 2011). In the prevention and treatment of cancer antioxidants and anti-obesity therapies play vital role. FX not only directly acts on tumor cell but also prevents the formation of cancer cells due to oxidative stress and obesity. Many of the studies showed that FX could be used as therapy for oxidative stress and obesity. FX acts directly on fat tissues and promote the heat production which depletes the fat deposition in adipose tissues.

Antioxidant Activity

Marine algae contain a wide variety of bioactive compounds; many of them have commercial applications in pharmaceutical, medical, cosmetic, nutraceutical, food and agricultural industries. Natural antioxidants, found in many algae play an important role against various diseases through protection of cells from oxidative damage (Kelman et al., 2012). Marine food products contain carotenoids (asthaxantin, lutein, beta-carotene, fucoxanthin), have shown an antioxidant effect in reducing oxidative markers stress (Riccioni, 2012).

FX has the ability to protect against oxidative stress induced by UV-B radiation and which might be applied to antioxidant and cosmeceutical industries (Heo and Jeon, 2009; Sangeetha et al., 2009) demonstrated that FX has greater potential than beta-carotene in modulating lipid peroxidation, catalase and glutathione transferase in plasma and liver of retinol deficiency rats. Fucoxanthin prevents skin photoaging in UVB-irradiated hairless mice, possibly via antioxidant and antiangiogenic effects on topical treatment (Urikura et al., 2011). FX showed strong antioxidant activity which is attributed to quenching singlet oxygen and scavenging free radicals (Miyashita, 2009).

FX extracts exhibited antioxidant activity in noncellular systems and in activated RAW 264.7 macrophages, as well as in ex vivo assays in plasma and erythrocytes, after the 4 week treatment in rats (Zaragoza et al., 2008). The antioxidant activities of FX was assessed in vitro with respect to radical scavenging and singlet oxygen quenching abilities and hydroxyl radical scavenging was assessed by the electron spin resonance (ESR) technique. Both analyses showed the superoxide radical scavenging activity (Sachindra et al., 2007).

Anti-obesity Activity

Obesity is the leading metabolic disorder with rapidly growing prevalence throughout the world. As it could

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lead to heart failure, Liver disease and cancer, there is an urgent need to find a suitable drug for lifelong use. Recent research shows only a few molecular targets are more successful for anti-obesity prevention and treatment. One of the keys is the action on the uncoupling proteins found in mitochondria of abdominal white adipose tissue (WAT) which oxidize fatty acids to produce heat (Miyashita et al., 2011).

In this direction the use of plants and edible seaweeds are better than synthetic drugs the later that cause adverse effects in long term treatment. Brown seaweeds contain Fucoxanthin is known to reduce excess fat. Administration of fucoxanthin produced anti-obesity effects by reducing the expression of uncoupling proteins UCP1 and UCP1 (Okada et al., 2011). Fucoxanthin is converted to fucoxanthinol and amarouciaxanthin-A. This metabolite of fucoxanthin in white adipose tissue suppresses adipocyte differentiation and development (Yim et al., 2011; Lai et al., 2012) investigated the inhibitory effects of fucoxanthin, on the differentiation of preadipocytes and recognized as triacylglycerol-lowering agent in humans which is also observed by (Hu et al., 2012).

Anticancer Mechanism

Carotenoids are natural fat-soluble pigments that provide bright coloration to plants and animals. Various carotenoids, such as beta-carotene, a-carotene, lycopene, lutein, zeaxanthin, beta-cryptoxanthin, fucoxanthin, canthaxanthin and astaxanthin, have been proven to have anti-carcinogenic activity in several tissues. Preclinical studies have shown that some carotenoids have potent antitumor effects both in vitro and in vivo models. Since chemoprevention is one of the most important strategies in the control of cancer development, molecular mechanism-based cancer chemoprevention using carotenoids seems to be an attractive approach (Tanaka et al., 2012).

Fucoxanthin inhibited the growth of LNCap prostate cancer cells in a dose-dependent manner. FX activated c-Jun N-terminal kinase (SAPK/JNK), while the inhibition of SAPK/JNK attenuated the induction of G (1) arrest and GADD45A expression by fucoxanthin (Satomi, 2012). Fucoxanthin treatments was found to induce apoptosis through caspase-3 activation in PC-3 human prostate cancer cells (Kotake-Nara et al., 2005). FX has strong antioxidant and cytotoxicity against breast cancer (MCF-7) with IC_{50}=11.5 mug/ml and concluded that FX could be used as antioxidant and as an antitumor compound (Ayyad et al., 2011). Human gastric adenocarcinoma MGC-803 cells when treated with FX, fucoxanthin (50 or 75 muM) increased the ratio of cell in G2/M phase and apoptotic MGC-803 cells on a dose-dependent manner (Yu et al., 2011). When a human prostate cancer cells, PC-3, DU 145 and LNCap, were evaluated with carotenoid-supplemented medium for 72 h at 20 micro mol/L, 5,6-monoepoxy carotenoids. Results suggested that fucoxanthin have the potential to reduce the risk of prostate cancer (Kotake-Nara et al., 2001).

Yamamoto et al. (2011) evaluated the anti-Primary effusion lymphoma (PEL) with FX and its metabolite, fucoxanthinol (FXOH). Treatment of PEL cells with FX or FXOH induced cell cycle was arrested during G phase and caspase-dependent apoptosis. They also silenced NF-kappa B, AP-1 and Akt activation, in conjunction with down-regulation of anti-apoptotic proteins and cell cycle regulators and resulted the reduced growth of PEL-cell tumors. Study showed that topical application of fucoxanthin (1%) significantly suppressed mRNA sexpression of cyclooxygenase (COX)-2, endothelin receptor A, p75 neurotrophin receptor (NTR), prostaglandin E receptor 1 (EP1), melanocortin 1 receptor (MC1R) and tyrosinase-related protein 1. The effect of FX on skin melanogenic mRNA expression was evaluated by real time reverse transcription polymerase chain reaction. FX inhibited tyrosinase activity, melanogenesis in melanoma and UVB-induced skin pigmentation (Shimoda et al., 2010). Fucoxanthin-induced apoptosis in human leukemia cell HL-60 cells triggered Bcl-xL signaling pathway in HL-60 cells. Study showed that ROS are generated during fucoxanthin-induced cytotoxicity and apoptosis in HL-60 cells. N-acetylcysteine (NAC), a ROS scavenger, was suppressed by fucoxanthin-induced cytotoxicity and apoptosis. Fucoxanthin induced the cleavage of caspases -3 and -7, and poly-ADP-ribose polymerase (PARP) and a decrease of Bcl-xL levels. It was demonstrated that FX generated ROS and that the accumulation of ROS performed a crucial role in the fucoxanthin-induced Bcl-xL signaling pathway (Kim et al., 2010).

Liu et al. (2009) hypothesized that fucoxanthin may cause cell cycle arrest and enhance gap junctional intercellular communication (GJIC) in SK-Hep-1 human hepatoma cells. Results revealed that FX strongly inhibited the proliferation of SK-Hep-1 cells at 24h of incubation. In SK-Hep-1 cells, fucoxanthin caused cell cycle arrest at G0/G1 phase and induced cell apoptosis. FX was found to be an antiproliferative against SK-Hep-1 cells and the effect is associated with up regulation of Cx32 and Cx43, which enhances GJIC of SK-Hep-1 cells.

Satomi and Nishino (2009) suggested that gadd45a is closely related with the G1 arrest induced by fucoxanthin, and that the pattern of MAPK involvement in the induction of gadd45a and G1 arrest by fucoxanthin differs its antiproliferative effect depending on the cell type. Zhang et al. (2008) determined antigrowth and apoptosis-induction activity of fucoxanthin from dietary Laminaria japonica against EJ-1 human bladder cancers. Fucoxanthin significantly reduced the cell viability in a dose- and time-dependent manner. The induction of apoptosis in EJ-1 cells was characterized by morphological changes, DNA ladder, and increased percentage of hypodiploid cells, activating caspase-3 activity.

Ishikawa et al. (2008) evaluated the anti- Adult T-cell leukemia (ATL) effects of fucoxanthin and its metabolite, fucoxanthinol. Both carotenoids inhibited cell viability of HTLV-1-infected T-cell lines and ATL cells, and fucoxanthinol was approximately twice more potent than fucoxanthin. Both carotenoids induced cell cycle arrest during G(1) phase by reducing the expression of cyclin D1, cyclin D2, CDK4 and CDK6, and inducing the expression of GADD45 alpha, and induced apoptosis by reducing the expression of Bcl-2, XIAP, cIAP2 and

survivin. The induced apoptosis was associated with activation of caspase-3, -8 and -9.

Safety Profile

As a part of safety evaluation, single and repeated oral dose toxicity study of FX was conducted (Beppu et al., 2009) In a single dose study, FX purified from seaweed was orally administered to male and female ICR mice at doses of 1,000 and 2,000 mg/kg. In a repeated doses study, FX at doses of 500 and 1,000 mg/kg was orally administered for 30 days. In both studies, no mortality and no abnormalities in gross appearance were observed. In the repeated doses study, histological observation revealed no abnormal changes in liver, kidney, spleen and gonadal tissues. FX extracts were shown to lack any relevant toxic effects in an acute toxicity test following a 4 week daily treatment in rats.

Novel Mode of Fucoxanthin Drug Delivery

Nano-suspensions have proved their efficiency in drug delivery system associated with water-insoluble and both water and lipid-insoluble drugs. They are unique because of their simplicity and best over other application strategies. They increase the dissolution velocity and saturation solubility of the drugs. Nano suspensions keeps pharmaceutical active ingredient as submicron colloidal particles in a liquid phase stabilized by added stabilizers.

Fucoxanthin is insoluble in water and least soluble (~10mg/ml) in Acetone/DMSO. It has good thermostability (80-100°C for one hour) and stable at wide pH range from acidic to basic condition. Acute toxicity (LD50) 60 mg/kg (2000 mg/kg for extract) was found to be non toxic. These high doses of Fucoxanthin extract and solubility properties are found to be hurdles in drug delivery system. This could be succeeded by Nano-suspensions formulation.

Conclusion

It is concluded that the literature reviewed showed the marine algae product fucoxanthin has significant antioxidant and anticancer activity. The experiments carried out by the most of the workers have established possible mechanism of action.

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