

Potential ability of xanthophylls to prevent obesity-associated cancer

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Abstract

Obesity-associated cancers, including colon cancer and breast cancer, are increasing in Asian countries with Westernized lifestyles as exemplified by reduced physical activity and increased fat/sugar consumption. An excessive accumulation of visceral adipose tissue causes insulin resistance, dyslipidemia and adipocytokine imbalance, and these factors are suggested to be involved in cancer promotion. To prevent obesity-associated cancers, researcher attention is increasing on the so-called "functional foods". In addition, new approaches to cancer control are in high demand, and using "functional foods" as supplemental or adjuvant agents in chemotherapy is thought to be a promising approach. One of these functional ingredients is xanthophylls, which are natural fat-soluble pigments found in fruits, vegetables, algae and other plants. Xanthophylls belong to the carotenoid class and have struc-

tures containing oxygen. Some studies have revealed that xanthophylls improve the inflammation status, serum triglyceride levels, blood pressure levels and liver function test values. Furthermore, recent studies show that xanthophylls possess high anti-cancer, anti-diabetic, anti-obesity and anti-oxidant properties. In this review, we highlight the recent findings for five xanthophylls, namely astaxanthin, β -cryptoxanthin, fucoxanthin, neoxanthin and zeaxanthin/lutein, and their relevance to cancer prevention.

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Key words: Cancer prevention; Xanthophylls

Core tip: Xanthophylls belong to the class of carotenoids, and are natural fat-soluble pigments found in fruits, vegetables, algae and so on. It has been shown that the versatile functions of xanthophylls have great potential for the prevention of metabolic syndrome and cancers. Xanthophylls have proved safety, and several xanthophylls provide other health benefits, including improvement of inflammation, dyslipidemia, hypertension and liver function. These findings indicate that xanthophylls could be useful to prevent obesity-associated cancer.

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INTRODUCTION

Obesity has recently attracted much interest as a risk factor for several cancers, such as breast cancer and colorectal cancer^[1,2]. Both metabolic syndrome that is characterized by obesity, hyperlipidemia, type 2 diabetes and hypertension

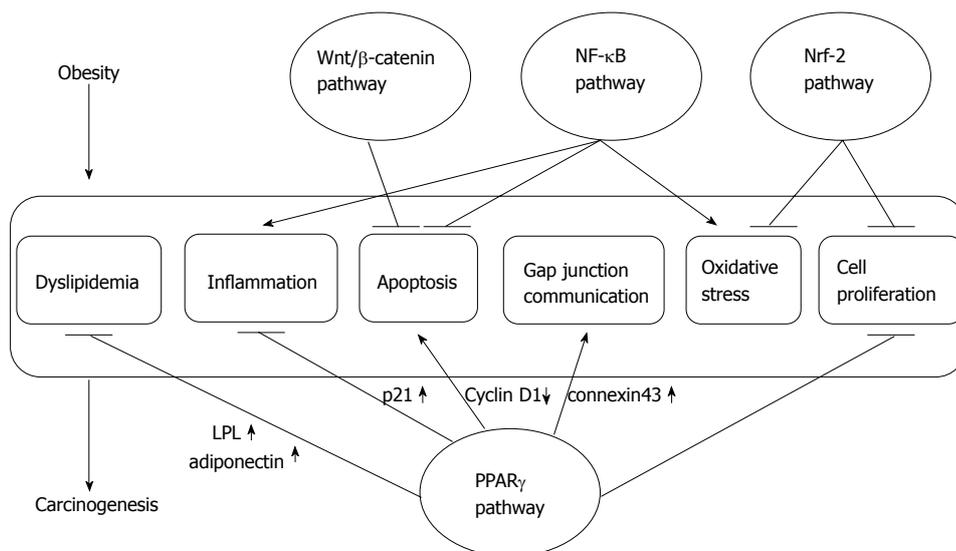


Figure 1 Possible mechanisms for obesity-associated cancer prevention. LPL: Lipoprotein lipase; NF-κB: Nuclear factor kappa B; Nrf2: Nuclear factor-erythroid 2 related factor 2; PPAR: Peroxisome proliferator-activated receptor.

Table 1 Obesity-associated cancers	
Type of cancer	
Breast (postmenopausal)	
Colorectum	
Endometrium	
Esophagus	
Gallbladder	
Kidney	
Pancreas	
Thyroid	

and obesity-associated cancers (Table 1) are extremely common in Western countries, and they are currently increasing in Eastern countries, including Japan. The factors linking obesity and cancer are becoming apparent, and they are insulin resistance, dyslipidemia and a subsequent adipocytokine imbalance (Figure 1)^[1,2]. Carotenoid intake is reported to be inversely associated with obesity and with the risk of many cancers^[3-6].

Carotenoids are fat-soluble pigments found in fruits, vegetables, algae and other plants. Humans cannot synthesize carotenoids, and we should therefore consume them as part of our diet. Carotenoids belong to the tetraterpenoid category, and they can be divided into xanthophylls and carotenes according to whether the structure contains oxygen or not. Carotenoids with structures containing oxygen are xanthophylls. As the name indicates, the color of xanthophylls is usually yellow, and they are usually lipophilic because of the long unsaturated aliphatic chain in their structure.

Because conventional chemotherapy has failed to reduce the mortality rates of common cancers, including obesity-associated cancers, new approaches to controlling the development of cancer are in great demand^[7]. One approach is the use of functional foods/plant-derived agents as supplemental or adjuvant agents in chemo-

therapy^[8,9]. Another approach is chemoprevention for the control of cancer development^[8,9]. In both methods, using xanthophylls seems to be an attractive approach. As shown in this review, xanthophylls provided health benefits, such as improvements in inflammation, dyslipidemia, hypertension and liver function. Moreover, the biological significance of xanthophylls as important candidates for the chemoprevention of cancer is becoming clearer, and the safety of xanthophylls has been affirmed, as described in this review. Another candidate called - carotene is the most abundant dietary carotenoid, and long-term supplementation with this compound has been shown to be ineffective for cancer chemoprevention in several recent large-scale intervention trials^[10-12].

In this review, we focus on recent findings for five xanthophylls as follows: astaxanthin, β-cryptoxanthin, fucoxanthin, neoxanthin and zeaxanthin/lutein, and their relevance to cancer prevention (Figure 2).

ASTAXANTHIN

Distribution and nature of astaxanthin

Astaxanthin (AX) is a natural fat-soluble red pigment and belongs to the xanthophyll subclass of carotenoids. Dietary sources of AX are eggs of salmon and trout, skin of red sea bream, crabs, shrimps and lobsters. AX is synthesized in microalgae (*Chlorella zofingiensis*, *Chlorococcum* and *Haematococcus pluvialis*). Krills (*Euphausia superba*) feed on the microalgae and in turn are fed upon by fishes. The microalga, *H. pluvialis*, is the main source of natural AX and is able to accumulate up to 4%AX on dry weight basis^[13-15]. AX extracted from *H. pluvialis* is used as a food dye in many countries. AX exists in stereoisomers and geometric isomers. *H. pluvialis* biosynthesizes the (3*S*, 3'*S*)-isomer, meanwhile *P. rhodozyma* biosynthesizes the (3*R*, 3'*R*)-isomer. AX has two hydroxyl groups and is able to react with fatty acids and proteins. AX is found as free, mono- and di-ester forms in organisms^[13].

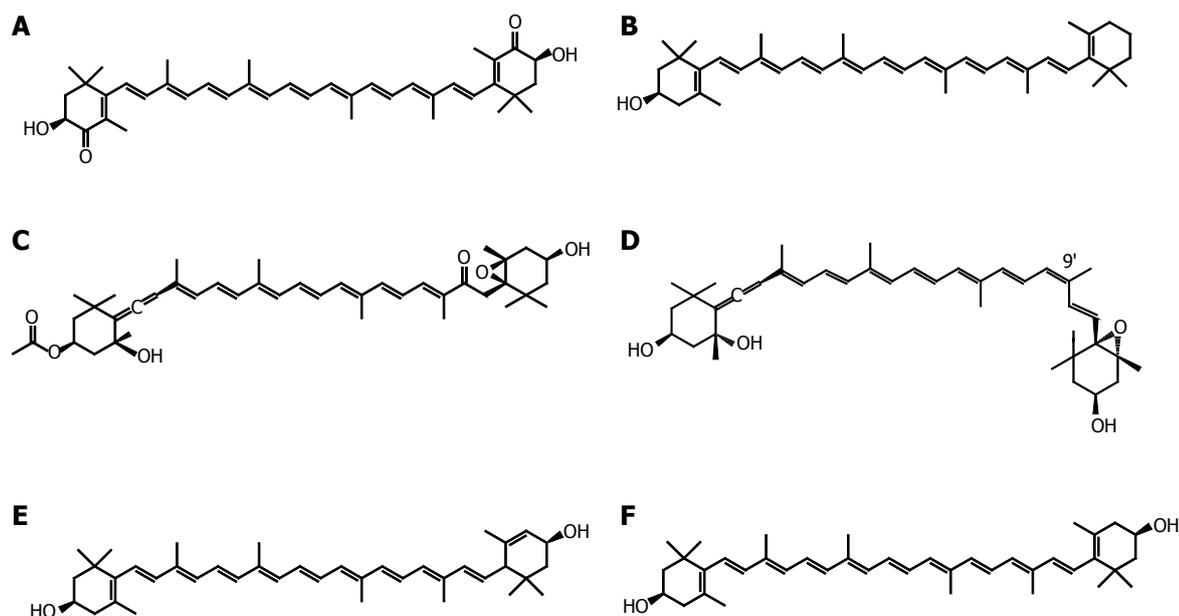


Figure 2 Structure of xanthophylls. A: Astaxanthin; B: β -cryptoxanthin; C: Fucoxanthin; D: 9'-cis-neoxanthin; E: Lutein; F: Zeaxanthin.

AX can take to transverse cell membrane orientation, and shows strong antioxidative activity^[13,15]. After oral administration of AX, AX changes to all-*E*, 9*Z*-, 13*Z*-geometrical isomers and 3*R*,3'*R*-, 3*R*,3'*S* meso-, 3*S*,3'*S*-optical isomers, all of which can be detected in human blood^[16].

Safety profile

Many experimental and clinical studies have demonstrated the safety of AX^[13,17]. In a subchronic toxicity study in rats, feeding AX-rich microalgae biomass corresponding to doses of 465 and 557 mg AX/kg per day for 90 d in male and female rats, respectively, revealed no adverse events^[18]. A randomized, double-blind, placebo-controlled study has demonstrated that it is safe to administer 6 mg/d AX in healthy adults for 8 wk^[19], and a significant decrease of triglycerides and increase of adiponectin and high density lipoprotein cholesterol in participants with mild dyslipidemia by administration of AX at doses of 12 mg/d and 18 mg/d for 12 wk^[20].

Preclinical studies and anti-cancer mechanisms

Oxidative stress and inflammation are closely related to carcinogenesis (Figure 1), and many antioxidants, including carotenoids have been demonstrated to decrease cancer development in experimental animal models^[14]. There are papers on preventive effects of AX on urinary bladder^[21], oral^[22,23], and colorectal^[24,25] carcinogenesis. In mouse urinary bladder cancer induced by *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (OH-BBN), AX administration at a dose of 50 ppm in water for 20 wk after OH-BBN exposure for 20 wk resulted in a decrease in the incidences of precancerous lesions and bladder cancer^[21]. In rat oral carcinogenesis induced by 4-nitroquinoline 1-oxide (4-NQO), the incidence of oral precancerous le-

sions in rats treated with 20 ppm 4-NQO and 100 ppm AX was smaller compared to those of the non-treatment group, and oral neoplasms did not observed in rats fed AX among the 4-NQO exposure^[22]. In these studies, AX decreased cell growth activity in the non-cancerous epithelial tissues of 4-NQO-exposed animals^[21,22]. AX has also been demonstrated to show preventive effects in 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced hamster buccal pouch carcinogenesis *via* nuclear factor-erythroid 2 related factor 2 (Nrf2) activation^[23]. Moreover, AX has been shown to inhibit nuclear factor kappa B (NF- κ B) and Wnt/ β -catenin signaling pathways^[26]. Related to colorectal carcinogenesis, AX at 500 ppm in diet significantly decreased the development of aberrant crypt foci (ACF) and the incidence and multiplicity of colorectal tumors induced by azoxymethane (AOM)^[24]. AX at 200 ppm in diet also suppressed mucosal ulcers induced by dextran sulfate sodium (DSS), and development of dysplastic ACF and colonic adenocarcinoma induced by both treatment of DSS and AOM^[25]. In addition, AX reduced the number and size of aflatoxin B1-induced liver preneoplastic foci in rats^[27]. Growth of WAZ-2T cells, mammary tumor cells, inoculated into the mice mammary fat pad was also inhibited by AX at 100 ppm or 400 ppm in diet^[28]. Lipid peroxidation activity in tumors was reduced in tumors treated with 400 ppm^[28]. AX markedly attenuated the promotion of hepatic metastasis of P815 mastocytoma cells in a syngenic graft model under restraint stress^[29]. In *in vitro* cell culture systems, AX suppressed invasion of rat ascites hepatoma AH109A cells^[30]. AX inhibited cell proliferation and decreased cell viability of leukemia K562 cells *via* induction of apoptosis along with up-regulation of peroxisome proliferator-activated receptor (PPAR) γ and p21, and down-regulation

of cyclin D1^[31]. Induction of connexin 43, gap junction protein, through activation of PPAR γ is suggested to be one of the anti-tumor mechanisms of AX^[32,33]. Up-regulation of the Nrf2 pathway is also involved in antioxidant activity of AX^[23,31,34], and may improve mitochondrial function^[35]. However, the role of Nrf2 activation in anti-tumorigenesis is controversial. The oncogenic *K-ras* gene induces Nrf2 expression, and detoxification of reactive oxygen species promotes tumor growth^[36]. Deficiency of Nrf2 has been reported to increase induction of tumors in urethane-induced mouse lung carcinogenesis, but reduce the number of malignant tumors harboring activated mutation in the *K-ras* gene, indicating that Nrf2 prevents initiation but accelerates progression under the activation of the K-ras signaling pathway^[37]. Indeed, there is a report that effects of AX differ at the stages of initiation and the stage of promotion in mammary tumors. AX fed before tumor initiation delayed mammary tumor growth and modulated immune response, but AX supplementation after tumor initiation resulted in more rapid tumor growth^[38]. Thus, use of antioxidants for cancer prevention is considered to be useful at the time before tumor initiation, but more caution is required in using them after the stage accompanied with activated K-ras signaling.

Clinical studies

A randomized, double-blind, placebo-controlled study has demonstrated that AX reduces oxidation of fatty acids^[39], decreases oxidative stress markers^[40] and inflammation^[41], and improves dyslipidemia^[20] and age-related dysfunction of eyes^[42,43] and brain^[44]. However, human cancer prevention studies using AX have not yet been reported.

β -CRYPTOXANTHIN

Distribution and nature of β -cryptoxanthin

β -cryptoxanthin (β -CRX) is one of the naturally occurring carotenoid pigments, and is also classified as a xanthophyll. Its unique character is that it is found in specific fruits and vegetables such as mango, papaya, loquat, Japanese persimmon, peach, sweet red peppers and citrus fruits of the mandarin family^[45,46]. Satsuma mandarin, *Citrus unshiu*, is one of the most β -CRX rich fruits in Japan. The content of β -CRX in *C. unshiu* reaches several mg/100g wet weight. The level of β -CRX in Valencia orange is very low and grapefruit has been found to be devoid of it.

In the human body, β -CRX is easily converted to vitamin A (retinol) and is therefore considered as a pro-vitamin A. It is also known that β -CRX might be easily absorbed^[47], and is accumulated in various organs^[48]. Moreover, it can be stored for several months in the human body^[49]. Serum β -CRX concentration could be around 96 $\mu\text{g}/\text{dL}$ ^[50]. It is also reported that β -CRX concentration in Japanese mother's milk and serum are nearly parallel with their intake of the Satsuma mandarin, and

are higher than other countries^[51,52].

Epidemiologic studies

Many epidemiological studies showed the intake of β -CRX was significantly associated with reduced risks of type 2 diabetes [relative risk (RR) = 0.58]^[53] and rheumatoid arthritis (RR = 0.59)^[54]. β -CRX supplementation significantly decreased cigarette smoke-induced lung squamous metaplasia and inflammation^[55]. Regarding cancer risk, several observational epidemiologic studies suggest that β -CRX could potentially prevent cancer development. The demonstrated cancer risks for lung, esophageal and bladder were 0.76 (RR), 0.16 [odds ratio (OR)] and 0.74 (RR), respectively, comparing the highest to lowest quintile of intake^[56-58]. A greater intake of β -CRX was also inversely associated with developing undetermined cervical atypical squamous cells (OR = 0.4)^[59]. Interestingly, the serum level of β -CRX is lower in the patients of liver cancer than that in healthy counterparts^[60]. These results suggest that a high serum β -CRX concentration or intake of β -CRX is beneficial to human health.

Safety profile

The scientific panel on additives and products or substances used in animal feed (FEEDAP) panel members considered β -CRX to appear not to be mutagenic and show no clastogenic activity^[61]. In subchronic studies, The FEEDAP panel could not find any adverse effects^[61]. Also an acceptable daily intake has not been determined^[61]. Previously, we have reported the chemoprevention effect of β -CRX against chemically-induced bladder carcinogenesis in ICR mice^[62]. Mice were fed with 1, 5 and 25 ppm of β -CRX for 24 wk, and no clinical signs of toxicity and poor condition, low survival or histopathological changes were found^[62]. Many epidemiological studies^[53-60,63-68] indicated that administration of β -CRX is safe for human health.

Preclinical studies and anti-cancer mechanisms

Various functions of β -CRX have been reported recently. β -CRX is an antioxidant phytochemical and may help prevent oxidative damage^[69]. Thus, it is believed that β -CRX has health benefits for people with risk of chronic diseases.

Numerous possible mechanisms for the anti-carcinogenic potential of β -CRX have been proposed. These include the antioxidant function that is associated with the enhancement of DNA repair^[55,69], suppression of efficacy of key proinflammatory cytokine expression, such as tumor necrosis factor- α ^[55] and an apoptotic induction effect^[70]. Also, β -CRX is known to stimulate the expression of the RB gene (a tumor-suppressor gene) and *p73* gene (a *p53*-related gene)^[71] and reduce the expression of NF- κ B and activator protein-1 (AP-1), that induces numerous genes including inflammation, cell proliferation, and apoptosis^[55]. These mechanisms indicate that β -CRX may be a promising chemopreventive agent against cancer. Indeed, β -CRX exerts an anti-tumor promoter action *in vitro*^[72] and

inhibits chemically induced carcinogenesis *in vivo*^[62,71,73,74]. Previously, we investigated the effects of β -CRX extracted from *C. unshiu* oranges on OH-BBN-induced urinary bladder carcinogenesis in male ICR mice^[62]. OH-BBN-exposed mice were fed with 1, 5 and 25 ppm of β -CRX for 24 wk starting 1 wk after the cessation of OH-BBN exposure. Feeding with β -CRX decreased the incidence and multiplicity of precancerous and cancerous urinary bladder lesions. Especially, 25 ppm β -CRX markedly reduced the occurrence of bladder cancer. Meanwhile, β -CRX is also reported to reduce mouse skin^[71], mouse lung^[74] and rat colon^[71] carcinogenesis. In our report, β -CRX lowered ratios of cyclin D1-positive cell in various urinary bladder lesions, meaning that reduction in the incidence of precancerous and cancerous urinary bladder lesions is due to reduced cell cycle progression^[62].

Clinical studies

The efficacy of β -CRX supplementation on obesity have been investigated^[75]. Seventeen postmenopausal obese women were provided 200 mL of a beverage containing β -CRX (1.56 mg/serving and 4.7 mg/d) for 3 wk^[75]. As a result, the levels of serum β -CRX were significantly elevated from 0.28 (initial period) to 1.15 mg/mL, and high molecular weight-adiponectin was also elevated from 9.8 to 11.1 mg/mL^[75]. At the end of the study, the levels of serum triglyceride ($P = 0.057$) and total plasminogen activator inhibitor-1 (PAI-1) ($P = 0.052$) tended to decrease. Nishino *et al.*^[60] reported an intervention study where β -CRX-rich mandarin orange juice (3 mg β -CRX in 80 mL) was provided for 12 wk to obese men or obese men with elevated serum γ -glutamyl transpeptidase (γ GTP) levels^[60]. After drinking β -CRX for 12 wk, body weight ($P < 0.001$), BMI ($P < 0.001$) and β -GTP levels ($P < 0.005$) were decreased.

An intervention trial regarding prevention of liver cancer has also been reported^[60]. Viral hepatitis with cirrhosis patients were randomly assigned into two groups in the trial. The treatment group was administered mandarin orange juice enriched with β -CRX and with the carotenoids mixture (lycopene, β -carotene and α -carotene). Patients in the control group were administered a carotenoids mixture alone. At year 2.5, cumulative incidence of liver cancer/hepatocellular carcinoma development in the mandarin orange juice group was lower than that of the carotenoids mixture alone group ($P = 0.05$). The combinational use of natural carotenoids containing β -CRX might be valuable for the prevention of liver cancer in hepatitis virus infected patients with cirrhosis.

FUCOXANTHIN

Distribution and nature of fucoxanthin

Brown seaweeds include *Undaria pinnatifida* (wakame), *Hizikia fusiforme* (hijiki), *Laminaria japonica* (ma-kombu) and *Sargassum fulvellum*. The Japanese have been estimated to intake wakame at 1 g/d^[76]. Brown seaweeds are known to contain many bioactive components, *i.e.*,

fucoxanthin (FX), fucoidan, vitamins, minerals, dietary fibers, proteins, ω -3 polyunsaturated fatty acids (PUFAs), polysaccharides, other carotenoids and various functional polyphenols. Fucoidan is a sulfated polysaccharide that is one of the major bioactive components in seaweed^[77,78], but we would like to focus on FX in this review. FX is a xanthophyll belonging to non-provitamin A carotenoids, constructed with an unusual allenic bond, an epoxide group, and a conjugated carbonyl group in a polyene chain^[79]. Some reports demonstrated that the FX content of *U. pinnatifida* is approximately 1.0-3.0 mg/g dry weight through one life cycle^[80,81]. It has been proven that mice convert FX into keto-carotenoids by oxidation of the secondary hydroxyl groups ($\text{FX} + \text{H}_2\text{O} \rightarrow \text{FuOH}$; $\text{FuOH} + \text{NAD}^+ \rightarrow \text{amarouci-xanthin A} + \text{NADH}$)^[79]. On the other hand, oral administration of kombu extract containing FX in humans revealed that the FuOH and the *cis*-isomer of FuOH could be found in the serum, detected by HPLC^[82].

Safety profile

FX has been proved to be safe with no side effects by single (1000 or 2000 mg/kg BW) and repeated (500 or 1000 mg/kg BW for 30 d) oral dose toxicity studies in male and female mice^[83]. In the repeated doses study, histological examination of the gonadal tissues, kidneys, liver and spleen revealed no abnormal changes^[83]. In rats, 13-wk oral subchronic toxicity studies suggested that more than 2000 mg/kg BW of microalgal FX oil induce the 50% lethal^[84].

Preclinical studies and anti-cancer mechanisms

Many studies suggested FX possesses anti-cancer potential, especially shown in colon cancer cell lines (Caco-2, DLD-1 and HT-29), liver cell lines (HepG2), prostate cancer cell lines (DU 145, LNCaP and PC-3) and urinary bladder^[85-88]. The main biomolecules involved in anti-cancer mechanism is assumed to be the biomolecules related to apoptosis and cell cycle^[89,90] and those may associate with antioxidant activity through their free radical scavenging action^[91]. Moreover, inhibition of PI3K/Akt and NF- κ B signals were reported in human cervical and breast cancer cells, respectively^[92,93].

Its metabolite fucoxanthinol (FuOH) also has inhibitory effects on cancer cell growth^[94,95], and 1,2-dimethylhydrazine-induced formation of colonic ACF in mice and AOM/DSS-induced colon carcinogenesis^[25,96]. To find new cancer prevention approaches, we investigated the combination effect of FuOH and 1 α ,25-dihydroxyvitamin D₃ (1 α ,25(OH)₂D₃), and found inhibition of cell viability and induction of apoptosis in DLD-1 and HT-29 cells^[97]. Down-regulation of PPAR γ and NF- κ B p52 were suggested to be involved in the inhibition of cell viability due to the combination of FuOH and 1 α ,25(OH)₂D₃. It has been shown that activation of PPAR γ suppresses intestinal polyp development in *Apc*-mutant mice and AOM-induced colonic ACF development in obese KK-*A*⁰ mice^[98,99].

Clinical studies

FX has been reported to provide health benefits in humans, such as improvement of obesity, reduction of inflammation, healthy triglyceride levels, and improvements in blood pressure levels^[100,101].

After daily intake of *U. pinnatifida*, FuOH is detectable in human plasma^[82]. Although metabolites of FX could be measured as a marker of exposure, effects of FX or FuOH in human carcinogenesis have not been reported to date. From the aspect of obesity-associated cancer, we here introduce one study that has been conducted to assess the effects of FX supplementation on weight loss. FX supplementation on obese patients with non-alcoholic fatty liver disease results in the improvement of liver inflammatory markers, such as alanine aminotransferase, aspartate aminotransferase, C-reactive protein, γ -glutamyltransferase (γ GT, GGT)^[101]. Of note, it has been demonstrated that increased of GGT plasma levels are associated with an increased risk of pancreatic cancer^[102,103], nevertheless GGT has no causative role itself.

It is also interesting to mention that intake of 5 g/d *U. pinnatifida* stimulated a significant 50% reduction in urinary urokinase-like plasminogen activator receptor (uPAR) proteins in postmenopausal women. uPAR, is the membrane receptor for uPA, responsible for extracellular membrane proteins degradation and PAI-1, responsible for the inhibition of plasminogen activation^[104]. Generally, uPAR is known to be higher in postmenopausal women as well as in breast cancer patients^[105]. Moreover, it has been reported that uPA and/or PAI-1 is positively correlated with poor prognosis in patients with breast cancer, *i.e.*, correlation with cancer metastatic potential^[106,107]. Thus, uPA, PAI-1 and uPAR might be used as prognostic markers for breast cancer^[108], and FX may reduce such a tumor marker.

NEOXANTHIN

Distribution and nature of Neoxanthin

Neoxanthin (NX), a non-provitamin A carotenoid, has an unusual allenic bond and a 5,6-monoepoxide as well as FX. NX is widely present in terrestrial and marine biota and the occurrence of two geometric *cis/trans* isomers is known to be species dependent^[109-111]. The 9'-*cis* form of NX (9'-*cis* NX) is mainly localized and used in the photosynthetic organs of spinach leaves and marine algae such as *Euglenophyta*. It is also used as a precursor of abscisic acid, a plant hormone^[112,113]. Whereas the all-*trans* form of NX is predominant in the petals of globeflower and yellow rose, this xanthophyll is not involved in the photosynthetic system^[111,114]. We mainly obtain the 9'-*cis* NX from leafy green vegetables. Fresh spinach contains 9'-*cis* NX around 5 mg/100 g in fresh leaf^[110]. It has been estimated that 9'-*cis* NX exists at 0.95 μ mol/L in digested fluid (9 L/d), when we ingest 100 g/d spinach.

The 5,6-monoepoxide moiety in 9'-*cis* NX is easily isomerized to 5,8-epoxide under the acidic conditions of the stomach and generates almost equal amounts of

(8'-R/S)-neochrome^[115,116]. After a 1-wk spinach intervention (3 mg 9'-*cis* NX/day), highly hydrophilic xanthophylls of 9'-*cis* NX and (8'-R and 8'-S)-neochromes appeared at a very low level in human plasma (about 1 nmol/L)^[117]. It is known that the uptake of various carotenoids by human colon cancer cells (Caco-2 cells) positively correlates with the lipophilicity of the carotenoids^[118]. The highly hydrophilic xanthophylls such as NX, FX and violaxanthin could be detected slightly in human plasma, when we intake purified forms and food matrices^[79,101,117,119-121]. Because of the poor intestinal absorption of NX, a considerable amount of ingested 9'-*cis* NX and (8'-R and 8'-S)-neochrome would be delivered to the colon, and even if absorbed in the small intestine, they would be metabolized easily.

Preclinical studies and anti-cancer mechanisms

It has been reported that both 9'-*cis* NX and all-*trans* NX possess strong potential of cell growth inhibition and apoptosis induction in human prostate cancer cells^[87,94,115,122], human colon cancer^[122-124], mouse melanoma^[122] and mouse embryonic mesenchymal cells^[125]. In addition, several researchers have reported that 9'-*cis* NX, all-*trans* NX and (8'-R/S)-neochrome have cancer preventive effects^[126], and also anti-tumor promoter functions^[70]. Moreover, induction of cell cycle arrest^[115], anti-oxidant properties^[127] and anti-obesity properties^[128] have been reported. Recently, we additionally demonstrated that 9'-*cis* NX rapidly accumulated in the mitochondria, caused mitochondria $\Delta\Psi$ loss and thereafter the release of cytochrome *c* and production of apoptosis-inducing factor in human colon cancer cells^[123]. It is regrettable that there is little information about the anti-cancer mechanisms of dietary NX in mammals, except for that described above.

Safety profile and clinical studies

No safety profile and clinical studies have been reported on 9'-*cis* NX, any -*trans* NX and (8'-R/S)-neochromes. However, epidemiological data show that higher intake of fruits and vegetables, rich in highly hydrophilic epoxyxanthophylls such as NX, is associated with a lower risk of colorectal cancer^[129,130]. Further studies are required to elucidate the clinical beneficial properties of NX.

ZEAXANTHIN/LUTEIN

Distribution and nature of zeaxanthin / lutein

Zeaxanthin (ZX) and lutein also belong to the xanthophyll family. Their unique character is that they are the only carotenoid among more than 600 species of carotenoid existing in eye tissue, especially in the retina^[131]. Lutein can be photochemically transformed to meso-ZX. They are stereoisomer of each other, differ by the location of a double bond. Lutein is abundant in egg yolk, and in dark-green leafy vegetables, such as broccoli, brussels sprouts, kale and spinach^[132]. In the human body, lutein is distributed at the skin, breasts, cervix uteri, and also found in serum in high amounts. Serum lutein and

ZX levels are reported to be around 180 and 20 ng/mL, respectively^[133]. They are assumed to play a critical role in ocular health because they act as strong anti-oxidants and filtered out high-energy blue light^[134]. Of note, no correlation between plasma concentrations of lutein/zeaxanthin and BMI or insulin resistance has been reported^[135].

Epidemiologic studies

In many papers, target organs for lutein are reported to be the eyeballs, the skin and the heart. Regarding ocular conditions, age-related macular degeneration, cataracts, and retina pigmentosa have been reported to have some correlation with lutein. Lutein also possesses a preventive function of cardiovascular diseases/stroke^[131,134,136,137].

Regarding lung cancer, some epidemiologic studies state lutein has an important cancer preventive function^[4,14]. A ten-year study of 120000 United States people revealed that lung cancer incidence was significantly reduced in those who ingested a high amount of total carotenoids, including lutein and ZX^[138]. Similar relationships were found in Fijians, when compared to the other South Pacific islands' people. Fijians intake 25 mg lutein daily on an average (200 g dark greens), whereas other 20 South Pacific countries intake less lutein in diets^[139]. Thus, there was a clear inverse association with lutein intake and lung cancer incidence.

Regarding colorectal cancer, inverse associations with dietary lutein intake have been reported^[124], and serum ZX concentration by Okuyama *et al.*^[140]. However, no association has been detected between the levels of plasma lutein and the risk of gastric cancer^[141].

Regarding skin cancer risk, the specific effects of lutein are not fully known. The only reported data is that a combination of carotenoids may protect erythema development in human skin^[142], and that may be correlated with the presence of skin cancer or precancerous lesions^[124].

Regarding breast cancer, there is some possibility for protective effects of lutein^[6,14,143]. Intake of lutein-rich foods significantly lowered the risk of premenopausal breast cancer. The Nurse's Health Study demonstrated a weak inverse association, but significant, between lutein and ZX intake and the breast cancer risk among premenopausal women^[6]. Of note, the protective effect of lutein and ZX was strongest in patients have a family history of breast cancer. Also there is a report that increasing serum levels of lutein and ZX were associated with a reduced breast cancer risk, but the trend was only marginally significant in a case-control study^[143]. There is a report comparing biopsy samples from breast cancer tissue and benign mammary tissue. In this report, increasing lutein and ZX concentrations tends to decrease the risk of breast cancer^[144]. Meanwhile, Other studies have shown that there are no differences of lutein and ZX concentrations in mammary adipose tissue between benign breast tumors and breast cancer^[145]. New York University Women's Health Study, a nested case-control prospective study, demonstrated an inverse relationship

between plasma levels of lutein, but not ZX, and risk of breast cancer^[146].

Regarding other cancers, significant inverse relations were observed for lutein and ZX in oral cavity and pharyngeal cancer^[147].

Safety profile

No toxicities or adverse reactions for intake of lutein/ZX have been reported at doses up to 40 mg/d for 2 mo^[131,148]. High doses of β -carotene supplements (> 30 mg/d) are well known to be associated with carotenodermia^[149], and the same could happen when we consume high doses of lutein and ZX. Also it has been demonstrated that lutein has no mutagenic effect in the Ames test^[150].

Preclinical study and anticancer mechanism

Lutein/ZX is thought to have a superior anti-oxidant ability to scavenge free radicals than other carotenoids. An *in vitro* study showed that lutein could quench peroxy radicals and play a guarding role against oxidative injury^[151,152]. In this experiment, a synergistic antioxidant effect was obtained with a combination of lutein and lycopene^[153]. Carotenoids also show a superb function for immune response^[154].

Lutein could also function as an anti-carcinogenic reagent, such as a modulator of cell growth and apoptosis signaling. Lutein induces cell cycle arrest in human prostate and esophageal cancer cell^[155,156]. Lutein induces apoptosis in transformed cancer cells but do not induce apoptosis in normal human mammary cells through modulating the ratio of Bcl-xL/Bax protein expression^[157]. Meanwhile, ZX, structural isomer of lutein, induced cell cycle arrest in human breast cancer cells^[158]. Lutein stimulates some genes involved in T-cell transformations activated by antigens, cytokines and mitogens^[159]. Lutein interacts with carcinogens such as 1-nitropyrene and aflatoxin B1, and lowered its carcinogenic activity^[150,160]. In a recent report, female BALB/c mice were fed a diet containing lutein for 14 d, and then inoculated with 0 to 2.5×10^3 mammary tumor cells. The results demonstrated that 0.002% and 0.02% lutein lowered both mammary tumor incidence and tumor growth^[161].

FUTURE ASPECTS

The versatile functions of xanthophylls have shown great potential for the prevention of metabolic syndrome and cancers, both *in vitro* and *in vivo*. Xanthophylls have been verified as safe with no side events, and several xanthophylls provide other health benefits, including improvements in inflammation, dyslipidemia, hypertension and liver function, as shown in this review. The accumulated evidence indicates the functionality of xanthophylls as anti-obesity and anti-insulin-resistance functional foods, implying that xanthophylls could be useful in preventing obesity-associated cancer.

The chemical synthesis of each xanthophyll is not impossible, but it may be very expensive. However, the

promising results obtained from *in vivo* studies encourage researchers to undertake more clinical studies in humans. We have some information about xanthophylls trials, and we should further promote human clinical studies to obtain information about the adequate dosage of xanthophylls needed to prevent cancers.

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