Cancer Prevention and Tumor Reduction

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**Growth-inhibitory effects of the astaxanthin-rich alga Haematococcus pluvialis in human colon cancer cells.**

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The growth-inhibitory effects of the astaxanthin-rich Haematococcus pluvialis were studied in HCT-116 colon cancer cells. H. pluvialis extract (5-25μg/ml) inhibited cell growth in a dose- and time-dependent manner, by arresting cell cycle progression and by promoting apoptosis. At 25μg/ml of H. pluvialis extract, an increase of p53, p21(WAF-1/CIP-1) and p27 expression (220%, 160%, 250%, respectively) was observed, concomitantly with a decrease of cyclin D1 expression (58%) and AKT phosphorylation (21%). Moreover, the extract, at the same concentration, strongly up-regulated apoptosis by modifying the ratio of Bax/Bcl-2 and Bcl-XL, and increased the phosphorylation of p38, JNK, and ERK1/2 by 160%, 242%, 280%, respectively. Growth-inhibitory effects by H. pluvialis were also observed in HT-29, LS-174, WiDr, SW-480 cells. This study suggests that H. pluvialis may protect from colon cancer.

PMID: 19423215 [PubMed - as supplied by publisher]
Antitumor Activity of Astaxanthin and Its Mode of Action
Harumi Jyonouchi, Sinine Sun, Koji Ijima, and Myron D. Gross

Astaxanthin, a carotenoid without Vitamin A activity, may exert antitumor activity through the enhancement of immune response. Here, we determined the effects of dietary astaxanthin on tumor growth and tumor immunity against transplantable methylcholanthrene-induces fibrosarcoma (Meth-A tumor) cells. These tumor cells express a tumor antigen that induces T cell-mediated immune responses in syngenic mice. BALB/c mice were fed astaxanthin (0.02%, 40 µg/kg body wt/day in a beadlet form) mixed in a chemically defined diet starting zero, one, and three weeks before subcutaneous inoculation with tumor cells (3 x 10^5 cells, 2 times the minimal tumorigenic dose). Three weeks after inoculation, tumor size and weight were determined. We also determined cytotoxic T lymphocyte (CTL) activity and interferon-γ (IFN-γ) production by tumor-draining lymph node (TDLN) and spleen cells by restimulating cells with Meth-A tumor cells in culture. The astaxanthin-fed mice had significantly lower tumor size and weight than controls when supplementation was started one and three weeks before tumor inoculation. This antitumor activity was paralleled with higher CTL activity and IFN-γ production by TNLN and spleen cells in the astaxanthin-fed mice. CTL activity by TDLN cells was highest in mice fed astaxanthin for three weeks before inoculation. When the astaxanthin-supplemented diet was started at the same time as tumor inoculation, none of these parameters were altered by dietary astaxanthin-supplemented diet was started at the same time as tumor inoculation, none of these parameters were altered by dietary astaxanthin, except IFN-γ production by spleen cells. Total serum astaxanthin concentrations were approximately 1.2 µmol/l when mice were fed astaxanthin (0.02%) for four weeks and appeared to increase in correlation with the length of astaxanthin supplementation. Our results indicate that dietary astaxanthin suppressed Meth-A tumor cell growth and stimulated immunity against Meth-A tumor antigen.
Astaxanthin inhibits cytotoxic and genotoxic effects of cyclophosphamide in mice germ cells.

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Cyclophosphamide (CP), an alkylating agent used in the treatment of several cancers as well as an immunosuppressant in rheumatoid arthritis. It is used against several cancers due to its broad spectrum efficacy, but at the same time possesses unwanted risks for occupational exposure as well as therapy related toxicities to patients. The present study was aimed to investigate the protective effect of astaxanthin (AST) a red carotenoid pigment on CP induced germ cell toxicity in male mice. CP was administered intraperitoneally (i.p.) at the dose of 50, 100 and 200mg/kg body weight to mice (20-25 g) once in a week for a period of five weeks. AST was given at the dose of 25mg/kg per oral (p.o.) for five consecutive days in a week for five weeks. The animals were sacrificed one week after the last injection of CP. The protective effect of AST against CP induced male germ cell toxicity was evaluated using body weight, testes and epididymis weight, sperm count, sperm head morphology, sperm comet assay, histology of testes and TUNEL assay. AST treatment significantly improved the testes weight, sperm count and sperm head morphology as compared to only CP treated animals. The result of comet assay showed that AST treatment significantly restored the sperm DNA damage induced by CP. Further, AST treatment showed protection against CP induced testicular toxicity as evident from testes histology and TUNEL assay. The present results indicate the chemoprotective potential of AST against CP induced germ cell toxicity in mice.

Publication Types:

PMID: 18485558 [PubMed - indexed for MEDLINE]
Visualization of astaxanthin localization in HT29 human colon adenocarcinoma cells by combined confocal resonance Raman and fluorescence microspectroscopy.

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Astaxanthin, a carotenoid found in plants and seafood, exhibits antiproliferative, antioxidant and anticarcinogenic properties. We show that astaxanthin delivered with tetrahydrofuran is effectively taken up by cultured colon adenocarcinoma cells and is localized mostly in the cytoplasm as detected by confocal resonance Raman and broad-band fluorescence microspectroscopy image analysis. Cells incubated with beta-carotene at the same concentration as astaxanthin (10 microM) showed about a 50-fold lower cellular amount of beta-carotene, as detected by HPLC. No detectable Raman signal of beta-carotene was found in cells, but a weak broad-band fluorescence signal of beta-carotene was observed. Beta-Carotene, like astaxanthin, was localized mostly in the cytoplasm. The heterogeneity of astaxanthin and beta-carotene cellular distribution in cells of intestinal origin suggests that the possible defense against reactive molecules by carotenoids in these cells may also be heterogeneous.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17039456 [PubMed - indexed for MEDLINE]
Molecular modeling of non-covalent binding of homochiral (3S,3'S)-astaxanthin to matrix metalloproteinase-13 (MMP-13).

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Inhibitors for matrix metalloproteinases (MMPs) are under investigation for the treatment of various important chronic illnesses, including cancer, arthritis, and cardiovascular disease (CVD). In particular, MMP-13 is currently being probed as a potential key target in CVD and malignant disease due to its documented effects on extracellular matrix (ECM) remodeling, important in the pathophysiology of these diseases. Within the family of related mammalian MMP enzymes, MMP-13 possesses a large hydrophobic binding pocket relative to that of other MMPs. Homochiral astaxanthin (3S,3'S-AST; 3S,3'S-dihydroxy-beta,beta-carotene-4,4'-dione), an important antioxidant and anti-inflammatory xanthophyll carotenoid, is an active metabolite of several novel soft drugs in clinical development; it is also extensively used and tested as a human nutraceutical. In the current study, the prediction of the geometry and energetics of its binding to human MMP-13 was conducted with molecular modeling. The method used was found to predict the energy of binding of known ligands of MMP-13 with great precision. Blind docking using the whole protein target was then used in order to identify the possible binding site(s) of AST. AST was predicted to bind at several sites in close proximity to the active center. Subsequent analyses focused on the binding site at the atomic (i.e., amino acid sequence) level suggested that AST can bind to MMP-13 with high affinity and favorable energetics. Therefore, the modeling study predicts potential direct enzyme-inhibitory activity of AST against MMP-13, a behavior that may be exploited in mammalian systems in which pathological upregulation of MMP activity is paramount.

PMID: 16716595 [PubMed - indexed for MEDLINE]
Antiproliferation and induction of cell death of Phaffia rhodozyma (Xanthophyllomyces dendrorhous) extract fermented by brewer malt waste on breast cancer cells.

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Astaxanthin has been shown to have antiproliferative activity on breast cancer and skin cancer cells. However, the high cost of production, isolation and purification of purified astaxanthin from natural sources or chemically synthetic methods limit its usage on cancer therapy. We show that astaxanthin could be produced by fermentating the Phaffia rhodozyma (Xanthophyllomyces dendrorhous) yeast cells with brewer malt waste using a 20 L B. Braun fermentor. The percentage composition of astaxanthin from the P. rhodozyma was >70% of total pigment as estimated by the high performance liquid chromatographic analysis. Furthermore, the antiproliferative activity of this P. rhodozyma cell extract (PRE) was demonstrated on breast cancer cell lines including the MCF-7 (estrogen receptor positive) and MDA-MB231 (estrogen receptor negative) by using the [3-(4,5-dimethylthiazol-2-yl)-5-(3-arboxymethoxyphenyl)-2- (4-sulfophenyl)-2H-tetrazolium] (MTS) assay. No apoptotic cell death, but growth inhibitory effect was induced after 48 h of PRE incubation as suggested by morphological investigation. Anchorage-dependent clonogenicity assay showed that PRE could reduce the colony formation potential of both breast cancer cell lines. Cell death was observed from both breast cancer cell lines after incubation with PRE for 6 days. Taken together, our results showed that by using an economic method of brewer malt waste fermentation, we obtained P. rhodozyma with a high yield of astaxanthin and the corresponding PRE could have short-term growth inhibition and long-term cell death activity on breast cancer cells.

Publication Types:

PMID: 16211266 [PubMed - indexed for MEDLINE]
Cancer prevention by retinoids and carotenoids: independent action on a common target.

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Virtually all human tumors are deficient in gap junctional communication (GJC) and the restoration of GJC by forced expression of connexins reduces indices of neoplasia. The expression of connexin 43 (Cx43) is upregulated by cancer-preventive retinoids and carotenoids which correlates with the suppression of carcinogen-induced transformation in 10T1/2 cells. However, the molecular mechanism for upregulated expression is poorly understood. The retinoic acid receptor antagonist, Ro 41-5253, suppressed retinoid-induced Cx43 protein expression in 10T1/2 cells and the induction of a Cx43 luciferase reporter construct in F9 cells, but did not suppress protein expression or reporter activity induced by the non-pro-vitamin A carotenoid astaxanthin. In contrast, Cx43 induction by astaxanthin, but not by a RAR-specific retinoid, was inhibited by GW9662, a PPAR-gamma antagonist. Neither compound required protein synthesis for the induction of Cx43 mRNA, nor was the 5.0 h half-life of Cx43 mRNA altered, indicating direct transcriptional activation. The responsive region was found within -158 bp and +209 bp of the transcription start site. Site directed mutagenesis of a GC-box in this region increased basal levels of transcription and loss of retinoid responsiveness. Simultaneous treatment with a retinoid and beta-carotene or astaxanthin resulted in supra-additive Cx43 expression, again indicating separate mechanisms of gene regulation.

Publication Types:

PMID: 15949684 [PubMed - indexed for MEDLINE]
Inhibition of chemically-induced neoplastic transformation by a novel tetrasodium diphosphate astaxanthin derivative.

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Carotenoids have been implicated in numerous epidemiological studies as being protective against cancer at many sites, and their chemopreventive properties have been confirmed in laboratory studies. Astaxanthin (AST), primarily a carotenoid of marine origin, responsible for the pink coloration of salmon, shrimp and lobster, has received relatively little attention. As with other carotenoids, its highly lipophilic properties complicate delivery to model systems. To overcome this issue we have synthesized a novel tetrasodium diphosphate astaxanthin (pAST) derivative with aqueous dispersibility of 25.21 mg/ml. pAST was delivered to C3H/10T1/2 cells in an aqueous/ethanol solution and compared with non-esterified AST dissolved in tetrahydrofuran. We show pAST to (i) upregulate connexin 43 (Cx43) protein expression; (ii) increase the formation of Cx43 immunoreactive plaques; (iii) upregulate gap junctional intercellular communication (GJIC); and (iv) cause 100% inhibition of methylcholanthrene-induced neoplastic transformation at 10(-6) M. In all these assays, pAST was superior to non-esterified AST itself; in fact, pAST exceeded the potency of all other previously tested carotenoids in this model system. Cleavage of pAST to non-esterified (free) AST and uptake into cells was also verified by HPLC; however, levels of free AST were approximately 100-fold lower than in cells treated with AST itself, suggesting that pAST possesses intrinsic activity. The dual properties of water dispersibility (enabling parenteral administration in vivo) and increased potency should prove extremely useful in the future development of cancer chemopreventive agents.

PMID: 15888493 [PubMed - indexed for MEDLINE]
Upregulation of connexin 43 protein expression and increased gap junctional communication by water soluble disodium disuccinate astaxanthin derivatives.

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Carotenoids are plant pigments whose consumption is associated with lower cancer rates in humans. Studies in experimental animal and cell systems have confirmed the cancer chemopreventive activity of these compounds. However, their extremely hydrophobic nature makes these compounds biologically unavailable unless delivered in organic solution to model systems. We have synthesized novel disodium salt disuccinate astaxanthin derivatives that possess high aqueous dispersibility. When delivered to mouse embryonic fibroblast C3H/10T1/2 cell cultures, either in aqueous or aqueous/ethanol solutions, these derivatives are biologically active. Biological activity was demonstrated by (1) upregulated expression of connexin 43 (Cx43) protein; (2) increased formation of Cx43 immunoreactive plaques in regions of the plasma membrane consistent with localization of gap junctions; (3) significantly upregulated gap junctional intercellular communication (GJIC) as demonstrated by Lucifer Yellow dye transfer after microinjection (P < 0.03; Fisher's Exact test). Enhanced expression of Cx43 and increased GJIC have been previously demonstrated to result in inhibition of in vitro neoplastic transformation of 10T1/2 cells as well as growth reduction of human tumors in xenografts. These novel derivatives possess increased utility as water soluble and water dispersible agents, allowing for aqueous delivery both in vitro and in vivo, properties that could enhance their potential clinical utility as potent cancer chemopreventive agents. Copyright 2004 Elsevier Ireland Ltd.

PMID: 15194214 [PubMed - indexed for MEDLINE]
Contribution of the antioxidative property of astaxanthin to its protective effect on the promotion of cancer metastasis in mice treated with restraint stress.

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We investigated the effects of astaxanthin on the antitumor effector activity of natural killer (NK) cells suppressed by stress in mice in order to define the immunological significance of astaxanthin (ASX) when combined with restraint stress treatment. When the mice were treated with restraint stress alone, the total number of spleen cells, and the level NK cell activity per spleen were reduced to a nadir on day 3. The stress also caused a significant increase in the lipid peroxidation of liver tissue. ASX (100 mg/kg/day, p.o., 4 days) improved the immunological dysfunction induced by restraint stress. On the other hand, metastatic nodules were observed in the livers of syngenic DBA/2 mice on day 12 after inoculation of P815 mastocytoma cells. Hepatic metastasis was promoted further by restraint stress when applied on day 3 before the inoculation of P815. Daily oral administration of ASX (1 mg/kg/day, p.o., 14 days) markedly attenuated the promotion of hepatic metastasis induced by restraint stress. These results suggested that astaxanthin improves antitumor immune responses by inhibiting of lipid peroxidation induced by stress.

PMID: 12173414 [PubMed - indexed for MEDLINE]
Antitumor activity of astaxanthin and its mode of action.

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Astaxanthin, a carotenoid without vitamin A activity, may exert antitumor activity through the enhancement of immune responses. Here, we determined the effects of dietary astaxanthin on tumor growth and tumor immunity against transplantable methylcholanthrene-induced fibrosarcoma (Meth-A tumor) cells. These tumor cells express a tumor antigen that induces T cell-mediated immune responses in syngenic mice. BALB/c mice were fed astaxanthin (0.02%, 40 micrograms/kg body wt/day in a beadlet form) mixed in a chemically defined diet starting zero, one, and three weeks before subcutaneous inoculation with tumor cells (3 x 10(5) cells, 2 times the minimal tumorigenic dose). Three weeks after inoculation, tumor size and weight were determined. We also determined cytotoxic T lymphocyte (CTL) activity and interferon-gamma (IFN-gamma) production by tumor-draining lymph node (TDLN) and spleen cells by restimulating cells with Meth-A tumor cells in culture. The astaxanthin-fed mice had significantly lower tumor size and weight than controls when supplementation was started one and three weeks before tumor inoculation. This antitumor activity was paralleled with higher CTL activity and IFN-gamma production by TDLN and spleen cells in the astaxanthin-fed mice. CTL activity by TDLN cells was highest in mice fed astaxanthin for three weeks before inoculation. When the astaxanthin-supplemented diet was started at the same time as tumor inoculation, none of these parameters were altered by dietary astaxanthin, except IFN-gamma production by spleen cells. Total serum astaxanthin concentrations were approximately 1.2 mumol/l when mice were fed astaxanthin (0.02%) for four weeks and appeared to increase in correlation with the length of astaxanthin supplementation. Our results indicate that dietary astaxanthin suppressed Meth-A tumor cell growth and stimulated immunity against Meth-A tumor antigen.

Publication Types:

PMID: 10798217 [PubMed - indexed for MEDLINE]
Inhibitory effects of carotenoids on the invasion of rat ascites hepatoma cells in culture.

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The effects of carotenoids--alpha-carotene, beta-carotene, lycopene, beta-cryptoxanthin, zeaxanthin, lutein, canthaxanthin, astaxanthin--on the invasion of rat ascites hepatoma AH109A cells were investigated by co-culturing the hepatoma cells with rat mesentery-derived mesothelial cells (M-cells). All the carotenoids examined inhibited AH109A invasion in a dose-dependent manner up to 5 microM. Cancer cells previously cultured with hypoxanthine (HX) and xanthine oxidase (XO) showed a highly invasive activity. Carotenoids, 5 microM of beta-carotene and astaxanthin, suppressed this reactive oxygen species-potentiated invasive capacity by simultaneously treating AH109A cells with the carotenoids, HX and XO. These results suggest that the antioxidative property of these carotenoids may be involved in their anti-invasive action.

Publication Types:

PMID: 10766430 [PubMed - indexed for MEDLINE]
Dietary beta-carotene and astaxanthin but not canthaxanthin stimulate splenocyte function in mice.

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The in vivo modulatory effect of beta-carotene, astaxanthin and canthaxanthin on lymphocyte function was investigated. Female BALB/c mice (8 wk old) were fed a basal diet containing 0, 0.1% or 0.4% beta-carotene, astaxanthin or canthaxanthin for 0, 2 or 4 wk (n = 8/diet/period). Splenic lymphocytes were isolated and mitogen-stimulated proliferation, IL-2 production and lymphocyte cytotoxicity were assessed. Body weight and feed intake were not different among dietary treatments. Plasma carotenoids were undetectable in unsupplemented mice but concentrations of the respective carotenoids were elevated in mice fed 0.1 or 0.4% beta-carotene (0.22 and 0.39 mumol/L), astaxanthin (16.4 and 50.2 mumol/L) and canthaxanthin (5.00 and 7.02 mumol/L) respectively. Mice fed both dietary levels of beta-carotene and astaxanthin had enhanced phytohemagglutinin-induced lymphoblastogenesis compared to unsupplemented mice (P < 0.03). No treatment difference was detected with concanavalin A- or lipopolysaccharide-induced lympho-proliferation nor with IL-2 production (P < 0.05). Astaxanthin (0.1%) also enhanced lymphocyte cytotoxic activity (P < 0.08). In contrast, canthaxanthin did not significantly influence any of the lymphocyte functions measured. Results indicate that beta-carotene and astaxanthin but not canthaxanthin exert enhanced splenic lymphocyte function in mice.

Publication Types:

PMID: 10697539 [PubMed - indexed for MEDLINE]
A comparison of the anticancer activities of dietary beta-carotene, canthaxanthin and astaxanthin in mice in vivo.

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The anticancer activities of beta-carotene, astaxanthin and canthaxanthin against the growth of mammary tumors were studied in female eight-wk-old BALB/c mice. The mice were fed a synthetic diet containing 0, 0.1 or 0.4% beta-carotene, astaxanthin or canthaxanthin. After 3 weeks, all mice were inoculated with 1 x 10(6) WAZ-2T tumor cells into the mammary fat pad. All animals were killed on 45 d after inoculation with the tumor cells. No carotenoids were detectable in the plasma or tumor tissues of unsupplemented mice. Concentrations of plasma astaxanthin (20 to 28 mumol/L) were greater (P < 0.05) than that of beta-carotene (0.1 to 0.2 mumol/L) and canthaxanthin (3 to 6 mmol/L). However, in tumor tissues, the concentration of canthaxanthin (4.9 to 6.0 nmol/g) was higher than that of beta-carotene (0.2 to 0.5 nmol/g) and astaxanthin (1.2 to 2.7 nmol/g). In general, all three carotenoids decreased mammary tumor volume. Mammary tumor growth inhibition by astaxanthin was dose-dependent and was higher than that of canthaxanthin and beta-carotene. Mice fed 0.4% beta-carotene or canthaxanthin did not show further increases in tumor growth inhibition compared to those fed 0.1% of each carotenoid. Lipid peroxidation activity in tumors was lower (P < 0.05) in mice fed 0.4% astaxanthin, but not in those fed beta-carotene and canthaxanthin. Therefore, beta-carotene, canthaxanthin and especially astaxanthin inhibit the growth of mammary tumors in mice; their anti-tumor activity is also influenced by the supplemental dose.

Publication Types:

PMID: 10470126 [PubMed - indexed for MEDLINE]
Effect of dietary supplementation with carotenoids on xenobiotic metabolizing enzymes in the liver, lung, kidney and small intestine of the rat.

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The effect of 16 d intake of 300 mg carotenoids/kg diet (beta-carotene (beta C), bixin (BX), lycopene (LY), lutein (LU), canthaxanthin (CX) or astaxanthin (AX) on xenobiotic metabolizing enzymes in the liver, lung, kidney and small intestine of male Wistar rats was assessed. A control group received the basal diet (AIN-76) without carotenoids and a positive control group for enzyme induction received 3-methylcholanthrene (3-MC) at 666 mg/kg diet. Cytochrome P450 activity was assessed using the substrates ethoxyresorufin for P450 1A1, methoxyresorufin for P450 1A2, pentoxyresorufin for P450 2B1/2 and benzyloxyresorufin for P450 types 1A1/2, 2B1/2 and 3A. Glutathione-S-transferase (EC 2.5.1.18) and reduced glutathione status were assessed. Carotenoid uptake by the tissues was also determined. 3-MC and the carotenoids BX, CX and AX led to significant increases compared with control in liver, lung and kidney ethoxyresorufin-O-deethylation. Methoxyresorufin-O-demethylation activity was significantly increased in liver and lung by BX, CX and AX but only CX and AX significantly increased activity in kidney. Pentoxyresorufin-O-depentylation and benzyloxyresorufin-O-dearylation increased in liver of 3-MC-, BX-, CX- and AX-treated rats, but to a much lesser degree than for the other two substrates. Benzyloxyresorufin-O-dearylation in lung was significantly decreased by all carotenoids. Activities of any of the measured enzymes in the small intestine were undetectable in all treatment groups except the 3-MC group. Glutathione status was unaffected by any of the treatments. This is the first study identifying the carotenoids BX, CX and AX as inducers of rat lung and kidney xenobiotic metabolizing enzymes.

Publication Types:

PMID: 10434850 [PubMed - indexed for MEDLINE]
Dietary carotenoids inhibit aflatoxin B1-induced liver preneoplastic foci and DNA damage in the rat: role of the modulation of aflatoxin B1 metabolism.

Gradelet S, Le Bon AM, Bergès R, Suschetet M, Astorg P.

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To study the effects of carotenoids on the initiation of liver carcinogenesis by aflatoxin B1 (AFB1), male weanling rats were fed beta-carotene, beta-apo-8'-carotenal, canthaxanthin, astaxanthin or lycopene (300 mg/kg diet), or an excess of vitamin A (21000 RE/kg diet), or were injected i.p. with 3-methylcholanthrene (3-MC) (6 x 20 mg/kg body wt) before and during i.p. treatment with AFB1 (2 x 1 mg/kg body wt). The rats were later submitted to 2-acetylaminofluorene treatment and partial hepatectomy, and placental glutathione S-transferase-positive liver foci were detected and quantified. The in vivo effects of carotenoids or of 3-MC on AFB1-induced liver DNA damage were evaluated using different endpoints: liver DNA single-strand breaks (SSB) induced by AFB1, and in vivo binding of [3H]AFB1 to liver DNA and plasma albumin. Finally, the modulation of AFB1 metabolism by carotenoids or by 3-MC was investigated in vitro by incubating [14C]AFB1 with liver microsomes from rats that had been fed with carotenoids or treated by 3-MC, and the metabolites formed by HPLC were analyzed. In contrast to lycopene or to an excess of vitamin A, both of which had no effect, beta-carotene, beta-apo-8'-carotenal, astaxanthin and canthaxanthin, as well as 3-MC, were very efficient in reducing the number and the size of liver preneoplastic foci. In a similar way as 3-MC, the P4501A-inducer carotenoids, beta-apo-8'-carotenal astaxanthin and canthaxanthin, as well as 3-MC, were very efficient in reducing the number and the size of liver preneoplastic foci. It is concluded that these carotenoids exert their protective effect through the deviation of AFB1 metabolism towards detoxication pathways. In contrast, beta-carotene did not protect hepatic DNA from AFB1-induced alterations, and caused only minor changes of AFB1 metabolism: seemingly, its protective effect against the initiation of liver preneoplastic foci by AFB1 is mediated by other mechanisms.

Publication Types:

PMID: 9525273 [PubMed - indexed for MEDLINE]
Modulation of aflatoxin B1 carcinogenicity, genotoxicity and metabolism in rat liver by dietary carotenoids: evidence for a protective effect of CYP1A inducers.

Gradelet S, Astorg P, Le Bon AM, Bergès R, Suschetet M.

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The effects of several carotenoids of vitamin A and of 3-methylcholanthrene have been tested on the initiation of hepatocarcinogenesis by aflatoxin B1, using the sequential protocol of Solt and Farber. AFB1-induced DNA single-strand breaks and AFB1-metabolism were also assessed. The P4501A inducer carotenoids (canthaxanthin, astaxanthin, beta-apo-8'-carotenal) and 3-methylcholanthrene reduce the carcinogenicity of AFB1, divert AFB1-metabolism into the less genotoxic aflatoxin M1 and reduce AFB1-induced DNA single-strand breaks: we conclude that these carotenoids exert their protective effect through the deviation of AFB1 metabolism towards detoxification pathways. beta-Carotene decreased AFB1 carcinogenicity but did not alter its metabolism, probably acting by other mechanisms.

Publication Types:

PMID: 9103297 [PubMed - indexed for MEDLINE]
Chemoprevention by naturally occurring and synthetic agents in oral, liver, and large bowel carcinogenesis.

Mori H, Tanaka T, Sugie S, Yoshimi N, Kawamori T, Hirose Y, Ohnishi M.

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A number of naturally occurring compounds and several related synthetic agents were confirmed to exert chemopreventive properties against carcinogenesis in the digestive organs. Phenolic compounds, widely distributed as plant constituents, possess chemopreventive activities in tongue, liver, and large bowel of rodents. Of them, a simple phenolic protocatechuic acid seems to be a promising compound. Organosulfur compounds contained in the cruciferous vegetables and known to activate detoxifying enzymes are regarded as a candidate group for cancer preventive agents. We proved a strong protective effect of S-methylmethanethiosulfonate, a constituent in these vegetables, on azoxymethane (AOM)-induced large bowel carcinogenesis. Some oxygenated carotenoids (xanthophylls) are reported to have antitumor effects. Naturally occurring xanthophylls astaxanthin and canthaxanthin have considerable preventive activities on 4-nitroquinoline-1-oxide (4-NQO)-induced tongue carcinogenesis and AOM-induced large bowel carcinogenesis. A novel synthesized retinoidal butenolide, KYN-54, which suppresses large bowel as well as tongue carcinogenesis could be a useful agent for prevention of digestive organ cancers. Some trace elements are known to have anticarcinogenic effects. Magnesium hydroxide, a protective agent in colorectal carcinogenesis, inhibits c-myc expression and ornithine decarboxylase activity in the mucosal epithelium of the intestine. Our results show that many agents with preventive effects in tongue, liver, and large bowel control carcinogen-induced hyperproliferation of cells in these organs. Carcinogens used to induce large bowel cancers also induce apoptosis in the target sites. Telomerase activity is increased in the tissues of preneoplastic as well as neoplastic lesions in experimental models such as dimethylbenz[a]anthracene-induced oral carcinogenesis in hamsters. These could be useful biomarkers in studies for cancer chemoprevention.

Publication Types:

PMID: 9591191 [PubMed - indexed for MEDLINE]
Suppression of azoxymethane-induced rat colon carcinogenesis by dietary administration of naturally occurring xanthophylls astaxanthin and canthaxanthin during the postinitiation phase.

Tanaka T, Kawamori T, Ohnishi M, Makita H, Mori H, Satoh K, Hara A.

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The modulating effects of dietary feeding of two xanthophylls, astaxanthin (AX) and canthaxanthin (CX) during the postinitiation phase on colon carcinogenesis initiated with azoxymethane (AOM) were investigated in male F344 rats. Animals were initiated with AOM by weekly s.c. injections of 15 mg/kg body wt for 3 weeks and then they were fed the diets containing AX or CX at concentrations of 100 and 500 p.p.m. for 34 weeks. The others contained the groups of rats treated with AX or CX alone and untreated. At the end of the study (week 37), the incidence and multiplicity of neoplasms (adenoma and adenocarcinoma) in the large intestine of rats initiated with AOM and followed by AX or CX containing diet at a high dose (500 p.p.m.) were significantly smaller than those of rats given AOM alone (P < 0.001). In addition, AX or CX feeding significantly inhibited the development of aberrant crypt foci induced by AOM. Dietary exposure to AX or CX also decreased cell proliferation activity as revealed by measuring 5'-bromodeoxyuridine-labeling index as crypt cells, colonic mucosal ornithine decarboxylase activity and blood polyamine levels. These results indicate that AX and CX are possible chemopreventers for carcinogenesis of colon in addition to urinary bladder and oral cavity and such effects may be partly due to suppression of cell proliferation.

Publication Types:

PMID: 8603470 [PubMed - indexed for MEDLINE]
Chemoprevention of rat oral carcinogenesis by naturally occurring xanthophylls, astaxanthin and canthaxanthin.

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The chemopreventive effects of two xanthophylls, astaxanthin (AX) and canthaxanthin (CX) on oral carcinogenesis induced by 4-nitroquinoline 1-oxide (4-NQO) was investigated in male F344 rats. Rats were given 20 ppm of 4-NQO in their drinking water for 8 weeks to induce oral neoplasms or preneoplasms. Animals were fed diets containing 100 ppm AX or CX during the initiation or postinitiation phase of 4-NQO-induced oral carcinogenesis. The others contained the groups of rats treated with AX or CX alone and untreated. At the end of the study (week 32), the incidences of preneoplastic lesions and neoplasms in the oral cavity of rats treated with 4-NQO and AX or CX were significantly smaller than those of rats given 4-NQO alone (P < 0.001). In particular, no oral neoplasms developed in rats fed AX and CX during the 4-NQO exposure and in those given CX after the 4-NQO administration. Similarly, the incidences of oral preneoplastic lesions (hyperplasia and dysplasia) in rats treated with 4-NQO and AX or CX were significantly smaller than that of the 4-NQO-alone group (P < 0.05). In addition to such tumor inhibitory potential, dietary exposure of AX or CX decreased cell proliferation activity in the nonlesional squamous epithelium exposed to 4-NQO as revealed by measuring the silver-stained nucleolar organizer regions protein number/nucleus and 5'-bromodeoxyuridine-labeling index. Also, dietary AX and CX could reduce polyamine levels of oral mucosal tissues exposed to 4-NQO. These results indicate that AX and CX are possible chemopreventers for oral carcinogenesis, and such effects may be partly due to suppression of cell proliferation.

Publication Types:

PMID: 7664280 [PubMed - indexed for MEDLINE]
Chemoprevention of mouse urinary bladder carcinogenesis by the naturally occurring carotenoid astaxanthin.

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The chemopreventive effects of two xanthophylls, astaxanthin (AX) and canthaxanthin (CX), on urinary bladder carcinogenesis induced by N-butyl-N(4-hydroxybutyl)nitrosamine (OH-BBN) was investigated in male ICR mice. Mice were given 250 p.p.m. OH-BBN in drinking water for 20 weeks and after a 1 week interval with tap water, water containing AX or CX at a concentration of 50 p.p.m. was administered during subsequent 20 weeks. Other groups of mice were treated with AX or CX alone or untreated. At the end of the study (week 41), the incidences of preneoplastic lesions and neoplasms in the bladder of mice treated with OH-BBN and AX or CX were smaller than those of mice given OH-BBN. In particular, AX administration after OH-BBN exposure significantly reduced the incidence of bladder cancer (transitional cell carcinoma) (P < 0.003). However, the inhibition of the frequencies of such lesions in mice treated with OH-BBN and CX was not significant. Treatment with AX or CX also decreased the number/nucleus of silver-stained nucleolar organizer region proteins (AgNORs), a new index of cell proliferation, in the transitional epithelium exposed to OH-BBN. Preneoplasms and neoplasms induced by OH-BBN, and the antiproliferative potential, was greater for AX than CX. These results indicate that AX is a possible chemopreventive agent for bladder carcinogenesis and such an effect of AX may be partly due to suppression of cell proliferation.

Publication Types:

PMID: 8293542 [PubMed - indexed for MEDLINE]
Preventive action of carotenoids on the development of lymphadenopathy and proteinuria in MRL-lpr/lpr mice.

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The chemopreventive action of carotenoids on proteinuria and lymphadenopathy were examined in autoimmune-prone MRL-lpr/lpr (MRL/l) mice. They were fed a synthetic full-fed diet (16-18 kcal/mouse/day) with supplementation of beta-carotene or astaxanthin (0.19 mumoles/mouse, 3 times a week), and the development of lymphadenopathy and proteinuria were examined. MRL/l mice fed a full-fed diet without the supplementation of carotenoids or those fed a calorie-restricted (CR) diet (10-11 kcal/mouse/day, 60% calorie intake of full-fed mice) were employed as controls. CR dramatically delayed the development of proteinuria and lymphadenopathy, as reported previously. Carotenoids also significantly delayed the onset of these symptoms in MRL/l mice fed a full-fed diet. Carotenoids were half as effective as CR and astaxanthin, a carotenoid without provitamin A activity, which appeared to exert more significant preventive actions than beta-carotene in delaying the development of these symptoms. Similar chemopreventive actions of carotenoids were also demonstrated in MRL/l mice fed a regular diet (Lab Chow). CR has been shown to augment IL-2 production and to decrease serum prolactin levels in this strain, which may be related to its dramatic preventive action of autoimmunity. However, carotenoids did not affect IL-2 production nor prolactin levels in full-fed MRL/l mice. The chemopreventive actions of carotenoids observed in autoimmune-prone MRL/l mice may be attributed to yet unknown mechanisms, apart from their provitamin A activity or oxygen-quenching activity.

Publication Types:

PMID: 8180322 [PubMed - indexed for MEDLINE]
Inhibition of benzo(a)pyrene-induced mouse forestomach neoplasia by astaxanthin containing egg yolks

Anticarcinogenic activity of astaxanthin-containing egg yolks (designate AEY) was investigated for benzo(a)pyrene (BP)-induced mouse forestomach tumorigenesis initiating regimen. Female ICR mouse (6-7 weeks of age) were housed in polycarbonated cages (5 mice/cage; 20 mice/treatment) in a humidity-and-temperature-controlled facility and permitted free access to water and food. One week later, four and 2 days prior to p.o. treatment with BP (2 mg/0.2 ml corn oil), mice were given 0.2 ml PBS containing 50 mg AEY, 100 mg AEY, 150 mg AEY, or 150 mg CEY. Control mice were only given 0.2 ml PBS. Three days later this sequence was repeated for a total of 4 times. Beginning with the first intubation and continuing thereafter, body weight and food intake were recorded once weekly. All surviving mice were sacrificed 24 weeks after the first dose of BP. Mice treated with AEY developed only about one third as many neoplasms/animal as mice in control or CEY-treated group (p<0.05). Reduction effect of tumor development by AEY was dependent upon doses applied. Tumor incidence was also reduced by AEY treatments, but significantly reduced only by 150 mg AEY treatment when compared to that by control or CEY. Food intake and body weight were not affected by AEY treatment. These results indicate that AEY inhibits tumorigenesis of mouse forestomach induced by BP.
Cancer prevention by astaxanthin, a natural carotenoid

MOU X Y (Kyoto Prefectural Univ. Medicine Graduate School Of Medical Sci.)

Astaxanthin is a natural carotenoid. The anticarcinogenic effect of astaxanthin was shown in mouse lung and liver models. The effect of astaxanthin on cell proliferation, cell cycle progression and apoptosis was examined in the HepG2 human liver cancer cell line. Astaxanthin significantly inhibited the proliferation of liver cancer cells in a dose-dependent manner. Flow cytometric analysis demonstrated that astaxanthin restrained the cell cycle progression at G1, and induced apoptosis. Further examinations by real-time quantitative RT-PCR revealed that astaxanthin enhanced the expression of p21CIP1/WAF1, GADD153 and c-myc genes. These results suggest that astaxanthin will be a promising agent for use in chemopreventive or therapeutics against cancer.
Inhibition of Sarcoma-180 Cell-induced Mouse Ascites Cancer by Astaxanthin-containing Egg Yolk
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Abstract
Anticarcinogenic activity of astaxanthin-containing egg yolk (designate AEY) was investigated for mouse ascites carcinogenesis induced by mouse Sarcoma-I80 (S-180) cells. Female ICR mice (8 mice/treatment, 7~8 weeks of age, 25±1g) were injected, i.p. with S-180 cells (1 x 10^7 cell/ml PBS). Two days later, each mouse was given 0.1ml PBS containing AEY (10, 25 or 50µg/g body weight) or control egg yolk (CEY: 50µg/g body weight) every other day for 7 times. Control mice were only given 0.1ml S-180 cells and 0.1ml PBS. Mice treated with 25µg/g body weight of AEY showed 24.8 days of life, which was equivalent to 138% of control mice's life (18.0 days). Based on dose-dependant experiment of AEY, mice treated with 10µg/g body weight showed slightly longer life (19.4 days) relative to mice treated with control mice, and mice treated with 50µg/g body weight exhibited 21.9 days of life. Mice treated with any dose of AEY exhibited longer life than mice with CEY 50µg/g body weight. Body weight of mice treated with AEY was reduced relative to that of control mice or CEY-treated mice. These results suggest that AEY inhibits the carcinogenesis of mouse ascites induced by S-180 cells.
Cancer prevention by carotenoids

Nishino, et al,

A review with 13 refs. Various natural carotenoids have been proven to have anticarcinogenic activity. Epidemiol. investigations have shown that cancer risk is inversely related to the consumption of green and yellow vegetables and fruits. As b-carotene is present in abundance in these vegetables and fruits, it has been investigated extensively as a possible cancer preventive agent. However, various carotenoids which coexist with b-carotene in vegetables and fruits also have anticarcinogenic activity, and some of these, such as a-carotene, lutein and lycopene, show a higher potency than b-carotene in suppressing exptl. carcinogenesis. Thus, we have carried out more extensive studies on cancer preventive activities of natural carotenoids in foods. For example, we found that b-cryptoxanthin showed antitumor initiating activity, as well as antitumor promoting activity. It is of interest that not only carotenoids distributed in vegetables and fruits, but also animal carot enoids, such as astaxanthin, are promising as cancer preventive agents. In the present study, the cancer preventive potential of phytoene was also confirmed. The establishment of NIH3T3 cells that produce phytoene by introducing the crtB gene provides evidence that resistance against transformation, imposed by transfection of activated H-ras oncogene, was acquired by phytoene prodn. Anal. of the action mechanism of these natural carotenoids is now in progress, and some interesting results have already been obtained; for example, various carotenoids were suggested to stimulate the expression of RB gene, an antioncogene.
Introduction
There are clear links between human cancers and diet.1,2 By some estimates, dietary risk factors rank higher than tobacco usage and much higher than pollution or occupational hazards in their association with cancer deaths.3 In addition to avoidance of tobacco smoke and carcinogenic food items, regular intake of chemopreventive compounds is a promising approach for reducing cancer incidence.3,4 A number of substances naturally occurring in foodstuffs, particularly antioxidant compounds in plant products, have shown promise as potential chemopreventive agents.3-6 Among these phytonutrients, the yellow, orange and red carotenoid pigments have recently sparked much interest. In epidemiological studies, vegetable and fruit consumption has consistently been associated with reduced incidence of various cancers, 5-7 and dietary carotenoid intake from these sources has similarly been correlated with reduced cancer risk.8-10 However, several recent large-scale intervention trials failed to find any chemopreventive effect of long-term supplementation with β-carotene, the most abundant dietary carotenoid.11-13 Several naturally occurring carotenoids other than β-carotene have exhibited anticancer activity,14-17 and are being considered further as potential chemopreventive agents. Among these carotenoids, the red pigment astaxanthin is of particular interest in health management due to its unique structural and chemical properties.18-20 This chapter will review the evidence for anticarcinogenic behavior of selected carotenoids, with an emphasis on the chemopreventive activities of astaxanthin.
A preliminary investigation of the enzymatic inhibition of 5alpha-reduction and growth of prostatic carcinoma cell line LNCap-FGC by natural astaxanthin and Saw Palmetto lipid extract in vitro.

Anderson ML.

Inhibition of 5alpha-reductase has been reported to decrease the symptoms of benign prostate hyperplasia (BPH) and possibly inhibit or help treat prostate cancer. Saw Palmetto berry lipid extract (SPLE) is reported to inhibit 5alpha-reductase and decrease the clinical symptoms of BPH. Epidemiologic studies report that carotenoids such as lycopene may inhibit prostate cancer. In this investigation the effect of the carotenoid astaxanthin, and SPLE were examined for their effect on 5alpha-reductase inhibition as well as the growth of prostatic carcinoma cells in vitro. The results show astaxanthin demonstrated 98% inhibition of 5alpha-reductase at 300 microg/mL in vitro. Alphastat, the combination of astaxanthin and SPLE, showed a 20% greater inhibition of 5alpha-reductase than SPLE alone in vitro. CONCLUSIONS: Low levels of carotenoid astaxanthin inhibit 5alpha-reductase and decrease the growth of human prostatic cancer cells in vitro. Astaxanthin added to SPLE shows greater inhibition of 5alpha-reductase than SPLE alone in vitro.
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Astaxanthin inhibits tumor invasion by decreasing extracellular matrix production and induces apoptosis in experimental rat colon carcinogenesis by modulating the expressions of ERK-2, NFkB and COX-2.

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Abstract

Colon cancer is the third most malignant neoplasm in the world and it remains an important cause of mortality in Asian and Western countries. Astaxanthin (AST), a major component of carotenoids possesses attractive remedial features. The purpose of this study is to investigate the possible mechanism of action of astaxanthin against 1, 2 dimethyl hydrazine (DMH)-induced rat colon carcinogenesis. Wistar male rats were randomized into five groups, group 1 were control rats, group 2 were rats that received AST (15 mg/kg body wt p.o. everyday), rats in group 3 were induced with DMH (40 mg/kg body wt, s.c.), DMH-induced rats in groups 4 and 5 were either pre or post initiated with AST, respectively as in group 2. DMH-induced rats exhibited elevated expressions of Nuclear factor kappa B-p65 (NF-kappaB-p65), Cyclooxygenase-2 (COX-2), Matrixmetallo proteinases (MMP) 2/9, Proliferating cell nuclear antigen (PCNA), and Extracellular signal-regulated kinase-2 (ERK-2) as confirmed by immunofluorescence. Further, Westernblot analysis of MMPs-2/9, ERK-2 and Protein kinase B (Akt) revealed increased expressions of these proteins in DMH-induced groups of rats. AST-treatment decreased the expressions of all these vital proteins, involved in colon carcinogenesis. The ability of AST to induce apoptosis in the colon of DMH-induced rats was confirmed by Annexin-V/PI staining in a confocal microscopy, DNA fragmentation analysis and expression of caspase-3 by Western blotting. In conclusion, astaxanthin exhibits anti-inflammatory and anti-cancer effects by inducing apoptosis in DMH-induced rat colon carcinogenesis by modulating the expressions of NFkB, COX-2, MMPs-2/9, Akt and ERK-2.

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Cancer Prevention
Intervention of astaxanthin against cyclophosphamide-induced oxidative stress and DNA damage: a study in mice.

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Abstract

Astaxanthin, a natural and nutritional red carotenoid pigment, is used as a dietary supplement. The intention of the present study was to investigate the beneficial effects of dietary pigment astaxanthin, against cyclophosphamide-induced oxidative stress and DNA damage. The endpoints of evaluation of the study included: (a) malondialdehyde, glutathione and superoxide dismutase concentration in liver to detect oxidative stress; (b) normal and modified alkaline comet assays (the latter includes lesion-specific enzymes formamidopyrimidine-DNA glycosylase and endonuclease-III) to detect normal and oxidative stress-induced DNA damage by cyclophosphamide in the mouse bone marrow and the peripheral blood lymphocytes. In addition, micronucleus assay and chromosomal aberration test capable of detecting the DNA damage were also carried out in peripheral blood and bone marrow of mice. Cyclophosphamide (100 mg/kg intra-peritoneal) treatment led to significant increase in liver malondialdehyde and decreased the antioxidant enzymes glutathione and superoxide dismutase. Further, cyclophosphamide also significantly increased the DNA damage as observed from normal and modified comet assays as well as micronucleus and chromosomal aberration assay. Pre-treatment with astaxanthin (12.5, 25 and 50 mg/kg/day for 5 days per oral) resulted in the restoration of oxidative stress markers such as malondialdehyde, glutathione and superoxide dismutase in liver. The amelioration of oxidative stress with astaxanthin pre-treatment correlated well with the decreased DNA damage as evident from normal and modified alkaline comet assays of bone marrow cells and peripheral blood lymphocytes. Further astaxanthin pre-treatment also reduced the frequency of chromosomal breakage and micronucleus formation in the mouse bone marrow cells and peripheral blood reticulocytes. It is thus concluded that pre-treatment with astaxanthin attenuates cyclophosphamide-induced oxidative stress and subsequent DNA damage in mice and it can be used as a chemoprotective agent against the toxicity of anticancer drug cyclophosphamide.

PMID: 19539803 [PubMed - indexed for MEDLINE]
Growth-inhibitory effects of the astaxanthin-rich alga Haematococcus pluvialis in human colon cancer cells.


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Abstract

The growth-inhibitory effects of the astaxanthin-rich Haematococcus pluvialis were studied in HCT-116 colon cancer cells. H. pluvialis extract (5-25 microg/ml) inhibited cell growth in a dose- and time-dependent manner, by arresting cell cycle progression and by promoting apoptosis. At 25 microg/ml of H. pluvialis extract, an increase of p53, p21(WAF-1/CIP-1) and p27 expression (220%, 160%, 250%, respectively) was observed, concomitantly with a decrease of cyclin D1 expression (58%) and AKT phosphorylation (21%). Moreover, the extract, at the same concentration, strongly up-regulated apoptosis by modifying the ratio of Bax/Bcl-2 and Bcl-XL, and increased the phosphorylation of p38, JNK, and ERK1/2 by 160%, 242%, 280%, respectively. Growth-inhibitory effects by H. pluvialis were also observed in HT-29, LS-174, WiDr, SW-480 cells. This study suggests that H. pluvialis may protect from colon cancer.

PMID: 19423215 [PubMed - indexed for MEDLINE]
Antioxidative and antiproliferative effects of astaxanthin during the initiation stages of 1,2-dimethyl hydrazine-induced experimental colon carcinogenesis.

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Abstract

Colon cancer is one of the major causes of cancer mortality worldwide. Several carotenoids with antioxidant properties are reported for their chemopreventive nature. In this study, we have evaluated the chemopreventive efficacy of astaxanthin on lipid peroxidation, antioxidant status, total number of aberrant crypt foci (ACF), and cell proliferation in 1,2 dimethylhydrazine (DMH)-induced colon carcinogenesis using a rat model. DMH was induced subcutaneously at a dosage of 40 mg/kg body weight, twice a week for 2 weeks. Astaxanthin was administered before and after the DMH induction, orally at a concentration of 15 mg/kg body weight throughout the experimental period. At the end of 16 weeks, pre-treatment with astaxanthin markedly reduced the degree of histological lesions, ACF development and also lowered the number of argyrophilic nucleolar organizer regions. Our results also showed the decreased levels of colon enzymic and non-enzymic antioxidants and increased levels of lipid peroxidation marker levels in DMH-induced rats, which were significantly reversed on astaxanthin administration. In conclusion, the results of this study suggest that astaxanthin has an affirmative and beneficial effect against chemically induced colonic pre-neoplastic progression in rats induced by DMH.

PMID: 19645817 [PubMed - indexed for MEDLINE]
Effect of dietary astaxanthin at different stages of mammary tumor initiation in BALB/c mice.

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Abstract

The effects of astaxanthin on tumor growth, cardiac function and immune response in mice were studied. Female BALB/c mice were fed a control diet (diet C) for 8 weeks, 0.005% astaxathin for 8 weeks (diet A), or diet C for weeks 1-5 followed by diet A thereafter (diet CA). Mice were injected with a mammary tumor cell line on day 7 and tumor growth was measured daily. Mice fed diet A had extended tumor latency and lower tumor volume (p<0.05). Interestingly, those fed diet CA showed the fastest tumor growth. Astaxanthin feeding elevated plasma astaxanthin concentrations; there was no difference in plasma astaxanthin between mice fed CA and those fed A. Mice fed diet A, but not CA, had a higher (p<0.05) natural killer cell subpopulation and plasma interferon-gamma concentration compared to those fed diet C. Astaxanthin delayed tumor growth and modulated immune response, but only when astaxanthin was given before tumor initiation. This suggests that an adequate blood astaxanthin status is needed to protect against tumor initiation; conversely, astaxanthin supplementation after tumor initiation may be contraindicated.

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