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Review article

The silver bullet for cancer prevention: Chemopreventive effects of carotenoids

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ABSTRACT

Cancer has been a leading cause of death in many countries. Chemoprevention of various types of human cancer using dietary nutrients has received a lot of attention and interest in the past decade. Recently, carotenoids have been shown to prevent tumor growth and progression. Carotenoids demonstrated chemopreventive capability by interrupting several stages of cancer including initiation, promotion, progression, and metastasis. The molecular mechanisms of actions are through the modulation of cell-signaling pathways and gene expression. The results of our study suggested that carotenoids could act as chemopreventive agents against the growth and progression of human cancer cells.

1. Introduction

Carotenoids are organic compounds naturally occurring in plants and photosynthetic organisms such as algae [1,2]. Present reports suggest that >600 carotenoids have been identified. However, as a result of selective uptake in digestive tract, only 14 carotenoids with their metabolites have been identified in human plasma and peripheral tissues [3]. Carotenoids are commonly divided into two major classes, namely, carotenes and xanthophylls [4]. The presence of these carotenoids has been reported in fruits and vegetables. Some of the common carotenes are lycopene, carotene (α, β, γ, δ), and phytoene. On the other hand, the most common xenophylls are cryptoxanthin (α, β), zeaxanthin, lutein, violaxanthin, and astaxanthin [4]. Because of their colorful nature, carotenoid-rich foods such as fruits and vegetables always attract people's interest and induce their appetite. Results of many studies indicated that diets rich in vegetables and fruits can reduce the risk of several chronic diseases including cancer, cardiovascular diseases, and diabetes [5,6]. Many phytochemicals and nutrients present in these plant foods, such as carotenoids, antioxidant vitamins, polyphenols, folate, plant sterols, indoles, and fibers, contribute to the risk reduction [5,6]. Among these phytochemicals, carotenoids have been studied widely because of their beneficial effects on the human tissues and the diverse options they provide in improving human health. In humans, some carotenoids, such as β-carotene and β-cryptoxanthin, are precursors of vitamin A. Besides β-carotene, various carotenoids show more potent activity to suppress the process of carcinogenesis. In this

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review, we will mainly discuss the chemopreventive effects of β-carotene, lycopene, and cryptoxanthin.

2. Carcinogenesis

Cancer is an important public health issue worldwide. It has been a leading cause of death in many countries [7]. During tumorigenesis, accumulation of multiple gene mutations would lead to the neoplastic transformation of a single cell. These aberrant mutations or overexpression of several important genes contribute to the initiation of cancer and progression of human malignancies. Neoplastic transformation commonly affects three major classes of genes: proto-oncogenes, tumor-suppressor genes, and DNA repair genes. Several cellular proto-oncogenes have been activated through mutation. For example, the *ras* proto-oncogenes were a typical subset of gene mutation. Because of neoplastic transformation, *ras* (oncogene) genes were activated and exhibited transforming properties. The mutations of *ras* augment the activity of guanosine-5′-triphosphatase and transmission of signals to *raf*. Furthermore, mutations of the *raf* genes could also drive the mitogen-activated protein kinase (MAPK) signaling pathway and induce tumor growth and progression [8]. Several oncoproteins such as RAS, RAF, MAPK, and phosphatidylinositol-3 kinase (PI-3 K), Akt are frequently mutated in cancer [9,10]. Meanwhile, PI-3 K mutations could activate Akt and mTOR cascades to enhance cell survivals and escape from cell apoptosis. Suppression of apoptotic pathways involving the downstream caspase-3 molecule could avoid cell death [11]. RAS, RAF, and PI-3 K mutations occur in many cancer patients. The incidence of these cancer-specific point mutations is particularly high in many types of cancer and has been linked to poor outcomes. The aberrant activation of RAS/RAF/MEK/MAPK signaling pathways stimulate key processes involved in tumor growth and progression, including proliferation, angiogenesis, invasion, and metastasis [8]. The activation of MAPK/extracellular signal–regulated kinase (ERK) signaling pathway could induce the expression of cyclooxygenase-2 (COX-2) protein, its principal metabolite prostaglandin E_2, and inflammatory response [12,13]. More than 50% of colorectal carcinomas have elevated levels of COX-2 protein. The aberrant activation of MAPK/ERK signaling pathway also plays an important role in the disassembly of E-cadherin adherens complex and augments nuclear accumulation of β-catenin transcription factors in several types of cancer. Abnormal accumulation of β-catenin is correlated with tumor growth and progression [14–16]. A recent study indicated that β-catenin could be an important biomarker of human cancer. During the activation of these signaling pathways, upregulation of cell cycle–related protein, such as cyclin D1, is strongly correlated with tumor growth.

During the progression of tumor, overexpression of matrix metalloproteinases (MMPs) is highly correlated with inflammatory response, tumor growth, angiogenesis, and metastasis [17]. MMPs could degrade extracellular matrix and create a microenvironment that could support tumor development [18]. Invasion of cancer cells into the surrounding stroma occurs through the augmented expression of MMPs [19]. Previous studies suggested that elevated expression of MMP-9 was strongly correlated with poor prognosis and low survival rate in cancer patients [20,21]. However, suppression of MMPs could prevent the development of tumor [22].

3. Chemopreventive effects of carotenoids

3.1. *β-Carotene*

β-Carotene has been shown to inhibit the proliferation of cancer cells by their antioxidant activity or by their conversion into vitamin A. Surprisingly, previous human studies demonstrated that high doses of β-carotene (20 mg/day) supplementation enhanced the prevalence of lung cancer, especially in current smokers or people exposed to asbestos [23]. In order to clarify these controversial findings, scientists conducted several *in vitro* and *in vivo* studies. Many conclusive results showed that high levels of β-carotene in the smoke-exposed animals were prone to have plenty of oxidative metabolites of β-carotene, which enhance the metabolism of retinoic acid followed by diminished retinoid signaling, and induced cell proliferation. These findings suggest that dietary intake of β-carotene is still beneficial to induce chemopreventive effects. However, overdose of β-carotene in smokers would induce the formation and growth of lung cancer. Furthermore, these findings attracted more attention to the study of carotenoids. In this review, more evidences will be provided to demonstrate whether the remaining carotenoids are capable of preventing tumor growth.

3.2. *Lycopene*

Results of various epidemiological studies indicated that dietary intake of lycopene-rich tomatoes and tomato products is correlated with lower risk of cancer [24,25]. Serum and tissue levels of lycopene are also inversely correlated with the risk of several types of cancer. To further understand the chemopreventive effects, several studies have been conducted to investigate the molecular actions of lycopene. Most noticeably, one of the studies indicated that lycopene supplementation (at doses of 1.1 and 4.3 mg/kg body weight/day) could inhibit the proliferation of lung squamous cancer cells by the induction of apoptosis and upregulation of insulin-like growth factor–binding protein-3 in cigarette smoke–exposed ferrets [26]. Moreover, recent studies suggested that lycopene effectively inhibited the proliferation of several types of cancer by different mechanisms. Lycopene (at doses of 2, 5, and 10 μM) significantly inhibited the proliferation of colon cancer cells *in vitro* [27]. The molecular mechanisms of action were through the suppression of proliferative PI-3 K/Akt signaling cascades and augmented apoptotic pathways. Moreover, intake of lycopene (at doses of 3 and 6 mg/kg body weight/day) inhibited tumor growth in a mouse xenograft model of colorectal cancer [28]. Lycopene could also stabilize the expression of adherent E-cadherin molecules in colon cancer cells. Moreover, concomitant consumption of lycopene and eicosapentaenoic acid could synergistically inhibit the proliferation of colon cancer cells [29]. Huang et al. showed that lycopene significantly inhibited the proliferation and

metastasis of hepatoma cancer cells by the reduction of MMP-9 and vascular endothelial growth factor (VEGF) molecules [30]. The molecular mechanisms of action were achieved by the suppression of nuclear factor-kappa B (NF-κB p65) and stimulating protein-1 [31]. These findings made people feel confident in taking carotenoids as chemopreventive agents. Furthermore, recent studies demonstrated that lycopene can be converted into apo-10′-lycopenals by carotene-9′, 10′-oxygenase in both *in vitro* and *in vivo* conditions. The cleaved apo-10′-lycopenals can be further converted into apo-10′-lycopenoic acid and apo-10′-lycopenol in liver and lung tissues. The major metabolite of lycopene, apo-10′-lycopenoic acid, effectively inhibited the proliferation of lung cancer cells *in vitro* and *in vivo* conditions [32].

3.3. *Fucoxanthin*

Fucoxanthin is an orange-pigmented carotenoid found in seaweed. Because of its distinct structure, fucoxanthin belongs to the group of non-provitamin A carotenoids. However, fucoxanthin is an excellent free radical quencher under anoxic conditions. As free radicals and oxidative stress are involved in the initiation stage of cancer development, nutritional studies have focused on the antioxidant activity of fucoxanthin in the prevention of cancer development in the past few years. Many studies suggested that fucoxanthin can effectively inhibit or prevent the proliferation of several types of cancer cell lines such as prostate cancer, leukemia, and colorectal cancer cells [33,34]. The molecular mechanisms of fucoxanthin were probably through the induction of cell cycle arrest, apoptosis, and even by the expression of gap junction molecules in these cell lines. Moreover, fucoxanthin can inhibit the expression of antiapoptotic molecules such as Bcl-2 and Bcl-xl proteins. Yu et al. showed that fucoxanthin (50 and 75 μM) inhibited the proliferation of human gastric adenocarcinoma MGC 803 cells. The results demonstrated that fucoxanthin induced cell cycle arrest at G_2/M phase by the suppression of cyclin B1 protein. In addition, fucoxanthin also induced cell apoptosis by the suppression of JAK/STAT signaling pathway [35].

3.4. *β-Cryptoxanthin*

The structure of β-cryptoxanthin is similar to that of β-carotene. Under the action of carotene monooxygenase, cleavage of β-cryptoxanthin can lead to the formation of retinol and retinoic acid. Therefore, β-carotene and β-cryptoxanthin are provitamin A carotenoids. Epidemiological studies indicated that high intake of β-cryptoxanthin is associated with reduced risk of lung cancer, especially for current smokers. In the *in vitro* study, β-cryptoxanthin significantly inhibited the proliferation of lung cancer cells. β-Cryptoxanthin exhibited its anticancer effects by the upregulation of retinoic acid receptor-β and by the transactivation of retinoic acid response element–driven promoter activity. Supplementing dose-dependent β-cryptoxanthin with lycopene prevents lung inflammation by suppressing the levels of tumor necrosis factor-α and squamous metaplasia in lung tissues in cigarette smoke–exposed animals [36]. Moreover, β-cryptoxanthin suppressed the levels of oxidative damage to DNA, 8-OHdG, the activation of NF-κB, and expression of activator protein 1 (AP-1) [36]. These results suggest that β-cryptoxanthin might play an important role in protecting the lung tissue from smoke-induced inflammation, DNA damage, and squamous metaplasia in experimental animals.

3.5. *Astaxanthin*

Astaxanthin is a marine carotenoid without vitamin A activity. Results from an earlier study of xenograft tumor mouse model demonstrated that pretreatment of astaxanthin (0.005% astaxanthin for 8 weeks) suppressed the growth of mammary tumor in BALB/c mice [37]. Mice fed with astaxanthin before tumor initiation had increased blood levels of natural killer cells and plasma levels of γ-interferon compared with those fed with control diet (i.e., without astaxanthin). Such an effect was not observed in mice fed with astaxanthin after the tumor initiation. This study suggests that adequate blood astaxanthin is essential to protect against tumor initiation. Other evidences showed that astaxanthin could play important roles in the suppression of tumor invasion and progression. An earlier study showed that astaxanthin acted as a chemopreventive agent against 1,2-dimethyl hydrazine (DMH)–induced rat colon carcinogenesis. When administered with DMH (40 mg/kg body weight, subcutaneously), control group of experimental animals had high expression of NF-κB p65, COX-2, MMP-2, MMP-9, proliferating cell nuclear antigen, protein kinase B (Akt), and ERK-2. However, the treatment group that received astaxanthin (15 mg/kg of body weight/day, orally) had lower tumor size and reduced levels of these tumor biomarkers. Furthermore, astaxanthin induced apoptosis in colorectal carcinoma tissues of DMH-induced rats. The effects were associated with increased expression of caspase-3 protein in those astaxanthin-fed mice [38]. These results suggest that astaxanthin acts as a chemopreventive agent against tumor growth, invasion, inflammation, and progression.

3.6. *Lutein and zeaxanthin*

Lutein and zeaxanthin have been demonstrated as strong antioxidants and are widely distributed in vegetables and fruits. Epidemiological studies indicated that high intake of lutein/zeaxanthin could reduce the risk of variety of cancers including lung and colon cancer [39,40]. Although the clear molecular mechanism of lutein and zeaxanthin has not been studied well yet, several studies already revealed their chemopreventive effects in animals. Dietary supplementation of lutein also reduces colon carcinogenesis in carcinogen (DMH)-treated animals [41]. The chemopreventive effects of lutein against colon cancer were by the suppression of k-Ras and β-catenin expression and by the activation of protein kinase B.

4. Conclusions

This review demonstrated the chemopreventive effects of carotenoids in different aspects (Fig. 1). Many evidences suggest that carotenoids play important roles in the prevention of tumor growth, invasion, metastasis, and progression. Carotenoids are widely distributed in fruits and vegetables. Daily consumption of fruits and vegetables can provide an excellent way to prevent tumorigenesis.

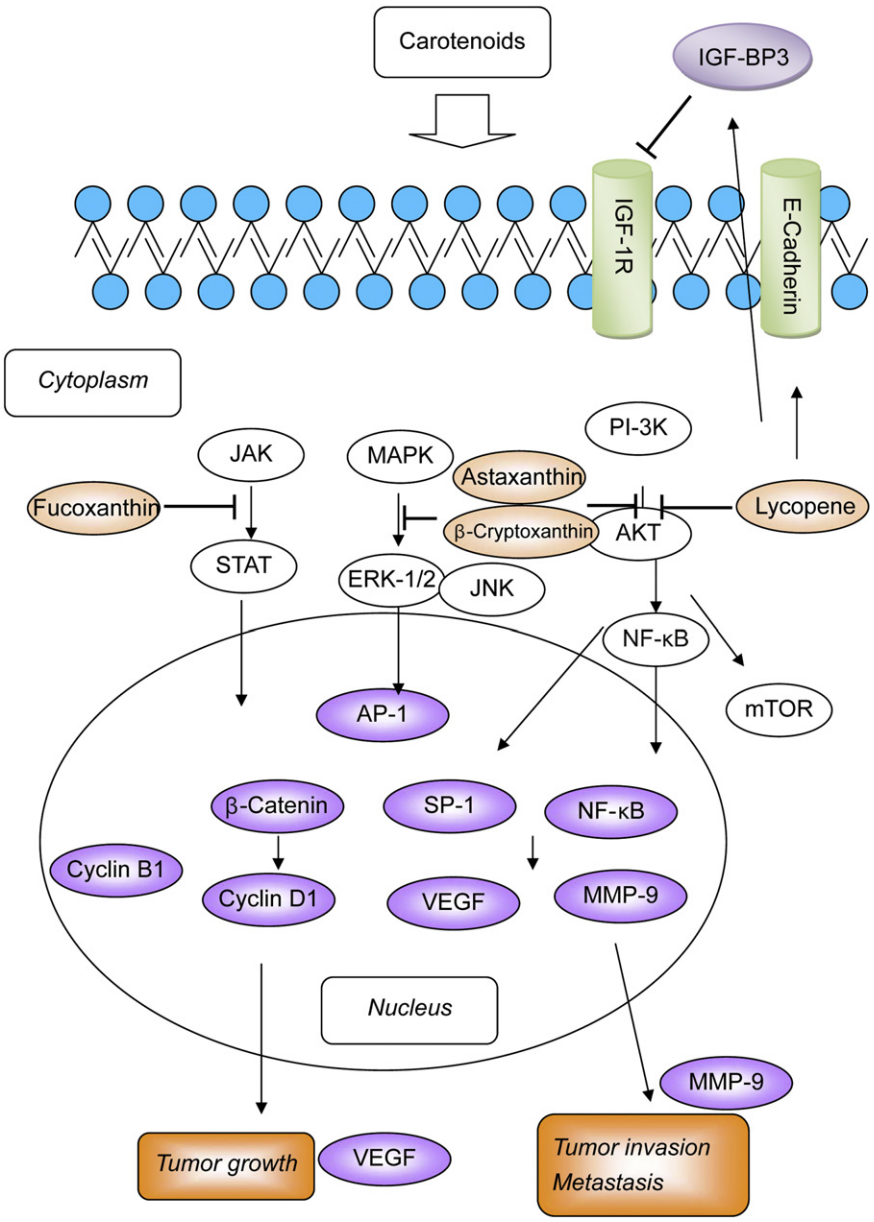

Fig. 1 – Proposed mechanisms of signaling pathways associated with carotenoids-mediated suppression of tumor growth and progression. ERK = extracellular signal–regulated kinase; IGF-1R = insulin-like growth factor 1; IGF-BP3 = insulin-like growth factor–binding protein-3; JAK = Janus kinase; JNK = c-Jun N-terminal kinase; MAPK = mitogen-activated protein kinase; MMP = matrix metalloproteinase; NF-κB = nuclear factor-kappa B; PI-3 K = phosphatidylinositol-3 kinase; SP-1 = stimulating protein-1; STAT = signal transducer and activator of transcription; VEGF = vascular endothelial growth factor.

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