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Carotenoids modulate the hallmarks of cancer cells

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Abbreviations: HL-60, human promyelocytic leukemia cell line; U-937, human leukemic monocyte lymphoma cell line; AtT20, mouse pituitary epithelial-like tumor cell line; DU145 and PC-3, human prostate cancer cell lines; LNCaP, androgen-sensitive human prostate adenocarcinoma cell line; Hep3B and HepG2, human hepatocellular carcinoma cell lines; HT-29, HCT-116, CaCo2, COLO 320 HSR, DLD-1, T-84 and WiDr, human colorectal adenocarcinoma cell lines; MCF-7, MDA-MB-468 and SK-BR-3, human breast adenocarcinoma cell lines; KB-1, human mouth epidermal carcinoma cell line; A549, human alveolar adenocarcinoma epithelial cell line; K562, human erythromyeloblastoid leukemia cell line; BxPC-3 and MIA-PaCa-2, human pancreatic adenocarcinoma cell lines; MGC-803 and AGS, human gastric adenocarcinoma cell lines; AH109A, rat ascites hepatoma cell line; SK-Hep-1, human hepatic adenocarcinoma cell line; YTMLC-90, human lung cancer cell line; SK-MEL-2, human melanoma cell line; SP6.6 and C918, human uveal melanoma cell lines; C3H10T1/2, mouse embryonic mesenchymal cell line; 143B, human osteosarcoma cell line; GOTO and SK-N-BE(2), human neuroblastoma cell lines; B16F-10, mouse melanoma cell line; TE-4, human esophageal carcinoma cell lines; EJ-1, human urinary bladder cancer cell line; HUVEC, human umbilical vein endothelial cells; ROS, reactive oxygen species; $ROO^{\bullet}$, peroxyl radical; $ABTS^{\bullet}$, 2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) radical; ICR, imprinted control region; Skp2, S-phase kinase associated protein 2; pRB, retinoblastoma protein; CK8/18, cytokeratin 8/18; CK19, cytokeratin 19; Cdc, cell division control protein; p21WAF1/Cip1, cyclin-dependent kinase inhibitor 1; CDK, cyclin-dependent kinase; p15INK4b, cyclin-dependent kinase 4 inhibitor B; $p27^{KIP}$, cyclin-dependent kinase inhibitor 1B; PCNA, proliferating cell nuclear antigen; Nrf2, nuclear factor erythroid 2-related factor 2; GADD45α and GADD153, growth arrest and DNA-damage-inducible proteins; Cx43 and Cx32, connexins; SAPT/JNK, stress-activated protein kinase/c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; PARP, poly-ADP-ribose polymerase; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2 associated X protein; Bcl-xL, B-cell lymphoma-extra large; BAD, Bcl-2-associated death promoter; PPAR-γ, peroxisome proliferator-activated receptor gamma; Akt, Akt-murine thymoma viral oncogene/protein kinase B; Rac 1, Ras-related C3 botulinum toxin substrate 1; Rho, Ras-like small GTPase protein; Nm23-H1, non-metastatic protein 23 homologue 1; ATM, ataxia-telangiectasia-mutated; NF-κB, nuclear factor kappa-B; uPA, urokinase plasminogen activator; PAI-1, plasminogen activator inhibitor-1; COX, cyclooxygenase; DR5, death receptor 5; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; AIF, apoptosis inducing factor; XIAP, X-linked inhibitor of apoptosis protein; JAK/STAT, Janus kinase/signal transducer and activator of transcription; EGFR, epidermal growth factor receptor; TRAIL, TNF-related apoptosis inducing ligand; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; GLUT-1, glucose transporter-1; HIF-1α, hypoxia-inducible factor- 1α; TIMP-1, tissue inhibitor of MMP-1; PI3K, phosphoinositide 3 kinase; CXR4, C-X-C chemokine receptor type 4; CD44, cluster of differentiation 44; DBA, dilute brown non-agouti; IL-12, interleukin-12; INF-γ, interferon gamma; VE-cadherin, vascular endothelial-specific cadherin; WHO, World Health Organization; PSA, prostate specific antigen; XRCC1, X-ray repair cross-complementing protein 1; ER, estrogen receptor; PR, progesterone receptor; DHA, docosahexaenoic acid; ODC, ornithine decarboxylase; CIN, cervical intra-epithelial neoplasia; HPV, human papilloma virus

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ABSTRACT

Biologically active compounds are considered as powerful food factors that elicit profound effects on the maintenance of human health, and disease prevention. The research into how bioactive compounds work and their role in disease prevention *in vitro* and *in vivo* is rapidly expanding. Carotenoids are one among several classes of biologically active compounds that have been reported to possess greater antioxidant and anti-cancer activity. Today, this emerging class of nutrients is the driving force in the nutritional supplement industry, and serves as a new frontier in cancer and cardiovascular research. Cancer is one of the leading causes of death worldwide. It is the second most common disease responsible for maximum mortality with about 8.2 million deaths, and the global cancer burden rises to 14.1 million new cases in 2012. This review mainly focused to summarize the anti-cancer therapeutic targets of carotenoids by highlighting the important hallmarks of cancer in terms of (i) cell cycle arrest, (ii) resistance to apoptosis, (iii) metastasis and (iv) angiogenesis alongside the relation of carotenoids in cancer epidemiology.

1. Introduction

Carotenoids are tetraterpenoids, mainly synthesized in plants and other photosynthetic organisms. They are also synthesized in some non-photosynthetic bacteria, yeasts and molds (Das et al., 2007; Dufosse et al., 2005; Mata-Gomez, Montanez, Mendez-Zavala, & Aguilar, 2014). The yellow, orange and red colors of many fruits and flowers are caused by carotenoid-containing chromoplasts that are usually devoid of chlorophyll, and considerable amounts of carotenoids are present in green parts of the plants including leaves where chlorophyll masks the carotenoids. Nearly 700 carotenoids are isolated from the natural sources, of which about 20 are present in human blood and tissues (Britton, Liaaen-Jensen, & Pfander, 2004; Rao & Rao, 2007). Carotenoids are classified into oxygen free carotenes (α-carotene, β-carotene and lycopene) and oxygen containing xanthophylls (zeaxanthin, neoxanthin and fucoxanthin). Most carotenoids exhibit a characteristic, symmetrical tetraterpene skeleton formed by the tail-to-tail linkage of the two C20 moieties (Fig. 1). The linear C40 hydrocarbon backbone is susceptible to diverse structural modifications. Some organisms produce partially degraded pigments known as apocarotenoids or norcarotenoids, and a few bacteria synthesize C_{45} or C_{50} carotenoids by further addition to the C_{40} backbone. The presence of numerous conjugated double bonds and cyclic end groups is crucial for the proper functioning of carotenoids, which is essentially light absorption in photosynthetic organisms and (photo)protection in all living organisms. During photosynthesis, carotenoids absorb radiant energy to chlorophyll molecules in a light harvesting function, dissipate excess energy via the xanthophyll cycle, and quench exited-state chlorophylls directly. One of the ultimate factors responsible for photooxidative damage to plant leaves is singlet oxygen ($^1O_2$). Carotenoids are the first line defense mechanism that quenches $^1O_2$ either physically by energy transfer mechanism or chemically by direct reaction with the radical (Amarowicz, 2011).

Although carotenoids are not synthesized by humans and animals, their presence in the body is due to dietary intake of carotenoid-containing foods. Carotenoids, being mostly fat soluble, follow the same intestinal absorption path as dietary fat. They are released from food matrices and solubilized in the gut. This is carried out in the presence of fat and conjugated bile acids. Chylomicrons are responsible for the transport of carotenoids from the intestinal mucosa to the bloodstream via the lymphatics for delivery to tissues. Then, carotenoids are transported in the plasma exclusively by lipoproteins (Parker, 1996). The delivery of carotenoids to extra hepatic tissues is accomplished through the interaction of lipoprotein particles with receptors and the degradation by lipoprotein lipase (Furr & Clark, 1997; Olson, 1994; Parker, 1996). Recently, facilitated diffusion has been reported to mediate the intestinal absorption of carotenoids in mammals (van Bennekum et al., 2005). However, the mechanism underlying this process is not well understood. Though some carotenoids act as precursors to vitamin A, many carotenoids act as powerful antioxidants and anti-cancer agents. Epidemiological and experimental studies have reported that intake of carotenoids is inversely related with the prevalence of cancer (Eliassen et al., 2012; Kim et al., 2014; Palozza, Simone, Catalano, & Mele, 2011; Sen et al., 2013; Takata et al., 2013; Vílchez et al., 2011). Carotenoids such as α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, zeaxanthin, violaxanthin, neoxanthain, canthaxanthin, astaxanthin, fucoxanthin and siphonaxanthin have been proven to have anti-cancer activity in different cancer cells such as colon, liver, breast, prostate, cervix and leukemia (Ajila & Brar, 2012; Gloria et al., 2014; Haddad et al., 2013; Nishino et al., 2000; Rokkaku et al., 2013; Sugawara, Ganesan, Li, Manabe, & Hirata, 2014; Tanaka, Shnimizu, & Moriwaki, 2012). The major mechanisms of cancer chemoprevention by carotenoids are changes in pathways leading to cell growth or cell death. These include immune modulation, hormone and growth factor signaling, regulatory mechanisms of cell cycle progression, cell differentiation and apoptosis (Sporn & Suh, 2002; Tanaka et al., 2012). This contribution mainly focuses to summarize recent reports on the anti-cancer mechanisms of carotenoids by targeting four important hallmarks of cancer cells.

2. Antioxidant potential of carotenoids

Reactive oxygen species (ROS) is the term used to specify a group of oxidants which comprise both free radical and non-free radical