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Carotenoids, inflammation, and oxidative stress—implications of cellular signaling pathways and relation to chronic disease prevention

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ABSTRACT

Several epidemiologic studies have shown that diets rich in fruits and vegetables reduce the risk of developing several chronic diseases, such as type 2 diabetes, atherosclerosis, and cancer. These diseases are linked with systemic, low-grade chronic inflammation. Although controversy persists on the bioactive ingredients, several secondary plant metabolites have been associated with these beneficial health effects. Carotenoids represent the most abundant lipid-soluble phytochemicals, and in vitro and in vivo studies have suggested that they have antioxidant, antiapoptotic, and anti-inflammatory properties. Recently, many of these properties have been linked to the effect of carotenoids on intracellular signaling cascades, thereby influencing gene expression and protein translation. By blocking the translocation of nuclear factor κB to the nucleus, carotenoids are able to interact with the nuclear factor κB pathway and thus inhibit the downstream production of inflammatory cytokines, such as interleukin-8 or prostaglandin E2. Carotenoids can also block oxidative stress by interacting with the nuclear factor erythroid 2–related factor 2 pathway, enhancing its translocation into the nucleus, and activating phase II enzymes and antioxidants, such as glutathione-S-transferases. In this review, which is organized into in vitro, animal, and human investigations, we summarized current knowledge on carotenoids and metabolites with respect to their ability to modulate inflammatory and oxidative stress pathways and discuss potential dose-health relations. Although many pathways involved in the bioactivity of carotenoids have been revealed, future research should be directed toward dose-response relations of carotenoids, their metabolites, and their effect on transcription factors and metabolism.

Abbreviations: AMD, age-related macular degeneration; ARE, antioxidant response element; BCDO2, β-carotene dioxygenase 2; BCO1, β-carotene 15,15′-oxygenase 1; CAT, catalase; CCL2, chemokine (C-C motif) ligand 2; COX-2, cyclooxygenase 2; CVD, cardiovascular disease; CXCL, chemokine (C-X-C motif) ligand 2; DMSO, dimethyl sulfoxide; GCL, glutamate cysteine ligase; GPx, glutathione peroxidase; GSH, glutathione; GSTs, glutathione-S-transferase; HMGB1, high-mobility group box 1; HO-1, heme oxygenase; ICAM-1, intracellular adhesion molecule 1; IGFBP3, insulin-like growth factor binding protein 3; IKK, IκB kinase; iNOS, nitric oxide synthase; Keap1, kelch-like ECH-associated protein 1; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein 1; MDA, malondialdehyde; NAD(P)H, nicotinamide adenine dinucleotide phosphate; NEMO, NF-κB essential modulator; NF-κB, nuclear factor κB; NO, nitric oxide; NOX-2/4, NAD(P)H oxidase; Nrf2, nuclear factor erythroid 2–related factor 2; NQO1, NAD(P)H quinone oxidoreductase 1; 8-OHdG, 8-oxo-2′ deoxyguanosine; PBMC, peripheral blood mononuclear cell; PGE2, prostaglandin E2; PGF2α, prostaglandin F2α; RA, retinoic acid; RAR, retinoic acid receptor; ROS, reactive oxygen species; SOD, superoxide dismutase; STAT, signal transducers and activators of transcription; THF, tetrahydrofuran; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion protein 1.

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1. Introduction: carotenoids as antioxidants

Many nutrition and health organizations recommend regular consumption of fruits and vegetables because it is supposed to decrease the incidence of several chronic diseases such as type 2 diabetes [1,2], cardiovascular diseases (CVDs) [3] such as atherosclerosis [4], and several types of cancer [5–7]. These chronic diseases are associated with a systemic, low-grade chronic inflammatory component that is characterized by elevated circulating inflammatory markers such as cytokines (eg, interleukin [IL]-8, IL-6, IL-1, IL-12) [8–10]; other inflammatory stimulating compounds such as prostaglandin E2 (PGE2) [11], tumor necrosis factor α (TNF-α) [10], and interferons [10]; acute-phase proteins such as C-reactive protein [12,13]; immune cells associated with inflammatory responses such as macrophages [14] or eosinophiles [15]; and elevated markers of oxidative stress, for example, prostaglandins [16], isoprostanes [17], oxidized cholesterol [18], or oxidized lipid compounds such as malondialdehyde (MDA) [19]. These factors may result in additional tissue damage [20] and eventually aggravate disease.

Despite other potential dietary confounding factors such as vitamin C, vitamin E, or dietary fiber, several studies have attributed observed beneficial health effects to the consumption of secondary plant compounds such as polyphenols [21,22] and carotenoids [23,24]. Among those, carotenoids reach the highest plasma and tissue concentrations, ca. 2 μM [25], despite their lower intake compared with, for example, polyphenols [26]. The most abundant carotenoids in plasma include lycopene, β-carotene, and lutein [25]. In addition, their plasma half-life is relatively long (days to weeks compared with 2-30 hours for polyphenols) because of their fat solubility, limited phase II metabolism, and decreased renal clearance [27–29]. Carotenoid consumption and tissue levels have been related to the prevention of cancer [30,31], diabetes [1,23,32], and inflammatory bowel diseases [33,34].

Carotenoids are liposoluble C-40–based isoprenoid pigments. They are characterized by an extended conjugated π-electron system that can only be synthesized by plants and microorganisms [35]. Animals, including humans, must rely on dietary uptake. To date, approximately 700 different carotenoid species have been identified, but only 50 have been reported to play a role in the human diet [36], with an intake of ca. 5-15 mg/d per capita [37]. Carotenoids can be separated into the oxygen-devoid carotenes and the oxygen-containing xanthophylls [3]. They can be further classified into provitamin A carotenoids (eg, β-carotene and β-cryptoxanthin) and the non–provitamin A carotenoids, which cannot be converted to retinal (eg, lycopene and lutein) [38].

The extended π-electron system is an important feature of carotenoids because it aids in stabilizing unpaired electrons after radical quenching [39]. Because of this conjugated double-bond structure, carotenoids are strong scavengers of singlet oxygen ($^1O_2$) and peroxyl radicals [40]. They either act via physical quenching, electron acceptance, or donation [41] or via hydrogen abstraction/acceptance [42]. Singlet oxygen scavenging by carotenoids depends largely on physical quenching, that is, a direct energy transfer between the 2 molecules. This scavenging depends on the number of conjugated double bonds [43]. Thus, carotenoids with more extended π-electron systems, such as lycopene, are generally reported to constitute stronger antioxidants compared with phytoene/phytofluene [44].

The carotenoids also play an important role in their orientation within biological membranes [45]. As lipid-soluble molecules, different carotenoid structures are found in lipophilic environments and lipid/water interfaces. Xanthophylls, which are less hydrophobic than carotenes, are found in cellular membranes at the lipid/aqueous interface, and they can scavenge lipid and aqueous phase radicals [41]. Carotenes scavenge radicals in the lipid phase, as they are mostly located deep in the apolar core of lipid membranes [46]. Thus, within cells, carotenoids are affiliated with various types of membranes, such as the outer cell membrane, but also the mitochondria and the nucleus [47]. They also can be found in liposomes [48], whereas their free occurrence in the cytosol is rather low [47]. As a consequence, carotenoids play an important role in protecting cellular membranes [49] and lipoproteins [50] against damage by peroxyl radicals.

In addition to their scavenging function toward several reactive oxygen species (ROS), there is growing awareness that carotenoids may also act via more indirect pathways. This indirect route may include interactions with cellular signaling cascades, such as nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK), or nuclear factor erythroid 2–related factor 2 (Nrf2) [51,52]. Because of their rather low tissue concentrations and the regulation of antioxidant balance by numerous other endogenous compounds, the capacity for scavenging radicals is of biological relevance. After their cellular uptake from mixed micelles and the resulting symmetric (β-carotene-oxygenase 1, or BCO1) and assymetric apocarotenoids (β-carotene-di-oxygenase 2, BCDO2, their activity depending on genetic factors and the administered dosage [53]), appear to be bioactive.

Presenting the findings from in vitro, animal, and human investigations, this review aims to summarize current knowledge on the part carotenoids may play in inhibiting inflammatory and oxidative stress related processes by interacting with cellular signaling cascades. Search criteria in PubMed included the terms “carotenoids” combined with one of the following: “inflammation,” “oxidative stress,” “meta-analyses,” “NF-κB,” “reactive oxygen species,” “MAPK,” “animal studies,” or “Nrf2”; the results were then further filtered manually. The literature was searched from inception of PubMed until the present (2014). The initial search yielded 1657 potential studies, with 215 of these selected for this review.

2. Oxidative stress, inflammation, and intracellular signaling cascades

Inflammation, under normal conditions, is a protective mechanism of tissues against endogenous and exogenous damage [54]. Several agents and conditions that could lead to inflammation are known, such as microbial and viral infections, autoimmune diseases, exposure to allergens or toxic chemicals, and even metabolic disturbances that include

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