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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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obesity [55]. Two stages of inflammation are distinguished, the acute and chronic phases. Acute inflammation is the initial stage that persists for only a short time, and it is normally beneficial to the host because it helps to reestablish normal homeostasis, for example by digesting foreign bacteria. However, if persisting over a prolonged period, this state is referred to as *chronic inflammation*. This is harmful for the body because it can result in abnormal physiological responses, increase the risk of cellular damage, and lead to the development of chronic diseases, such as cancer [55].

During inflammation, cells of the immune system such as macrophages and leucocytes are recruited to the site of damage. This results in a "respiratory burst," an overproduction of ROS, and leads to oxidative stress and damage of important biomolecules, such as proteins or DNA [54]. The inflamed cells also produce soluble mediators such as cytokines, chemokines, and metabolites of arachidonic acid (ie, prostaglandins), which further recruit macrophages and are important key activators of different signal transduction cascades and transcription factors, such as NF-κB or Nrf2 (Figure). The activation of these cascades and transcription factors then results in the production and secretion of cellular stress responses such as cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS), chemokines, and cytokines [55]. Transcription factors, specifically NF-κB and Nrf2, have been associated with inflammation and oxidative stress responses, respectively.

Nuclear factor κB is responsible for the transcription of a variety of genes that regulate inflammatory responses. When cells are not stimulated, NF-κB is bound to its inhibitory

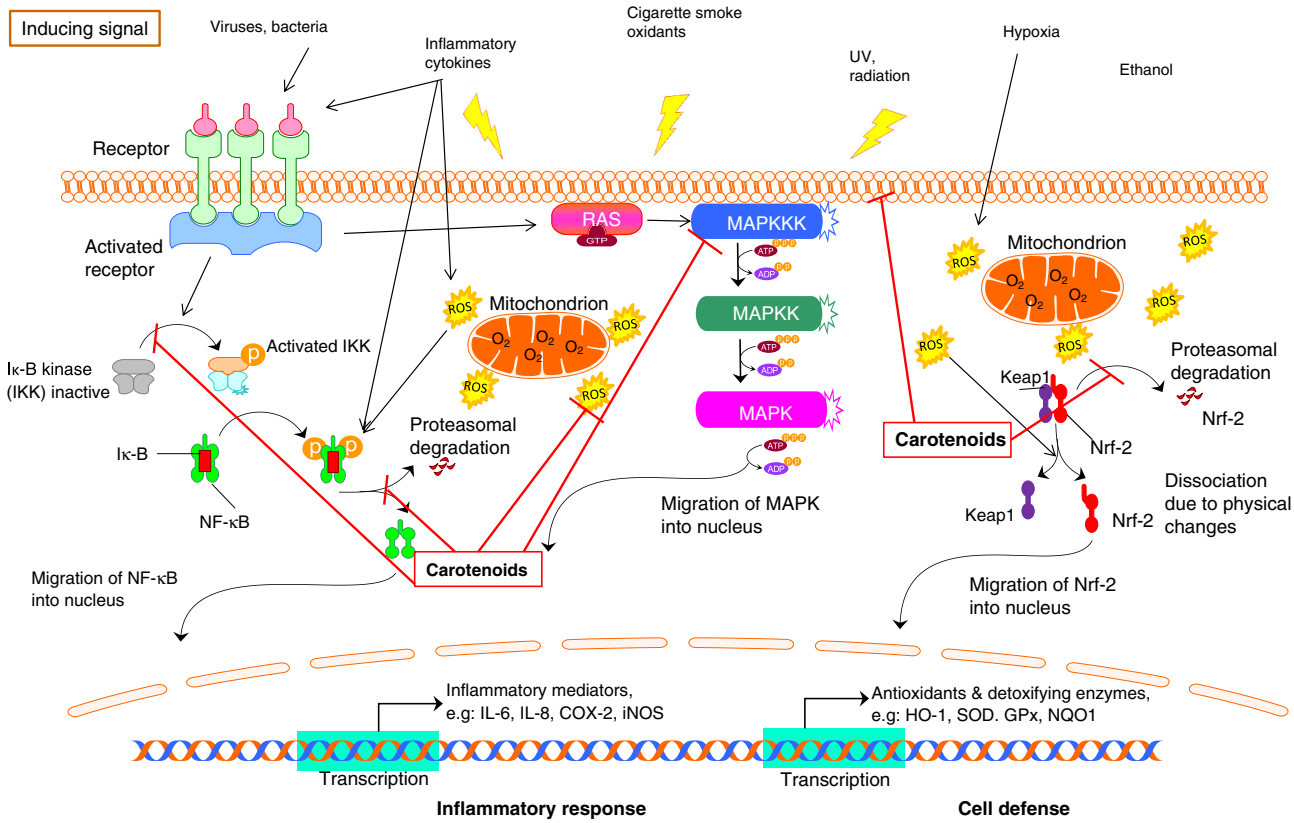

Figure – Inflammatory signaling pathways and carotenoids. Under resting conditions, inactive NF-κB is bound to its inhibitory protein IκB in the cytoplasm. After stimulation with, that is, oxidative stress, inflammatory cytokines, or hypoxia, IκB protein is phosphorylated by the IKK complex leading to the ubiquitination and proteasomal degradation of the IκB protein. This releases NF-κB, which can then translocate to the nucleus and the transcription of inflammatory cytokines can start [213]. It could be hypothesized that carotenoids or their derivatives can interact with cysteine residues of the IKK and/or NF-κB subunits and, as such, inactivate the NF-κB pathway [93]. Nrf2 is kept inactive by Keap1 in the cytosol by poly-ubiquitination and rapid degradation through the proteasome. During redox imbalance, the Keap1-Nrf2 association is disrupted and Nrf2 can dissociate from Keap1, entering the nucleus, and leading to the transcription of antioxidant and detoxifying enzymes, which promotes cytoprotection [58]. Carotenoids and their derivatives seem to interact with Keap1 by changing its physical properties [214]. Mitogen-activated protein kinases are a family of Ser/Thr protein kinases. MAPK signaling cascades are organized hierarchically into a 3-kinase architecture. MAPKs are phosphorylated and activated by MAPK-kinases (MAPKKs), which in turn are phosphorylated and activated by MAPKK-kinases (MAPKKKs). The MAPKKKs are in turn activated by interaction with the family of small GTPases and/or other protein kinases, connecting the MAPK module to cell surface receptors or external stimuli [215]. It is not known how carotenoids interact with the MAPK pathway. Part of the images from Motifolio drawing toolkits (www.motifolio.com) were used, with permission, in the figure preparation.

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protein, κB (eg, IκB-α, IκB-β, IκB-γ, IκB-ε), which resides in the cytoplasm. Specific (TNF-α, IL-1β), as well as unspecific (oxidative stress, UV radiation), signals can activate the NF-κB pathway (Figure), starting with the dissociation of the inhibitor from the NF-κB-complex and the entrance of NF-κB into the nucleus. Here, the NF-κB complex can bind to DNA and activate the transcription of various target genes [56], many of which are inflammatory and immunoregulatory [57]. Blocking NF-κB activation, anywhere in the cascade, will lead to a repression of the transcription of the target genes and thus reduced inflammation.

The Keap1-Nrf2 pathway (Figure) plays an important role in the cellular defense against endogenous or exogenous stress caused by ROS [58]. Under normal conditions, Nrf2 is bound to its repressor protein Keap1 in the cytosol, which leads to its degradation by ubiquitinylation [59]. Keap1 is a cysteine-rich protein with 27 cysteine residues, and its conformation can be modified by different oxidants and electrophiles, thereby leading to the liberation of Nrf2 and its translocation to the nucleus [58]. Modifications of the thiol residues of Keap1 lead either to a disrupted interaction with Nrf2, which can no longer be ubiquitinlyated, or to a dissociation of Nrf2 from Keap1. Either way, Keap1 is inactivated, and the newly synthetized Nrf2 can then translocate to the nucleus. It binds to the antioxidant response element (ARE), which leads to the expression of antioxidant and cytoprotective enzymes, for example, heme oxygenase 1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutamate cysteine ligase (GCL), or glutathione-S-transferases (GSTs) [59].

Mitogen-activated protein kinases are serine/threonine kinases. Their functions and regulations have been conserved from unicellular organisms to multicellular organisms. Mammalians have 3 well-characterized MAPK cascades (Figure): extracellular signal-regulated kinases (ERK1/ERK2), c-Jun N-terminal kinases (JNK1, JNK2, and JNK3), and p38 kinases [60]. Mitogen-activated protein kinases are typically organized in a "3-kinase architecture" that is activated by various extracellular stimuli, including IL-1β, TNF-α, lipopolysaccharide (LPS), and oxidative stress [61]. The 3-kinase architecture is composed of MAPK, a MAPK activator (MEK, MKK, MAPK kinase), and a MEK activator (MEK kinase or MAPK kinase kinase). As they form a kinase cascade, each downstream kinase serves as a substrate for the upstream activator [62].

3. In vitro studies

3.1. *General considerations and implications of ROS*

Many in vitro studies (Table 1), especially those that include cellular models, have aided in establishing a link between carotenoids, oxidative stress, and inflammation. There are several advantages in employing cellular models to investigate the effects of carotenoids on inflammation-related pathways. These include the ability to investigate, under well-defined conditions, specified carotenoid concentrations and specific types of cells and therefore allowing for a large number of investigations that are suitable for hypothesis building and studying mechanistic effects.

Most studies have investigated the more abundant carotenoids (eg, β-carotene, lutein, and lycopene), and occasionally, less frequently ingested ones, such as astaxanthin, are examined. The limitations of these cellular studies include the difficulty to conduct long-term studies due to limited cell-life, the missing interactions with other cells present in vivo, and the way of administration, that is, using carotenoids in solvents (eg, tetrahydrofuran and dimethylsulfoxide) rather than in lipoproteins or mixed micelles. This may also have percussions on their stability and cellular uptake, which normally occurs either passively or via transporters (SRBI, CD36, NPC1L1). In addition, many studies have used non-physiological high concentrations, that is, greater than ca. 2 μM [25] (plasma and tissues) and ca. 20 μM (gut) [63]. Another controversy exists regarding the way in which inflammation is stimulated. Tumor necrosis factor α[64], LPSs [65–67], IL-1β [68,69], H_2O_2[70,71], and bacterial [72,73] or viral stimulation [74,75] are among the most common stimuli in vivo. Typically, several of these factors are involved, activating multiple rather than individual pathways of inflammation [76].

Several cellular models for studying potential anti-inflammatory effects of carotenoids have been established. As carotenoid concentration is highest in the gut, several studies have focused on gastrointestinal epithelial cells such as Caco-2 [77], HT-29 cells [78], and human gastric epithelial adenocarcinoma (AGS) [79]. Because of their implication in many inflammatory mechanisms, monocytes/macrophages are another interesting target of carotenoids [80]. Carotenoids are mainly stored in adipose tissue and adipocytes (3T3-L1) [81,82], and keratinocytes (human primary keratinocyte [HPK]) [83] have been used in several studies. Retinal pigment epithelial cells (ARPE-19) may also accumulate in the skin and in the retina.

Reactive oxygen species could cause inflammation, and several in vitro studies have shown that β-carotene, lycopene, and lutein were able to reduce ROS production [84]. Lycopene has been suggested as a potent compound to decrease ROS, such as that generated by smoke, and to modulate redox-sensitive cell targets which include protein tyrosine phosphatases, protein kinases, MAPKs, and transcription factors [85]. For instance, lycopene at 2 μM was able to reduce the effect of smoke on molecular pathways involved in inflammation, cell proliferation, and apoptosis as well as on carcinogen-activating enzymes, and it also inhibited the formation of smoke-induced DNA adducts and smoke-stimulated insulin-like growth factor signaling [85]. In another study, 2 μM of lycopene significantly reduced ROS levels by 60% in human monocytes (THP-1) when stimulated with cigarette smoke [86]. Lutein (20 μM) and β-carotene (20 μM) showed a significant reduction (20% and 10%, respectively) of ROS in AGS cells after stimulation with H_2O_2[87]. Similarly, β-carotene (10 and 20 μM) significantly reduced ROS in AGS cells following *Helicobacter pylori* stimulation [88].

Reactive oxygen species can also be produced by poor coupling of the P450 catalytic cycle [89]. Several carotenoids, especially lycopene, have been shown to modulate liver metabolizing enzymes, such as cytochrome P4502E1, thus resulting in anticancerous activity. In one example, lycopene reduced ROS production through the interaction with NAD(P)H oxidase and NOX-4 (a homologue of NAD(P)H) [90].

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Table 1 – Effects of carotenoids on different inflammatory mediators investigated in cell cultures

Carotenoids investigated	Cell type	Inflammatory stimulus	Carotenoid concentration	Inflammatory effects [a]	Reference
Astaxanthin	HPKs	UVB irradiation (80 mJ/cm^2)	8 μM	NF-κB associated: reduced gene expression of COX-2 and IL-8, decreased PGE-2 and IL-8 secretion. No effect on NF-κB translocation to the nucleus MAPK associated: decrease of p38 and ERK phosphorylation, no effect on JNK phosphorylation	Terazawa et al [83]
Astaxanthin	U397 (human macrophage-like cells)	H_2O_2 (100 μM)	10 μM	NF-κB associated: decrease of IL-1β, Il-6 secretion. Blockage of NF-κB nuclear translocation	Speranza et al [94]
Astaxanthin	ARPE-19 (retinal pigment epithelia cells)	H_2O_2 (200 μM)	5-20 μM	ROS: reduced level of ROS Nrf2 associated: Increased mRNA expression of NQO1, HO-1, GCLM, and GCLC. Increased nuclear localization of Nrf2	Li et al [105]
Astaxanthin	PC-12 (pheochromocytoma cell line)	MPP (N-methyl-4-phenylpyridinium; 500 μM)	10 μM	ROS: reduced level of ROS by 22% Nrf2 associated: decreased mRNA expression of NOX-2 by 24%. Increased mRNA expression of HO-1 by 117%. Increased Nrf2 protein by 100%	Ye et al [107]
β-Carotene	AGS (human gastric epithelial cells)	*H. pylori* (bacterium/cell ratio 300:1)	10 and 20 μM	ROS: reduced level of ROS NF-κB associated: 90% decrease of iNOS and COX-2 mRNA expression and NO and PGE2 protein levels. Dose-dependent decreased DNA binding activity of NF-κB, via prevention of IκB degradation MAPK associated: inhibition of p38, ERK, and JNK phosphorylation	Jang et al [88]
3-hydroxy-β-damascone	HT-29 (human colon adenocarcinoma cells)	n.i.	20 and 50 μM	Nrf2 associated: induction of NQO1. Increased Nrf2 transcriptional activity	Gerhäuser et al [100]
RA	SH-SY5Y (human neuroblastoma cell line)	n.i.	10 μM	Nrf2 associated: Increased mRNA expression of Nrf2 and NQO1	Zhao et al [101]
ATRA	SK-N-SH (human neuroblastoma cell line)	n.i	10 μM	NF-κB associated: Degraded IκB-β and increased NF-κB DNA binding activity	Kiningham et al [206]
RA	MCF-7 (human mammary cancer cells)	n.i.	1 μM	Nrf2 associated: decreased binding activity of Nrf2 to ARE	Wang et al [103]
β-Carotene or lutein	AGS (human gastric epithelial cells)	H_2O_2 (100 μM)	20 μM	ROS: 10% reduction of ROS by β-carotene and 20 % reduction by lutein NF-κB associated: reduced IL-8 mRNA expression and protein levels. Lutein 10% higher effect. Decreased DNA-binding activity of NF-κB	Kim et al [87]
β-Carotene or astaxanthin or capsanthin or bixin	K562 (human myelogenous leukemia cells)	n.i.	5-50 μM	Nrf2 associated: up-regulation of Nrf2 expression	Zhang et al [98]
Lutein or zeaxanthin	ARPE-19 (human retinal pigment epithelial cells)	A2E (lipofuscin fluorophore) (10 μM)	10 μM	NF-κB associated: decrease of IL-8 mRNA expression and protein levels	Bian et al [207]
Lycopene	RAW264.7 (murine macrophages)	LPS (1 ng/mL)	0.5; 1; 2 μM	NF-κB associated: 30%-40% reduction of IL-6 and IL-1β mRNA expression MAPK associated: decrease of JNK phosphorylation (no effect on p38 and ERK1/2 phosphorylation)	Marcotorchino et al [82]

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Table 1 (continued)

Carotenoids investigated	Cell type	Inflammatory stimulus	Carotenoid concentration	Inflammatory effects [a]	Reference
Lycopene	THP-1 (human monocytic cell line)	Cigarette smoke (0.5%)	2 μM	ROS: reduced ROS production NF-κB associated: decrease of IL-8 mRNA expression and protein levels. Decrease of NF-κB DNA binding activity	Simone et al [86]
Lycopene	RAW264.7 (murine macrophages)	LPS (1 μg/mL)	1-10 μM	NF-κB associated: decreased mRNA of NO and IL-6. Inhibition of NO and IL-6. Inhibition of IκB and phosphorylation and degradation and NF-κB translocation MAPK associated: decrease of p38 and ERK phosphorylation but no effect on JNK phosphorylation	Feng et al [111]
Lycopene	THP-1 (human monocytic cell line)	7-ketocholesterol (25 μM)	2 μM	ROS: reduced ROS production through reduction of NOX-4 and NAD(P)H oxidase. MAPK associated: decrease of p38, ERK and JNK phosphorylation	Palozza et al [110]
Lycopene	3T3-L1 (murine preadipocytes)	TNF-α (15 ng/mL)	2 μM	NF-κB associated: decreased mRNA of IL-6 by 40 %. Inhibition of IKKα/β phosphorylation	Gouranton et al [81]
Fucoxanthin	BNL CL.2 (mouse hepatic cells)	n.i.	0.5-5 μM	ROS: significant increase of ROS Nrf2 associated: increase of nuclear Nrf2 protein, increased binding of Nrf2 to ARE. Increased mRNA of HO-1, NQO1 MAPK associated: increased phosphorylation of ERK/p38	Liu et al [104]
Lycopene or β-carotene or phytoene or astaxanthin	HepG2 (human hepatocellular carcinoma cells) and MCF-7	n.i.	2-50 μM	Nrf2 associated: increase of Nrf2-translocation to the nucleus in HepG2 cells. Activation of ARE by 3 to 4 fold in MCF-7 and HepG2 cells (lycopene concentration of 6 μM)	Ben-Dor et al [51]

Abbreviations: n.i., no information; NO, nitric oxide; GCLM, glutamate cysteine ligase modulatory subunit; GCLC, glutamate cysteine ligase catalytic subunit; NOX-2/4, NAD(P)H oxidase; NADPH, nicotinamide adenine dinucleotide phosphate.
[a] All effects were significant.

3.2. *Inflammation factors associated with NF-κB*

Several studies have shown that carotenoids can reduce NF-κB activation [52,86,91,92], although it could be hypothesized that not (only) the intact carotenoids but also their derivatives are the key players in NF-κB regulation. Carotenoid derivatives, such as apocarotenals, contain electrophilic groups that can interact with the cysteine residues of IκB kinase (IKK) and NF-κB subunits (p65), thereby inactivating the NF-κB pathway [93].

Whichever the causal agent, it has been shown that β-carotene at 2 to 20 μM reduced the expression of several downstream targets of NF-κB, including iNOS and COX-2, by 90% in bacterially infected AGS cells [88]. In the same study, β-carotene also decreased the secretion of nitric oxide (NO) and PGE2. Lycopene, at much lower concentrations (0.5-2 μM), showed similar effects on inflammatory cytokines and signaling pathways, by reducing IL-6 and Il-1β secretion by 30% to 40% in LPS-stimulated RAW264.7 cells [82]. Lycopene (2 μM) decreased the IL-6 messenger RNA (mRNA) expression in preadipocytes (3T3-L1) by 40% and in mature adipocytes (3T3-L1) by 37% [81], suggesting that it may play an important role in the homeostasis of adipose tissue. At 2 μM, lycopene reduced IL-8 mRNA expression and protein levels, as well as NF-κB DNA binding and the production of ROS in cigarette smoke–stimulated human monocytic (and macrophage-like) cells (THP-1) [86], therefore supporting that the idea that lycopene may be an interesting candidate for further testing in vivo, such as in smokers. Another research group analyzed the effect of astaxanthin on several inflammatory mediators and NF-κB in H_2O_2-stimulated human macrophage-like cells (U397) and found that it lowered IL-1β and IL-6 secretion and blocked NF-κB translocation to the nucleus [94]. In addition to blocking translocation, studies demonstrated that β-carotene could inhibit H_2O_2 and *H. pylori*–induced NF-κB–DNA binding in the nucleus of AGS [87,88] and macrophage cells [95] at concentrations of around 2 to 25 μM. This was accomplished via the prevention of the degradation of the inhibitor IκB [88] in the cytosol, thus suggesting further downstream general anti-inflammatory effects.

Some studies have investigated the relationship between carotenoids and UV-induced inflammation, because carotenoids may be distributed in the human skin [96,97]. Studies in UV-B–irradiated HPKs revealed that astaxanthin at 8 μM reduced COX-2 and IL-8 gene expression and also PGE2 and IL-8 protein secretion [83]. It was also tested whether astaxanthin influenced NF-κB translocation, but no effect was seen, perhaps due to transient effects of the latter.

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3.3. *Inflammation factors associated with Nrf2 and MAPK*

Recently, due to the typical strong antioxidant effects of lycopene, the effects of lycopene on Nrf2 have been reviewed [90], and it was noted that lycopene was able to up-regulate the Nrf2 binding ARE system in several cell types such as MCF-7 breast cancer and HepG7 liver cells [51]. In a study by Zhang et al [98], β-carotene, astaxanthin, capsanthin, and bixin at 5 to 50 μM up-regulated the expression of Nrf2 in K562 leukemia cells. In a study by Ben-Dor et al [51] that focused on MCF-7 cells, expressions of reporter genes fused with ARE sequences after various carotenoid treatments (lycopene, phytoene, β-carotene, and astaxanthin) at 2 to 10 μM were compared. Their results showed that lycopene had the strongest effect and, hence, suggested that it is a good activator for the nuclear translocation of Nrf2. This may seem somewhat surprising due to its low cytosolic solubility and apolarity, which constitutes a poor activator of Keap1, and it may shed further doubts on whether lycopene, rather than its apocarotenal metabolites, are the bioactive constituents. Because carotenoids such as lycopene lack an electrophilic group, which appears to be required to react with Keap1, it is suggested that not the parental carotenoids, but metabolites following BCO1 and BCDO2 cleavage are the responsible bioactives [99]. An example includes the 10,10′-apocarotenal derivative of lycopene, which is shown to be active in MCF-7 and prostate adenocarcinoma (LNCaP) cells. In general, apocarotenals showed higher activity than apocarotenoid acids in terms of EpRE/ARE transactivation. In another study, 3-hydroxy-β-damascone, a carotenoid derived polar flavor (apocarotenoid), induced NQO1 in HT-29 cells after 10-, 20-, or 50-μM exposure [100], with the latter 2 concentrations being significant. It also appears that retinoic acid (RA), after cleavage of β-carotene by BCO1, is effective in enhancing Nrf2 translocation. Similarly, in a study on neuroblastoma cells (SH-SY5Y), RA at 5 to 40 μM induced mRNA expression of Nrf2 and NQO1, dose dependently [101]. Thus, all these studies are supportive of the idea that more polar carotenoid metabolites can activate Nrf2 translocation.

It also appears that oxidative stress, caused by rather high concentrations (>10 μM) of RA, stimulates Nrf2 translocation [102], whereas lower concentrations (0.1-1.0 μM) may inhibit Nrf2 translocation, indicating a biphasic activity behavior [102,103]. However, this is not confirmed in all studies. For example, in the study by Ben-Dor et al [51], ARE activation did not depend on the level of intracellular ROS or reduced glutathione, thus suggesting that this activation was not related to antioxidant activity. At comparable low concentrations, fucoxanthin (above 0.5 μM) in hepatic cells (BNL CL.2) increased nuclear Nrf2 protein accumulation, and levels of mRNA and protein expression of downstream HO-1 and NQO1 [104]. Of note, fucoxanthin also increased ROS levels and phosphorylated ERK and p38 intracellularly indicating that prooxidant properties could result in beneficial effects.

In a recent study by Li et al [105], astaxanthin protected retinal epithelial cells (ARPE-19) from H_2O_2 induced oxidative stress by inducing nuclear localization of Nrf2, reducing intracellular ROS, and up-regulating NQO1, HO-1, glutamate cysteine ligase modulatory subunit, and glutamate cysteine ligase catalytic subunit mRNA expression, although astaxanthin concentrations were comparatively high at 5 to 20 μM. In the same study, the involvement of P-Act and its downstream target Nrf2 was further suggested by inhibitors of P-Act, diminishing the positive effects of astaxanthin in ARPE-19 cells. The influence on retinal cells has been met with increasing interest due to the relation of age-related macular degeneration (AMD) and retinal carotenoid concentrations [106]. As carotenoids are also able to cross the blood-brain barrier and are found in brain cells, several cellular models of neuroprotection exist, such as for Parkinson's disease. In a recent study on neuronal PC-12 cells [107], astaxanthin protected against *N*-methyl-4-phenylpyridinium–induced oxidative stress at 10 μM, reduced intracellular ROS and NOX2, and increased Nrf2 and HO-1 protein expression; however, realistic concentrations in this tissue are expected to be lower (up to 0.5 μM) [108].

Only a few studies have investigated the effect of carotenoid cellular exposure on targets of the MAPK pathway, although interactions have been shown for lutein, zeaxanthin, and lycopene at the MEK activator level in the 3 different MAPK cascades [109]. It has been demonstrated that astaxanthin (4 or 8 μM) decreased the phosphorylation of p38 and ERK, but no effect was found on JNK in human keratinocytes [83]. Similar effects were seen for β-carotene, preventing the phosphorylation of ERK, JNK, and p38 [88] in the cytosol. In a study by Palozza et al [110], lycopene suppressed MAPK phosphorylation in oxysterol stimulated macrophages and prostate cancer cells. In another study, lycopene decreased JNK phosphorylation but showed no effect on p38 and ERK phosphorylation in LPS-stimulated RAW264.7 cells [82]. This finding contrasts with an investigation where lycopene blocked p38 and ERK phosphorylation but did not affect JNK phosphorylation in RAW264.7 cells [111]. A possible explanation might be the slightly different concentrations of lycopene, which ranged from 0.5 to 2 μM in one [82] and 1 to 10 μM in the other study [111]. Also, the time of exposure (often varying between 6 and 48 hours) and the cell passage number could have affected the results.

3.4. *Summary and outlook*

Despite the limitations of cellular studies to model complex in vivo environments, in conjunction with the often high concentrations of carotenoids that are investigated, several carotenoids, at concentrations that are physiologically plausible, have indicated that they are able to reduce ROS. Because of the relation of ROS and inflammation, it is not too surprising that carotenoids were also found to positively modulate markers of inflammation and oxidative stress, especially those related to the NF-κB or Nrf2 pathway, respectively. This occurred by blocking NF-κB translocation to the nucleus and removal of the Nrf2 repressor Keap1. The strength of the effect across various carotenoids appears difficult to predict, as studies often differ in many parameters, which include cell type, incubation time, and concentration, and the effects may not strictly be related to intracellular oxidative stress. An important factor deserving further investigation is the potential carotenoid metabolites which, also depending on the cell type and the ability to cleave carotenoids via eg, BCO1 or BCDO2 into apocarotenals, appear

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Table 2 – Effects of carotenoids on inflammation in animal models

Animals involved	Carotenoid investigated	Concentration of carotenoid	Stimuli	Treatment length	Tissue/cells sampled	Main effects	Reference
Rats	Annatto extract or β-carotene	0.1 % in the diet	n.i.	7 d	Neutrophils	ROS: reduced ROS production. Increased mRNA expression of SOD CAT, p22, p47	Rossoni Junior et al [114]
Rats	Lycopene	10 mg/kg bw	Sodium fluoride	5 wk	Red blood cells, heart and brain	ROS: reduced MDA, total nitrate/nitrite and glutathione	Mansour et al [117]
Rats	Lycopene	40 mg/kg bw	Mercury chloride	Single doses	Renal tissues	ROS: decreased ROS levels by 16%. Decreased MDA and GSH. Increased GPx and SOD	Yang et al [118]
Rats	Astaxanthin	20 mg/kg bw	Alloxan	30 d	Neutrophils	ROS: reduced TBARS and H_2O_2 levels	Marin et al [119]
Rats	Lycopene	1-4 mg/kg bw	Streptozotocin	10 wk	Serum	NF-κB associated: reduced TNF-α production	Kuhad et al [130]
Rats	Lycopene	10, 15, and 20 mg/kg bw	n.i.	12 wk	Serum	NF-κB associated: reduced VCAM-1, MCP-1, IL-8	Liu et al [131]
Rats	Lutein	1-100 mg/kg bw	Streptozotocin	Single injection	Aqueous humor	NF-κB associated: inhibited NF-κB activation. Decrease of NO, PGE2, IL-6, TNF-α, CCL2 and CXCL2	Kijlstra et al [134]
Rats	Fucoxanthin	0.1, 1 or 10 mg/kg bw	LPS	Single injection	Aqueous humor	NF-κB associated: reduced PGE2, NO, TNF-α levels	Shiratori et al [136]
Rats	Lycopene	1.1 or 3.3 mg/kg bw	Alcohol	11 wk	Plasma and liver	NF-κB associated: induction of CYP2E1 protein and TNF-α mRNA	Veeramachaneni et al [143]
Rats	Lycopene	6 mg/kg bw	Cisplatin	Single injection	Kidney cells	ROS: increased levels of SOD, GPx and CAT. NF-κB associated: decrease of NF-κB expression. Nrf2 associated: increased Nrf2 and HO-1 expression	Sahin et al [145]
Rats	Astaxanthin	25 mg/kg bw	Cyclophosphamide	10 d	Liver	Nrf2 associated: increase of NQO-1 and HO-1.	Tripathi et al [146]
Rats	Crocin	10 mg/kg bw	Cyclophosphamide	6 d	Liver and serum	ROS: increase in SOD, CAT, GSTs, GPx.	Jnaneshwari et al [138]
Rats	Crocin	10 or 20 mg/kg bw	Freund's complete adjuvant	14 d	Serum, liver, and spleen tissue	NF-κB associated: decreased IL-1β, IL-6, TNF-α and COX-2 and PGE2 levels ROS: ROS decrease by 98 %. Reverted GSH levels	Hemshekhar et al [139]
Rats	Crocetin	50 mg/kg bw	hemorrhagic shock	Single administration	Renal blood	NF-κB associated: decreased NO, TNF-α and IL-6	Wang et al [140]
Rats	β-Carotene	0.05 % in diet	azoxymethane	33 wk	Colonic mucosa	NF-κB associated: slight reduction of COX-2 expression	Choi et al [141]
Mice	β-Carotene or lycopene	0.5 g/kg bw	Cigarette smoke	4 wk	Lung	ROS: regulated expression of cytochrome P450	Aung et al [126]
Mice	β-Carotene	0.6 % in diet	n.i.	10, 15, or 20 wk	Liver	NF-κB associated: reduced mRNA of	Harari et al [127]

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Table 2 (*continued*)

Animals involved	Carotenoid investigated	Concentration of carotenoid	Stimuli	Treatment length	Tissue/cells sampled	Main effects	Reference
						VCAM-1, Il-1α, MCP-1, IFN-γ	
Mice	β-Carotene	150 mg/kg bw	n.i.	14 wk	Lung, liver, and white adipose tissue	NF-κB associated: decreased expression of genes involved in interferon production/ regulation	Van Helden et al [128]
Mice	RA	0.5 mg/kg bw	n.i.	9 wk	CD4(+) cells and arthritic joints	NF-κB associated: decreased IL-17, IL-6, IL-1β and iNOS expression. Down-regulated NF-κB	Kwok et al [92]
Mice	Lycogen	1 mg/kg bw	Dextran sodium sulfate	6 d	Plasma	NF-κB associated: reduced expression of TNF-α and IL-1β	Liu et al [129]
Mice	Astaxanthin	1, 10 or 100 mg/kg bw	n.i.	3 d, injections	Retinal pigment epithelium-choroid tissue	NF-κB associated: reduced IL-6, VEGF, MCP-1 and ICAM-1. Suppression of NF-κB activation, translocation and IκB degradation	Izumi-Nagai et al [137]
Mice	Lutein	1, 10, and 100 mg/kg	LPS	Single administration	Aqueous humor and iris-ciliary body	NF-κB associated: dose dependent reduction of NO, TNF-α, IL-6, PGE2 concentration; NF-κB activation	Jin et al [135]
Mice	Lutein	0.1 % in diet	Streptozotocin	1 mo	Retina	ROS: reduced ROS production MAPK associated: inhibit ERK activation	Sasaki et al [120]
Mice	Astaxanthin	100 mg/kg bw	H_2O_2	4 times	Retina	ROS: reduced retinal damage and oxidative DNA damage	Nakajima et al [121]
Mice	Vitamin A and RA	10:1 molar ratio	Hyperoxia	7 or 14 d	Lung	Nrf2 associated: decreased DNA damage. Reduction of Nrf2 proteins. Decrease of INF-γ and macrophage inflammatory protein 2-α mRNA	James et al [147]
Mice	RA	0.5 mg/mouse	n.i.	n.i.	T cells	Other pathways: suppression of IFN-γ producing CD4(+) and CD8(+) T cells. Suppression of STAT4 expression	Van et al [152]
Mice	RA	400 μg/mouse	Ovalbumin	Single administration	Lymphocytes	Other pathways: inhibition of Th-2 cells and Th17 related cytokines	Wu et al [208]
Mice	Lycopene	8 or 16 mg/kg bw	Ovalbumin	3 d	Lung	Other pathways: decreased IL-4 mRNA. Increased IFN-γ and T-bet mRNA	Lee et al [156]
Mice	Vitamin A	250 IU/g diet	Ovalbumin	3 wk	Lung	Other pathways: decreased Il-4 and IL-5 release	Schuster et al [209]
Mice	Lycopene	100 mg/kg bw	n.i.	Single dose	Different organs	Other pathways: induction of RARE-mediated cell signaling	Aydemir et al [153]

(*continued on next page*)

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Table 2 (continued)

Animals involved	Carotenoid investigated	Concentration of carotenoid	Stimuli	Treatment length	Tissue/cells sampled	Main effects	Reference
Mice	Lycopene	0-20 μM	LPS	Single administration	Endothelial cells	Other pathways: inhibition of HMGB1 release and HMGB1-mediated TNF-secretory phospholipase A2-IIA and HMGB1-mediated proinflammatory responses	Lee et al [210]
Dogs	Astaxanthin	20 mg/d	n.i.	16 wk	Leukocytes	ROS: improved mitochondrial function and plasma GPx and NO levels	Park et al [122]
Chicken	Astaxanthin	100 ppm	LPS	2 wk	Liver and spleen	NF-κB associated: increase in iNOS, IL-1, IL-6 and IFN-γ mRNA expression	Takahashi et al [142]

Abbreviations: n.i., not investigated; CCL2, chemokine (C-C motif) ligand 2; CXCL2, chemokine (C-X-C motif) ligand 2; IFN-γ, interferon γ; VEGF, vascular endothelial growth factor; RARE, RA response element; TBARS, thiobarbituric acid reactive substance.

to be in part responsible for the observed anti-inflammatory reactions. This is plausible given that free carotenoid concentration in the cytosol (where Nrf2 and NF-κB reside) are typically low and require binding to cysteine residues of these transcription factors, therefore favoring polar compounds. Also, carotenoid concentration in such studies is likely to influence the results. Although Nrf2 translocation appears to be more prominent at rather higher concentrations (>1 μM), possibly via increasing oxidative stress due to prooxidant effects of carotenoids or their metabolites, lower concentrations may have rather inhibitive effects on Nrf2.

4. Animal studies

4.1. *General aspects and implications of ROS*

Compared with cellular trials, animal models (Table 2) allow for studying the effects under more complex, that is, realistic, physiological conditions. Compared with human studies, they are easier to coordinate under more standardized conditions and allow for a higher accessibility to tissues. As a drawback, many animals metabolize carotenoids differently from humans [112]; their cleavage rate by BCO1 and BCDO2, such as in mice (being much higher), can be quite altered compared with humans. In addition, in many animal models, carotenoids were administered at supraphysiological doses that were comparable to ca. 6 mg/kg body weight (bw) when setting 0.5 mg/kg bw in humans as a limit for a physiological dose, applying the human equivalent dose formula for comparing doses across species [113]. Animal models resembling the human carotenoid metabolism include *Mongolian gerbils* and various types of monkeys [112].

By providing foods rich in carotenoids, several studies have aimed to reduce ROS and their negative impact on inflammation. For example, annatto extract or β-carotene added at 0.1% to the diet of rats for 7 days decreased ROS production in neutrophils and increased mRNA concentrations of superoxide dismutase (SOD), catalase (CAT), p22(phox), and p47(phox), which are components of the electron transfer elements of nicotinamide adenine dinucleotide phosphate oxidase [114].

However, most studies investigated isolated carotenoids that were added to the diet. Administration of lycopene in isolated form has received some attention because of its strong antioxidant effects in vitro [115]. Similar to cellular studies, lycopene ameliorated the negative effects of ROS produced during anticancer chemotherapy [116]. In another study on rats, daily lycopene administration of 10 mg/kg bw for 5 weeks normalized oxidative stress (caused by sodium fluoride exposure), assessed as plasma MDA and total nitrate/nitrite [117]. Lycopene also ameliorated oxidative stress in tissues, for example, in renal tissues (glutathione [GSH], MDA, SOD), when administered as a single dose (40 mg/kg bw) prior to mercury poisoning [118].

Astaxanthin (20 mg/kg), administered to diabetic rats for 30 days, reduced oxidative stress (measured by thiobarbituric acid reactive substance, H_2O_2) in neutrophils, although it did not go back to basal levels [119]. In another diabetes model, lutein (0.1% in the diet) in rats prevented ROS-related retina degeneration after 4 months of supplementation [120]. Positive effects on the retina were also found for astaxanthin in mice, but they received very high doses, that is 4 times 100 mg/kg [121]. These results support the positive effects of carotenoids for eye health. In larger animals, for example, dogs, 20 mg/d of astaxanthin for 16 weeks improved mitochondrial function and markers of oxidative stress, including plasma glutathione peroxidase (GPx) and NO [122]. These observations were attributed, in addition to indirect effects on intracellular signaling (especially Nrf2) to the following: (*a*) quenching of singlet oxygen, (*b*) reaction with free radicals, (*c*) acting as an antioxidant via reactivating vitamin E or vitamin C, or (*d*) reducing DNA damage [123]. Further additional modes of action may exist. Several animal studies have suggested that carotenoids can up-regulate the P450 cytochrome monooxygenase family and may come into play when detoxifying

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xenobiotic compounds. For instance, several enzymes such as P450E1 in rat liver [124] or CYP 1A1/2 2B1/2 and 3A [125] were up-regulated in a dose-dependent manner by lycopene, and both lycopene and β-carotene activated the P450 A1 gene in mice [126].

4.2. *Implication of the NF-κB pathway*

In cellular studies, NF-κB or downstream cytokines have been among the most studied markers of inflammation in animal studies after carotenoid exposure. Positive effects on inflammatory genes, such as those implicated in the expression of IL-1α, INF-γ, monocyte chemotactic protein 1 (MCP-1), and vascular cell adhesion protein 1 (VCAM-1), were found after feeding a diet of 0.6% β-carotene (50% in 9-*cis* form) to rats (in which atherosclerotic lesions were induced by a high-fat diet) for 11 weeks [127]. In another study with BCO1-deficient mice, 14-day β-carotene supplementation (150 mg/kg in diet) reduced mRNA expression of proinflammatory genes involved in interferon production/regulation in the lung, liver, and white adipose tissue [128]. This suggests that effects were independent from vitamin A active compounds, although BCDO2 may still have been active. As with cellular models, metabolites of carotenoids have been shown to be effective in altering the inflammatory processes. In arthritis mice models [92], RA intraperitoneal (IP) at 0.5 mg/kg for 9 weeks reduced several inflammatory parameters, including IL-17 in CD4(+) T cells and serum IgG/IgG2, down-regulated NF-κB in CD4(+) T cells, and reduced iNOS, IL-6, and IL-1β in tissues.

Carotenoids other than β-carotene also received some attention. In a rodent study, colitis induced in mice by dextran–sodium sulfate was reduced by the administration of lycogen (at 1 mg/kg for 6 days), which is a trademark extract rich in carotenoids. Both TNF-α and IL-1β in plasma were also reduced [129]. In diabetic induced rats, lycopene given at 1 to 4 mg/kg for 10 weeks reduced inflammation, as measured by TNF-α in serum, and limited cognitive decline, as indicated by the Morris water maze test [130]. In a hyperhomocysteinemic rat model, lycopene at 10, 15, and 20 mg/kg taken for 12 weeks reduced serum markers of inflammation such as VCAM-1, MCP-1, and IL-8, thus indicating antiatherogenic effects [131].

Because AMD is related to inflammation processes [132], and lutein and zeaxanthin have been especially related to AMD [133], many animal models focusing on the retina have investigated the potential benefits of carotenoids. As reviewed by Kijlstra [134], lutein intravenous injections (doses between 1 and 100 mg/kg) reduced aqueous humor NO, PGE2, IL-6, TNF-α, various chemokines, and NF-κB activation in the Iris ciliary body in a rat model, when administered prior to endotoxin induced uveitis [135]. In a similar rat model of LPS-induced uveitis, fucoxanthin injected intravenously at 0.1, 1.0, or 10 mg/kg after LPS administration reduced PGE2, NO, and TNF-α concentration in the aqueous humor [136]. In a mouse model of AMD, astaxanthin given ip to mice (10 or 100 mg/kg bw) reduced NF-κB activation and inflammation-related molecules such as vascular endothelial growth factor, IL-6, ICAM-1, and MCP-1 in retinal pigment epithelium tissues [137]. Taken together, these results suggest that inflammatory processes in the retina involved in AMD may be altered by considerable doses of carotenoids.

A further hint toward the bioactivity of polar carotenoids and their metabolites comes from studies with crocin. This natural, more polar carotenoid attenuated cyclophosphamide induced hepatotoxicity in rats after a 6-day administration of 10 mg/kg. In addition to various markers of oxidative stress, inflammatory markers that included cytokines were significantly decreased [138]. In a rat model of arthritis (induced by *Mycobacterium tuberculosis*), 10 or 20 mg/kg crocin for 14 days reduced plasma levels of inflammatory markers, including TNF-α, IL-1β, IL-6, COX-2, and PGE2, as well as markers of ROS, such as GSH [139]. In rats, crocin administered at 50 mg/kg after hemorrhagic shock–induced acute renal failure reduced negative effects by decreasing NO, TNF-α, and IL-6 and also attenuating NF-κB expression [140].

Some conflicting results exist and deserve to be mentioned because there is the possibility of severe underreporting of nonsignificant or even negative results. In a study by Choi et al [141], β-carotene given at 0.5 % for 33 weeks to rats with induced colon carcinogenesis failed to reduce inflammatory markers such as COX-2. In a broiler study by Takahashi et al [142], the addition of astaxanthin at 100 ppm to the diet showed no positive effect on inflammation, but it aggravated LPS-stimulated inflammation, which was measured by mRNA expression of iNOS, IL-1, IL-6, and IFN-γ in the liver. The reasons for these observations remain unknown, but altered metabolism of carotenoids in birds, low dosing of carotenoids, or overlayering effects with the co-consumed corn (also containing carotenoids) could have played a role.

Even negative effects of carotenoids have been reported. When feeding physiological doses of 1.1 or 3.3 mg/kg bw (equivalent to ca. 45 mg/kg in a 70-kg human) for 11 weeks to rats receiving high doses of ethanol, the higher lycopene dose increased hepatic TNF-α mRNA, thus suggesting a prudent approach when administering carotenoids when chronic alcohol abuse is involved [143]. Although the reasons remain unknown, in the same study, it was suggested that alcohol slowed down BCDO2 enzymatic activity and the formation of lycopene metabolites. The resulting elevated tissue concentrations of the native carotenoid could have caused prooxidative effects [144].

4.3. *Implication of the Nrf2 and other pathways*

As the importance of Nrf2 in oxidative stress and inflammation related pathways has only recently been discovered, very few carotenoid studies investigating Nrf2 have been conducted in animals. As cancer chemotherapy may cause oxidative stress, a few studies have attempted to ameliorate this undesired side effect. In a study with cisplatin (used in chemotherapy), lycopene ameliorated nuclear Nrf2 and HO-1 decreases in rats receiving 6% lycopene and 1.5% other carotenoids at 6 mg/kg (phytoene, phytofluene) in their diet for 6 days (ie, 360 μg/kg final lycopene) [145]. Expression of NF-κB p65 was also reduced, and the formation of downstream SOD, GPx, and CAT was up-regulated in kidney cells. In another rat study, astaxanthin increased NQO-1 and HO-1 expression in rats, after exposure to either cyclophosphamide with or without pretreatment of 25 mg/kg astaxanthin [146]. In line with cellular studies, vitamin A active carotenoid metabolites (ie, RA) improved hyperoxia induced depressed

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lung function in mice, reduced DNA damage, protein oxidation, interferon-γ, and macrophage inflammatory protein-2α mRNA, thus reducing Nrf2 proteins [147].

In addition to primary inflamed cells, it should not be overlooked that cytokines may also attract cells of the immune system, such as macrophages, which can then further stimulate inflammation responses. Carotenoids may also have effects on these attracted immune cells. It is well acknowledged that RA and other vitamin A active compounds are required for optimal functioning and maturation of the immune system [148], and studies have shown that at a later age, they can have pronounced effects on the immune system, such as on CD4(+) and CD8(+) T cells, for example, reducing their inflammatory potential [149,150]. However, it is possible that pathways other than NF-κB and Nrf2 also play a role, such as signal transducers and activators of transcription (STAT) [151]. For example, in a model of type 1 diabetes, all-trans retinol at 0.5 mg/mouse reduced STAT4 expression required for IFN-γ production and immune cell response [152]. These activities of RA are of interest because other carotenoid metabolites may also show similar behavior. In a mouse study by Aydemir et al [153], it was shown that lycopene can also activate the RA receptor (RAR) and the RA response element. Similar results were found by Harrison et al [154]. This study demonstrated that various β-apocarotenoids were able to bind to RARα, RARβ, and RARγ receptors, thereby opening the door to many immune-related reactions of carotenoid metabolites.

Possibly due to similar activities, swelling and inflammation of the paw in mice (induced by carrageenan) receiving a pepper carotenoid extract (a mixture of carotenoids, ie, β-carotene, violaxanthin, capsanthin, and capsorubin) were significantly reduced at 5, 20, or 80 mg/kg [155]. Such reduced involvement of inflammatory stimulating cells was also seen after lycopene administration. In a murine model of asthma (induced by ovalbumin), lycopene (8 or 16 mg injected IP for 3 days) reduced inflammation, as measured by infiltration of inflammatory cells (neutrophils, eosinophils, lymphocytes, and macrophages), into the peribrochilar and perivascular regions. It also decreased mRNA levels of IL-4 in bronchoalveolar lavage fluid but increased IFN-γ and T-bet (encoding for transcription factors responsible for development and also for IFN-γ production), thus suggesting an overall anti-inflammatory activity in upper airway diseases [156]. Lycopene administration (0-20 μM) also reduced permeability and migration of leukocytes to the peritoneal cavity in mice. This was explained by its influence on the high-mobility group box 1 (HMGB1), which is a nuclear protein responsible for the mediation of proinflammatory stimuli such as of multiple cytokines and chemoattraction of stem cells [157]. Further data on the effect of carotenoids on this protein are limited though.

4.4. *Summary and outlook*

A large number of animal trials have strongly suggested the implication of NF-κB, Nrf2, and additional transcription factors, such as STAT, in anti-inflammatory effects of carotenoids, and thereby influencing many downstream targets such as cytokine formation. Furthermore, the effects were correlated with results from several studies, several studies focusing on the decreased activation of proinflammatory cell types such as CD4(+), CD8(+), and neutrophils, and possibly even involving (via their metabolites) other nuclear receptors such as RAR. This represents a novel area to be further scrutinized. Although often supraphysiological doses were used to achieve this response, there are also indications that lower and rather chronically applied concentrations are likewise effective, although more studies are needed in this domain. An interesting approach in using in vivo models could be the use and development of novel, more water-soluble carotenoids, such as crocin and disodium disuccinate astaxanthin. Disodium disuccinate astaxanthin has been investigated for cardioprotection and has been shown to reduce some inflammatory (and oxidative stress) markers (eg, prostaglandin F2α [PGF2α], 5-hydroxyeicosatetraenoic acid, 8-isoprostane F2α) in a peritoneal mouse inflammation model, although doses were extremely high (500 mg/kg for 7 days) [158].

5. Human studies

5.1. *Markers of inflammation and oxidative stress and general aspects*

Human intervention studies (Table 3), especially when conducted as a randomized, double-blind, and placebo-controlled design, are still considered the “gold standard” in nutritional sciences for testing health effects of dietary compounds. Among other reasons, studies that include disease outcome add much more evidence toward proving a potential relationship between carotenoid consumption and disease incidence. However, with respect to studying secondary plant compounds including carotenoids, human studies are faced with a dilemma. When administering carotenoid-rich foods, such as certain fruits and vegetables, many confounding factors prevail that include dietary fiber, minerals, and vitamins, which are also present in the food matrix. However, when giving individual compounds such as in the form of supplements, synergistic effects between carotenoids and micronutrients (eg, between vitamin C and vitamin E), aspects of overdosing, or altered bioavailability (missing food matrix aiding eg, in emulsification) may result in different release kinetics, uptake, and biodistribution than carotenoids bound to the food matrix.

An indirect indication of the potential health benefits of carotenoids may be found in epidemiologic studies, although aspects of inflammation in such studies are not typically assessed. In addition, epidemiologic studies cannot demonstrate causality. Furthermore, due to a large number of confounding factors, it is difficult to predict the effect of individual food constituents. Nevertheless, a number of large-scale prospective cohort studies such as the EPIC study [159], the Los Angeles Artheriosclerosis Study [160], and the study by Kabagambe et al [161] have produced interesting and robust data with respect to “hard end points.” Most of these studies have been reviewed in further detail elsewhere [84,162]. They suggest that there are significant health benefits when consuming 3 to 8 servings of fruits and vegetables per day, whereas a lower number of servings often showed to be

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Table 3 – Effects of carotenoids or carotenoid rich food items on inflammatory mediators and oxidative stress in humans

Study type	Cell type or specimen	Test meals	Time frame	No. of subjects	Carotenoids investigated	Aspects studied	Main effects	Reference
Intervention studies with food items	PBMCs	Fruits and vegetables (2 or 8 servings/d)	8 wk	64 men	n.i.	Fruit/ vegetable consumption and immunologic markers	Consumption of fruits/vegetables: no impact on TNF-α, IL-12 (2 and 8 servings/d) and C-reactive protein (2 servings/d). Consumption of 8 servings/d lowered C-reactive protein	Watzl et al [198]
	Urine and serum	Vegetables (2, 5, or 10 servings/d = 130 g, 237 g, 614 g)	3 wk	49 women	n.i.	Vegetable consumption and oxidative stress, inflammation	Consumption of vegetables: no effect on urinary 8-isoprostane F2α and serum C-reactive protein	Crane et al [199]
	PBMCs	68 g avocado	1 consumption	11 individuals	n.i.	Avocado and inflammatory responses	Avocado consumption reduced IL-6 secretion and NF-κB activation	Li et al [211]
	–	Fruits and vegetables	12 y	73286 women	α-and β-carotene, lycopene, lutein/ zeaxanthin β-cryptoxanthin	Dietary carotenoids and CAD	Significant inverse relation between intake of β-carotene and α-carotene–rich foods and coronary artery disease	Osganian et al [212]
	–	Carotenoid-rich foods (mostly carrot)	15 y	559 men	α-carotene, β-carotene	Carotenoid-rich foods and CVD	α- and β-carotene–rich food: lowered CVD mortality. Other carotenoids: no effect	Buijsse et al [165]
	–	Tomato products	–	–	Lycopene	Tomato and prostate cancer	Tomato and tomato products might play a role in prostate cancer, when highly consumed	Etminan et al [166]
	–	Food rich in carotenoids	7-16 y	399 765 individuals	α-and β-carotene, lycopene lutein/ zeaxanthin, β-cryptoxanthin	Carotenoid-rich food and lung cancer	Intake of β-cryptoxanthin–rich food: inversely associated with lung cancer risk	Mannisto et al [167]
	White blood cells	Tomatoes (360-728 g/d)	1 single dose	5 individuals	n.i.	DNA oxidation	Tomato consumption decreased levels of 8-hydroxyguanine	Rehman et al [180]
	Peripheral lymphocytes	Tomato juice (330 mL/d 3-4 wk) Carrot juice (330 mL/d, 5-6 wk) Dried spinach in milk/water (10 g/d, 7-8 wk)	8 wk in total	23 men	Lycopene, β-carotene, α-carotene lutein	DNA oxidation	Reduction of strand breaks in lymphocyte DNA. Reduction of oxidative base damage measured via COMET assay through the carrot juice	Pool et al [178]
	Urine	Tomato products	3 wk	12 women	Lycopene	Tomato products and markers of lipid oxidation	Significant reduction of 8-iso-PGF2α due to tomato products consumption	Visioli et al [181]
	Leucocytes	Tomato	3 wk	32 men	Lycopene	Tomato	Tomato sauce	Chen

(continued on next page)

Table 3 (continued)

Study type	Cell type or specimen	Test meals	Time frame	No. of subjects	Carotenoids investigated	Aspects studied	Main effects	Reference
	and prostate tissue	sauce (30 mg lycopene/d)				sauce and prostate cancer	reduced oxidative DNA damage in leucocytes and in prostate tissue	et al [182]
	Plasma	Tomato juice (500 mL/d)	4 wk	57 diabetic subjects	Lycopene	Tomato juice and LDL oxidation	Tomato juice consumption increased the resistance of LDL to oxidation	Upritchard et al [184]
	Skin	Tomato paste (55 g/d including 16 mg lycopene)	12 wk	20 women	Lycopene	Tomato paste and cutaneous photodamage	Protection against cutaneous photodamage through reducing mitochondrial DNA damage	Rizwan et al [186]
	PBMCs	Tomato juice (330 mL/d, 47.1 mg lycopene)	8 wk	53 individuals	Lycopene	Tomato juice and cell-mediated immunity	Tomato juice decreased IL-2 and IL-4 secretion	Watzl et al [191]
	Whole blood	Tomato drink (5.7 mg lycopene, 3.7 mg phytoene, 2.7 mg phytofluene, 1 mg β-carotene, 1.7 mg α-tocopherol)	26 d	26 individuals	Lycopene	Tomato-based drink and markers of inflammation	Tomato-based drink decreased TNF-α levels	Riso et al [192]
	Serum	Tomato paste (200 g/d, 16 mg lycopene); pure lycopene (16 mg/d)	1 wk	30 men	Lycopene	Tomato paste and lycopene and different target genes of prostate cancer cells	Tomato paste: up-regulated IGFBP3 and Bax/Bcl-2 ratio and down-regulated cyclin D1, p53 and Nrf2. Lycopene con-sumption up-regulated IGFBP3, c-fos, and μPAR.	Talvas et al [200]
	Lymphocytes	Passata sauce (170 g pasta, ca. 7 mg/d lycopene)	3 wk	24 men	Lycopene	Passata sauce on oxidative stress	Consumption of passata sauce: no effect on HO-1 in lymphocytes	Markovitch et al [201]
Intervention studies with isolated carotenoids/ suppl.	–	β-Carotene (20 mg/d) and vitamin E (50 mg/d) suppl.	8 y	29133 smokers and nonsmokers	β-Carotene	β-Carotene and vitamin E and lung cancer	Increased lung cancer risk in smokers	Albanes et al [172]
	–	β-Carotene (30 mg/d) and retinyl palmitate (25000 IU) suppl.	5 y	18 314 smokers and nonsmokers	β-Carotene	β-Carotene and vitamin A and lung cancer incidence	Increased lung cancer incidence in smokers	Omenn et al [171]
	–	β-Carotene (20 mg/d) and vitamin E (50 mg/d) suppl.	6 y	28 519 men	β-Carotene	Effect on stroke incidence in smokers	Increased risk of intracerebral hemorrhage	Leppälä et al [174]
	–	vitamin C (120 mg/d) and E (30 mg/d) and β-carotene (6 mg/d) and Se (100 μg/d) and Zn (20 mg/d)	7.5 y	13 017 individuals	β-Carotene	Effect on cancer incidence and all-cause mortality	Decrease in total cancer incidence and all-cause mortality in men but not in women	Hercberg et al [177]

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Table 3 (*continued*)

Study type	Cell type or specimen	Test meals	Time frame	No. of subjects	Carotenoids investigated	Aspects studied	Main effects	Reference
	–	suppl. β-Carotene (15 mg/d) and Se (50 μg/d) and vitamin E (30 mg/d)	5.25 y	30 000 individuals	β-Carotene	Effect on cancer incidence	Decrease in total mortality and in cancer mortality	Blot et al [176]
	–	β-Carotene (17.8 mg/d)	3.3 y (mean)	232 606 individuals	β-Carotene	β-Carotene and CVD	β-Carotene supplementation increased slightly the risk to develop CVD	Bjelakovic et al [169]
	–	β-Carotene (4 μg/d) or lutein 1.5 μg/d	10 y	77 126 individuals	β-Carotene lutein	Effect of carotenoids on lung cancer	β-carotene: increased risk of small cell lung cancer. Lutein supplementation: increased risk of non–small cell lung cancer	Satia et al [173]
	–	Lutein (20 mg/d)	3 mo	65 individuals	Lutein	Lutein, serum cytokines, lipid profile	Supplementation with lutein: decreased levels of IL-6 and MCP-1, also of LDL and TG	Xu et al [196]
	Plasma	Lycopene (6 or 15 mg/d)	8 wk	126 men	Lycopene	Lycopene and endothelial health, oxidative stress	Lycopene supplementation (15 mg/d): increased SOD plasma activity, decreased lymphocyte DNA comet tail length	Kim et al [183]
	Plasma and urine	Lycopene (0,6.5, 15 and 30 mg/d)	8 wk	77 individuals	Lycopene	Lycopene and biomarkers of oxidative stress	Lycopene supplementation: no effect on urinary F2-isoprostanes, MDA, LDL oxidation. 30 mg/d: decreased lymphocyte DNA damage and urinary 8-OHdG	Devaraj et al [187]
	Serum	Lycopene (10 mg/d)	2 mo	35 diabetic patients	Lycopene	Lycopene and oxidative stress	Lycopene supplementation: no effect on antioxidant capacity, oxidized LDL, but increased MDA	Neyestani et al [188]
	Plasma	Lycopene (12 mg/d)	56 d	37 women	Lycopene	Lycopene and lymphocyte DNA damage	Lycopene consumption reduced DNA damage in lymphocytes but did not prevent it.	Zhao et al [189]
	Plasma	Lycopene (15 mg/d)	1 wk	8 individuals	Lycopene	Lycopene and lymphocyte DNA damage	Lycopene consumption prevented DNA damage in lymphocytes.	Torbergsen et al [190]
	Prostate cancer	Lycopene (15 mg/d)	3 wk	26 men	Lycopene	Lycopene and prostate cancer	Lycopene consumption: no effect on apoptotic markers	Kucuk et al [193]
	Plasma	Lycopene	1 wk	18 men and 9 women	Lycopene	Lycopene and biomarkers of endothelial health	Lycopene: no effect on MDA levels	Denniss et al [194]

Abbreviations: n.i., not investigated; suppl., supplements; CHD, coronary heart disease; 8-OHdG, 8-oxo-2′ deoxyguanosine; CAD, coronary artery disease; TG, triglycerides.

ineffective [163,164]. Likewise, several prospective studies have suggested that carotenoid consumption in the diet was associated with a reduced risk of cardiovascular mortality [165], or developing type 2 diabetes [23], prostate cancer [166], and lung cancer [167]. Similar results were also found for tissue levels and chronic diseases [168].

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In contrast to epidemiologic studies that assess the relationship of whole fruits/vegetables and their positive effects on chronic diseases, many intervention studies with isolated carotenoids have failed to demonstrate health benefits. Instead, they appear to show that the risk for developing CVD [169], lung cancer [170–173], or stroke [174] increased. However, a few trials have revealed beneficial effects after carotenoid supplementation, especially when given to populations marginally deficient in carotenoids [175–177], highlighting that administration of potential prooxidants to nonhealthy subjects bears several risks.

5.2. *Carotenoids, oxidative stress, NF-κB, Nrf2, and other pathways*

Compared with in vitro studies, it is more difficult to measure the antioxidant effects of carotenoids in vivo, as many factors govern the antioxidant system [84] and only small or transient effects are expected (Table 3). Pool et al [178] showed that consuming 330 mL tomato juice (40 mg lycopene) or 330 mL carrot juice (containing 22 mg β-carotene and 16 mg α-carotene) or consuming 10 g dried spinach powder in water/milk resulted in a significant decrease in endogenous levels of strand breaks in lymphocyte DNA. The carrot juice intervention was the only intervention in this study that significantly reduced oxidative damage. In another carrot juice intervention [179], 240 mL carrot juice for 3 weeks provided to breast cancer survivors significantly reduced 8-iso PGF2α, although the study was without a control group. Another study by Rehman et al [180] (5 individuals) showed that a single serving of tomatoes (360-728 g/d) reduced oxidative DNA base damage level in white blood cells within 24 hours. It has also been shown that the intake of tomato products for 21 days decreased urinary 8-*iso*-PGF2α by 50% [181]. The consumption of lycopene-rich tomato products (sauce, paste, or juice) for 4 to 8 weeks decreased oxidative DNA [182] and lymphocyte DNA damage in healthy patients [183], and it increased the resistance of low-density lipoprotein (LDL) to oxidation in diabetic patients [184], similar to another study [185]. Lycopene-rich tomato paste also protected against cutaneous photodamage by reducing mitochondrial DNA damage [186].

Some positive, but more mixed results were seen in studies including carotenoid supplements. Although taking lycopene (6.5, 15, 30 mg/d) in pure form for 8 weeks had no effect on urinary F2-isoprostanes, MDA, and LDL oxidation rate, 30 mg/d reduced lymphocyte DNA damage and urinary 8-OHdG in healthy subjects [187]. A similar result was found in diabetic patients receiving 10 mg/d of lycopene. The supplementation had no effect on total antioxidant capacity or oxidized LDL, but reduced MDA in serum [188]. Supplementing 12 mg/d lycopene for 56 days reduced H_2O_2-induced DNA damage in lymphocytes, but it did not prevent DNA damage [189], although supplementation with 15 mg/d lycopene for 1 week prevented H_2O_2-induced DNA damage in lymphocytes [190].

A few studies have investigated carotenoid supplementation and their effect on factors involved in the NF-κB pathway. Lycopene-rich foods have received the most attention, possibly due to the relation to tomatoes and the Mediterranean diet. For example, tomato juice administered for 2 weeks to human subjects reduced IL-2 and IL-4 secretion of peripheral blood mononuclear cells (PBMCs) [191], and the consumption of a tomato-based drink for 26 days lowered TNF-α secretion by 34% [192]. Although these results are promising, other studies with lycopene supplementation or tomato products showed rather limited effects, that is, no effect on apoptotic markers [193], MDA [194], C-reactive protein [195], and nitrite/nitrate [194]. In early arthrosis patients, supplementing 20 mg lutein per day for 3 months reduced plasma IL-6 and MCP-1 and improved serum lipids, when compared with subjects receiving a placebo. This indirectly indicated that NF-κB may have been involved [196]. In subjects receiving enteral nutrition, carotenoid enrichment (3 mg/1500 kcal) reduced NF-κB lymphocyte expression, after 3 months of intervention, as compared with a control group [197].

In contrast, 2 or 8 servings/d of fruits and vegetables for 4 weeks did not show any effect on TNF-α and IL-12 production, and the same was observed for C-reactive protein concentrations. However, consuming more than 8 servings/d reduced C-reactive protein concentration [198]. In overweight or obese postmenopausal woman, consuming 2, 5, or 10 servings of vegetables/d for 3 weeks had no effect on urinary 8-isoprostane F2α or serum C-reactive protein [199], despite a clear increase in carotenoid plasma levels. Perhaps the short time of intervention limited observable effects on the inflammation markers.

Only a few human studies have investigated the relationship of carotenoids and Nrf2 expression. A recent study by Talvas et al [200] showed that cells incubated with sera from men who consumed red tomato paste had a significant up-regulation of insulin-like growth factor binding protein 3 (IGFBP3) and Bax/Bcl-2 ratio and down-regulation of cyclin-D1, p53, and Nrf2. These are all genes implicated in the cell cycle, cell stress response, apoptosis, or cell proliferation. Moreover, the study showed that cells incubated with sera from men who consumed purified lycopene had significant up-regulated IGFBP3, c-fos, and μPAR, which are genes implicated in cell proliferation and carcinogenesis. In another recent study, lycopene supplementation (7 mg/d for 3 weeks) was unable to modulate HO-1 in lymphocytes of young men, perhaps because they were already healthy [201]. Middle-aged, moderately overweight subjects who received a lycopene-rich diet (224-350 mg) or lycopene supplements (70 mg/week) for 12 weeks showed significantly improved serum-amyloid A, which is a marker of systemic and high-density lipoprotein–associated inflammation [202].

6. Conclusions, gaps of knowledge, and future research

Many mechanistic (ie, in vitro studies) investigating the effect of carotenoids on various markers of oxidative stress and inflammation have indicated beneficial health effects, by influencing transcription factors, such as NF-κB or Nrf2, and their downstream targets, such as IL-8 and PGE2 or HO-1, SOD, respectively. However, other, less well-studied molecular targets, such as RAR, may also play a role.

Thus, although several pathways possibly related to carotenoids, inflammation, and oxidative stress have been

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uncovered, many aspects remain poorly understood and require more research. This research should include the synergistic aspects between different carotenoids and other compounds such as vitamins, their dosing, and the role of carotenoid breakdown products or metabolites. Taking carotenoid supplements alone has often failed or even indicated negative effects on disease risk in some trials, especially in subjects at risk for oxidative stress, such as smokers. Although this remains controversial, it may be explained by the absence of synergistic effects with compounds normally present in whole foods, such as other antioxidants like vitamin E or C, [203,204]. Carotenoids, when taken as a supplement and not in a food matrix, especially when taken in significant doses, may act as prooxidants, which would be in line with the effects seen in vitro [205].

Future research should investigate which carotenoids and their metabolites, such as apocarotenoids or water-soluble derivatives, may constitute suitable modulators to alter pathways related to oxidative stress and inflammation. Research should also focus on the effects that other matrix components may have on their metabolism and potential anti-inflammatory properties. Such studies will likely advance understanding into the potential dose-relation effects. Further, studying of molecular targets of this promising group of secondary plant compounds are warranted.

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