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Review

Carotenoids as Multifunctional Nutritional Modulators in Alzheimer's Disease: A Mini-Review of Parallel Effects on Oxidative Stress, Connexin 43, and Amyloid-β Aggregation

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Abstract

Alzheimer's disease (AD) is characterized by the accumulation of amyloid-beta (Aβ) plaques and associated oxidative and inflammatory neurotoxicity. Carotenoids are being investigated as promising nutritional candidates that may attenuate Aβ-induced damage through multiple parallel mechanisms, including reducing oxidative stress, modulating gap junction intercellular communication (GJIC), and interfering with Aβ aggregation. Microglial activation and subsequent release of reactive oxygen species (ROS) and cytokine together alter astrocytic connexin 43 (Cx43) function, disrupt GJIC, and drive excitotoxic signaling that further increases Aβ production. Carotenoids exhibit antioxidant activity through free radical scavenging and support of mitochondrial function and have been associated with modulation of Cx43 expression and astrocytic coupling under conditions of oxidative and inflammatory stress, potentially helping to maintain neuronal energy balance and ion homeostasis. These effects may also influence redox- and cytokine-dependent pathways implicated in pathological hemichannel activity. In addition, certain carotenoids can directly interact with Aβ in experimental models, inhibiting fibril formation and attenuating Aβ-associated inflammatory responses. Overall, the current evidence base is dominated by *in vitro*, animal, and observational studies. Notably, while clinical evidence remains limited, a preliminary interventional study in AD patients reported that a combination of lutein, zeaxanthin, meso-zeaxanthin, and omega-3 fatty acids was associated with slower functional decline and improvements in certain behavioral and clinical measures, whereas carotenoids alone had a smaller impact. A subsequent randomized clinical trial using a similar carotenoid–omega-3 formulation plus vitamin E showed modest benefits on selected memory and clinical outcomes. In contrast, omega-3 fatty acids or vitamin E, administered without concomitant carotenoids in other trials, have not consistently shown clear benefits for AD progression. In addition, a randomized trial of lutein/zeaxanthin supplementation in community-dwelling older adults with self-reported cognitive complaints suggested modest, domain-specific improvements, particularly in visual memory and learning. This mini-review summarizes current experimental and clinical evidence for these antioxidant, gap-junction-modulating, and anti-aggregatory actions in the context of Aβ-driven neurodegeneration and highlights the potential role of these carotenoids as multifunctional agents in nutritional strategies against AD.

Keywords: Alzheimer's disease; dietary carotenoids; amyloid-beta neurotoxicity; oxidative stress; Aβ aggregation; connexin 43 hemichannels; lutein; β-carotene; zeaxanthin; meso-zeaxanthin

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder in the world and is marked by progressive cognitive decline together with the abnormal accumulation of amyloid-beta (Aβ) plaques in the brain [1,2]. Current projections estimate that by 2050, 152.8 million people worldwide will be living with dementia, with AD being the most common form [3,4]. Current therapies for Alzheimer's mainly rely on symptomatic drugs such as cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) antagonists, which offer modest cognitive and functional benefits without reliably halting disease progression [1,5]. Newer disease-modifying approaches, including monoclonal antibodies targeting Aβ plaques and neurofibrillary tangles as well as gene and immunotherapy strategies, show promise in slowing underlying pathology but are still limited by efficacy, safety, cost, and access challenges [1]. In parallel with pharmacologic strategies, nutritional and lifestyle factors have attracted increasing attention as potential modulators of AD risk and progression. Recently, the Lancet dementia commission concluded that tackling modifiable life-course and vascular risk factors through broad lifestyle and public-health measures could prevent a large fraction of dementia cases, making prevention-focused strategies more impactful than relying on drug treatments alone [6].

Carotenoids are dietary lipophilic pigments with strong antioxidant properties, and there is growing evidence for their neuroprotective effects [7]. Most carotenoids are generally well tolerated at dietary and commonly used supplemental doses, with an excellent safety record outside of high-dose β-carotene in smokers [8]. Their bioavailability, however, is modest and strongly influenced by

formulation and diet; processing that disrupts the plant matrix and co-ingestion with dietary lipids, as well as oil-based or emulsified supplement forms, substantially enhance intestinal absorption and systemic exposure [9,10]. Notably, xanthophyll carotenoids, particularly lutein, are more efficiently delivered to and preferentially accumulated in brain tissue than carotenes such as β-carotene [11]. Mechanistically, carotenoids appear to influence several interlocking pathways that are now recognized as central to AD pathogenesis: they scavenge reactive oxygen and nitrogen species and modulate redox-sensitive signalling, dampen microglial and astrocytic inflammatory responses, help preserve mitochondrial function and synaptic plasticity, and in some cases directly interfere with Aβ aggregation and membrane-disruptive Aβ oligomers [7,12,13,14,15,16]. More recently, experimental work has also begun to link carotenoid actions to increased connexin expression and connexin-mediated glial communication, suggesting that these compounds may act at the level of glial–neuronal network organization as well as classical oxidative and inflammatory cascades [17,18,19,20,21]. Observational studies and neuropathological series consistently report that individuals with higher intakes or circulating levels of carotenoids, particularly the xanthophylls lutein and zeaxanthin, tend to show better cognitive performance, lower incidence of dementia, and, in some cohorts, reduced AD-type neuropathology, whereas AD patients often exhibit relatively low carotenoid status in serum and brain tissue [22,23,24]. Small randomized trials further suggest that supplementation with lutein and zeaxanthin, alone or in combination with other nutrients such as omega-3 fatty acids and vitamin E, may be associated with modest improvements in selected outcomes in people with cognitive complaints or established AD, although larger and longer-term studies are still needed to confirm these effects [25,26,27].

This mini-review first outlines how carotenoids intersect with oxidative, nitrosative, and inflammatory pathways that shape early Alzheimer's pathology in section 2. It then examines their influence on microglia–astrocyte–neuron signalling networks, with a particular focus on connexin 43 (Cx43)-dependent communication and hemichannel gating in section 3 and finally, considers experimental and clinical evidence that carotenoids can alter Aβ-related toxicity in section 4, framing these actions within their broader promise as nutritional strategies for AD prevention and management.

2. Carotenoids in Oxidative, Nitrosative, and Inflammatory Pathways in Early Alzheimer's Disease

2.1 Oxidative and Nitrosative Stress as Early Amplifiers of Aβ Pathology

Experimental and clinical work increasingly supports a model in which oxidative and nitrosative stress arise early in the Alzheimer's cascade and reinforce Aβ production rather than simply reflecting plaque burden [28,29]. Reviews of AD pathogenesis emphasize that Aβ accumulation, mitochondrial injury, and chronic neuroinflammation form a self-amplifying loop in which reactive oxygen species (ROS), reactive nitrogen species (RNS), and cytokines drive synaptic failure and tau pathology [28,30]. Building on this framework, mitochondria-derived ROS have been shown to shift amyloid precursor protein (APP) processing toward the Aβ-generating pathway, increaseβ-site amyloid precursor protein cleaving enzyme 1 (BACE1) activity via activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and elevate Aβ monomer production, with antioxidant treatment reversing these effects [31,32]. ROS drive peroxidation of membrane polyunsaturated fatty acids to generate the lipid aldehyde 4-hydroxy-2-nonenal (4-HNE), which then forms covalent adducts on the β-subunit of the low-density lipoprotein receptor-related protein 1 (LRP1), a key Aβ efflux receptor at the blood–brain barrier (BBB), thereby impairing LRP1-mediated Aβ clearance [33,34]. Loss or dysfunction of LRP1 at the BBB and in vascular smooth muscle cells reduces vascular efflux of soluble Aβ, leading to increased brain Aβ burden that is thought to favor accumulation of neurotoxic soluble Aβ oligomers [35]. These oligomeric Aβ species, in turn, interfere with neuronal survival pathways by dampening phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling, weakening Akt-dependent trophic and metabolic support, permitting activation of downstream pro-apoptotic mechanisms, and glycogen synthase kinase-3β (GSK3β)–dependent tau-phosphorylating processes [36]. Consistent with a feed-forward loop between redox imbalance and survival signaling, ROS generated in response to Aβ can further inhibit PI3K/Akt through redox-sensitive changes in PI3K and Akt phosphorylation [36,37]. Interventions that lower ROS have been reported to reduce Aβ levels and oligomer burden, restore PI3K/Akt activity and glucose transporter 1 (GLUT1)–dependent energy metabolism, and enhance Aβ clearance [38].

Microglia are also a major source of reactive oxygen and nitrogen species in the brain; upon sensing infection or injury, they become activated and upregulate NADPH oxidase and inducible nitric oxide synthase (iNOS), resulting in robust production of ROS and nitric oxide (NO) [39]. In AD, microglia exposed to Aβ become chronically primed by oxidative and nitrosative stress: fibrillar Aβ engages a microglial receptor complex (including CD36) that activates NADPH oxidase and iNOS, thereby further increasing ROS and NO generation; these species combine to form peroxynitrite and other reactive intermediates that both injure nearby neurons and reinforce microglial activation, thereby amplifying Aβ-driven neurotoxicity [40,41]. Consistent with this, studies of glutathione depletion and metal-mediated oxidative damage indicate that redox alter-

ations precede overt plaque and tangle formation in AD brain tissue, supporting a model in which oxidative and nitrosative stress are not merely byproducts of Aβ pathology but early, dynamic amplifiers that couple mitochondrial dysfunction, impaired Aβ clearance, and maladaptive glial activation into a self-reinforcing cascade of synaptic and neuronal injury [29,42].

2.2 Antioxidant and Anti-Inflammatory Actions of Carotenoids in Neural Tissue

Across experimental systems, carotenoids act as lipophilic antioxidants that quench singlet oxygen, scavenge peroxyl radicals, stabilize membranes, and modulate redox-sensitive transcription factors such as nuclear factor erythroid 2–related factor 2 (Nrf2) and NF-κB, with xanthophylls like lutein and zeaxanthin particularly well documented in neural tissues [7,12,13]. Evidence from neurodegenerative contexts indicates that these actions translate into lower ROS/RNS, reduced lipid peroxidation, and better mitochondrial function in brain tissue, often accompanied by dampened microglial activation and cytokine output [7,12,14,43]. Physiologically, Nrf2 is restrained by Kelch-like ECH-associated protein 1 (KEAP1) and released under oxidative or electrophilic stress to induce heme oxygenase-1 (HO-1) and a battery of antioxidant and phase II detoxifying enzymes, thereby strengthening glutathione metabolism, mitochondrial redox buffering, and resistance to ROS/RNS [44]. In AD-relevant settings, defective Nrf2/HO-1 responses are linked to increased lipid peroxidation, mitochondrial dysfunction, and a pro-inflammatory cytokine profile [45,46]. In a severe traumatic brain injury (STBI) rat model characterized by increased ROS production and neuroinflammation similar to AD models, lutein reduced ROS levels and the pro-inflammatory mediators tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) while concomitantly elevating Nrf2 expression and the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) [47]. Similarly, in mouse models of cerebral ischemia/reperfusion injury, a condition marked by pronounced ROS and RNS generation typical of stroke reperfusion, lutein lowered nitrotyrosine (NT), a marker of nitrosative stress, inhibited NF-κB activation, enhanced PI3K/Akt pathway signaling, and increased the antioxidant enzymes SOD, GPx, and catalase [48,49]. Carotenoid-driven activation of Nrf2/HO-1, together with inhibition of NF-κB directly addresses the redox and inflammatory abnormalities that lower the threshold for Aβ-related neurotoxicity [45,46,50]. In bacterial lipopolysaccharide (LPS)-stimulated microglia, β-carotene suppresses NO production and iNOS expression through retinoic acid receptor (RAR) dependent pathways, pointing to a direct carotenoid influence on NO/iNOS signaling in inflammatory glia [19]. Although much of the detailed cellular work comes from retina and peripheral tissues, studies in retinal degeneration show that lutein can preserve synaptic proteins, maintain brain-derived neurotrophic factor (BDNF), limit DNA damage, and restrain extracellular signal-regulated kinase (ERK) overactivation, illustrating how carotenoids support neuronal structure and trophic signaling in vulnerable neural circuits [51].

Experimental work in AD relevant models supports the view that oxidative stress is an early event that facilitates Aβ oligomerization and tau pathology, rather than a mere byproduct of plaques, and that boosting endogenous antioxidant capacity can mitigate these downstream effects. For example, in neuronal cultures, pretreatment with the carotenoid fucoxanthin lowers basal ROS and strengthens endogenous antioxidant defenses, so that a subsequent Aβ oligomer challenge produces less oxidative damage, apoptosis, and signaling through pro-inflammatory pathways [37]. Similarly, β-carotene administered to mice before streptozotocin-induced AD-like pathology attenuates memory impairment, reduces oxidative stress markers and decreases Aβ protein levels [52]. In an AD-relevant rat model, lycopene supplementation lowered hippocampal $A\beta_{1-42}$, the oxidative stress marker malondialdehyde, nitrite, and pro-inflammatory cytokines while boosting Nrf2, SOD, GPx, and the anti-inflammatory mediators interleukin-10 (IL-10) and transforming growth factor beta 1 (TGF-β1), and this biochemical improvement correlated with better cognitive performance and synaptic marker preservation [14]. Together, these data support carotenoids as upstream modulators that rebalance redox and inflammatory tone before and after Aβ exposure, raising the threshold for excitotoxic damage.

3. Carotenoid Modulation of Microglia–Astrocyte–Neuron Signaling and Cx43 Dependent Communication

3.1 Connexin Expression in Astrocytes and Microglia and Carotenoid Driven Transcriptional Changes

Astrocytes mainly express Cx43 but also some connexin 30 (Cx30) which couple them with each other and coordinate metabolic and ionic support to neurons while microglia express low levels of connexin 36 (Cx36) which connect them to each other and to neurons and allow surveillance signaling under normal physiological conditions [53,54,55,56,57]. Connexin expression in glial cells is strongly context-dependent: under resting conditions, microglia form very little functional gap-junctional coupling, whereas astrocytes are extensively coupled through Cx43 or Cx30 based networks that support neurometabolic coupling [53,55,56,58]. Dye-coupling studies *in vivo* show that activated microglia in AD models do not connect via functional gap junctions to each other or to astrocytes, oligodendrocytes, or neurons, suggesting that most microglial connexin signaling in disease proceeds through hemichannels and pannexins rather than classic gap junction intercellular communication (GJIC) [53,58]. Specifically, a recent study showed that microglia around Aβ plaques start to ex-

press Cx43 hemichannels and similar upregulation occurs when microglia are treated with certain cytokines [59,60]. Astrocytes under stress also start to express pannexins and open Cx43 hemichannels [61,62], while non-stressed networks rely on functional Cx43 and Cx30 mediated coupling to distribute glucose and lactate and to buffer ions during high synaptic activity; when this gap-junctional scaffold is disrupted, neurons lose access to distant energy substrates and synaptic transmission fails [55,56]. Mitochondrial status can tune this coupling: opening astrocytic mitochondrial adenosine triphosphate-sensitive potassium channels (K_{ATP}) enhances Cx43 dependent electrical coupling through ROS- and ERK-dependent pathways, indicating that metabolic cues are wired directly into connexin regulation [63].

Retinoids and certain carotenoids add a transcriptional layer by regulating Cx43 expression in diverse cell types. Work in canine lens and kidney epithelial cells, mouse embryonic fibroblasts, and human endometrial stroma and oral cancer cells shows that all-trans retinoic acid (ATRA) and related retinoids increase Cx43 mRNA and protein and enhance GJIC via RAR-dependent mechanisms, while some non-provitamin A carotenoids can also upregulate Cx43 in specific cell types, whereas non-carotenoid antioxidants do not, implying a specific signaling route from retinoid and carotenoid structure to connexin transcription [64,65,66,67,68,69]. Detailed promoter analyses reveal that both retinoids and select carotenoids converge on a GC-box motif in the Cx43 promoter bound by Sp1/Sp3, increasing transcription without changing mRNA stability [65,66]. Retinoid effects are RAR-dependent and can be blocked by antagonists, while non-provitamin A carotenoids can still induce Cx43 in the presence of RAR blockade, pointing to alternate receptors, such as peroxisome proliferator-activated receptor gamma (PPARγ) or related nuclear factors, that converge on the same promoter element [65,66,70]. This division of labor allows retinoids and some carotenoids to cooperate or substitute at the level of Cx43 expression: retinoids provide RAR-driven control tightly linked to vitamin A status, and certain carotenoids provide a parallel, RAR-independent route that may be particularly relevant in tissues like the brain where local vitamin A metabolism is tightly regulated [65,66]. However, studies showing retinoid or carotenoid driven upregulation of Cx43 in astrocytes are rare, with one Chinese study showing that ATRA upregulates Cx43 expression in neonatal Sprague-Dawley rat astrocytes [71] and another study showing that lycopene can upregulate Cx43 in rat spinal astrocytes under inflammatory conditions, but in a post-transcriptional way [17], raising the possibility that carotenoids capable of accessing the central nervous system (CNS) could similarly preserve gap-junctional connectivity and resilience in Aβ-stressed astrocytes in an AD-relevant model.

3.2 Carotenoid Effects on Cx43 Hemichannel Opening and Gap Junction Coupling Under Stress

Pathologic opening of Cx43 hemichannels is now recognized as a key amplifier of glial and neuronal injury in AD and related conditions [72]. In amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice, and human AD brain, astrocytic Cx43 expression and hemichannel activity are increased around plaques, where they drive adenosine triphosphate (ATP) and glutamate release, sustain astrocytic calcium elevation, increase oxidative stress, and drive structural degeneration in adjacent neurons; conditional deletion of astrocytic Cx43 reduces hemichannel activity and markedly lessens neuronal damage [73,74]. Recently, it was also found that treating APP/PS1 mice with TAT-Cx43@LNPs, which is a peptide that blocks microglial Cx43 hemichannels and is delivered using lipid nanoparticles, turns microglia neuroprotective instead of pro-inflammatory and rescues neuropathology and cognitive impairment [59]. Work across ischemia, anesthesia, and oxygen-glucose deprivation/reperfusion models shows a consistent pattern: stressors reduce Cx43-mediated GJIC while enhancing hemichannel opening, and interventions that either block hemichannels or selectively boost gap-junctional Cx43 coupling mitigate neuroinflammation and cognitive deficits [75,76,77,78,79]. In isoflurane-exposed mice, for example, pharmacologic enhancement of Cx43 networks, using the small molecule ZP1609, restores coupling, lowers IL-1β/IL-6, and rescues behavior without increasing hemichannel activity, highlighting how shifting Cx43 from an open hemichannel to a coupled gap-junction state can be neuroprotective [76].

Pro-inflammatory mediators and redox changes are potent drivers of this channel reconfiguration. Reviews of brain hemichannels show that cytokines, LPS, ischemia, and Aβ all converge on increased Cx43 and Cx36 hemichannel activity alongside reduced GJIC, leading to ATP and glutamate efflux, Ca^{2+} dysregulation, and propagation of injury signals through glial networks [30,77,78,80,81]. NO-dependent mechanisms again play a central role: astrocytic Ca^{2+} elevations activate NOS, and the resulting NO can open Cx43 hemichannels via S-nitrosylation, forming a feed-forward loop in which Ca^{2+} and NO reinforce hemichannel opening and neurovascular/neuronal dysfunction [18,82,83]. Mechanistic work in osteocytes corroborates this redox sensitivity: oxidative stress–induced Ca^{2+} surges drive both hemichannel opening and increased Cx43 surface trafficking [84].

Taken together, these studies show that carotenoids are best viewed as indirect modulators of Cx43 channel state. By suppressing microglial NO/iNOS and dampening NF-κB-driven cytokine release, carotenoids are expected to reduce the NO and inflammatory signals that promote Cx43 S-nitrosylation and hemichannel activation, although this has not yet been demonstrated directly in AD-relevant astrocytes [18,19,20,21,85]. Their ability to stabilize mi-

tochondrial function and limit ROS/RNS production could further lower the redox and calcium loads that bias Cx43 toward open hemichannels. At the same time, upregulation of Cx43 could favor a network architecture in which astrocytes remain strongly gap-junction-coupled, supporting neurometabolic buffering rather than releasing toxic gliotransmitters. Finally, pharmacologic work demonstrating that hemichannel blockade can slow disease progression in APP/PS1 mice and amyotrophic lateral sclerosis (ALS) models underscores that even partial shifts in Cx43 channel behavior, from open hemichannels back toward closed hemichannels and intact GJIC, can have meaningful effects on neuronal survival, providing a mechanistic rationale for carotenoid-mediated protection at this node.

4. Carotenoids and Aβ Related Toxicity: Experimental and Clinical Evidence

4.1 Carotenoid Mediated Modulation of Aβ Aggregation and Neurotoxicity

Mechanistic studies of Aβ toxicity emphasize that high-molecular-weight $A\beta_{1–42}$ oligomers, rather than mature fibrils, are major drivers of neuronal death through plasma membrane disruption, massive Ca^{2+} influx, and loss of ionic homeostasis, with downstream tau cleavage and aggregation [86]. In this context, polar xanthophyll carotenoids that span phospholipid bilayers and bind Aβ oligomerization domains are well placed to reduce both the formation and the impact of these toxic species, whereas non-polar carotenes may act more via systemic antioxidant effects than by direct membrane stabilization. Multiple experimental approaches indicate that several structurally diverse carotenoids can interact directly with Aβ and blunt its toxicity in addition to upstream redox and inflammatory actions. Docking and *in vitro* aggregation studies suggest that xanthophylls such as lutein and zeaxanthin, as well as astaxanthin and crocin, bind aggregation-prone regions of Aβ and interfere with oligomer and fibril formation, while non-polar carotenes like lycopene and β-carotene also show anti-aggregation effects in some assays but may do so at higher or less physiologically relevant concentrations [12,15,16]. Work with egg-derived lutein demonstrates that this carotenoid reduces Thioflavin T (ThT)-positive Aβ aggregates and oligomer/fibril formation while simultaneously attenuating Aβ-induced inflammatory responses in THP-1 macrophages, providing a clear example of dual peptide- and cell-level protection [16]. Carotenoids also protect cells from Aβ-induced oxidative membrane damage: in human erythrocytes, Aβ triggers hemolysis and membrane perturbation that are substantially mitigated by several carotenoids, showing that these compounds can stabilize plasma membranes and reduce ROS in the face of direct Aβ insult [87].

In vivo, specific carotenoids improve Aβ-related cognitive and pathological readouts. Zeaxanthin supplementation in $A\beta_{1–42}$-injected rats improves spatial learning and memory, restores synaptic markers, and lowers hippocampal oxidative stress and inflammatory mediators relative to Aβ-only animals [88]. Lycopene treatment in $A\beta_{1–42}$-based AD models reduces brain $A\beta_{1–42}$ levels, oxidative and nitrosative markers, and pro-inflammatory cytokines while normalizing synaptophysin and metabolic enzyme expression, and these changes track with better performance in learning and memory tasks [14]. Retinoid-centric work complements these findings: ATRA in APP/PS1 mice reduces plaque burden and soluble Aβ, downregulates β-site amyloid precursor protein cleaving enzyme 1 (BACE1), and dampens microglial activation, and it also repairs Aβ-induced DNA double-strand breaks in neural cells and neocortex, enhancing neuronal survival and synaptic integrity [70,89,90]. Broader retinoid reviews report consistent attenuation of Aβ production, tau phosphorylation, and glial inflammatory signaling in AD models, suggesting that vitamin A–related pathways provide a mechanistic template that carotenoids partially mirror with lower toxicity [70,89,91]. Together, these data support a multi-tiered model in which carotenoids and retinoids reduce Aβ burden, neutralize oligomer-driven membrane damage, and preserve neuronal genome and synapse integrity in the face of Aβ stress. To summarize these findings across carotenoid classes, Table 1 (Ref. [12,14,15,16,17,19,20,21,37,85,88,89,90,92,93,94,95,96,97,98,99]) provides an overview of major carotenoids discussed in this and previous sections, highlighting their principal mechanisms, representative experimental data, and implications in relation to Aβ-related toxicity and Alzheimer's disease.

4.2 Clinical and Epidemiological Evidence for Carotenoid Linked Cognitive Protection

Human data, although heterogeneous, consistently suggest a protective association between higher carotenoid status, particularly lutein and zeaxanthin, and lower dementia risk or better cognitive performance, while also leaving room for reverse causation [23,100]. Prospective cohorts show that higher serum lutein, zeaxanthin, and β-cryptoxanthin are associated with reduced incidence of all-cause dementia and, less robustly, AD, with suggestions that combinations of carotenoids may matter more than single compounds [24]. A systematic review and meta-analysis of plasma/serum carotenoids concludes that AD patients have significantly lower lutein and zeaxanthin than controls, whereas other carotenoids show inconsistent differences, highlighting xanthophylls as the carotenoids most reliably inversely linked to AD; however, these cross-sectional differences could also reflect reduced dietary intake, weight loss, or altered lipid transport secondary to AD pathology rather than a purely causal protective effect [100]. Cohort work from the Rush Memory and Aging Project further connects higher dietary total carotenoid intake, and particularly lutein-zeaxanthin, to a

Table 1. Carotenoids and Aβ-related neurotoxicity: key mechanisms.

Carotenoid/group	Main mechanisms relevant to Aβ toxicity	Representative experimental evidence	Implication for AD mechanisms
Lutein, zeaxanthin, meso-zeaxanthin	Potent membrane-associated antioxidants; reduction of ROS/RNS and lipid peroxidation; modulation of Nrf2/HO-1 and NF-κB signaling; attenuation of microglial and macrophage inflammatory responses; protection of synaptic proteins and BDNF; interference with Aβ aggregation and oligomer-induced membrane damage.	Lutein from egg yolk inhibits $A\beta_{1-42}$ aggregation and reduces Aβ-induced inflammation in human THP-1 macrophages [16]. Docking and *in vitro* aggregation studies indicate that lutein and zeaxanthin bind aggregation-prone regions of Aβ and interfere with oligomer and fibril formation [12,15]. Lutein lowers oxidative and nitrosative stress and cytokine release from activated microglia [92] and Zeaxanthin and Lutein lower oxidative stress and neuroinflammation in rodent models of AD [88,93].	Supports a multi-level protective role against Aβ-driven oxidative damage, inflammation, and synaptic dysfunction, with additional direct interference in Aβ oligomer/fibril formation.
β-carotene and other provitamin A carotenes	Antioxidant activity; suppression of iNOS and NO production via NF-κB and retinoic acid receptor-dependent pathways; provision of retinoid precursors that modulate APP processing, Aβ generation, and DNA damage responses.	β-carotene down-regulates iNOS, NO, and inflammatory mediators in LPS-stimulated microglia and macrophages [19,94]. Docking and aggregation assays suggest β-carotene can inhibit Aβ fibril formation, although often at higher or less physiologically relevant concentrations than xanthophylls [15,95]. Retinoic acid derivatives decrease Aβ deposition, BACE1 expression, and Aβ-induced DNA double-strand breaks and preserve synaptic integrity in AD-like mouse models [89,90].	Indicates that provitamin A carotenes can indirectly counter Aβ toxicity via NO/iNOS and retinoid pathways and may exert additional, albeit weaker, direct anti-aggregatory effects on Aβ.
Lycopene	Efficient quenching of singlet oxygen and lipid radicals; activation of Nrf2-dependent antioxidant defenses; reduction of pro-inflammatory cytokines and nitrosative stress; upregulation of Cx43 expression in spinal astrocytes.	In $A\beta_{1-42}$-based rodent models, lycopene lowers hippocampal $A\beta_{1-42}$, malondialdehyde, nitrite, and pro-inflammatory cytokines, boosts antioxidant enzymes, and improves learning and memory [12,14]. Docking and *in vitro* aggregation studies report anti-aggregatory effects of lycopene on Aβ, though typically at higher concentrations than those required for xanthophylls [15]. In spinal astrocytes, lycopene increases Cx43 expression under inflammatory conditions [17].	Suggests that lycopene can simultaneously reduce Aβ burden, oxidative/nitrosative injury, and potentially support brain astrocytic gap-junction networks, with some capacity to interfere directly with Aβ aggregation.
Astaxanthin, fucoxanthin, crocin/crocetin and related marine/plant carotenoids	Strong ROS/RNS scavenging; inhibition of NF-κB, iNOS, and pro-inflammatory cytokines; modulation of PI3K/Akt and ERK pathways; attenuation of Aβ oligomer-induced apoptosis and membrane damage.	Astaxanthin and crocetin/crocin reduce NO/iNOS and inflammatory mediators in activated microglia and macrophages [20,21,96,97]. Docking and *in vitro* aggregation studies show that astaxanthin and crocin bind aggregation-prone domains of Aβ and inhibit oligomer and fibril formation [15,98]. Fucoxanthin protects SH-SY5Y cells from Aβ oligomer-induced oxidative damage and apoptosis via PI3K/Akt and ERK pathways [37].	Highlights a broader set of carotenoids with potent anti-oxidative and anti-inflammatory actions and direct binding to Aβ, limiting oligomer and fibril formation and downstream toxicity.
Mixed carotenoid preparations	Combined antioxidant and anti-inflammatory effects; stabilization of membranes; possible convergence on Nrf2 and NF-κB signaling and on multiple Aβ-related injury pathways.	Mixed carotenoid extracts from microalgae or other sources reduce ROS/RNS, iNOS expression, and cytokine release in neuroinflammatory models and mitigate oxidative toxicity in neuronal cultures [85,99].	Supports the idea that carotenoid mixtures may provide broader, synergistic modulation of Aβ-linked oxidative, inflammatory, and aggregation-related cascades than single compounds.

Aβ, amyloid-beta; AD, Alzheimer's disease; ROS, reactive oxygen species; RNS, reactive nitrogen species; Nrf2, nuclear factor erythroid 2–related factor 2; HO-1, heme oxygenase-1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; BDNF, brain-derived neurotrophic factor; iNOS, inducible nitric oxide synthase; APP, amyloid precursor protein; Cx43, connexin 43; PI3K, phosphoinositide 3-kinase; ERK, extracellular signal-regulated kinase; NO, nitric oxide; BACE1, β-site amyloid precursor protein cleaving enzyme 1; LPS, lipopolysaccharide; THP-1, a human monocyte cell line.

substantially lower hazard of incident AD, and shows that higher intakes of total carotenoids, lutein-zeaxanthin, and lycopene are associated with lower global AD neuropathology at autopsy, including lower neuritic plaque and neurofibrillary tangle burden for lutein-zeaxanthin, even after adjustment for major demographic, lifestyle, and vascular factors [23]. In the Three-City Bordeaux cohort, higher baseline plasma lutein normalized to lipids was associated with about 20% lower dementia risk per one standard deviation increase after adjustment for sociodemographic factors, vascular risk, and baseline cognition, strengthening the case for lutein as a key circulating carotenoid marker of cognitive resilience, while acknowledging that residual confounding and reverse causation cannot be fully excluded [22].

Intervention studies, though still limited in size and duration, demonstrate that raising carotenoid status can influence specific cognitive domains [25,26,27]. A randomized, double-blind trial in adults with mild cognitive complaints reports that six months of 10 mg lutein plus 2 mg zeaxanthin once a day improves visual episodic memory and visual learning relative to placebo, with good tolerability [25]. Broader clinical reviews of carotenoid supplementation in AD and mild cognitive impairment (MCI) that summarize in silico, preclinical, and early trial data suggest that several carotenoids cross the BBB, reduce oxidative and inflammatory markers, and in some studies modestly slow some measures of cognitive decline, though robust randomized controlled trial evidence is strongest for macular carotenoids and still emerging for others like astaxanthin and fucoxanthin [7,12,14,22,101,102]. In people already living with AD, preliminary intervention work suggests that carotenoids may be more effective when combined with other neuroactive nutrients: a small series of trials comparing a xanthophyll-only formulation to the same carotenoids plus omega-3 fatty acids reported greater rises in blood xanthophylls when combined with docosahexaenoic acid (DHA)/eicosapentaenoic acid (EPA), with caregivers noting benefits in select measures of memory, mood, and visual function in the combination arm [26]. It should be noted that similar interventions with only omega-3 fatty acids in patients with comparable AD severity (moderate) did not show significant improvement [103]. A larger 12-month randomized trial found that daily supplementation with 10 mg meso-zeaxanthin, 10 mg lutein, 2 mg zeaxanthin, omega-3 fatty acids, and vitamin E increased carotenoid and omega-3 fatty acids levels and was associated with modest but significantly better outcomes on select measures of AD severity, memory, and mood compared with placebo [27]. Importantly, systematic review evidence from blinded randomized trials of vitamin E monotherapy in AD and MCI shows no clinically meaningful benefit on cognitive outcomes, suggesting that carotenoids and omega-3's are working synergistically with vitamin E [104]. Finally, studies in eye and retinal disease, including large trials improving macular pigment and visual outcomes with lutein/zeaxanthin, reinforce the concepts of long-term safety, bioavailability, and targeted neural accumulation of these xanthophylls, features that make them attractive candidates for nutritional strategies aimed at preserving brain function in at-risk and early-stage AD populations [12,13,25,51,102]. Table 2 (Ref. [22,23,24,25,26,27,100,101]) summarizes the human studies of carotenoids in relation to AD and cognitive outcomes.

5. Conclusions and Perspectives

Carotenoids emerge as multifunctional modulators that engage several early drivers of Alzheimer's pathology rather than acting at a single downstream node. They buffer oxidative and nitrosative stress, attenuate microglial and astrocytic inflammatory signaling, and help stabilize mitochondrial function, thereby raising the threshold for excitotoxic injury and Aβ-driven network failure. In parallel, specific carotenoids and retinoids converge on the Cx43 promoter and increase astrocytic gap-junction coupling while redox and NO/iNOS pathways that can open Cx43 hemichannels are simultaneously dampened potentially shifting glial signaling away from a leaky, hemichannel-dominant state toward a coupled astrocytic syncytium that better supports neurometabolic demands and ion homeostasis under stress. *In vitro* studies confirming this plausible hypothesis in Aβ-stressed astrocytic models are needed to determine which carotenoids are best at modulating Cx43 expression and states under these specific conditions.

At the level of Aβ itself, several carotenoids can bind aggregation-prone domains, limit oligomer and fibril formation, and protect membranes and cells from oligomer-induced oxidative damage, with *in vivo* studies of zeaxanthin, lycopene, and retinoic acid showing improved cognition, reduced Aβ burden, and preserved synaptic markers in Aβ-based models. Longitudinal cohorts and biomarker studies consistently implicate lutein and zeaxanthin as the carotenoids most strongly linked to lower dementia risk and lower AD neuropathology, and emerging randomized trials now suggest that multi-nutrient formulations combining xanthophyll carotenoids with omega-3 fatty acids and vitamin E can modestly slow select measures of clinical progression and also modestly improve specific tests of memory and mood in patients with established AD, especially when carotenoids are given as part of a broader nutrient formulation rather than in isolation.

Key next steps will be to test whether carotenoids can reduce hemichannel activity and preserve gap-junctional coupling in AD-relevant astrocyte models, and, if so, which specific carotenoids are most effective. In parallel, the pharmacological delivery of these candidate carotenoids to the brain could be optimized using nanocarriers, intranasal formulations, or systems that pair carotenoids with dietary nutrients known to enhance intestinal uptake and transport [105,106]. Intravenous administration strategies, such

Table 2. Key human studies on carotenoids and Alzheimer's disease.

Study	Study design/population	Carotenoids/exposure	Main AD-related outcomes	Key findings
Feart et al. [22] 2016	Prospective cohort, elderly French adults	Baseline plasma carotenoids	Incident dementia (incl. AD)	Higher plasma carotenoids, especially lutein, were inversely associated with risk of dementia over follow-up.
Yuan et al. [23] 2021	Community-based cohort (Rush MAP), older adults with autopsy subset	Dietary carotenoid intake (total, lutein-zeaxanthin, lycopene)	Incident AD; post-mortem AD neuropathology	Higher total carotenoids and lutein-zeaxanthin intake were associated with lower risk of incident AD and lower neuritic plaque and neurofibrillary tangle burden at autopsy.
Beydoun et al. [24] 2022	Prospective US cohort (NHANES-linked), mid- to older-aged adults	Serum antioxidant vitamins and carotenoids	Incident AD and all-cause dementia	Higher serum lutein, zeaxanthin, and β-cryptoxanthin were associated with reduced risk of AD and all-cause dementia, strongest for combined antioxidant profiles.
Qu et al. [100] 2021	Systematic review and meta-analysis of case-control and cohort studies	Plasma/serum carotenoids	AD diagnosis vs controls	AD patients had significantly lower lutein and zeaxanthin than cognitively healthy controls; other carotenoids showed less consistent differences.
Lopresti et al. [25] 2022	Randomized, double-blind, placebo-controlled trial; adults with mild cognitive complaints	Lutein (10 mg) + zeaxanthin (2 mg) daily, 6 months	Cognitive performance (memory, learning)	Supplementation improved visual episodic memory and visual learning compared with placebo, with good tolerability.
Nolan et al. [26] 2018	Clinical trial (Phase I/II) nutritional intervention study; includes small intervention studies in AD/MCI	Xanthophyll carotenoids (lutein, zeaxanthin, meso-zeaxanthin) ± omega-3 fatty acids	Cognitive decline and AD risk (summarized)	Supplementation with xanthophyll carotenoids plus fish oil produced larger increases in blood xanthophylls than carotenoids alone. Caregivers and clinicians in the combination group reported improvements in memory, sight, mood, and day-to-day function relative to baseline.
Nolan et al. [27] 2022	12-month randomized trial; patients with mild-moderate AD	Lutein (10 mg), zeaxanthin (2 mg), meso-zeaxanthin (10 mg) + omega-3 fatty acids + vitamin E vs placebo	AD severity, memory, mood	In patients with mild–moderate Alzheimer's disease, 12-month supplementation with carotenoids, omega-3 fatty acids, and vitamin E produced higher nutrient biomarkers than placebo and showed statistically significant group differences in clinical collateral for memory measures and non-significant improvements in objective measures of AD severity including memory and mood.
Flieger et al. [101] 2024	Narrative review of human carotenoid supplementation in AD/MCI	Various carotenoids and formulations	AD symptoms and progression (summarized)	Concluded that several carotenoids (particularly lutein and zeaxanthin, often combined with other nutrients) have been associated with changes in cognitive and symptom measures in AD/MCI, but the human evidence remains limited and preliminary.

MCI, mild cognitive impairment; Rush MAP, Rush Memory and Aging Project; NHANES, National Health and Nutrition Examination Survey.

as the use of water-soluble γ-cyclodextrin inclusion complexes that increase crocetin delivery across the BBB by approximately five-fold compared with oral dosing, could also be adapted for other individual carotenoids or rational combinations [107]. On the dietary side, studies comparing different fat sources and physical forms indicate that emul-

sified olive oil can substantially enhance the absorption of salad carotenoids, illustrating how the food matrix can be leveraged to improve carotenoid bioavailability [108]. Further work systematically probing food combinations and dosing patterns that maximize carotenoid absorption and brain delivery will be important to translate these mechanistic insights into practical nutritional strategies. Overall, the evidence synthesized here supports carotenoids as plausible, low-toxicity nutritional agents, with lutein- and zeaxanthin-rich regimens as a current focus but with scope for other carotenoids to contribute as delivery technologies and dietary strategies improve. Their capacity to potentially stabilize glial–neuronal networks and slow Aβ-related neurodegeneration will depend on both their diverse actions on oxidative, inflammatory, gap-junctional, and aggregation pathways and on optimized approaches that maximize their access to vulnerable brain regions, warranting further targeted mechanistic studies and rigorously designed clinical trials.

Author Contributions

The single author prepared the figure or conducted the literature search for the manuscript, and wrote the paper. JM has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Perplexity (Perplexity AI, Pro version) to check spelling and grammar in the abstract, introduction, and main text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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