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CAROTENOIDS AND HUMAN HEALTH: A MULTIFACETED APPROACH TO DISEASE PREVENTION

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ABSTRACT: Carotenoids, a class of essential phytonutrients widely distributed among plants, algae, bacteria, and fungi, serve diverse functions in various biological processes. Notably, they encompass pro-vitamin A compounds that significantly contribute to the promotion of human health and the prevention of diseases. This comprehensive review delves into the current state of knowledge concerning the health benefits associated with specific carotenoids, including β-carotene, α-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin, with a particular emphasis on their potential in the prevention and management of chronic diseases. Scientific evidence indicates that carotenoids exhibit multifaceted potential in mitigating the risk of chronic diseases such as cardiovascular diseases, cancer, age-related macular degeneration, and various other chronic conditions. Their mechanisms of action encompass antioxidant properties, anti-inflammatory effects, modulation of the immune system, and specific disease-targeted mechanisms. Nevertheless, a more comprehensive understanding of the precise mechanisms underlying the beneficial effects of carotenoids and the determination of optimal dosages and formulations for specific health outcomes necessitate further investigation. The amassed evidence underscores the significance of carotenoids as vital nutrients for human health, suggesting that their incorporation into dietary practices may offer substantial support in the prevention and treatment of an array of chronic diseases. This review provides a scholarly overview of the multifaceted roles played by carotenoids in disease prevention and health promotion, highlighting the imperative need for ongoing research to elucidate their full potential.

Keywords; Antioxidant, Carotenoid, Health benefits, Chronic diseases, Anti-inflammatory effects, Immune system modulation**.**

BIOACTIVE COMPOUNDS; CAROTENOIDS

Carotenoids, present in various organisms such as plants, algae, bacteria, and fungi, are essential phytonutrients with diverse roles. These elements are essential for plants, contributing to processes like photosynthesis, pigmentation, and signalling, and are used in a variety of sectors such as food, feed, cosmetics, and pharmaceuticals (Addi *et al.*, 2022). In general, animals do not synthesise carotenoids from scratch, so those found in animals are either obtained directly from food or partially altered through metabolic reactions. The primary metabolic transformations of carotenoids within animal organisms encompass processes such as oxidation, reduction, shifting of double bonds, oxidative fragmentation of double bonds, and the cleavage of epoxy bonds. (Britton, 2022; Harrison, 2022).

Humans rely on external sources of vitamin A since our bodies cannot produce vital compounds like retinol, retinal, or retinoic acid. Carotenoids with unmodified β-ionone rings, such as β-carotene, α-carotene, β-cryptoxanthin, and β, ψ-carotene (γ-carotene), are well-known precursors of retinoids and are termed pro-vitamin A compounds. β-carotene, a specific carotenoid, is enzymatically converted into retinal in the intestine, which can subsequently be oxidized into retinoic acid or reduced to retinol through various metabolic processes (Harrison, 2022).

Of the 50 carotenoids in common human foods, 20 are detectable in the bloodstream in humans, with β-carotene, α-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin being the most abundant (Bohn, 2018). These also accumulate in erythrocytes, and their oxidative byproducts are seen in plasma. While capsanthin is absorbed and partially metabolized, epoxy carotenoids are not detected in the bloodstream, likely due to degradation in the stomach (Cervantes *et al*., 2016). Moreover, insects exhibit a wide range of structural diversity in their carotenoids, primarily including β-carotene, β-cryptoxanthin, lutein, and zeaxanthin, which are derived from their dietary intake and metabolic processes (Maoka, 2020).

Carotenoids in aquatic animals, including β-carotene, fucoxanthin, peridinin, diatoxanthin, alloxanthin, and astaxanthin, are primarily derived from algae (Galasso *et al.,* 2017). Marine animals undergo metabolic processes to transform and store dietary carotenoids in their organs, enhancing the antioxidative and photo-protective properties of these compounds. Fucoxanthin is the most common carotenoid in diatoms and undergoes metabolic transformations in aquatic animals, including the conversion of allenic bonds to acetylenic bonds, the hydrolysis of the epoxy group, and the oxidation of the epoxy group (Maoka, 2011). Furthermore, carotenoids play crucial roles in animals, serving as photoprotective agents, antioxidants, immune boosters, and contributors to reproductive processes (Chacón *et al.,* 2019; Swapnil *et al.,* 2021a).

To date, over 750 carotenoids have been documented in the context of promoting health and preventing diseases (Grainger *et al.*, 2022). The consumption of foods rich in carotenoids is associated with a reduced risk of heart disease, cancer, macular degeneration, and various other eye-related issues (Sauer *et al.,* 2019) Gao *et al.,* 2021). Conversely, a deficiency in carotenoids can lead to pathological conditions like Xerophthalmia, nyctalopia, cornea softening, ulcers, and scar formation, ultimately culminating in irreversible blindness (Milani *et al.,* 2017).

STRUCTURAL CHARACTERISTICS OF CAROTENOIDS

Carotenoids are an isoprenoid compound subclass with long carbon chain structures typically of 40 carbons as they are derived from the linear tetraterpene phytoene (Vila *et al.,* 2019). The lengthy system of conjugated double bonds in which Pi electrons (π electrons) are efficiently delocalized along the length of the polyene chain is the distinctive property of carotenoid molecules. Because of isomerism around the C=C bonds, carotenoids can exist in a variety of configurations (Llansola-Portoles *et al.,* 2022). Carotenoids, which include both xanthophylls and carotenes, have a diverse structural landscape and play significant roles in a variety of biological processes (Llansola-Portoles *et al.,* 2022; Sun *et al.,* 2022). For instance, β-carotene has two β-rings at both ends of the molecule, while lutein and zeaxanthin have oxygen-containing functional groups in their structures as shown in *Figure 1*. The configurations surrounding a double bond are denoted by the letters E or Z, which normally correspond to trans and cis, respectively; however, there are notable exceptions (Llansola-Portoles *et al.,* 2017). These structural differences contribute to their diverse bioactivities (Wurtzel, 2019; Zhao et al., 2017).

Trans isomers are thermodynamically more stable than cis isomers, owing to sterical hindrance between nearby hydrogens and methyl groups. As a result, all-trans carotenoids are more common in nature. Additionally, rotation around each single C-C bond is feasible, allowing carotenoid molecules to take on a variety of forms and conformations. The connected polyene chain is stable primarily due to the presence of coplanar double bonds. Many different geometries may be generated by free rotation around the C-6,7 single bond in carotenoids with cyclic-end groups as exhibited in *Figure 1*. It is reasonable to believe that coplanarity between the ring and chain causes steric crowding (Pinto, 2013).

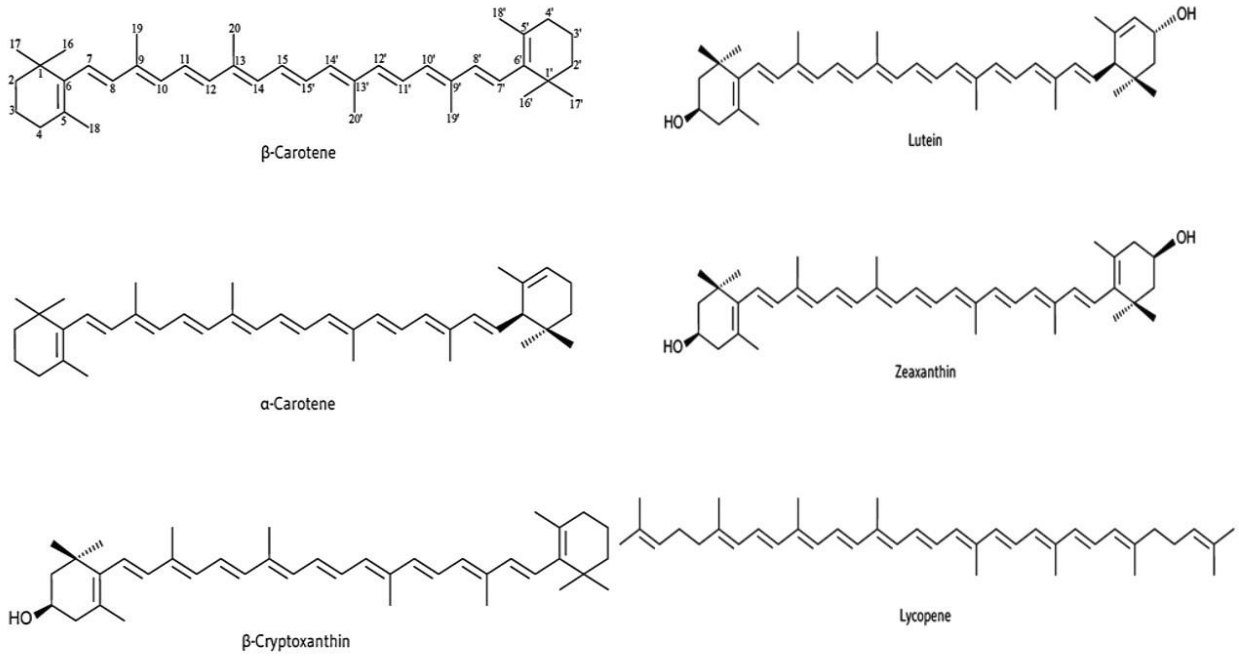


Figure 1: Molecular structure of a few carotenoids.

Thus, the optimal conformation is 6-s-cis, but a 40-degree deviation from planarity is required to remove steric inhibition in between the methyl group on ring carbon-5 and the carbon-8 hydrogen from the polyene chain. All-trans carotenoids are linear and stiff molecules with a prolonged conjugated double-bond structure. Cis-isomers, on the other hand, have distinct molecular geometries, are not linear molecules, and hence their capacity to operate inside cellular compartments may be substantially altered. Since cis-isomers are more soluble than trans-isomers, they may be absorbed and transported more easily inside cellular compartments (Latowski *et al.,* 2014). It is well known that carotenoids that contain unsubstituted β-ionone ring such as β-carotene, α-carotene, β-cryptoxanthin, and β, ψ-carotene (γ-carotene) are precursor of retinoids and are called pro-vitamin A.

The caretogenic compounds have gained attention for their potential health benefits as shown in *Figure 2* (Kulczyński *et al.,* 2017; Akepach *et al.,* 2022)). The most researched carotenoids, such as β-carotene, lycopene, lutein, and zeaxanthin, have demonstrated their significance in health promotion and disease prevention (Ashokkumar *et al.,* 2023). Furthermore, astaxanthin and β-cryptoxanthin have garnered interest due to their potential preventive properties against illnesses such as cardiovascular disease, diabetes, and inflammation (Fujita *et al.,* 2023; Narayanan *et al.,* 2021).

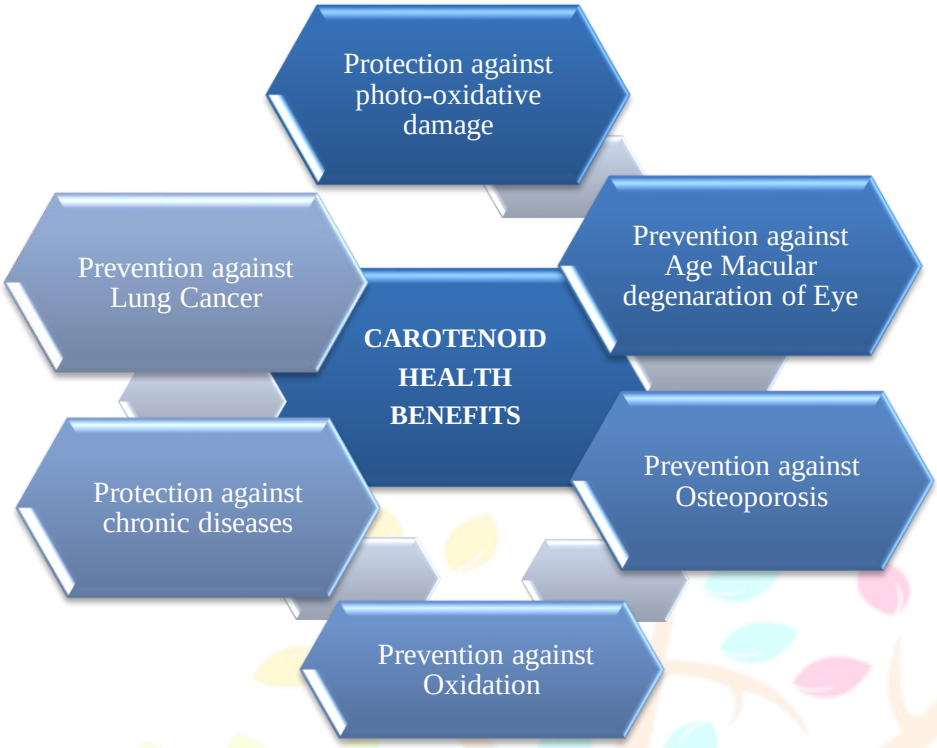


Figure 2; The health benefits of carotenoids.

CAROTENOIDS' RELATION TO DISEASE PREVENTION

The relationship between carotenoids and disease treatment is an area of growing interest in scientific research. These carotenoids have demonstrated various health benefits and potential roles in disease treatment as shown in *Figure 3*.

Some key points of carotenoids' relation to disease treatment include:

i. Antioxidant Properties

Carotenoids possess potent antioxidant properties due to their ability to neutralize harmful reactive oxygen species (ROS) in cells (Wang *et al.*, 2022; M. Li & Kim, 2023). Recent research has highlighted their role in reducing oxidative stress, which is implicated in various diseases, including cardiovascular diseases, neurodegenerative disorders, and cancer. Studies have shown that carotenoids can scavenge free radicals and protect cellular components from oxidative damage, thus potentially mitigating the progression of these diseases (Chisté *et al.*, 2014; Lu *et al.*, 2022; Felipini *et al.*, 2023).

Figure 3; Carotenoids relation to disease treatment.

The antioxidant activity of carotenoids depends on the following factors. First of all, their structure is crucial, the way they incorporate in biological membranes, how they interact with reactive species and the presence of other co-antioxidants (e.g., α-tocopherol) (Britton, 2022).

In general, the quenching activity of carotenoids is affected by:

- The number of conjugated double bonds.
- The end groups (cyclic or acyclic) (*Figure 4*).
- The nature of substituents in carotenoids containing cyclic end groups.

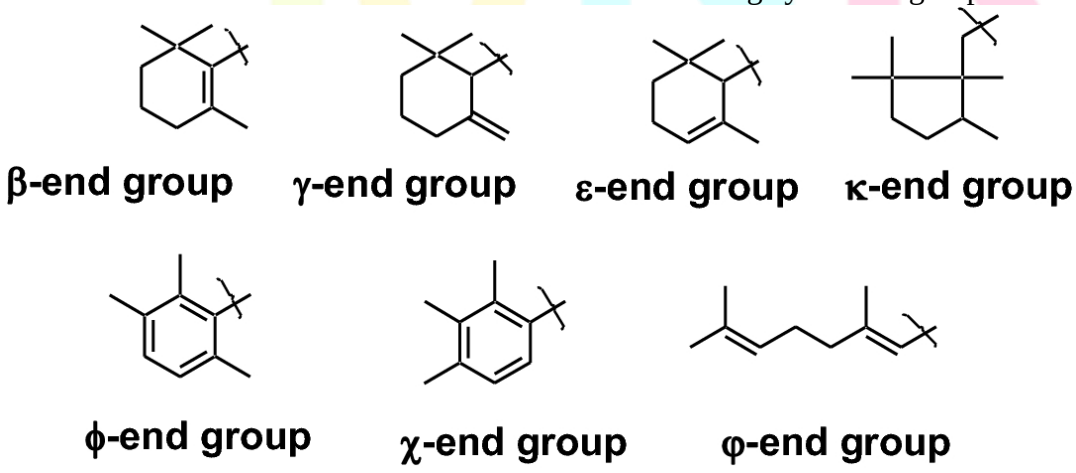


Figure 4; Basic structures of carotenoid end group.

The unsaturated nature of carotenoids, characterized by conjugated double bonds within their molecular structure, creates a system of alternating single and double bonds. This structural feature makes them more prone to auto-oxidation, allowing them to efficiently quench reactive oxygen species (ROS). Carotenoids play a vital role in protecting cells and tissues from oxidative damage and contribute to their therapeutic potential in disease treatment (Reboul *et al.*, 2006; Swapnil *et al.*, 2021b).

β-carotene, one of the prominent carotenoids, has been extensively studied for its antioxidant properties. Gao *et al.*, 2021 demonstrated that β-carotene effectively scavenges ROS, reducing oxidative stress and preventing cellular damage.

In Pedroza-García *et al.*, 2023, they investigated the bioactive role of beta-carotene as a key modulator of oxidative stress in rat models. These rats were intraperitoneally treated with a uniquely high dose of beta-carotene. Their findings shed light on the notion that riboflavin may play a significant role in reducing oxidative stress species, Malondialdehyde levels, along with the restoration of Superoxide dismutase activity, providing valuable insights into the potential therapeutic applications of beta-carotene in oxidative stress management.

In laboratory experiments, fucoxanthin has shown its ability to neutralize various types of harmful free radicals, including hydroxyls, superoxide, peroxyl radicals, and lipid peroxides (Y. Zhang *et al.*, 2014; J. Zhang *et al.*, 2014). Its antioxidant properties have been observed in studies involving different cell types, such as monkey kidney fibroblast cells, human hepatic L02 cells, and human HaCaT keratinocytes (Heo *et al.*, 2008; Zheng *et al.*, 2013; Zheng *et al.*, 2014). Furthermore, fucoxanthin has been found to enhance its antioxidant effects, leading to reduced levels of ROS (Reactive Oxygen Species) and malondialdehyde (MDA) in HepG2 cells, as reported in the scientific literature (J. Zeng *et al.*, 2018).

The antioxidant activity is increased as the number of conjugated double bonds increases. e.g., astaxanthin, which contains 13 conjugated double bonds should have higher singlet oxygen scavenging activity than those of β carotene which contains parallel conjugated double bonds (Nemzer *et al*., 2019). According to a study by Sowmya and colleagues, 2017, astaxanthin at 20 µM has a significant pro-oxidant effect on MCF-7 cells (53.3 per cent increase in ROS, compared to 17.3 per cent increase in control), and this effect is synergistically amplified when cells are subjected with a mixture of astaxanthin, β-carotene, and lutein (68.1 per cent increase in ROS) (Sowmya *et al.*, 2017).

Shang *et al.*, 2022 demonstrated the anticancer activities of β-cryptoxanthin were mediated through pro-oxidant actions. These actions enhanced ROS generation and led to increased expression of caspase-3, -7, and -9, Bax, and p-53 at the mRNA level, while simultaneously suppressing the antiapoptotic Bcl-2. These events initiated nuclear condensation, loss of mitochondrial membrane potential, activation of caspase-3 proteins, and ultimately, cleavage of nuclear DNA.

Linnewiel-Hermoni *et al.*, 2014 study showed that synthetic carotenoid derivatives inhibited nuclear factor kappa B (NF-κB) activity in bone and cancer cells by targeting key thiol groups. They used two derivatives: 10,10′-diapocarotene-10,10′-dial (10,10′) and 6,14′ diapocarotene-6,14′-dial (6,14′). The carotenoid derivatives inhibited NF-κB transcription in T47D mammary cancer cells and in two bone osteoblast lines: human HOS cells and mouse MC3T3-E1 preosteoblasts. These findings suggest that carotenoids may be beneficial for both cancer prevention and bone health.

ii. Immune System Modulation

Carotenoids can modulate the immune system by influencing the activity of immune cells. Recent research has explored the potential of carotenoids to boost immunity, which has implications for disease prevention and treatment, particularly in infectious diseases. Beta-carotene, for instance, has been shown to enhance the immune response by promoting the proliferation and function of T lymphocytes (Bacanlı *et al.*, 2015). Recent findings by Grainger et al., 2022 indicated that β-cryptoxanthin, abundant in citrus fruits, promotes immune cell proliferation and enhances immune responses. In numerous investigations, there have been indications that metabolites of lycopene may engage with RXR (retinoid X receptors) and RAR (Retinoic acid receptors), which play crucial roles in regulating various functions, including the immune system (Bohn et al., 2023).

Astaxanthin has been demonstrated to preserve B-cell insulin secretion function, lower elevated blood glucose levels in individuals with diabetes, and shield mesangial cells from oxidative signalling induced by hyperglycaemia (Gowd

et al., 2021). Tan *et al.*, 2020 study unveiled that incorporating astaxanthin into the diet was linked to an elevation in phenol oxidase activity and the total haemocyte count.

The protective benefits of lycopene have been studied encompassing its capacity to safeguard against chronic illnesses through various mechanisms, such as the regulation of gene expression, modulation of gap junctions, antiproliferative properties, and immune and hormonal modulation (Elvira *et al.*, 2019).

Donoso *et al.*, 2021 demonstrated that all three stereoisomers of astaxanthin (ASTA), (3S,3'S)-trans-ASTA, (3R,3'R)-trans-ASTA, and meso-trans-ASTA, significantly enhanced lymphocyte proliferation, phagocytic capacity of peritoneal exudate cells, and cytotoxicity of natural killer (NK) cells at a concentration of 20 μmol/L.

Milani *et al.*, 2017 study exhibited that the intake of lutein supplements at a dosage of approximately 20 mg per day led to a notable reduction in serum IL-6 and monocyte chemoattractant protein-1 (MCP-1), as well as triglyceride (TG) and LDL levels, during three months in individuals with early atherosclerosis.

W. Li et al., 2019 research suggested that lycopene inhibited lipopolysaccharide (LPS)-induced pro-inflammatory responses by improving vascular barrier integrity, reducing barrier permeability and cell adhesion molecule (CAM) expression, and preventing leukocyte adhesion and transendothelial migration. Notably, high lycopene concentrations (10 μmol/L) exhibited potent anti-angiogenic effects, due to the upregulation of IL-12 (~163%) and IFN-γ (~531%) in human umbilical vein endothelial cells (HUVECs) (Huang *et al.*, 2013).

iii. Anti-Inflammatory Effects

Inflammation is a hallmark of many chronic diseases, as it plays a crucial role in the development of chronic diseases. Carotenoids, particularly xanthophylls, have shown anti-inflammatory effects by modulating pro-inflammatory signalling pathways. Recent studies have elucidated the molecular mechanisms by which these carotenoids modulate inflammatory pathways, providing insights into their therapeutic potential (Jain & Katti, 2015; Caruso *et al.*, 2021); Lu *et al.*, 2022)

A study by Eroglu and colleagues in 2023 highlighted the anti-inflammatory potential of carotenoids in reducing cytokine production and inflammatory markers. Beta-cryptoxanthin has been linked to reduced levels of pro-inflammatory cytokines. Lutein and zeaxanthin, have shown promise in alleviating ocular inflammation and protecting against age-related macular degeneration (AMD).

Fucoxanthin and its derivatives have emerged as potential enhancers of immune system performance. Research conducted in controlled laboratory settings has demonstrated that both fucoxanthin and its metabolite, fucoxanthinol, exhibited the ability to reduce the expression of mRNA associated with pro-inflammatory molecules such as TNF-α, iNOS, and COX-2 in RAW264.7 macrophage-like cells (X. Li *et al.*, 2021). Furthermore, they were found to diminish IL-6 levels in human pulmonary fibroblasts stimulated with transforming growth factor-beta1 (TGF-β1) (Ma *et al.*, 2017). In addition, these compounds were observed to have a downregulating effect on IL-6 and IL-8 levels in inflammatory human tracheal epithelial BEAS-2B cells (Wu *et al.*, 2021).
In vitro studies have also shown that carotenoids can help reduce oxidative stress and inflammation, which are associated with neurodegenerative diseases such as Alzheimer's and Parkinson's disease (Z. Liu *et al.*, 2017). Carotenoids have been shown to have anti-inflammatory, neuroprotective properties that could be used to slow the progression of Alzheimer's disease (Manochkumar *et al.*, 2021).

In a 2015 study by Liu and co-workers, they investigated the anti-metastatic effects of α-carotene in Lewis lung carcinoma (LLC) cells and mice. In cell culture experiments, α-carotene at 2.5 μM significantly inhibited invasion, migration, and the activities of matrix metalloproteinases (MMP)-2, -9, and urokinase plasminogen activator. Additionally, α-carotene suppressed integrin β1-mediated phosphorylation of focal adhesion kinase (FAK), which led to reduced phosphorylation of MAPK family proteins. These findings suggested that α-carotene has potential as an anti-metastatic agent or as an adjunct to anti-cancer treatments.

Lycopene has been reported to have a stronger antioxidant potential than other carotenoids due to its conjugated dienes (Shin *et al.*, 2020). Additionally, (Thies *et al.*, 2017) found that lycopene consumption reduces high-density lipoprotein (HDL)-associated inflammation, which may protect against cardiovascular diseases.

iv. Disease-Specific Effects

Carotenoids help in reducing the risk of developing conditions such as T2D (Jiang *et al.*, 2021), CVD (Kulczyński *et al.*, 2017), obesity (X. Li *et al.*, 2021), and cancer (Saini *et al.*, 2022). Recent evidence suggests that carotenoids may have disease-specific effects. For instance, beta-cryptoxanthin has shown promise in reducing the risk of lung cancer, particularly in smokers (X. Liu *et al.*, 2021; Islam *et al.*, 2022). Lutein and zeaxanthin have been associated with a lower risk of age-related macular degeneration. The mechanisms underlying these disease-specific effects are an active area of research, and ongoing studies aim to elucidate the molecular pathways involved.

- ***Bone Health***

Beta-cryptoxanthin may contribute to bone health by promoting bone mineral density and reducing the risk of osteoporosis (Zacarías-García *et al.*, 2021). The research conducted by Linnewiel-Hermoni and colleagues in 2014 demonstrated that electrophilic carotenoid derivatives have a positive impact on both cancer prevention and the maintenance of bone health. They achieve this by inhibiting the NFkB transcription system, with a significant role attributed to the essential thiol groups found in both IKK and p65.

Furthermore, in a series of epidemiological investigations carried out by Charkos and colleagues in 2020, a meta-analysis was conducted to explore the relationship between β-carotene consumption and the likelihood of experiencing fractures. The results indicated a 95% probability that β-carotene intake could reduce the risk of hip fracture and fractures of any type by more than 20%.

- ***Diabetes Management***

Some studies suggest that carotenoids can improve insulin sensitivity and reduce the risk of type 2 diabetes or help manage the condition in diabetic individuals (Lima *et al.*, 2019; Alhabeeb *et al.*, 2022; Subodh *et al.*, 2023). Studies using animal models have shown that certain carotenoids can help reduce plasma glucose, glycemia, insulinemia, and LDL-C, VLDL-C, and TG levels, which are associated with metabolic syndrome and type 2 diabetes (Z. Zeng *et al.*, 2017). In a different investigation, a three-week dietary supplementation of (9-cis, all-trans) β-carotene at a daily dosage of 60 mg was administered to a group of patients (n = 20) with long-standing non-insulin-dependent diabetes mellitus (NIDDM). The results of this supplementation revealed that low-density lipoproteins in NIDDM patients who received β-carotene exhibited enhanced resistance to oxidation. Additionally, there was a notable reduction in the levels of malondialdehyde (MDA) in these individuals (Levy et al., 2000).

In a study by Chen *et al.*, 2018, it was observed that Astaxanthin had the potential to mitigate diabetic nephropathy in diabetic db mice, a rodent model for type II diabetes. The mice treated with astaxanthin exhibited reduced blood glucose levels in comparison to the untreated group, and a significant improvement in the mesangial region was noted in the treated group.

- ***Eye Health***

Lutein and zeaxanthin are known to accumulate in the retina and support vision. Carotenoids also reduce the risk of age-related macular degeneration (AMD) and cataracts (Sauer *et al.*, 2019).
Numerous research findings indicate that therapies involving carotenoid vitamins offer significant combined protection to the neurosensory retina. This suggests their potential use as complementary nutraceutical treatments for established AMD, although the extent of these benefits might differ based on the disease's stage (Kim *et al.*, 2011); Gul *et al.*, 2015; Lem *et al.*, 2021).

Z. Li *et al.*, 2013 showed that astaxanthin protected retinal epithelial cells from oxidative stress induced by H_2O_2. Astaxanthin promoted the nuclear translocation of Nrf2 and reduced intracellular ROS levels. This protection was mediated by the PI3K/Akt signalling pathway, which upregulated the expression of Phase II enzymes.

Astaxanthin has been identified as having the capacity to reduce UVB-induced lipid peroxidation and stress signalling in human lens epithelial cells more effectively than alpha-tocopherol (Donoso *et al.*, 2021). Additionally, astaxanthin improves accommodation amplitude for visual displays in terminal workers and the intake of a supplement comprising astaxanthin, lutein, and zeaxanthin helps alleviate the reduction in eye-hand coordination following VDT (Visual Display Terminal) operation (Yoshida *et al.*, 2023).

Yang *et al.*, 2016 research demonstrated the effectiveness of lycopene in reducing TNF-α-induced monocyte adhesion and mitigating cell damage induced by H_2O_2 in RPE cells. Additionally, lycopene exhibited inhibitory effects on ICAM-1 expression and effectively suppressed NF-κB activation for a duration of up to 12 hours in TNFα-treated RPE cells, specifically in human retinal pigment epithelial cells.

- ***Skin Protection***

Carotenoids have the potential to offer protection against skin damage caused by UV radiation. Research conducted in 2023 suggested that including β-carotene and lutein in one's diet can effectively decrease UV-induced skin redness (erythema) and shield the skin from oxidative stress (Anbualakan *et al.*, 2023a)
A systematic review of the literature to explore the effects of certain carotenoids in preventing skin photodamage was done via the electronic Medline (Ovid) and PubMed databases for relevant studies published between 2002 and 2022. Out of 434 articles retrieved, 40 were identified as potentially relevant. All the studies reported positive effects of carotenoid-containing plant extract on UV-induced skin damage (Anbualakan *et al.*, 2023b).

- ***Anti-ageing***

β-cryptoxanthin and lutein have demonstrated remarkable anti-ageing properties through their potent antioxidant activity. These carotenoids scavenge harmful free radicals and reactive oxygen species (ROS), which are major contributors to skin ageing, by neutralizing their damaging effects. Additionally, they support collagen production and skin hydration, contributing to improved skin elasticity and a reduction in the appearance of wrinkles and fine lines (Addi *et al.*, 2022). Recent studies, like the one conducted by Anbualakan *et al.*, 2023b have highlighted the protective role of carotenoids in preventing premature ageing and maintaining youthful skin, making them valuable compounds in the pursuit of anti-ageing skincare solutions.

- ***Covid-19***

Carotenoids and their derivatives show promise in reducing oxidative stress resulting from viral infections, inhibiting the overproduction of pro-inflammatory cytokines to mitigate cytokine storms (Kaulmann & Bohn, 2014), and potentially obstructing ACE2, which serves as the entry point for SARS-CoV-2 (Yim *et al.*, 2021). These actions could offer potential advantages to individuals with COVID-19. Numerous prior investigations have suggested that carotenoids may have a positive impact on enhancing lung function and immunity (Lapa, 2011).

KEY MOLECULAR MECHANISMS OF ANTIOXIDANT POTENTIAL IN BIO-ACTIVE CAROTENOIDS

The concept of antioxidant activity refers to the ability of bioactive molecules to safeguard cell integrity and function by effectively neutralizing free radicals, regulating lipid peroxidation pathways, and preventing other oxidative damages (Saini *et al.*, 2022).

Carotenoids have been demonstrated to have repercussions in the prevention of several diseases, such as cardiovascular, cancer, and metabolic, among others. It is thought that these effects are related to their antioxidant activity, a consequence of the ability of the conjugated double-bond structure to delocalise unpaired electrons. Findings suggested that oxidation products formed from carotenoids (epoxides'), rather than the intact carotenoid, inhibit cell growth (Chacón-Ordóñez *et al.*, 2017).

Carotenoids may exert their antioxidant activity through multiple mechanisms: electron transfer, hydrogen abstraction, radical addition, metal chelation, quenching of molecular oxygen, scavenging reactive species [e.g., reactive oxygen and nitrogen species (ROS and RNS, respectively), or lipid peroxidation prevention (Ringwal *et al.*, 2022).

High redox potential oxidising radical species (R^+) can take an electron from the carotenoid molecule (Car) to create carotenoid radical cations (Car^+) ((Chisté *et al.*, 2014)).

$$Car + R^+ \longrightarrow Car^+ + R \qquad \text{(Eq. 1)}$$

Carotenoids were reduced, resulting in the creation of a carotenoid radical anion (Car).

$Car + e^- \longrightarrow Car^-$ (Eq. 2)

Abstraction of hydrogen atoms from carotenoids leads to the creation of a resonance-stabilized radical (Car + RH)

$Car[H] + R \longrightarrow Car + RH$ (Eq. 3)

Further processes involved the addition of radical species [(e.g., peroxyl (ROO), hydroxyl (HO)] to the polyene chain, resulting in an association with carotenoids ([Car-ROO]) (Eq. 4). With a minimal oxygen level, this oxidized form can react with another radical species, ROO, to form a non-radical derivative (ROO-Car-ROO) (radical chain-breaking mechanism) (Eq. 5).

$Car + ROO \longrightarrow [Car\text{-}ROO]$ (Eq. 4).

$[Car\text{-}ROO] + ROO \longrightarrow ROO\text{-}Car\text{-}ROO$ (Eq. 5).

With increased oxygen concentrations, the carotenoid radical combined with dioxygen (O_2) to form a carotenoid peroxyl radical (Car-OO) (auto-oxidation). Because they induced lipid (LH) peroxidation and enhanced oxidative damage in other biomolecules like DNA and proteins, these radicals operated as pro-oxidants as shown in Jomova and Valko, 2013 study. LOO, a hydrophobic lipid, combined with carotenoids to create oxidation products that were then metabolised and expelled from the body as shown in *Figure 5.*

β-carotene, depicted in *Figure 5*, functions as an antioxidant by countering reactive oxygen species (ROS), interrupting harmful free radical cascades, and regulating genes associated with oxidative stress (Nie *et al.*, 2019; Ba *et al.*, 2020). β-carotene's antioxidative effects are linked to reduced ROS formation, decreased cellular apoptosis, and the restoration of various cellular processes, including actin expression, cortical granule-free domains, mitochondria dispersion, and nuclear maturation (Gammone *et al.*, 2015; Brahma & Dutta, 2022).

The molecular structure of beta-carotene, with its conjugated double bonds, gives it strong antioxidative properties. Beta-carotene can neutralize singlet oxygen and various reactive oxygen species (ROS), as well as free radicals. By donating electrons to free radicals and other oxidants, it acts as a chain-breaking antioxidant, effectively preventing lipid peroxidation and other oxidative harm to cells and tissues. This capability to scavenge these reactive substances is the key to its effectiveness in protecting against diseases linked to oxidative stress, including cardiovascular disease, cancer, and neurodegenerative conditions (Chisté *et al.*, 2014).

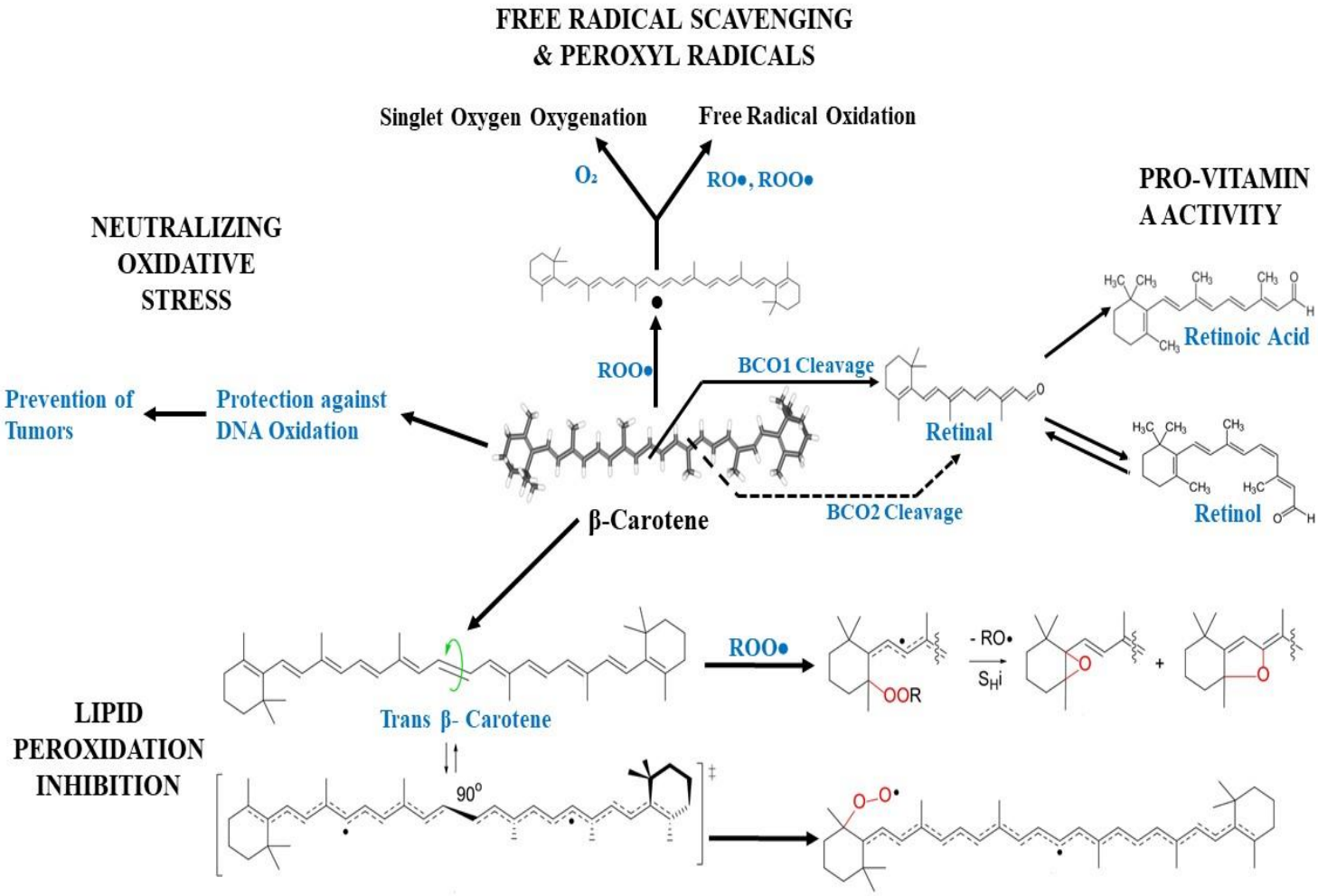


Figure 5; Schematic of antioxidant effects of β-Carotene. Provitamin A activity; Beta-carotene acts as an antioxidant, quenching harmful ROS, protecting cells, and serving as a vitamin A precursor, Neutralizing Oxidative stress; Beta-carotene counteracts oxidative stress by donating electrons to ROS, averting cell damage, Lipid Peroxidation; Initiation and epoxide formation, and Free Radical scavenging & Peroxyl Radicals; Reaction of beta-carotene with peroxyl radicals.

Beta-carotene has demonstrated its antioxidative characteristics in various in vitro settings. This includes its ability to scavenge free radicals like DPPH and O_2•−, its capacity for reducing potential, its metal-chelating properties, and its effectiveness in scavenging ABTS•+ (Netlak *et al.*, 2023). Additionally, it can function as a chain-breaking antioxidant against lipid ROO• and efficiently scavenge $^1O_2$ when oxygen concentrations are low. It's worth noting that at high oxygen concentrations, beta-carotene may exhibit pro-oxidant activity (Rowles & Erdman, 2020).

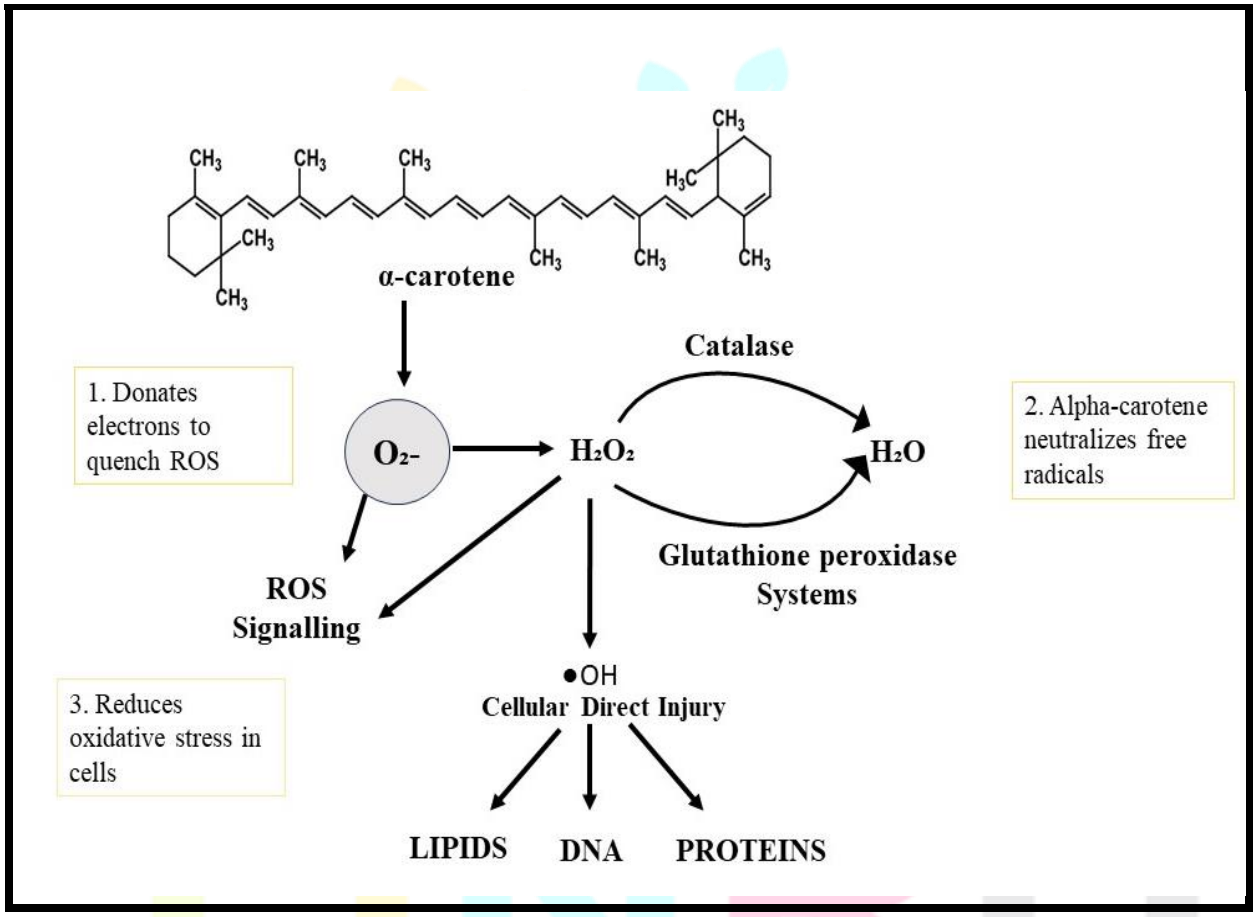


***Figure 6*;** Generation of free radicals and mechanism of ROS removal by Alpha Carotene.

Alpha-carotene, as seen in *Figure 6*, acts as an antioxidant by providing electrons to counteract ROS, preventing chain reactions initiated by these radicals (Gao et al., 2021). Research suggests its potential therapeutic use in neurodegenerative disorders (Kabir *et al.*, 2022). Its unique molecular arrangement, characterized by multiple conjugated double bonds and cyclic ring structures, enables alpha-carotene to donate electrons to ROS, thereby mitigating their reactivity and reducing potential oxidative damage to cellular components.

The xanthophylls also effectively quench ROS by donating electrons, preventing oxidative damage to lipids, proteins, and DNA (Kim *et al.*, 2011). They play a crucial role in the therapy and treatment of age-related macular degeneration, cataracts, and cardiovascular disease due to their antioxidative and anti-inflammatory attributes. ***Lutein and zeaxanthin***, presented in *Figure 7*, are recognized antioxidants due to their distinct chemical structures, localization in the eye's macular region, and electron-donating abilities. Zeaxanthin has been described as a direct and/or indirect antioxidant, regulating glutathione synthesis and levels, and ameliorating the intracellular redox status upon oxidative

stress while reducing susceptibility to (H_2O_2)-induced cell death (Sauer *et al.*, 2019). Lutein has been found to have a higher antioxidant activity than beta-carotene and vitamin E in some *in vitro* studies (Lem *et al.*, 2021).

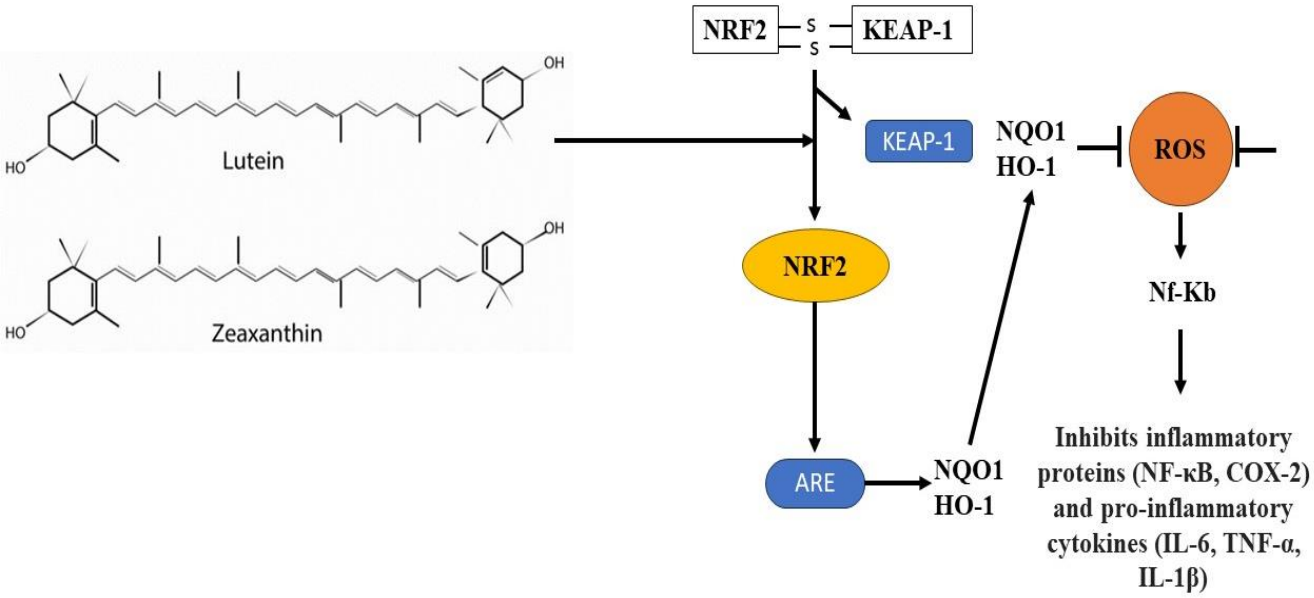
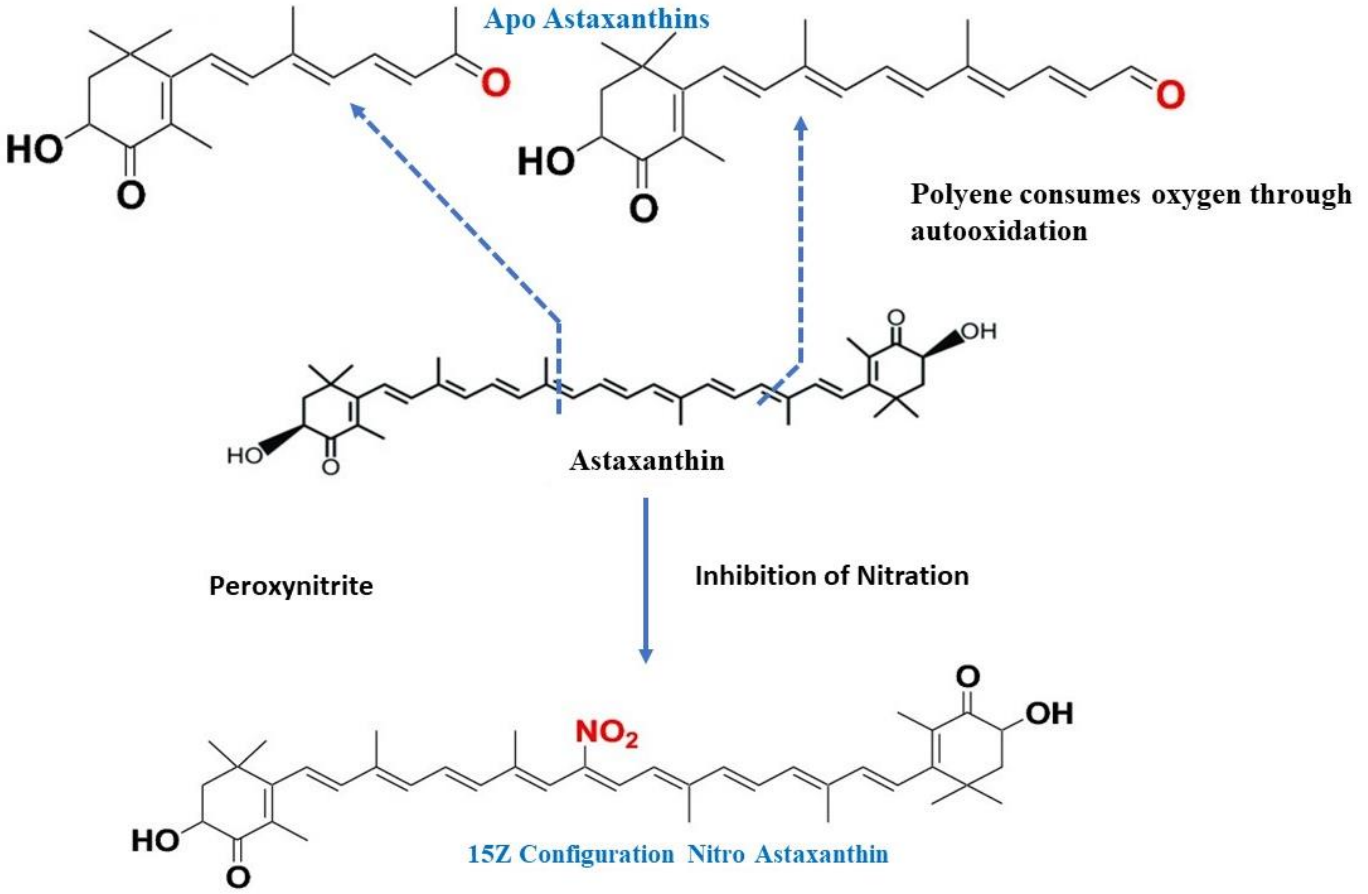


Figure 7; The mechanism by which lutein combats oxidative stress-induced inflammation involves reducing ROS levels and inhibiting ROS-mediated activation of NF-kB, leading to decreased expression of inflammatory mediators (IL-1β, IL-6, TNF-α, COX-2). Lutein also enhances the dissociation of Keap1 from the Nrf2/Keap1 complex, facilitating the nuclear translocation of Nrf2. Nrf2 then forms a heterodimer with sMaf protein and binds to the DNA regulatory region known as ARE, thereby inducing the expression of Nrf2-target antioxidant genes (HO-1, NQO1).

Astaxanthin, with carbonyl functional groups on both ionone rings and numerous unsaturated bonds, plays a critical role in combating free radicals and primarily serves as an antioxidant, mitigating cellular and tissue damage inflicted by free radicals (Manochkumar *et al.*, 2021). Research suggests its potential use as a mitochondrial-focused antioxidant therapy for ageing and cardiovascular disease (Pereira *et al.*, 2021). Astaxanthin's unique structure enhances its electron-attracting capabilities, reducing the energy required for reduction compared to other carotenoids and, consequently, inhibiting the generation of reactive oxygen species (ROS).

Figure 8; Products resulting from the auto-oxidation of astaxanthin and the reaction between astaxanthin and peroxynitrite.



Astaxanthin demonstrates efficient singlet oxygen, superoxide anion radical, and hydroxy radical quenching capabilities. Through LC/PDA ESI–MS analysis, it was determined that the primary reaction products with superoxide anion radicals and hydroxyl radicals were astaxanthin epoxides, whereas astaxanthin endoperoxides were the predominant products when interacting with singlet oxygen (Tasaka et al., 2023). Similar findings were observed for β-carotene, zeaxanthin, and capsanthin (Maoka, 2020). These results suggest that carotenoids can neutralize singlet oxygen, superoxide anion radicals, and hydroxyl radicals through the formation of endoperoxides or epoxides.

Astaxanthin, in various in vitro and in vivo studies, demonstrated robust antioxidative properties as shown in *Figure 8*. It exhibited the capability to neutralize free radicals and other oxidants, safeguard the lipid bilayer against peroxidation, and inhibit H_2O_2-induced activation of the transcription factor nuclear factor kappa B (NF-κB). Notably, astaxanthin displayed an antioxidant potency 10 times greater than lutein, canthaxanthin, and β-carotene. Furthermore, it was linked to neuroprotective effects in an in vivo experiment, where it enhanced the activity of catalase, superoxide dismutase, and glutathione (GSH) levels in the mouse brain (Sztretye *et al*., 2019)

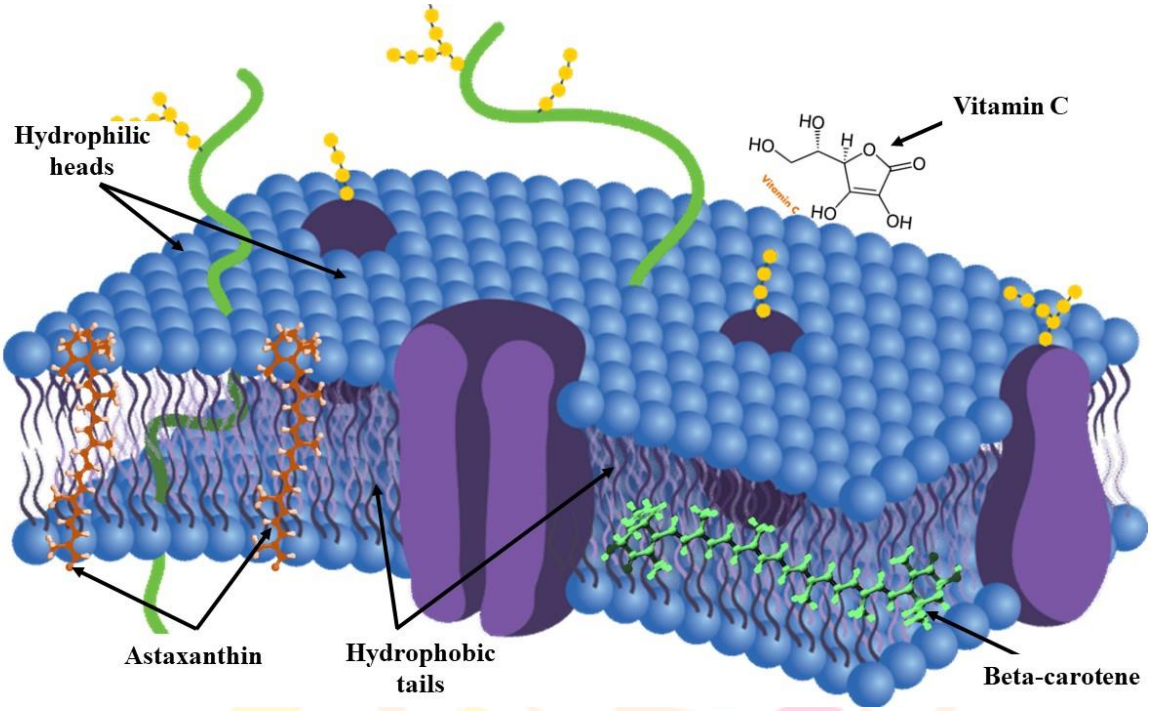


Figure 9; Molecular mechanism describing the antioxidative mechanism of astaxanthin.

Astaxanthin scavenges free radicals and other oxidants and protects the lipid bilayer from peroxidation. In *Figure 9*, the molecular mechanism underlying astaxanthin's antioxidative action is illustrated. Its distinctive molecular structure, featuring dual hydroxyl and keto moieties, allows astaxanthin to traverse cell bilayer membranes and facilitate electron transfer from inside to outside the cell, as well as quench lipid oxidation on the membrane surface (Jomova & Valko, 2013).

CONCLUSION

Carotenoids are a diverse group of plant pigments with a wide range of biological activities, including antioxidant, anti-inflammatory, and anticancer effects. They are found in many fruits, vegetables, and algae, and are essential for human health. This review has summarized the current state of knowledge on the health benefits of carotenoids, with a focus on their potential role in preventing and treating chronic diseases. The evidence suggests that carotenoids may play a role in reducing the risk of cardiovascular disease, cancer, age-related macular degeneration, and other chronic conditions. Overall, the evidence suggests that carotenoids are important nutrients for human health and that their consumption may help to prevent and treat a variety of chronic diseases.

In conclusion, the key antioxidant mechanisms of bioactive carotenoids involve a multifaceted approach to neutralizing free radicals and preventing oxidative damage. Carotenoids, such as beta-carotene and alpha-carotene, exert their antioxidant effects through diverse mechanisms, including electron transfer, hydrogen abstraction, radical addition, metal chelation and quenching of reactive oxygen species. The conjugated double-bond structure of carotenoids allows for the delocalization of unpaired electrons, effectively neutralizing free radicals and preventing oxidative damage to cells and tissues. Beta-carotene, with its ability to neutralize various reactive oxygen species, acts as a chain-breaking antioxidant, preventing lipid peroxidation and cellular damage. Additionally, xanthophylls like lutein and zeaxanthin play crucial roles in combating oxidative stress, with lutein exhibiting higher antioxidant activity than beta-carotene and vitamin E. Astaxanthin, with its unique structure and electron-attracting capabilities, demonstrates robust antioxidative properties, showcasing potential therapeutic applications for ageing and cardiovascular diseases. The antioxidative mechanisms of carotenoids extend beyond scavenging free radicals to include lipid bilayer protection, inhibition of peroxidation, and modulation of cellular processes, highlighting their significance in maintaining cellular integrity and preventing diseases associated with oxidative stress.

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