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Review

Carotenoids in Skin Photoaging: Unveiling Protective Effects, Molecular Insights, and Safety and Bioavailability Frontiers

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Abstract: Skin photoaging, driven primarily by ultraviolet radiation, remains a critical dermatological concern. Carotenoids, a class of natural pigments with potent antioxidant properties, have emerged as promising agents for preventing and mitigating photoaging. This review comprehensively integrates current understanding regarding the triggers of skin photoaging, oxidative stress and their associated signal pathways, the photoprotective roles and mechanisms of carotenoids, as well as their bioavailability. Common C_{40} carotenoids, such as β-carotene, lycopene, astaxanthin, lutein, and zeaxanthin demonstrate remarkable antioxidant activity, primarily attributed to their conjugated double bond structures. Many studies have demonstrated that both oral and topical administration of these C_{40} carotenoids can effectively alleviate skin photoaging. Specifically, they play a crucial role in promoting the formation of a new skin barrier and enhancing the production of collagen and elastin, key structural proteins essential for maintaining skin integrity and elasticity. Mechanistically, these carotenoids combat photoaging by effectively scavenging reactive oxygen species and modulating oxidative stress responsive signal pathways, including MAPK, Nrf2, and NF-κB. Notably, we also anticipate the anti-photoaging potential of novel carotenoids, with a particular emphasis on bacterioruberin, a C_{50} carotenoid derived from halophilic archaea. Bacterioruberin exhibits a superior radical scavenging capacity, outperforming the conventional C_{40} carotenoids. Furthermore, when considering the application of carotenoids, aspects such as safe dosage, bioavailability, and possible long term usage issues, including allergies and pigmentation disorders, must be taken into account. This review underscores the anti-photoaging mechanism of carotenoids, providing strategies and theoretical basis for the prevention and treatment of photoaging.

Keywords: carotenoids; photoaging; oxidative stress; ultraviolet radiation; bacterioruberin

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1. Introduction

The skin, composed of the epidermis, dermis, and subcutaneous tissues, plays a crucial role in barrier function, temperature regulation, tactile perception, and immune monitoring [1]. Skin aging is the most visible manifestation of the aging process, and extrinsic aging is a significant subtype within it [2]. Extrinsic aging is primarily induced by long-term exposure to various environmental factors, such as ultraviolet (UV) radiation, air pollution,

ionizing radiation, and toxins. This exposure leads to a series of skin problems, including sunburn, roughness, sagging, dullness, deep wrinkles, telangiectasia, mottled pigmentation, reduction in elasticity, delayed wound healing, and an increased susceptibility to cancer [3,4]. Among these factors, UV radiation is responsible for 80–90% of the visible signs of extrinsic aging, making it one of the most common causes of photoaging [5,6]. When the skin is exposed to UV rays, it stimulates cells to generate excessive reactive oxygen species (ROS), which disrupt the normal redox balance and trigger an oxidative stress response. This oxidative stress can cause damage to cellular components, including DNA, proteins, and lipids, ultimately accelerating the photoaging process.

In the quest to combat skin photoaging, natural antioxidants have emerged as promising candidates. Compounds such as luteolin [7], tannic acid [8], and protocatechuic acid [9], chlorogenic acid and resveratrol [10], curcumin [11], and catechins [12] have been shown to effectively scavenge ROS, reduce oxidative damage, and delay the progression of photoaging. Among the natural antioxidants, carotenoids, widely distributed in microorganisms (e.g., microalgae, halophilic bacterial, and archaea) [13], plants (e.g., carrot, tomato, broccoli, corn, pumpkin, lettuce, orange, cherry, mango) [14–16], and aquatic animals (e.g., fish, shrimps, and crabs) [17] have gained significant interest due to their diverse biological activities. They possess multiple functions, including anti-inflammation [18], antitumor [19–21], anti-diabetes [22], and blood vessels protection [23], with their antioxidant activity being particularly remarkable [24] (Figure 1). A substantial number of studies have evidenced that carotenoids can alleviate photoaging [25–27]. However, there are no comprehensive reviews on the existing knowledge regarding the effects of carotenoids on photoaging. This review aims to comprehensively explore the effect of carotenoids on photoaging and provide valuable insights into scientific research, clinical practice, and public health improvement.

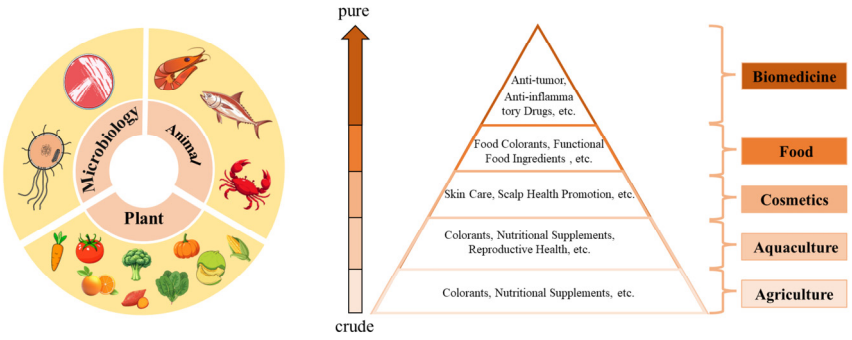

Figure 1. Sources and applications of carotenoids. (**a**) Source of carotenoids. (**b**) Applications of carotenoids.

2. Skin Photoaging

2.1. Ultraviolet Radiation as the Primary Trigger of Skin Photoaging

UV radiation, the principal contributor to skin aging, is categorized into three subtypes based on wavelength: UVA (315–400 nm), UVB (280–315 nm), and UVC (100–280 nm) [28]. The ozone layer absorbs nearly all UVC and over 95% of UVB, allowing only approximately 5% of UVB and 95% of UVA to reach the Earth's surface [29,30]. UVB primarily affects the epidermal layer of the skin. Approximately 70% of UVB is absorbed by the stratum corneum, 20% reaches differentiated epidermal regions (e.g., the granular layer), and only 10% penetrates to the superficial dermis [31] (Figure 2). UVB directly induces DNA damage through the formation of cyclobutane pyrimidine dimers (CPDs) and 6-4 pyrimidine photoproducts (6-4PPs), leading to genomic instability and cell death [32].

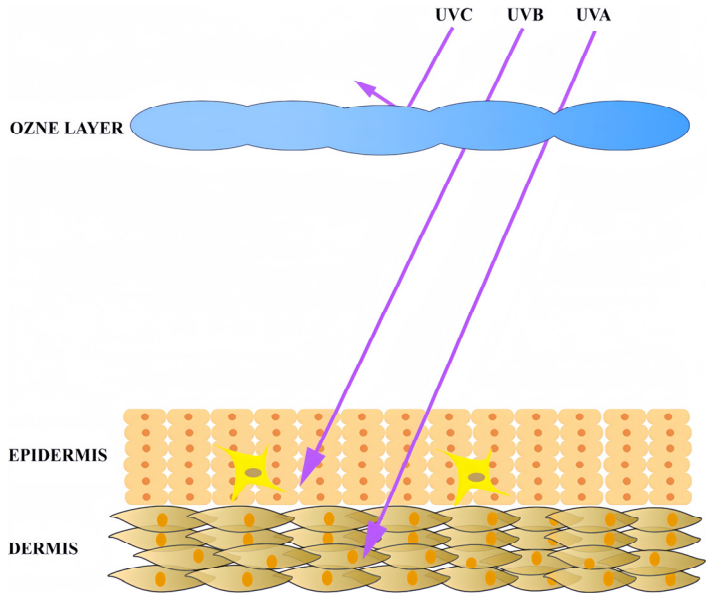

Figure 2. Ultraviolet radiation penetration in skin tissue.

UVA, with its longer wavelength, exhibits deeper skin penetration and plays a crucial role in photoaging by targeting both the epidermis and dermis. In the epidermis, UVA induces oxidative stress, DNA damage, and apoptosis in keratinocytes, the most abundant cells in the epidermis [33]. This process contributes to impaired skin barrier function and an increased risk of carcinogenesis, such as melanoma [34]. Within the dermis, collagen and elastin, the key structural proteins responsible for skin firmness and elasticity, are degraded upon UVA exposure [35,36]. Studies demonstrate that UVA disrupts collagen fiber synthesis and promotes elastic fiber fragmentation [37–39]. Furthermore, UVA stimulates dermal cells to generate excessive ROS, triggering oxidative stress, inflammatory cascades, and apoptotic pathways. These cumulative effects underscore UVA as the critical driver of skin photoaging.

2.2. Skin Photoaging and Oxidative Stress

Continuous exposure to UV radiation induces excessive accumulation of ROS in cutaneous tissues. ROS are a group of atoms or molecules possessing one or more unpaired electrons and can be classified into radical oxides (e.g., superoxide anion radical and hydroxyl radical) and non-radical oxides (e.g., singlet oxygen and hydrogen peroxide) [40]. Radical oxides have the ability to break single-strand DNA, whereas non-radical oxides typically oxidize DNA bases [41,42]. Given that excess ROS cannot be scavenged in a short period of time, a chemical imbalance between the production and consumption of oxidants in biological systems is induced, which activates the oxidative stress response [43]. This activation results in the oxidation of bio-macromolecules and the activation of signal pathways, ultimately leading to a series of skin photoaging symptoms [44–46].

2.2.1. Bio-Macromolecule Damage by Oxidative Stress

DNA, lipids, and proteins are crucial biological macromolecules in organisms, involving a wide array of biochemical reactions. UV radiation generates ROS, which can induce oxidative damage on nuclear DNA. This damage is induced through diverse molecular pathways, including single-base modifications (notably purine alterations), DNA interstrand cross-links, DNA–protein cross-links, and the generation of apurinic/apyrimidinic sites via depurination or depyrimidination processes. As a consequence, large quantities of thymine glycol and 8-hydroxyguanine are produced [45,47]. Base excision repair is a

mechanism capable of rectifying this type of DNA damage. However, with advancing age, the efficiency of various DNA repair mechanisms declines, including nucleotide excision repair, base excision repair, double-strand break repair, and mismatch repair [48]. The decrease in age-related repair efficiency exacerbates the accumulation of DNA damage induced by ROS.

In addition to DNA damage, ROS also target cell membrane lipids. Unsaturated fatty acids with double bonds in the cell membrane are particularly susceptible to attack by hydroxyl radicals (·OH) and peroxynitrite ($ONOO^-$). For instance, the hydroxyl radical (·OH) initiates lipid peroxidation cascades through hydrogen atom abstraction from polyunsaturated fatty acid, generating lipid radicals. Under aerobic conditions, these lipid radicals initiate lipid peroxidation. Lipid peroxidation has been shown to alter the membrane structure, affect its fluidity, and disrupt its integrity [49]. The lipid peroxides formed during this process can further break down into polyreactive aldehydes. These aldehydes react with DNA bases, generating unrepairable polymers that may ultimately lead to the development of diseases. Malondialdehyde (MDA), a common product of lipid peroxidation, plays a significant role in cellular damage. It causes cross-linking polymerization between membrane proteins and phospholipids, directly disrupting the phospholipid bilayer of the cell membrane [50]. This disruption leads to irreversible denaturation of membrane proteins. Moreover, MDA can react with DNA bases, potentially causing gene mutations [51].

ROS also have a detrimental impact on proteins. Hydrogen peroxide (H_2O_2) and superoxide anions (O_2^-) can directly interact with the active center of cysteine containing proteins, resulting in protein inactivation [52]. Additionally, ROS can damage proteins through various means. They can directly attack the protein backbone, oxidize amino acid residues, cleave peptide bonds, form protein aggregates, and generate oxidative stress by-products [53,54]. These effects lead to the loss of activity of many enzymes and the disruption of metabolic pathways.

In summary, UV-induced ROS can cause extensive oxidative damage to DNA, lipids, and proteins. The senescence-associated attenuation of DNA repair systems further exacerbates oxidative damage. The damage to lipids and proteins not only disrupts cellular structure and function but also has the potential to cause genetic mutations, highlighting the complex effects of ROS in the process of skin photoaging.

2.2.2. Signal Pathways Activated by Oxidative Stress

Studies have shown that ROS, acting as second messengers, can activate diverse signal transduction pathways. These pathways further regulate the expression of downstream genes, ultimately resulting in skin photoaging.

Activation of the MAPK Signal Pathway. UV irradiation generates excessive ROS, which initiate photo damage through sequential activation of the mitogen-activated protein kinase (MAPK) signaling cascade [55]. This process begins with ROS-mediated phosphorylation of the epidermal growth factor receptor (EGFR), triggering downstream MAPK activation. The MAPK family, comprising serine/threonine kinases, is subdivided into three major subfamilies based on stimulus specificity and functional divergence, including extracellular signal-regulated kinases (ERK), p38 MAPK, and c- Jun N-terminal kinases (JNK) [56]. Among these, UVA-induced ROS activate p38 and JNK through phosphorylation cascades originating from cytokine receptors, EGFR, and Ras GTPase [57]. These kinases phosphorylate upstream regulators (e.g., ASK1, MKK4/7), culminating in nuclear translocation of activated MAPKs. Activated MAPK proteins enter the nucleus and activate multiple transcription factors, such as adaptor protein complex-1 (AP-1), nuclear factor kappa-B (NF-κB), cyclooxygenase-2 (COX-2), and myc proto-oncogene protein (c-Myc) [57–59]. This

activation induces the expression of matrix metalloproteinases (MMPs), upregulates the expression of inflammatory factors like interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α), and downregulates the expression of transforming growth factor beta (TGF-β), resulting in photo damage [60]. Critically, these transcriptional events establish a self-reinforcing loop, ROS-induced MAPK activation enhances inflammatory mediator production, which further elevates intracellular ROS via NADPH oxidase activation [61].

Activation of the Nrf2 Signal Pathway. The nuclear factor erythroid 2-related factor 2 (Nrf2) signal pathway constitutes a master regulatory system for cellular redox homeostasis. Under physiological conditions, Nrf2 is constitutively sequestered in the cytoplasm through its interaction with Kelch-like ECH-associated protein 1 (Keap1), which functions as a substrate adaptor for the Cullin 3 (Cul3)-based E3 ubiquitin ligase complex [62,63]. This Keap1-Cul3-E3 ligase complex directs Nrf2 for polyubiquitination and subsequent proteasomal degradation, thereby maintaining low basal levels of Nrf2 under unstressed conditions. Mild oxidative stress triggers a biphasic regulatory mechanism: low-dose ROS promote the dissociation of the Keap1-Nrf2 complex, facilitating their nuclear co-translocation. Within the nucleus, Nrf2 heterodimerizes with small Maf proteins (e.g., MafG/K) and binds to antioxidant response elements (AREs) in the promoter regions of target genes, initiating the transcription of phase II detoxifying enzymes (e.g., NQO1, HO-1) and antioxidant proteins (e.g., glutathione synthetase), which collectively restore redox equilibrium [64–66]. Paradoxically, sustained oxidative stress disrupts this adaptive response through redox-sensitive modifications. Excessive ROS induce hyperoxidation of critical cysteine residues (e.g., Cys151, Cys273, Cys288) within Keap1, stabilizing its interaction with Nrf2 and enhancing Cul3-mediated ubiquitination [67]. Concurrently, oxidative modifications of Nrf2 itself (e.g., cysteine sulfenylation) impair its nuclear translocation and DNA-binding capacity, leading to transcriptional silencing of antioxidant genes. This dual inhibition mechanism exacerbates photoaging by depleting cellular defenses against UV-induced oxidative damage.

Activation of the NF-κB Signal Pathway. The NF-κB pathway serves as a pivotal mediator in cellular responses to oxidative stress, exhibiting dual regulatory roles in both pro-inflammatory and antioxidant processes [68,69]. As a transcription factor, NF-κB governs critical biological functions including cell proliferation, apoptosis, and stress adaptation to diverse pathological stimuli [70,71]. Under basal conditions, NF-κB remains sequestered in the cytoplasm as an inactive complex through its interaction with inhibitor proteins IκB, which binds specifically to the Rel homology domain (RHD) of NF-κB [72]. Upon oxidative stress, excessive ROS activate IκB kinase (IKK), triggering phosphorylation of serine residues on IκB. The post-translational modification, typically phosphorylation at specific serine residues on IκB, serves as a molecular signal that targets IκB for proteasomal degradation. As a result, the NF-κB heterodimer, composed of p50 and p65 subunits, is liberated from its inhibitory binding to IκB. Once free, the NF-κB heterodimer exposes its nuclear localization signals. This exposure enables the NF-κB complex to interact with importin proteins, facilitating its translocation into the nucleus, where it can then regulate gene expression. Within the nucleus, NF-κB initiates transcription of pro-inflammatory cytokines (e.g., IL-2, IL-8) and enzymes such as cyclooxygenase-2 (COX-2), thereby driving inflammation and tumorigenesis [72]. Notably, this inflammatory cascade establishes a feedforward loop, as secreted cytokines (e.g., TNF-α) further amplify NF-κB activation through receptor-mediated signaling. Paradoxically, NF-κB activation also confers adaptive antioxidant responses under oxidative stress. It transcriptionally upregulates antioxidant enzymes including superoxide dismutase (SOD) and glutathione peroxidase (GPx), whose enzymatic activities counteract ROS accumulation and restore redox homeostasis. The balanced NF-κB activity determines cellular fate under oxidative stress conditions [73,74].

3. The Anti-Photoaging Effect and Mechanism of Carotenoids

Oxidative stress typically activates the skin's antioxidative system, which includes antioxidases and non-enzymatic antioxidants. Research has indicated that singlet oxygen ($^1O_2$) generated by UV radiation can deactivate antioxidases [75,76]. In such circumstances, non-enzymatic antioxidants, like carotenoids, glutathione, and coenzyme Q10, play a crucial role in responding to oxidative stress. Among these, carotenoids exhibit distinct advantages over other antioxidants.

Carotenoids, as natural products, are widely distributed in various living organisms, including plants, microalgae, bacteria, fungi, and archaea. To date, more than 800 natural carotenoids have been identified [77]. This wide distribution makes them easily accessible. Structurally, carotenoids are composed of isoprene units, a structure that confers good stability (Figure 3). This structure also endows carotenoids with a certain degree of lipophilicity, enabling them to better bind to cell membranes and improve their bioavailability. In addition, carotenoid molecules feature a large number of conjugated double bonds. For example, β-carotene and lycopene have eleven conjugated double bonds, while astaxanthin and bacterioruberin have thirteen [78]. The antioxidant efficacy of carotenoids is fundamentally governed by the number of conjugated double bond, wherein a higher density proportionally amplifies their antioxidant capacity. This is because the conjugated double bond structure allows for efficient electron delocalization, which is crucial for neutralizing reactive species [79]. Carotenoids has been confirmed to possess a potent radical scavenging capacity and can effectively eliminate a wide spectrum of radicals, including 1,1-Diphenyl-2-picrylhydrazyl (DPPH), 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and ROS. Many studies have confirmed that carotenoids have a greater ability to scavenge DPPH, ABTS, and ROS radicals compared to the chemical antioxidants such as ascorbic acid, α-tocopherol, and butylhydroxytoluene (BHT) [80–83]. According to their elemental composition, carotenoids can be classified into two main categories: carotenes, which consist solely of hydrocarbon atoms, and xanthophyll, which contain hydrocarbon and oxygen atoms. Additionally, the terminal groups of carotenoids, such as hydroxyl and carbonyl groups, can further enhance their antioxidant capacity. For instance, astaxanthin has over 10 times the $^1O_2$ quenching capacity of β-carotene [84]. Except for the antioxidant activity, carotenoids also have antitumor [19,85–88], antibacterial [89–91], antihemolytic [86], photoprotective activity [24,92], immunomodulation [93], regulation of lipid metabolism [94], anti-atherosclerosis [95], vision protection [95], etc., allowing its wide application in food, dietary supplement, and pharmaceutical industries. Moreover, studies have shown that appropriate intake or topical application of carotenoids can effectively protect the skin from UV radiation, showing great promise in anti-photoaging [96].

3.1. The Anti-Photoaging Effect and Mechanism of C_{40} Carotenoids

C_{40} carotenoids are highly prevalent, with β-carotene, lycopene, astaxanthin, lutein, and zeaxanthin being prominent examples. These carotenoids are extensively utilized in various industrial applications, thus attracting numerous research efforts. Among them, β-carotene and lycopene fall into the category of carotene, while astaxanthin, lutein, and zeaxanthin are classified as a xanthophyll. C_{40} carotenoids such as lutein, zeaxanthin, and lycopene are excellent antioxidants, a fact that has also been demonstrated by testing the oxidized products of these carotenoids in the blood [97]. Studies have indicated that C_{40} carotenoids play a significant role in alleviating cardiovascular diseases, neurodegenerative disorders, obesity, and diabetes. In addition, carotenoids (e.g., β-carotene, lycopene, and lutein) and their oxidation products have been found in human skin [98], and they have been reported to possess anti-photoaging properties (Table 1).

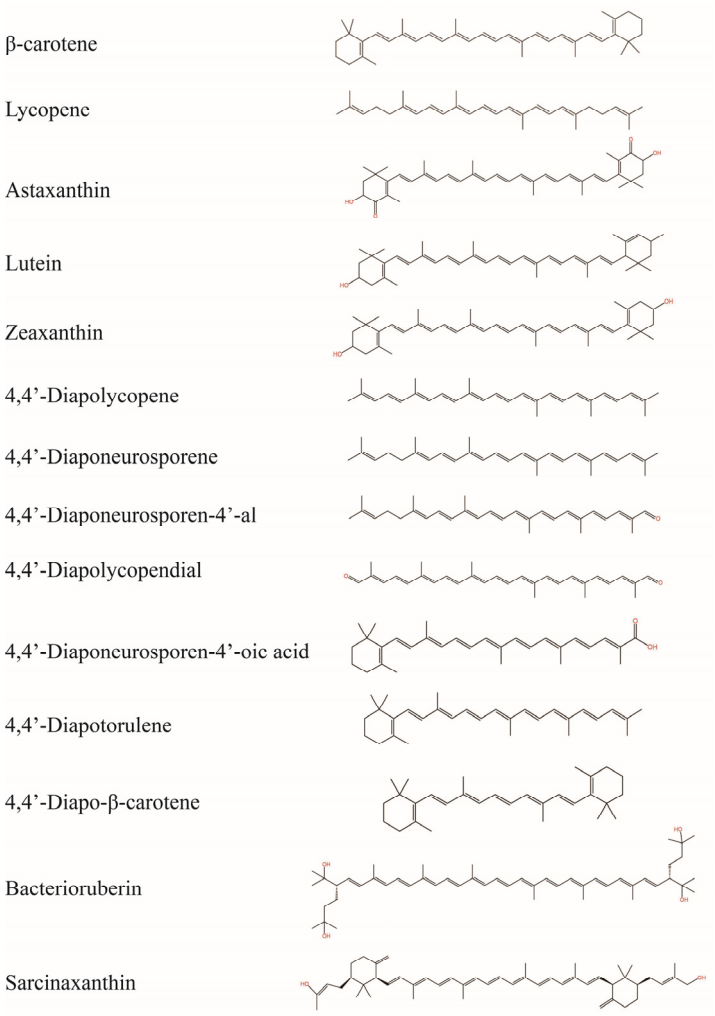

Figure 3. Chemical structures of related carotenoids.

3.1.1. The Anti-Photoaging Effects and Mechanism of β-Carotene

β-Carotene ($C_{40}H_{56}$, molecular weight of 536.87), a prominent member of the carotenoid family, is ubiquitously distributed in nature. It has been mainly found in vegetables (e.g., carrots, potatoes, spinach, lettuce, broccoli) and fruits (e.g., orange, cantaloupe, mango) [14]. As a pro-vitamin A carotenoid, β-carotene also serves as a critical dietary precursor for retinol biosynthesis, undergoing enzymatic cleavage to meet the body's vitamin A requirements [99]. The antioxidant properties of β-carotene are intrinsically linked to its unique polyene structure, featuring 11 conjugated double bonds and two β-ionone rings [100]. In addition to its antioxidant properties, β-carotene demonstrates diverse biological functions, such as anti-inflammatory effects [101], angiogenesis [102], photoprotective activity [103], and immunomodulation [104], enabling its extensive utilization in cosmetics, pharmaceuticals, and nutraceutical industries.

Clinical evidence highlights β-carotene's efficacy as a systemic photoprotective agent (Table 1). Research displayed that β-carotene can improve facial wrinkles and elasticity, reduce erythema, increase mRNA levels of collagen I, inhibit the expression of MMP-9, and reduce UV-induced DNA damage, thereby delaying skin aging [105–107]. Moreover, in patients with erythropoietic protoporphyria (EPP) and polymorphic light eruption (PMLE), prolonged supplementation (>10 weeks) of β-carotene at doses exceeding 12 mg/day significantly reduces UV-induced erythema and photo-dermatosis severity [108,109]. The delayed progression of this therapeutic effect is associated with the accumulation of β-carotene in tissues. To achieve optimal skin photoprotection, sustained treatment is neces-

sary [110]. Mechanistic studies further clarify the multimodal actions of β-carotene. Firstly, β-carotene can scavenge $^1O_2$ and inhibit lipid peroxidation. Additionally, in vitro models demonstrate that β-carotene supplementation enhances cellular antioxidant capacity by activating catalase (CAT) and SOD while concurrently downregulating MMP expression in dermal fibroblasts [111,112]. These regulations preserve extracellular matrix (ECM) architecture by reducing collagen degradation and counteracting UV-induced photoaging. In terms of mechanism, β-carotene can delay cellular aging by activating the Nrf2/ARE signal pathway, inducing the expression of antioxidant enzymes and phase II detoxification enzymes, and enhancing cellular antioxidant and detoxification capacity [113]. In addition, research showed that β-carotene can regulate the process of autophagy and apoptosis through the PI3K/AKT/mTOR signal pathway and reduce cell damage [114]. Furthermore, Wu et al. found that β-carotene can reduce malondialdehyde, TNF-α, and IL-6 levels and increase glutathione peroxidase and superoxide dismutase levels through NF-κB, MAPK, and Nrf 2 signal pathways [115]. β-carotene can also be converted to vitamin A through the KAT7-P15 signaling axis, which can be involved in the metabolism of retinol in order to slow down the aging of cells [116–118] (Figure 4). Current interventional trials support β-carotene's role in mitigating cutaneous damage in these contexts, though precise dosing protocols require further standardization [119].

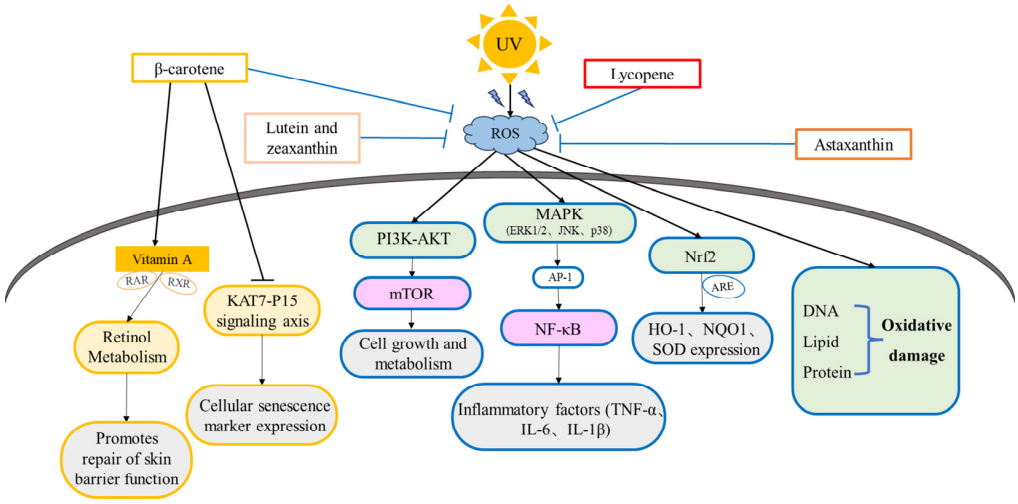

Figure 4. The mechanisms of C_{40} carotenoids on anti-photoaging. Note: Blue boxes indicate signal pathways common to the three carotenoids; orange boxes indicate β-carotenoid-specific signal pathways. UV: ultraviolet; ROS: reactive oxygen species; RAR: retinoic acid receptor; RXR: retinoid X receptor; mTOR: mammalian target of rapamycin; ERK1/2: extracellular signal-regulated kinase 1/2; JNK: c-Jun N-terminal kinase; p38: p38 mitogen-activated protein kinase; AP-1: activator protein 1; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element; HO-1: heme oxygenase 1; NQO1: NAD (P) H: quinone oxidoreductase 1; SOD: superoxide dismutase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6; IL-1β: interleukin 1 beta.

3.1.2. The Anti-Photoaging Effects and Mechanism of Lycopene

Lycopene ($C_{40}H_{56}$, molecular weight of 536.87), a non-oxygenated carotenoid, exists as needle-like deep red crystals in its pure form. This compound is predominantly found in red fruits and vegetables such as tomatoes, watermelon, apricots, and guava, with tomatoes exhibiting the highest natural abundance [120,121]. Recent advances in metabolic engineering and synthetic biology have enabled the heterologous biosynthesis of lycopene in engineered microbial systems, including *Escherichia coli* [122], *Saccharomyces cerevisiae* [123], *Yarrowia lipolytica* [124], and *Deinococcus radiodurans* [125]. Through targeted modification of

microbial metabolic pathways, these microorganisms have been transformed into efficient cellular factories for high-yield lycopene production.

Although lycopene shares the same molecular formula as β-carotene, their structures exhibit distinct differences. Specifically, lycopene features a linear structure, whereas β-carotene has two rings at its terminals. Lycopene, with its structural configuration of eleven conjugated and two non-conjugated double bonds, endows it with exceptional radical scavenging capacity. Among dietary carotenoids, lycopene demonstrates superior $^1O_2$ quenching efficiency, surpassing β-carotene and vitamin E by 47-fold and 100-fold, respectively [126,127]. Lycopene has an important role in slowing down apoptosis and skin aging (Table 1). It reduces ROS, β-galactosidase and advanced glycation end products (AGE), and increases mitochondrial membrane potential and attenuates apoptosis [128,129]. It improves skin elasticity, firmness, brightness, tone as well as fine lines and wrinkles, reduces erythema, decreases inflammatory oxidative indicators, enhances anti-elastase activity, anti-melanogenic activity, and anti-tyrosinase activity, inhibits melanin precursor darkening, and reduces UV-induced skin damage [130–136]. Moreover, lycopene combined with vitamin E enhances the inhibition of MMP-1 expression after UVA irradiation [137]. Mechanistically, lycopene attenuates oxidative stress and apoptosis by activating the PI3K/Akt/Nrf2 signal pathway [138], upregulating the expression of antioxidant and anti-apoptotic proteins and downregulating the expression of pro-apoptotic proteins [139]. In addition, lycopene protects the skin by inhibiting the MAPK and NF-κB signal pathways and reducing the inflammatory response [140] (Figure 4). These findings collectively establish lycopene-rich dietary interventions as effective strategies against acute photo damage and potential long-term photoaging sequelae.

3.1.3. The Anti-Photoaging Effects and Mechanism of Astaxanthin

Astaxanthin ($C_{40}H_{52}O_4$, molecular weight of 596.85), a xanthophyll-class carotenoid, is a lipid-soluble red pigment. Ubiquitously distributed in nature, astaxanthin is biosynthesized by microalgae (e.g., *Haematococcus pluvialis*) and bacteria, and it accumulates in higher trophic organisms such as crustaceans through dietary transfer [141,142]. Commercial production primarily relies on microbial fermentation of *H. pluvialis* [143], rather than direct extraction from other organisms, due to yield and purity advantages. Astaxanthin is characterized by a unique molecular architecture: two β-ionone rings at the termini interconnected by a conjugated polyene chain of four isoprene units. This structural configuration, particularly the extended conjugated double-bond system and terminal cyclic moieties, confers exceptional antioxidant capacity. Pharmacologically, astaxanthin exhibits multiple bioactivities, including antitumor [144,145], antidiabetic [146], anti-atherosclerotic [147], and anti-inflammatory effects [148].

Notably, its protective role against UV-induced photoaging has garnered significant attention (Table 1). In vivo studies using UVA-irradiated hairless mice demonstrated that oral astaxanthin administration (10–40 mg/kg/day) reduced wrinkle formation by 30–50%, suppressed ROS generation and enhanced dermal collagen density via MMP-13 downregulation and aquaporin-3/steroid sulfatase modulation [77,78]. Astaxanthin is also able to improve skin elasticity and hydration, as well as improve wrinkles, elasticity, transepidermal water loss (TEWL), moisture content, and sebum oil content [149,150]. In vitro analyses further revealed the effects of astaxanthin, which was found to inhibit cellular damage caused by free radicals, reduce UVA radiation-induced increases in IL6 expression levels, and reduce ROS generation [151]. Inhibition of keratinocyte apoptosis occurred through the reduction in iNOS and COX-2 [152]. Mechanistically, astaxanthin can act through PI3K/Akt, Nrf2, NF-κB, and MAPK signal pathways. For example, it has been found that astaxanthin reduces ROS production and inhibits apoptosis in mouse photoreceptor cells through the

PI3K/Akt/Nrf2 signal pathway [153]. Hama et al. found that astaxanthin reduced UV-induced collagen degradation and elastic fiber damage through Nrf2, NF-κB, and MAPK signal pathways, reduced the expression of MMPs (such as MMP-1, MMP-3, MMP-9), and resulted in delaying skin aging [154] (Figure 4). Current evidence substantiates astaxanthin as a potent nutraceutical agent for integrative dermatological interventions.

3.1.4. The Anti-Photoaging Effects and Mechanism of Lutein and Zeaxanthin

Lutein and zeaxanthin ($C_{40}H_{56}O_2$, molecular weight of 566.88) are two important carotenoids, primarily of plant origin, that have a variety of health benefits, especially in eye health [155]. Despite sharing an identical molecular formula, these isomers are distinguished by a single positional difference in the conjugated double-bond system: lutein contains one β-ionone ring and one ε-ionone ring, whereas zeaxanthin possesses two β-ionone rings. In rat tracheal epithelial cells, their synergetic scavenging of ROS enhances cellular viability, suppresses NF-κB mediated inflammatory signaling (including IL-1β and COX-2 downregulation), and mitigates UVA-induced DNA damage [156,157] (Figure 4). In skin aging models, these carotenoids exhibit photoprotective efficacy by improving epidermal barrier function (enhanced hydration and elasticity) and reducing wrinkle formation. Notably, murine studies demonstrate their capacity to inhibit UVB-triggered epidermal hyperplasia and acute inflammatory responses, while alleviating xerosis [158–160] (Table 1).

Table 1. The anti-photoaging effect and mechanism of C_{40} carotenoids.

Name	Antioxidant Capacity	In Vitro Experiment	In Vivo Experiment	Signal Pathways	References
β-carotene	Singlet oxygen (all-E-isomer-rich, IC_{50} 0.38 μg/mL; Z-isomer-rich IC_{50} = 0.95 μg/mL)	Human skin fibroblasts (HSFs), human229 neonatal skin fibroblasts (NB1RGB), and B16274 mouse melanoma cells: enhancing hyaluronic acid production, promoting proliferation, anti-elastase activity, anti-melanogenic activity and anti-tyrosinase activity, inhibition of type I collagen production, and inhibition of melanin precursor darkening	-	-	[130]
	-	Keratinocyte: inhibition of UVA-induced ECM degradation and enhancement of UVA-induced expression of tanning-related protease-activated receptor 2, promotes cell differentiation	-	-	[117,118]
	-	Mesenchymal stem cells (MSCs): reducing the expression of cellular senescence markers (e.g., SA-β-gal, p21, p53), enhancing cellular antioxidant capacity, and reducing oxidative stress-induced cell damage	C57 mice: improving the aging state of many tissues and organs, reducing expression of inflammatory factors	KAT7-P15	[116]
	-	Human mammary cancer cells (MCF-7) and human hepatocellular carcinoma cells (HepG 2): activating ARE, inducing the expression of antioxidant enzymes and phase II detoxification enzymes, and enhancing cellular antioxidant and detoxification capacity	-	Nrf2/ARE	[113]
	-	Rat Small Intestine Crypt Epithelial Cells (IEC): Down-regulation of caspase-3, Bax levels and LC3II/I ratio, and up-regulation of Bcl-2 and p62 levels were used to reduce autophagy and inhibit apoptosis	-	PI3K/AKT/mTOR	[114]

Table 1. *Cont.*

Name	Antioxidant Capacity	In Vitro Experiment	In Vivo Experiment	Signal Pathways	References
	-	-	Mice: decreasing malondialdehyde, TNF-α and IL-6 levels, and increasing glutathione peroxidase and superoxide dismutase levels	NF-κB/MAPK/Nrf2	[115]
	-	-	Healthy female subjects: improving facial wrinkles and elasticity, increases collagen type I mRNA levels, reduces UV-induced DNA damage	-	[105]
	-	-	Hairless mice: inhibiting MMP-9 expression and reducing skin wrinkles and sagging	-	[107]
	-	-	11 male and 11 female subjects: protecting human skin from UVA and UVB-induced erythema, reducing serum lipid peroxidation	-	[106]
Lycopene	Singlet oxygen (all-E-isomer-rich IC_{50} 0.26 μg/mL, Z-isomer-rich IC_{50} 1.06 μg/mL)	HSF: Enhancing hyaluronic acid production, promoting proliferation	Anti-elastase activity, anti-melanogenic activity, and anti-tyrosinase activity, inhibition of melanin precursor darkening	-	[130]
	-	-	Human oral intake: reducing erythematous reaction	-	[131]
	-	Chinese hamster ovary cell (M146L cell): reduction in oxidative stress and apoptosis, upregulation of antioxidant and anti-apoptotic proteins, downregulation of pro-apoptotic proteins	-	PI3K/Akt/Nrf2	[139]
	-	Macrophages: inhibiting LPS-induced IκB phosphorylation, IκB degradation, and NF-κB translocation, blocking phosphorylation of ERK1/2 and p38 MAP kinase	-	MAPK/NF-κB	[140]

Table 1. *Cont.*

Name	Antioxidant Capacity	In Vitro Experiment	In Vivo Experiment	Signal Pathways	References
	-	Primary mouse neurons cell: enhancing cell viability, restoring mitochondrial membrane potential, and reducing ROS production	-	PI3K/Akt	[138]
	-	HSF: decreasing the content of ROS, β-galactosidases, and AGEs and increases mitochondrial membrane potential	-	-	[128]
	-	Human neuroblastoma cells (SH-SY5Y): blocking neuro-inflammation and apoptosis	-	-	[129]
	-	HSF: Combined with vitamin E, enhancing the inhibition of MMP-1 expression after UVA radiation	-	-	[137]
	-	-	60 female subjects: improving skin elasticity, firmness, brightness, tone, and fine lines and wrinkles	-	[132]
	-	-	5 male and 5 female subjects: reduction in markers of inflammatory oxidative damage (e.g., malondialdehyde, protein carbonyls, etc.) and low-density lipoprotein peroxidase protein levels	-	[133]
	-	-	33 healthy male volunteers aged 20 to 30 years old: enhancing skin hydration and elasticity, reducing erythema, melanin, and sebum levels	-	[134]
	-	-	20 volunteers between 40 and 50 years of age: reducing the number of wrinkles and roughness	-	[135]
Astaxanthin	ABTS(IC_{50} 7.7 μg/mL); DPPH(IC_{50} 17.5 μg/mL)	-	-	-	[161]

Table 1. *Cont.*

Name	Antioxidant Capacity	In Vitro Experiment	In Vivo Experiment	Signal Pathways	References
	ABTS(IC_{50} 17.56 μg/mL); DPPH(IC_{50} 50.93 μg/mL)	-	-	-	[162]
	-	HSF: inhibiting cellular damage caused by free radicals and reducing UVA radiation-induced elevation of IL6 expression	-	-	[151]
	-	Mouse photoreceptor cells (661W): reducing ROS production and attenuating apoptosis	-	PI3K/Akt/Nrf2	[153]
	-	-	Male hairless mice: reducing UV-induced collagen degradation and elastic fiber damage, reducing the expression of MMPs (e.g., MMP-1, MMP-3, MMP-9)	Nrf2/NF-κB/MAPK	[154]
	-	HaCaT keratinocytes: inhibition of cell apoptosis by reducing INOS and COX-2	-	-	[152]
	-	-	Between 30 and 56 years of age, 21 women and 2 men: improving skin elasticity and hydration	-	[149]
	-	-	30 healthy female subjects: improving wrinkles, elasticity, transepidermal water loss, moisture content, and sebum oil levels	-	[150]
Lutein and zeaxanthin	-	Human RPE cell: directly quenching ROS and facilitating glutathione synthesis	-	-	[156]
	-	Rat tracheal epithelial cells: reduction in UVA radiation-induced DNA damage	-	-	[157]
	-	-	Human subjects: improving skin hydration, elasticity, and photoprotective activity	-	[158]
	-	-	Hairless mice: decreasing UVB-induced epidermal hyper-proliferation and acute inflammation in hairless mice	-	[159]
	-	-	Mice: reducing wrinkles and dryness	-	[160]

3.2. The Potential of Novel Carotenoids on Anti-Photoaging

3.2.1. C_{30} Carotenoids

C_{30} carotenoids, lipophilic tetraterpenoids composed of six isoprene subunits, are 30-carbon pigments biosynthesized by microorganisms, including *Pseudomonas rhodos* (4,4′-Diapocaroten-4′-al-4-oic acid, $C_{30}H_{36}O_3$), *Staphylococcus aureus* (4,4′-Diapolycopen-4-al (4, 4′-Diapolycopenal), $C_{30}H_{38}O$), *Halobacillus halophilus* (Methyl hydroxy-3,4-dehydro-apo-8′-lycopenoate, $C_{31}H_{42}O_3$), *Streptococcus faecium* (4-Hydroxy-4,4′-diaponeurosporene, $C_{30}H_{42}O$), and *Heliobacteria spp.* (4,4′-Diaponeurosporene, $C_{30}H_{42}$) (Table 2) [163]. Unlike the ubiquitous C_{40} carotenoids, C_{30} variants are phylogenetically restricted, exhibiting structural diversity through hydroxyl, ketone, aldehyde, or carboxyl functional groups. Their radical scavenging efficacy correlates positively with conjugated double bond count (3–13 in known derivatives), wherein extended π-electron delocalization enhances antioxidant potency. Current research prioritizes elucidating their physicochemical properties [163–165]. For instance, 4,4′-diaponeurosporene, a C_{30} carotenoid isolated from *Lactiplantibacillus plantarum* subsp. *plantarum* KCCP11226, demonstrated superior DPPH radical scavenging activity compared to BHT [164]. Another study also confirmed that C_{30} carotenoids have good DPPH radical scavenging activity [166].The superior antioxidant capacity of C_{30} carotenoids, combined with their intrinsic lipophilicity that facilitates cutaneous absorption, renders these compounds promising therapeutic agents for counteracting UV-induced photoaging.

Table 2. The antioxidant activity of C_{30} carotenoids [166].

Name	DPPH IC_{50} (μM)
4,4′-Diapolycopene	8.7
4,4′-Diaponeurosporene	11.6
4,4′-Diaponeurosporen-4′-al	10.2
4,4′-Diapolycopendial	7.5
4,4′-Diaponeurosporen-4′-oic acid	9.7
4,4′-Diapotorulene	70.3
4,4′-Diapo-β-carotene	77.8

3.2.2. C_{50} Carotenoids

C_{50} carotenoids, a novel class of natural pigments predominantly synthesized by halophilic archaea (e.g., *Halorubrum*, *Haloarcula*, and *Haloferax*), mainly existed in hypersaline environments (up to 300 g/L NaCl) [167–169]. C_{50} carotenoids include bacterioruberin and its derivatives, such as monoanhydro-bacterioruberin, bisanhydro-bacterioruberin, and trianhydro-bacterioruberin [13,170]. Structurally, bacterioruberin comprises a linear isoprenoid backbone with 13 conjugated double bonds and four hydroxyl groups at both termini. This configuration enables its integration into archaeal cell membranes, where it augments membrane rigidity [171]. In addition, the elongated π-electron conjugation in C_{50} carotenoids confers superior antioxidant capacity compared to C_{40} counterparts (e.g., β-carotene and astaxanthin). Previous studies have shown that C_{50} carotenoids have excellent ABTS and DPPH radical scavenging activity [172,173]. The ABTS radical scavenging assay revealed that bacterioruberin extracts exhibited antioxidant activity 9-fold higher than β-carotene and 26-fold higher than astaxanthin [174]. Furthermore, bacterioruberin demonstrated superior antioxidant efficacy compared to non-pigmented antioxidants, including α-tocopherol, ascorbic acid, and BHT [169]. Be-

yond its antioxidant properties, bacterioruberin exhibits multiple bioactivities, including antitumor, antihemolytic, antimicrobial, and anti-hepatitis viral [85,86,91]. Mechanistic studies demonstrated that bacterioruberin extracts significantly reduced the viability of HepG2 hepatocellular carcinoma cells and suppressed their metastatic potential [85,86]. Furthermore, bacterioruberin exerts broad-spectrum inhibitory effects against bacterial and fungal pathogens [82,91]. In H_2O_2-induced erythrocyte hemolysis models, crude extracts exhibited 3.9- to 6.3-fold higher antihemolytic activity than β-carotene [86]. Notably, bacterioruberin outperformed lamivudine and sofosbuvir, antiviral agents for hepatitis B (HBV) and hepatitis C (HCV) in viral clearance efficacy, as evidenced by superior reduction rates of HBV/HCV titers [87]. Additionally, bacterioruberin extracts were able to protect cells from oxidative DNA damaging agents, protect erythrocytes from H_2O_2, and reduce levels of pro-inflammatory cytokines such as TNF-α and IL-6 [86,92,175]. In addition to bacterioruberin, a structurally distinct C_{50} carotenoid, sarcinaxanthin (isolated from *Kocuria palustris*), demonstrated notable in vitro photoprotective efficacy, achieving a sun protection factor (SPF) of 9.36 ± 0.52 [176].These findings underscore that C_{50} carotenoids have broad application potential, particularly in the mitigation of photoaging (Table 3).

Table 3. The anti-photoaging potential of C_{50} carotenoids.

Name	Antioxidant Capacity	In Vitro Experiment	References
Bacterioruberin	ABTS (IC_{50} 9.8 μg/mL), FRAP (IC_{50} 2.1 μg/mL)	-	[172]
	DPPH (IC_{50} 86.67 μg/mL)	-	[173]
	-	Protection of cells against oxidizing DNA damaging agent	[92]
	-	Protection of erythrocytes from H_2O_2	[86]
	ABTS (IC_{50} 20.5 μg/mL),	Macrophages: reducing ROS levels and reducing levels of pro-inflammatory cytokines TNF-α and IL-6	[175]
Sarcinaxanthin	$^1O_2$	Displaying an SPF of 9.36 ± 0.52, exhibiting in vitro photoprotective activity	[176]

4. Safety and Bioavailability of Carotenoids

Carotenoids, while offering significant therapeutic potential, present safety and bioavailability challenges that require careful evaluation. This section critically examines their safety profiles and absorption limitations across administration routes.

4.1. Oral Administration: Safety Considerations

Excessive oral intake of carotenoid supplements may pose safety risks. One significant concern is carotenemia, a condition characterized by skin yellowing resulting from over-consumption of carotenoids. High-dose carotenoid intake can also induce digestive problems, including bloating, diarrhea, or constipation [177]. Additionally, some studies suggest that high-dose β-carotene supplements might increase the risk of lung cancer in smokers [178]. And the antioxidant properties of carotenoids might potentially mask the symptoms of underlying health issues, such as liver disease. By neutralizing free radicals and reducing oxidative stress, carotenoids may delay the detection of these conditions, thereby postponing diagnosis and treatment.

4.2. Topical Application: Efficacy and Safety Profile

Carotenoids can be applied topically, and products containing these pigments are generally regarded as relatively safe. This is because topical application acts directly on the skin surface without involving the digestive system (Figure 5). Nevertheless, there are still some potential safety concerns and side effects associated with topical use. For example, allergic reactions may occur, leading to skin redness, itching, or rashes. Prolonged or excessive use of carotenoid products may also cause changes in skin pigmentation, such as hypopigmentation (loss of color), hyperpigmentation (darkening of the skin), and the formation of discoloration patches. Existing studies have provided some insights into the safety of some carotenoids. For example, Edwards et al. reviewed the genotoxicity and carcinogenicity of astaxanthin in rats by integrating and analyzing data from numerous clinical trials. Their findings indicated that astaxanthin did not exhibit carcinogenicity in the entire life cycle of rat [179]. However, more research is required to fully understand the long-term safety of using carotenoid products, especially at high doses.

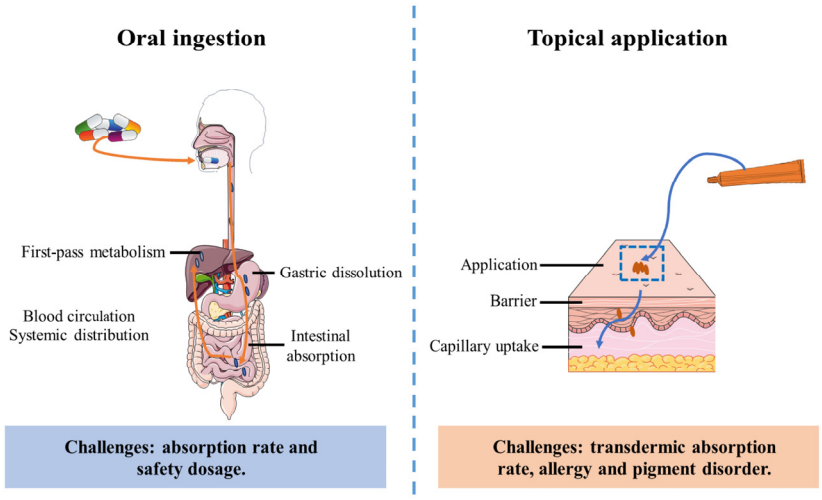

Figure 5. Schematic diagram of carotenoid administration pathways.

Carotenoids encounter several limitations in terms of bioavailability, which can impact their efficacy and practical applications. For oral intake, the primary constraint is their lipid-soluble nature. Carotenoids are insoluble in water and require mixing with lipids for absorption by the body. This property restricts their release from the food matrix and subsequent absorption. During digestion, carotenoids must be emulsified and incorporated into micelles for intestinal absorption. However, this process can be subject to degradation, generally resulting in low bioavailability [180]. Factors such as the presence of dietary fats, the type of food matrix, and individual digestive variations can further affect the absorption efficiency of carotenoids.

Topical delivery confronts distinct barriers, primarily stratum corneum impermeability. Carotenoids need to penetrate the skin barrier for absorption, a process influenced by the skin's structure and the chemical properties of the carotenoids themselves. The stratum corneum, the outermost layer of the skin, serves as a significant barrier to the penetration of many substances [181]. Additionally, external environmental factors like light, oxygen, and temperature can degrade carotenoids, reducing their stability and effectiveness. The formulation of carotenoid products, including the choice of carrier and excipients, can also impact the release of carotenoids and their ability to penetrate the skin [182]. To address these challenges and enhance the stability and bioavailability of carotenoids, researchers have been exploring various stabilization techniques in recent years. These include microencapsulation [183], liposome preparation [184], and nanoemulsion formulation [185].

These techniques involve physical treatment or chemical modification of carotenoids to enhance their stability within the application system. For example, microencapsulation can protect carotenoids from degradation by encapsulating them in a protective shell, while liposomes and nanoemulsions can improve their solubility and absorption efficiency [186].

5. Conclusions and Outlooks

This review systematically reveals the key role of carotenoids in combating skin photoaging induced by UV radiation. Extensive research has demonstrated that C_{40} carotenoids (e.g., β-carotene, lycopene, astaxanthin) can effectively inhibit UV-induced oxidative damage and collagen degradation. These carotenoids achieve protection against UV radiation by scavenging ROS and regulating signaling pathways such as MAPK, Nrf2, and NF-κB. Notably, novel C_{50} carotenoids (especially bacterioruberin) exhibit stronger antioxidant activity than C_{40} carotenoids, allowing potential in anti-photoaging.

Although carotenoids exhibit substantial potential in countering photoaging, numerous challenges and opportunities persist in their application and innovation. Future research should prioritize the following directions: (1) Optimizing delivery systems for enhanced bioavailability. Developing advanced delivery systems is crucial to overcome the bioavailability limitations of carotenoids. Technologies such as microencapsulation, liposome encapsulation, and nanoemulsion formulation can play a pivotal role, which need to be optimized to ensure efficient delivery of carotenoids to their target sites. (2) Unveiling the anti-photoaging mechanisms of novel carotenoids. Novel carotenoids, like bacterioruberin, possess unique anti-photoaging properties that require in-depth exploration. Multi-omics techniques, including genomics, proteomics, and metabolomics, could be employed to comprehensively elucidate their underlying mechanisms. (3) Establishing safety thresholds through dose–response matrices. To ensure the safe use of carotenoids, it is essential to establish accurate safety thresholds. Dose–response matrices should be formulated, considering various factors such as different routes of administration (oral, topical, etc.), individual variability in metabolism, and potential interactions with other substances. (4) Investigating the synergistic effects of carotenoids with other antioxidants. The combination of carotenoids with other antioxidants, such as coenzyme Q10 and vitamin E, may lead to synergistic effects in combating photoaging. These studies will deepen our understanding of the role that carotenoids play in photoaging, thereby providing more robust support for the application of carotenoids in promoting skin health.

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