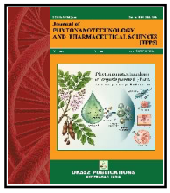
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Plant derived carotenoids as phytomedicines: Sources, biosynthesis, bioavailability and health promoting potential

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Abstract

Carotenoids are C40 isoprenoid pigments synthesised by plants, algae and some microorganisms, and they impart yellow, orange and red colours to fruits, flowers, roots and leaves. More than 1,100 natural carotenoids have been described, of which about 40 occur regularly in the human diet. Plants are the principal dietary source, with carrot, tomato, leafy greens, marigold, saffron, annatto, capsicum and *Moringa oleifer*a Lam. being commercially and medicinally important. In plants, carotenoids are formed in plastids from precursors supplied by the methylerythritol 4-phosphate (MEP) pathway, with phytoene synthase as the main rate-limiting enzyme and lycopene cyclisation directing flux towards the α- and β-branches. Because they are lipophilic, carotenoid absorption in humans is variable and depends on the food matrix, processing, dietary fat, carotenoid interactions and host genetics. Biologically, carotenoids quench singlet oxygen and scavenge free radicals, serve as precursors of vitamin A, modulate redox-sensitive signalling pathways such as Nrf2 and NF-κB, and Accumulate selectively in tissues such as the *Macula lutea*. Epidemiological and clinical evidence links carotenoid intake with lower risk of age-related macular degeneration, cardiovascular disease, certain cancers, photodamage of skin and cognitive decline. However, high-dose β-carotene supplements increased lung cancer incidence among smokers, underlining the importance of dose, source and target population. This review summarises the chemistry, plant sources, biosynthesis, extraction, bioavailability and health-promoting potential of plant-derived carotenoids, and outlines biofortification and nanoencapsulation as routes for developing carotenoid-based phytomedicines.

1. Introduction

Plants produce a wide range of secondary metabolites that have long formed the basis of traditional and modern medicine. Among them, carotenoids are one of the most widely distributed groups of natural pigments, responsible for the yellow, orange and red colours of many fruits, vegetables, flowers and spices (Britton, 1995). In photosynthetic tissues, carotenoids harvest light, protect the photosynthetic apparatus from photo-oxidative damage and serve as precursors of the plant hormones abscisic acid and strigolactones (Nisar *et al.*, 2015; Sun *et al.*, 2018).

Humans and other animals cannot synthesise carotenoids *de novo* and must obtain them from the diet (Rao and Rao, 2007). Of the more than 1,100 carotenoids identified in nature (Yabuzaki, 2017), about 40 are regularly consumed in the human diet, and β-carotene, α-carotene, β-cryptoxanthin, lycopene, lutein and zeaxanthin together account for most of the carotenoids found in human blood and tissues (Maiani *et al.*, 2009; Rodriguez-Concepcion *et al.*, 2018).

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β-Carotene, α-carotene and β-cryptoxanthin also act as provitamin A, making plant foods the main source of vitamin A for a large part of the world's population (Grune *et al.*, 2010).

Interest in carotenoids as phytomedicines has grown steadily because of their antioxidant, anti-inflammatory, immunomodulatory, photoprotective and anticancer properties (Fiedor and Burda, 2014; Milani *et al.*, 2017). They are now used in dietary supplements, functional foods, cosmetics and pharmaceuticals, and the global market for carotenoids continues to expand (Eggersdorfer and Wyss, 2018). At the same time, clinical trials have shown that their effects depend strongly on dose, formulation and the population studied (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Omenn *et al.*, 1996).

The therapeutic value of carotenoids is limited by their poor water solubility, chemical instability and highly variable bioavailability (Boon *et al.*, 2010; Desmarchelier and Borel, 2017). Understanding where carotenoids come from, how plants make them, and how they are absorbed and act in the human body is therefore essential for developing effective carotenoid-based phytomedicines. This review brings together current knowledge on the chemistry, plant sources, biosynthesis, extraction, bioavailability and health-promoting potential of plant-derived carotenoids, and discusses challenges and future directions.

2. Chemistry and classification of carotenoids

Carotenoids are tetraterpenoids built from eight isoprene (C5) units, giving a C40 backbone with a central polyene chain of conjugated double bonds (Britton, 1995). This conjugated system is the chromophore that absorbs light in the 400-500 nm range and gives carotenoids their colour; it also underlies their ability to quench singlet oxygen and react with free radicals (Stahl and Sies, 2003). The ends of the chain may be open (acyclic, as in lycopene) or closed into β- or ε-ionone rings (as in β-carotene and lutein).

Based on chemical composition, carotenoids are divided into two main groups (Rodriguez-Amaya, 2016; Maoka, 2020):

i. **Carotenes:** Pure hydrocarbons containing only carbon and hydrogen, such as phytoene, phytofluene, lycopene, α-carotene and β-carotene. They are highly non-polar and are usually found in the core of plastoglobules and lipid droplets.

ii. **Xanthophylls:** Oxygenated derivatives bearing hydroxyl, epoxy, keto or other functional groups, such as lutein, zeaxanthin, β-cryptoxanthin, violaxanthin, neoxanthin and capsanthin. Their polarity is higher, and in many fruits and flowers they occur esterified with fatty acids.

Carotenoids may also be grouped by nutritional function into provitamin A carotenoids, which carry at least one unsubstituted β-ionone ring (*e.g.*, β-carotene, α-carotene and β-cryptoxanthin), and non-provitamin A carotenoids (*e.g.*, lycopene, lutein and zeaxanthin) (Bohn, 2008; Grune *et al.*, 2010). Oxidative cleavage of carotenoids yields apocarotenoids, including retinal, abscisic acid, bixin, crocetin and its glycosides (crocins), several of which have their own medicinal value (Meléndez-Martínez, 2019).

In nature, most carotenoids exist in the all-*trans* configuration, but heat, light and processing can produce *cis*-isomers. *Cis*-isomers of lycopene, for example, are more readily incorporated into bile acid micelles and are absorbed more efficiently than the all-*trans* form (Boon *et al.*, 2010; Kopec and Failla, 2018).

3. Plant sources of carotenoids

Carotenoids occur in all photosynthetic plant tissues and accumulate in large amounts in many fruits, roots, flowers and seeds. Green leaves contain a fairly constant profile dominated by lutein, β-carotene, violaxanthin and neoxanthin, whereas non-green tissues show much greater diversity, including lycopene in tomato, capsanthin and capsorubin in red pepper, and bixin in annatto seeds (Saini *et al.*, 2015; Rodriguez-Concepcion *et al.*, 2018). The carotenoid content of a given crop varies with cultivar, maturity, growing conditions, post-harvest handling and processing (Maiani *et al.*, 2009).

Several medicinal and aromatic plants are also rich carotenoid sources. Saffron (*Crocus sativus* L.) stigmas contain the water-soluble apo-carotenoid crocin and the bitter glycoside picrocrocin, which underlie many of its pharmacological activities (Bathaie and Mousavi, 2010). Marigold (*Tagetes erecta* L.) petals are the main commercial source of lutein (Lin *et al.*, 2015), while *Moringa oleifera* Lam. leaves are an inexpensive source of â-carotene and lutein in tropical diets (Saini *et al.*, 2016). Important plant sources are summarised in Table 1.

Table 1: Major plant sources of carotenoids and their principal compounds

Plant (botanical name)	Family	Part used	Principal carotenoids	References
Carrot (*Daucus carota* L.)	Apiaceae	Root	β-Carotene, α-carotene, lutein	Rodriguez-Amaya (2016)
Tomato (*Solanum lycopersicum* L.)	Solanaceae	Fruit	Lycopene, β-carotene, phytoene	Giovannucci (1999)
Red pepper (*Capsicum annuum* L.)	Solanaceae	Fruit	Capsanthin, capsorubin, β-carotene, zeaxanthin	Maoka (2020)
Spinach (*Spinacia oleracea* L.)	Amaranthaceae	Leaf	Lutein, β-carotene, violaxanthin, neoxanthin	Saini *et al.* (2015)
Drumstick (*Moringa oleifera* Lam.)	Moringaceae	Leaf	β-Carotene, lutein	Saini *et al.* (2016)
Marigold (*Tagetes erecta* L.)	Asteraceae	Flower	Lutein esters, zeaxanthin	Lin *et al.* (2015)
Saffron (*Crocus sativus* L.)	Iridaceae	Stigma	Crocins, crocetin (apocarotenoids)	Bathaie and Mousavi (2010)
Annatto (*Bixa orellana* L.)	Bixaceae	Seed aril	Bixin, norbixin (apocarotenoids)	Meléndez-Martínez (2019)
Mango (*Mangifera indica* L.)	Anacardiaceae	Fruit pulp	β-Carotene, violaxanthin	Saini *et al.* (2015)
Papaya (*Carica papaya* L.)	Caricaceae	Fruit pulp	Lycopene, β-cryptoxanthin, β-carotene	Saini *et al.* (2015)
Sweet potato (*Ipomoea batatas* (L.) Lam., orange-fleshed)	Convolvulaceae	Tuber	β-Carotene	Rodriguez-Amaya (2016)
Maize (*Zea mays* L., yellow)	Poaceae	Grain	Lutein, zeaxanthin, β-cryptoxanthin	Maiani *et al.* (2009)
Mandarin (*Citrus reticulata* Blanco)	Rutaceae	Fruit pulp	β-Cryptoxanthin	Maiani *et al.* (2009)
Pumpkin (*Cucurbita moschata* Duchesne)	Cucurbitaceae	Fruit	β-Carotene, α-carotene, lutein	Rodriguez-Amaya (2016)

4. Biosynthesis and regulation of carotenoids in plants

4.1 Biosynthetic pathway

In plants, carotenoids are synthesised in plastids from the C5 precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), which are supplied by the methylerythritol 4-phosphate (MEP) pathway (Cazzonelli and Pogson, 2010; Ruiz-Sola and Rodríguez-Concepción, 2012). Geranylgeranyl diphosphate synthase (GGPPS) joins these units into the C20 compound

geranylgeranyl diphosphate (GGPP). The first committed step is the head-to-head condensation of two GGPP molecules by phytoene synthase (PSY) to form the colourless C40 carotene 15-cis-phytoene (Hirschberg, 2001).

Phytoene is then desaturated and isomerised by phytoene desaturase (PDS), ζ-carotene isomerase (Z-ISO), ζ-carotene desaturase (ZDS) and carotenoid isomerase (CRTISO) to produce red all-*trans*-lycopene (Nisar *et al.*, 2015). Cyclisation of lycopene is the main branch point. Lycopene β-cyclase (LCYB) acting on both ends gives β-carotene, while the combined action of lycopene ε-cyclase (LCYE) and LCYB gives α-carotene (Cazzonelli and Pogson, 2010).

Hydroxylation of the rings produces xanthophylls. β-Carotene hydroxylases (BCH) convert β-carotene to zeaxanthin through β-cryptoxanthin, while cytochrome P450 hydroxylases (CYP97A and CYP97C) convert α-carotene to lutein. Zeaxanthin epoxidase (ZEP) converts zeaxanthin to violaxanthin through antheraxanthin, and violaxanthin de-epoxidase (VDE) reverses this under high light in the xanthophyll cycle. Neoxanthin synthase (NSY) converts violaxanthin to neoxanthin, a precursor of abscisic acid (Ruiz-Sola and Rodríguez-Concepción, 2012). Carotenoid cleavage dioxygenases (CCDs) and 9-*cis*-epoxycarotenoid dioxygenases (NCEDs) cleave carotenoids into apocarotenoids such as abscisic acid, strigolactones, β-ionone, bixin and crocetin (Meléndez-Martínez, 2019). The pathway is summarised in Figure 1.

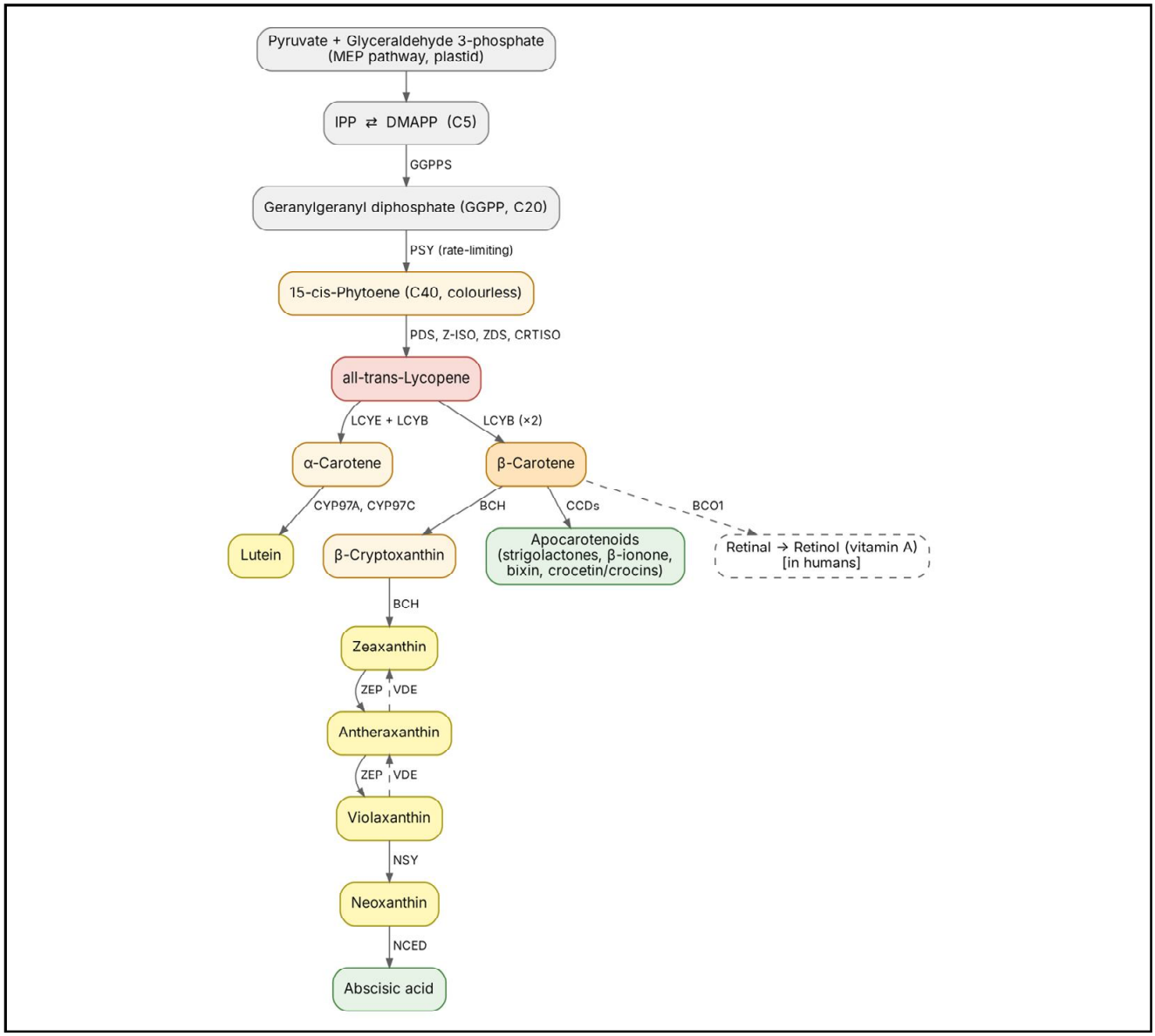


Figure 1: Simplified carotenoid biosynthetic pathway in plant plastids. GGPPS, geranylgeranyl diphosphate synthase; PSY, phytoene synthase; PDS, phytoene desaturase; Z-ISO, ζ-carotene isomerase; ZDS, ζ-carotene desaturase; CRTISO, carotenoid isomerase; LCYB/LCYE, lycopene β-/ε-cyclase; BCH, β-carotene hydroxylase; CYP97A/C, cytochrome P450 carotene hydroxylases; ZEP, zeaxanthin epoxidase; VDE, violaxanthin de-epoxidase (dashed arrows, xanthophyll cycle); NSY, neoxanthin synthase; NCED, 9-*cis*-epoxycarotenoid dioxygenase; CCDs, carotenoid cleavage dioxygenases; BCO1, β-carotene 15,152 -oxygenase (Developed image using Canva).

4.2 Regulation of carotenoid accumulation

Carotenoid levels in plant tissues depend on the balance between synthesis, degradation and storage. PSY is the main rate-limiting enzyme, and its expression is controlled by light, development and hormones through transcription factors such as phytochrome-interacting factors (PIFs) and ELONGATED HYPOCOTYL 5 (HY5) (Cazzonelli and Pogson, 2010; Sun *et al.*, 2018). The ORANGE (OR) protein stabilises PSY after translation and promotes the formation of chromoplasts, which act as storage sinks for carotenoids in fruits, roots and flowers (Sun *et al.*, 2018). Degradation by CCD enzymes and the capacity of plastoglobules and chromoplast structures to sequester pigments further determine the final carotenoid content (Nisar *et al.*, 2015).

This knowledge has been used to improve the carotenoid content of crops. Golden rice, developed by introducing *psy* and the bacterial *crtI* genes into rice endosperm, accumulates β-carotene in the grain (Ye *et al.*, 2000), and a second-generation version using maize *psy* raised total carotenoid content by up to 23-fold, mostly as β-carotene (Paine *et al.*, 2005).

5. Extraction and analysis of carotenoids

Because carotenoids are sensitive to light, heat, oxygen and acids, extraction is carried out quickly, under subdued light and often with antioxidants such as butylated hydroxytoluene (Rodriguez-Amaya, 2001). Conventional extraction uses organic solvents such as acetone, ethanol, hexane, tetrahydrofuran or their mixtures, followed by saponification when chlorophylls and lipids must be removed or xanthophyll esters must be hydrolysed (Saini and Keum, 2018).

Greener and more efficient methods are increasingly preferred. These include supercritical carbon dioxide extraction (often with ethanol as co-solvent), ultrasound-assisted extraction, microwave-assisted extraction, pressurised liquid extraction, enzyme-assisted extraction and the use of edible oils or deep eutectic solvents (Saini and Keum, 2018). These techniques reduce solvent use and extraction time, and supercritical CO_2 is particularly suited to producing food and pharmaceutical-grade extracts.

Total carotenoids are commonly estimated by UV-visible spectrophotometry using specific absorption coefficients. Individual carotenoids and their isomers are separated and quantified by high-performance liquid chromatography (HPLC) with photodiode array detection, often on C30 reversed-phase columns, and identified by liquid chromatography-mass spectrometry (LC-MS) (Rodriguez-Amaya, 2001; Saini *et al.*, 2015). Isomerisation and degradation during sample handling are major sources of analytical error and must be controlled.

6. Bioavailability and metabolism

6.1 Absorption and transport

Carotenoids follow the absorption route of dietary lipids. They must first be released from the food matrix, then dissolved in lipid droplets and incorporated into mixed micelles formed with bile salts in the small intestine (Castenmiller and West, 1998). Uptake into enterocytes is partly passive and partly mediated by membrane transporters, including scavenger receptor class B type I (SR-BI), cluster determinant 36 (CD36) and Niemann-Pick C1-like 1 (NPC1L1) (Desmarchelier and Borel, 2017). Inside the enterocyte, provitamin A carotenoids are cleaved by β-carotene 15,152 -oxygenase (BCO1) to retinal, which is converted to retinol and retinyl esters, while β-carotene 92 ,102 -oxygenase (BCO2) carries out asymmetric cleavage (von Lintig, 2010). Intact carotenoids and retinyl esters are packaged into chylomicrons and secreted into the lymph. In the circulation, carotenes are carried mainly in low-density lipoproteins, and xanthophylls are distributed between low and high density lipoproteins, before accumulating in the liver, adipose tissue, skin, adrenal glands and, in the case of lutein and zeaxanthin, the macula of the eye (Bernstein *et al.*, 2016).

6.2 Factors affecting bioavailability

Carotenoid bioavailability from plant foods is generally low and highly variable. The factors involved have been summarised by the mnemonic SLAMENGHI: Species of carotenoid, molecular Linkage, Amount consumed, Matrix, Effectors of absorption, Nutrient status, Genetic factors, Host-related factors and Interactions (Castenmiller and West, 1998). Important practical points include the following:

- **Food matrix and processing:** Carotenoids bound in the chloroplasts of leafy vegetables or present in crystalline form in raw carrot are poorly released; mild heat treatment, homogenisation and cooking break cell walls and improve release. Processed tomato products give higher lycopene bioavailability than raw tomatoes (Kopec and Failla, 2018).
- **Dietary fat:** A modest amount of fat in the same meal is needed for micelle formation and greatly improves carotenoid absorption (van het Hof *et al.*, 2000).
- **Dietary fibre and other inhibitors:** Pectin and some other fibres, plant sterols and fat substitutes can reduce absorption (van het Hof *et al.*, 2000; Bohn, 2008).
- **Carotenoid interactions:** Large doses of one carotenoid can compete with others for micellar incorporation and uptake (Desmarchelier and Borel, 2017).
- **Host factors:** Vitamin A status, intestinal health and genetic variation in genes such as BCO1, SCARB1 (encoding SR-BI) and CD36 explain much of the person-to-person variability in carotenoid response (Desmarchelier and Borel, 2017).

Formulation strategies such as emulsions, nanoemulsions, solid lipid nanoparticles, liposomes and inclusion complexes improve carotenoid stability, water dispersibility and bioavailability, and are central to the development of carotenoid-based phytomedicines (Gul *et al.*, 2015; Soukoulis and Bohn, 2018).

7. Health promoting and therapeutic potential

Carotenoids act on several biological targets at once, and their effects range from general antioxidant protection to tissue-specific functions in the eye, skin and brain. The main activities of individual carotenoids are summarised in Table 2 and discussed below.

7.1 Antioxidant and photoprotective activity

Carotenoids are among the most efficient natural quenchers of singlet oxygen ($^1O_2$). They deactivate $^1O_2$ mainly by physical quenching, in which the excitation energy is transferred to the carotenoid and released as heat, leaving the molecule intact and able to act again (Stahl and Sies, 2003). Quenching efficiency rises with the number of conjugated double bonds, and lycopene was identified as the most

efficient biological carotenoid quencher of singlet oxygen (Di Mascio *et al.*, 1989). Carotenoids also scavenge peroxyl radicals and protect membrane lipids from peroxidation, often acting together with vitamins E and C (Fiedor and Burda, 2014). At high concentrations or high oxygen partial pressure, however, carotenoids may behave as pro-oxidants, which may partly explain the inconsistent results of high-dose supplementation (Stahl and Sies, 2003).

Dietary β-carotene, lycopene and lutein accumulate in the skin and provide modest protection against ultraviolet-induced erythema. This protection develops only after about 10 weeks of regular intake and is weaker than that of topical sunscreens, so dietary carotenoids are best regarded as a supplement to, rather than a substitute for, conventional sun protection (Stahl and Sies, 2012).

7.2 Provitamin A activity and immune function

Vitamin A is essential for vision, epithelial integrity, growth and immunity. Central cleavage of β-carotene by BCO1 yields two molecules of retinal, whereas α-carotene and β-cryptoxanthin yield one. Conversion efficiency varies widely with food matrix and vitamin A status, and is regulated by feedback so that provitamin A carotenoids from plant foods do not cause vitamin A toxicity (Grune *et al.*, 2010; Tanumihardjo, 2011). In regions where vitamin A deficiency remains a public health problem, provitamin A carotenoids from plant foods are the main dietary source of vitamin A, and biofortified crops such as orange-fleshed sweet potato and Golden Rice are being promoted to close this gap (Paine *et al.*, 2005; Grune *et al.*, 2010).

7.3 Eye health

Lutein, zeaxanthin and meso-zeaxanthin, which is formed from lutein in the retina, are concentrated in the macula lutea, where they form the macular pigment. They filter high-energy blue light and quench reactive oxygen species in photoreceptor cells (Ma and Lin, 2010; Bernstein *et al.*, 2016). In the age-related eye disease study, adding lutein (10 mg) and zeaxanthin (2 mg) to the original AREDS formulation did not further reduce progression to advanced age-related macular degeneration in the primary analysis, but the combination was judged an appropriate replacement for β-carotene, which had been linked to lung cancer in former smokers. Higher macular pigment density is also associated with better cognitive performance in older adults (Johnson, 2014).

7.4 Anticancer and chemopreventive effects

Observational studies have associated higher intake of tomatoes and tomato products with lower risk of prostate cancer and some other cancers (Giovannucci, 1999). Proposed mechanisms include protection of DNA from oxidative damage, up-regulation of connexin 43 and gap junctional intercellular communication (Bertram and Vine, 2005), regulation of the cell cycle and apoptosis, and modulation of growth factor signalling. Oxidative metabolites of lycopene, such as apo-lycopenals, may contribute to these effects (Mein *et al.*, 2008; Tanaka *et al.*, 2012). Crocin and crocetin from saffron have shown antiproliferative and pro-apoptotic effects in several cancer cell lines (Bathaie and Mousavi, 2010).

These benefits do not extend to high-dose supplements of isolated β-carotene. In the α-tocopherol, β-carotene cancer prevention study, 20 mg/day of β-carotene increased lung cancer incidence among male smokers by 18% (The α-tocopherol, β-Carotene Cancer prevention study group, 1994). In the β-carotene and retinol efficacy trial (CARET), β-carotene combined with retinyl palmitate raised lung cancer risk among smokers and asbestos-exposed workers by 28%, and the trial was stopped early (Omenn *et al.*, 1996). Carotenoid-rich whole foods and moderate doses therefore remain the preferred approach.

Table 2: Health-promoting activities of major plant-derived carotenoids

Carotenoid	Major plant sources	Reported activities	Proposed mechanisms	References
β-carotene	Carrot, sweet potato, *Moringa* leaves, mango	Provitamin A, antioxidant, photoprotection, immune support	BCO1 cleavage to retinal; $^1O_2$ quenching	Grune *et al.* (2010); Stahl and Sies (2012)
α-carotene	Carrot, pumpkin	Provitamin A, antioxidant	Retinal formation; radical scavenging	Grune *et al.* (2010); Fiedor and Burda (2014)
β-cryptoxanthin	Mandarin, papaya, maize	Provitamin A, antioxidant	Retinal formation	Maiani *et al.* (2009); Grune *et al.* (2010)
Lycopene	Tomato, watermelon, papaya, pink guava	Antioxidant, chemopreventive (prostate), cardioprotective	$^1O_2$ quenching; gap junction communication; protection of LDL	Di Mascio *et al.* (1989); Giovannucci (1999); Rao and Agarwal (2000)
Lutein	Marigold, spinach, maize	Macular protection, cognitive support, anti-inflammatory	Blue-light filtering; antioxidant action in retina and brain	Ma and Lin (2010); Johnson (2014)
Zeaxanthin	Maize, red pepper	Macular protection	Blue-light filtering; antioxidant	Bernstein *et al.* (2016)
Capsanthin	Red pepper	Antioxidant, anti-inflammatory	Radical scavenging	Maoka (2020)
Crocins and crocetin	Saffron, gardenia fruit	Antidepressant, neuroprotective, antiproliferative, hypolipidaemic	Antioxidant; modulation of neurotransmission and apoptosis	Bathaie and Mousavi (2010)
Bixin and norbixin	Annatto seeds	Antioxidant; natural colourant	Radical scavenging	Meléndez-Martínez (2019)

7.5 Anti-inflammatory and cell-signalling effects

Carotenoids and their oxidative metabolites modulate redox-sensitive transcription factors. They inhibit activation of nuclear factor-κB (NF-κB), lowering the production of pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin-6 and interleukin-8, and they activate nuclear factor erythroid 2-related factor 2 (Nrf2), which induces antioxidant and phase II detoxifying enzymes such as haem oxygenase-1 (Kaulmann and Bohn, 2014). Electrophilic apocarotenoids formed by carotenoid oxidation are thought to be important mediators of these effects (Kaulmann and Bohn, 2014).

7.6 Cardiovascular and metabolic health

Lycopene and other carotenoids are transported in low-density lipoproteins and may protect them from oxidation, a key early event in atherosclerosis. Observational studies have linked higher dietary or serum lycopene with lower risk of cardiovascular disease (Rao and Agarwal, 2000; Rao and Rao, 2007), although results of randomised trials remain mixed (Milani *et al.*, 2017). Saffron and crocin have shown hypolipidaemic and antidiabetic effects in experimental studies (Bathaie and Mousavi, 2010).

7.7 Neuroprotective and cognitive effects

Lutein is the predominant carotenoid in the human brain, and lutein status has been associated with cognitive performance across the lifespan (Johnson, 2014). Saffron and its constituents crocin and crocetin have shown antidepressant, anxiolytic and memory-enhancing effects in experimental and clinical studies (Bathaie and Mousavi, 2010).

8. Safety, challenges and future prospects

8.1 Safety

Carotenoids consumed as part of fruits, vegetables and spices are considered safe. Very high intakes can cause carotenodermia, a harmless yellowing of the skin that disappears when intake is reduced (Milani *et al.*, 2017). The main safety concern relates to high-dose isolated β-carotene supplements in smokers and asbestos-exposed individuals, as shown in the ATBC and CARET trials (The α-tocopherol, β-carotene Cancer prevention study group, 1994; Omenn *et al.*, 1996).

8.2 Challenges

Several obstacles limit the development of carotenoids as phytomedicines. They degrade readily during processing and storage, and their bioavailability is low and varies widely between individuals (Boon *et al.*, 2010; Desmarchelier and Borel, 2017). Commercial extracts are often poorly standardised, and long-term randomised controlled trials with clear clinical endpoints are scarce. Observational associations are also difficult to separate from the effects of the whole diet, since carotenoid intake is a marker of fruit and vegetable consumption.

8.3 Future prospects

Research priorities that could strengthen the use of carotenoids as phytomedicines include the following:

- Biofortification and metabolic engineering of crops, including manipulation of PSY and the ORANGE protein, to raise carotenoid content in staple foods (Paine *et al.*, 2005; Sun *et al.*, 2018).
- Nano and micro-encapsulation systems that improve stability, dispersibility and bioavailability (Soukoulis and Bohn, 2018).
- Green extraction of carotenoids from agro-industrial by-products such as fruit and vegetable peels (Saini and Keum, 2018).
- Personalised nutrition that considers genetic variation in carotenoid absorption and conversion (Desmarchelier and Borel, 2017).
- Well-designed randomised trials using food-based interventions, standardised extracts and validated biomarkers.
- Exploration of underutilised medicinal, wild and tree species, including those grown in agroforestry systems, as sustainable carotenoid sources.

9. Conclusion

Plant-derived carotenoids are versatile bioactive pigments with clear roles in human nutrition and growing promise as phytomedicines. Plants supply nearly all dietary carotenoids, and advances in understanding their biosynthesis and regulation have made it possible to raise carotenoid levels in crops. Their health benefits, including provitamin A activity, antioxidant and anti-inflammatory action, protection of the eye and skin, and possible roles in preventing cancer, cardiovascular disease and cognitive decline, are best supported for carotenoid-rich foods consumed in moderate amounts. Low and variable bioavailability, instability and the risks of high-dose β-carotene in smokers remain important limitations. Combining biofortification, green extraction, advanced delivery systems and well-designed clinical trials will be key to turning carotenoids into reliable, evidence-based phytomedicines.

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Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

H. B. Roghan and P. Ravi Raja Simman: Conceptualization, academic oversight, critical review and validation of scientific content; **V. Kabinesh**: Software handling and data curation.

Consent for publication

All authors gave full consent for publication and submission to this journal.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest relevant to this article.

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