Carotenoids: Considerations for Their Use in Functional Foods, Nutraceuticals, Nutricosmetics, Supplements, Botanicals, and Novel Foods in the Context of Sustainability, Circular Economy, and Climate Change

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Abstract

Carotenoids are versatile isoprenoids that are important in food quality and health promotion. The need to establish recommended dietary intakes/nutritional reference values for carotenoids is being advocated. Research on carotenoids in agro-food and health is being propelled by the two multidisciplinary international networks, the Ibero-American Network for the Study of Carotenoids as Functional Foods Ingredients (IBERCAROT; http://www.cyted.org) and the European Network to Advance Carotenoid Research and Applications in Agro-Food and Health (EUROCAROTEN; http://www.eurocaroten.eu). In this review, considerations for their safe and sustainable use in products mostly intended for health promotion are provided. Specifically, information about sources, intakes, and factors affecting bioavailability is summarized. Furthermore, their health-promoting actions and importance in public health in relation to the contribution of reducing the risk of diverse ailments are synthesized. Definitions and regulatory and safety information for carotenoid-containing products are provided. Lastly, recent trends in research in the context of sustainable healthy diets are summarized.

INTRODUCTION

Carotenoids are versatile isoprenoids of great importance in agro-food and health. They are essential for photosynthesis, the engine of life on Earth, and also for plant development, as they are precursors of the phytohormones abscisic acid and strigolactones. They are also critical for plant propagation, as their colors and carotenoid-derived aromas are attractants of pollinators and seed dispersers (Britton et al. 2008, Esteban et al. 2015). Because plants are essential for animal and human diets, carotenoids are undoubtedly a key for food security. Beyond their colorant properties and the role of some of them as precursors of vitamin A, there is ample evidence that carotenoids (and/or derivatives) contribute to health-promoting actions or even to aesthetic benefits (Eggersdorfer & Wyss 2018, Meléndez-Martínez 2019, Meléndez-Martínez et al. 2019). Carotenoids are precursors of compounds **[**AU: more versatile than what?**]** important in light harvesting, photoprotection, communication between species, vision, stabilization of membranes, and protection against oxidizing agents (Britton et al. 2008, Esteban et al. 2015, Rodriguez-Concepcion et al. 2018). A key difference is that some carotenoids are precursors of vitamin A, an essential nutrient. Hence, provitamin A carotenoid-rich products (carrots, palm oil, gac oil, buriti, mango, sweet potato, apricot, and green vegetables) are key in combating vitamin A deficiency, one of the most important public health problems related to poor nutrition (Dias et al. 2018, Meléndez-Martínez 2019). Carotenoids (more specifically lutein) are among the bioactives for which the need to establish recommended dietary intakes (RDIs) is being discussed (Ranard et al. 2017). This review sumarizes the importance of carotenoids in agro-food and health and stresses key aspects to be considered for their sustainable production and rational use of products intended for health promotion.

DIETARY SOURCES AND CONSIDERATIONS REGARDING INTAKES

Typical diets can provide approximately 50 carotenoids, although only some are found in humans (Britton & Khachik 2009, Meléndez-Martínez 2019, Rodriguez-Concepcion et al. 2018). Dietary carotenoids are most commonly obtained from plant-derived foods, although they are also present in animal-derived foods (e.g., egg yolk, salmon flesh, and mussels) (Meléndez-Martínez 2019). Some are approved as food colorants and can also be obtained from supplements (Meléndez-Martínez et al. 2018, Mortensen 2009). **Table 1** summarizes some common rich fruit, vegetable, and aromatic plant sources of the main carotenoids found in humans (Meléndez-Martínez 2019). Mean values or intervals of mean values are presented only for the sources for which the processing and sample preparation (saponification performed or not) were clearly indicated.

Britton & Khachik (2009) suggested a criterion for the categorization of carotenoid content in a particular food so that the level of a specific carotenoid can be classified into four different concentration groups: low (0–0.1 mg/100 g), moderate (0.1–0.5 mg/100 g), high (0.5–2 mg/100 g), and very high (>2 mg/100 g). Another key aspect for the rational design of health-promoting carotenoid-containing products is to consider normal daily dietary intakes, which are usually below 4 mg/day, whereas those of β-carotene and lycopene can be considerably higher (values of 8.80 and 9.43 mg/day, respectively, have been reported). Important regional and temporal differences have been reported both within and across countries (Meléndez-Martínez 2019, Rodriguez-Concepcion et al. 2018).

LOCATION AND DEPOSITION FORMS OF CAROTENOIDS IN FOODS

In plants, carotenoids are contained in subcellular structures collectively named plastids, such that both the cell walls and membranes of these structures need to be disrupted for efficient carotenoid release. Carotenoids in chloroplasts form part of pigment–protein complexes. Chromoplasts can be found in diverse plant structures and display different colors and morphologies. Regarding crystalline chromoplasts, their formation is dependent on the carotenoid accumulated. Examples are the β-carotene- and lycopene-rich chromoplasts of orange carrot roots and red tomato fruits, respectively (Howitt & Pogson 2006, Schweiggert & Carle 2017).

Concerning animal foods, egg yolk carotenoids are thought to be found largely in a lipid-dissolved state and to a much lesser extent weakly associated with membrane lipoproteins. Carotenoids of milk are mostly dissolved in lipids in the core of fat globules, although some can be associated with the monolayer of polar lipids. **[**AU: AR house style requires that "on the other hand" be preceded by "on one hand."**]**Carotenoids in salmonid muscle tissue are thought to be bound to the the myofibrillar protein α-actinin (Schweiggert & Carle 2017).

The importance of the study of the location (e.g., muscle, fat, fruit, root), deposition form (e.g., crystals or fat globules), and associations (e.g., with proteins or lipoproteins) of carotenoids in foods is very important, as such factors influence the efficiency of carotenoid release during digestion and therefore their bioavailability (Schweiggert & Carle 2017).

CONSIDERATIONS REGARDING BIOAVAILABILITY

Bioavailability can be defined as the fraction of an ingested compound that is absorbed into the circulation system, available for use in normal physiological functions or for storage and dependent on food and host-related factors. One key related concept is bioaccessibility, defined as the amount of the compound released from the matrix during digestion and potentially available for further uptake and absorption. Concerning carotenoids, bioaccessibility usually refers to the fraction of ingested carotenoid that is incorporated into micelles. Another concept, bioaccesible content is being currently proposed to designate the actual quantity of carotenoid that is potentially absorbable per , weight/volume, or typical food serving (Bohn et al. 2015, Mapelli-Brahm et al. 2018, Rodriguez-Concepcion et al. 2018).

Bioavailable Carotenoids and Presence in Fluids and Tissues

The major plasma carotenoids are lutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, lycopene, phytoene, and phytofluene, although others such as ζ-carotene have also been detected (Meléndez-Martínez et al. 2017)**[**AU: Reviewer Comment: Reference?**]**. Carotenoids (in some cases, even different geometrical isomers) have also been detected in milk and semen as well as in adipose and mammary tissue and the skin, prostate, brain, lung, cervix, colon, liver, and adrenals, among other tissues. Apocarotenoids and other oxidized derivatives of some carotenoids have been detected in plasma and the eye. Neither epoxides of xanthophylls nor xanthophyll esters are normally found at detectable levels in human plasma and tissues. The factors related to the bioavailability of carotenoids are varied and dependent on the carotenoids (polarity, isomeric form, esterification, quantity ingested), characteristics of the matrix (type, formulation, processing), other dietary components (e.g., fat, fiber, vitamin E, minerals, phytosterols), and the individual (vitamin A status, sex, age, diseases and infections, alcohol intake, smoking, genetic differences) (Meléndez-Martínez et al. 2017).

Effect of Food Processing and Cooking on Bioavailability

The bioavailability of carotenoids can be modulated through processes such as mechanical disintegration, enzymatic maceration of matrix compounds, the addition of lipids, and thermal treatments (**Supplemental Table 1**). However, these processes have a variable impact on carotenoid. Thus, cooking and industrial processing may improve carotenoid release and solubility during digestion but also favour their degradation**[**AU: As written, "…processing may improve carotenoid release and solubility during…their degradation." OK?**]**. Thermal treatments and mechanical forces (e.g., those used for powdering) can lead to a total decrease of carotenoids but an important increase in the release of carotenoids due to damages in the cells and the plastids. Whether the net result (decrease of total carotenoid content versus increase in release) leads to enhanced bioavailability depends on the conditions used (Kaulmann et al. 2014, Mapelli-Brahm et al. 2018a). Furthermore, cooking by incorporating lipids can facilitate the absorption of carotenoids, with likely differences depending on the nature of the predominant fatty acids.**[**AU: These are "greater than" symbols. Should they be replaced with arrows?**]** Uptake and basolateral secretion of the carotenoid tested (lutein and β-carotene) were higher in cells pre-treated with unsaturated fatty acid–rich matrices compared to the saturated fatty acid counterparts, and the effects were mediated by increased assembly and secretion of chylomicrons. The results show that perhaps fats/oils rich in unsaturated fatty acids promote the bioavailability of those carotenoids by favoring their micellarization and intestinal transport (Failla et al. 2014).

Nonthermal technologies can satisfy the increased demand of consumers for quality products that do not compromise nutritional and sensorial features (Rodríguez-Roque et al. 2016). As an alternative to conventional food processing technologies, innovative technologies such as high hydrostatic pressure, pulsed electric fields, and ultrasound have been reported to degrade carotenoids in foods to a lesser extent than thermal treatments. For example, the use of high pressure (HP) processing has been reported to increase carotenoid bioaccessibility because of the disruption of the cell structure present in tomato chromoplasts and cell clusters (Bot et al. 2018, Palermo et al. 2013).

HEALTH-PROMOTING BIOLOGICAL ACTIONS OF CAROTENOIDS: MECHANISMS FOR AND CONTRIBUTIONS TO REDUCED RISK OF DISEASES [**AU: AS WRITTEN, THIS READS AS "REDUCED RISK OF HEALTH CLAIMS. OK?**]

Mechanisms

Although the possible health benefits of carotenoids are still usually attributed to direct antioxidant mechanisms (quenching, scavenging), which are very difficult to demonstrate in vivo, there may be other mechanisms that create these health benefits. For instance, prooxidant mechanisms, enhancement of gap junctional intercellular communication, modulation of signaling pathways or immune function, and absorption of visible light (or UV in the case of the colorless carotenoids phytoene and phytofluene), and all these may interact. As a result, different effects can take place (e.g., antioxidative, prooxidative, or anti-inflammatory). The biological actions of carotenoids may be due to some extent to apocarotenoids and other carotenoid derivatives, which can be present at low levels in foods and formed in the body. Mention apart deserve the role of some carotenoids as precursors of retinoids exhibiting vitamin A activity (retinol, retinal, and retinoic acid). More detailed information about biological actions, mechanistic and structural aspects can be found in recent reviews (Eggersdorfer & Wyss 2018, Meléndez-Martínez 2019, Meléndez-Martínez et al. 2019, Rodriguez-Concepcion et al. 2018).

Contribution to Reduced Risk of Diseases

Beyond the role of some carotenoids as vitamin A precursors, during the past four decades ample evidence suggests that carotenoids and their derivatives could be involved in health-promoting biological actions and contributing to reduce the risk of noncommunicable diseases, including several types of cancers (prostate, breast, cervical, ovarian, colorectal, gastric, oral, laryngeal), cardiovascular diseases (atherosclerosis, coronary disease), and bone, skin, or eye disorders. Research in the past few years is eliciting interest in the posible beneficial role of carotenoids in cognitive performance, Parkinson’s disease, respiratory conditions, betes mellitus, obesity, and other related metabolic disorders as well as during pregnancy and early life (Böhm 2012, Britton & Khachik 2009, Ciccone et al. 2013, Eggersdorfer & Wyss 2018, Harari et al. 2019, Johnson 2014, Meléndez-Martínez 2019, Rodriguez-Concepcion et al. 2018, Visioli & Artaria 2017).

FUNCTIONAL FOODS, NUTRACEUTICALS, NUTRICOSMETICS, SUPPLEMENTS, BOTANICALS, AND NOVEL FOODS

Given their versatility, carotenoids can be used in many products intended for human consumption, which are dealt with in brief below.

Concept

According to concerted action from Functional Food Science in Europe (FUFOSE) project, a food can be considered functional if it demonstrates that beneficial influence on one or more target functions of the body, beyond its pure value nutritional, in a way that is relevant to the improvement health and well-being and/or to reduce the risk of disease. It must also remain a food (i.e., not a pill, capsule, or supplement) and demonstrate its effect in quantities that are consumed within a normal food pattern. Different types of functional foods have been identified, including unmodified foods and others subjected to different treatments (Howlett 2008).

Nutrition and Health Claims

The term nutrition claim refers to any claim that states, suggests, or implies that a food has particular beneficial nutritional properties. Nutritional claims related to provitamin A carotenoids are “source of vitamin A” (i.e., used in products with a significant amount of vitamin as defined in the relevant legislation) and “high vitamin A” (i.e., used in products that contain at least twice the value of products defined as a “source of vitamin A”).

The term health claim refers to any claim that states, suggests, or implies that a relationship exists between a food category, a food, or one of its constituents and health. For vitamin A, the Commission Regulation (EU) No 432/2012 adopted six functional health claims related to its contribution to normal iron metabolism, maintenance of normal mucus membranes, skin, vision, and immune system as well as its role in the process of cell specialization.

To date there are not approved health claims for carotenoids in the European Union (EU), which does not mean that carotenoids do not provide health benefits but rather that they have not been categorically demonstrated in humans. Their properties, wide distribution in foods, constant intake, presence in fluids and tissues of humans, and the conclusions of many studies suggest that carotenoids are important health-promoting compounds. The compelling demonstration of this assumption is daunting because of the complexity of human physiology and diets (which contain thousands of other bioactives), influence of genetic and ambient factors, and limitations of the different types of studies. Becuse high levels of dietary carotenoids are usually provided by healthy dietary patterns, such as high intake of fruits and vegetables, which also contain many other bioactives, it seems reasonable to argue that carotenoids are among a group of compounds that can promote health (Britton et al. 2008, Krinsky & Johnson 2005, Meléndez-Martínez 2019, Wood et al. 2014).

Compared to other compounds (such as cocoa flavonoids or olive oil polyphenols) for which health claims are approved, a major drawback for the categorical demonstration of health benefits for carotenoids is that they are widespread in foods and ingested on a daily basis. It is noteworthy that humans have always fed on fruits and vegetables containing carotenoids, and they are already provided to newborns through the mother's milk (Sommerburg et al. 2000). Also, it appears that the skin can act as a peripheral buffer that helps maintain plasma carotenoid levels (Meléndez-Martínez et al. 2019). These facts add more difficulty to intervention studies aimed at demonstrating health benefits derived from their intake, as it is very difficult to deplete carotenoids.

Nutraceuticals

Nutraceuticals do not have a clear legal framework. DeFelice (1995) **[**AU: Please provide page number of quote**]**defined them as "any substance that is a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease. Such products may range from isolated nutrients, dietary supplements and specific diets to genetically engineered designer foods, herbal products, and processed foods such as cereals, soups and beverages" (p.59) **[**AU: As almost all of this paragraph is a quote from DeFelice, it's unclear why Santini is cited here**]**.

Nutricosmetics

Nutricosmetics and related terms (e.g., beauty pills, beauty foods, and oral cosmetics) refer to products for oral consumption that contain food components and are intended to provide cosmetic benefits (Meléndez-Martínez et al. 2019).

Supplements

Dietary supplements include macronutrients, vitamins, and minerals that are essential to human health as well as a wide variety of nonessential nutrients, such as certain phytochemicals, hormones, and herbs (Norman et al. 2003). They have a specific legislation in the EU. According to Directive of the European Parliament and of the Council (2002) no. 2002/46/EC, they are foodstuffs aimed at supplementing the normal diet and are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in diverse dosage forms (capsules, pastilles, tablets, pills, sachets of powder, ampoules of liquids, drop dispensing bottles, etc.) designed to be taken in measured small unit quantities. Directive 2002/46/EC deals with vitamins and minerals, in the forms listed, which may be used for the manufacture of food supplements as well as with labeling. Regarding vitamin A, only retinol, retinyl acetate, retinyl palmitate, or β-carotene can be used for s supplements **[**AU: What does “their” refer to? As written, seems to refer back to Vitamin A and thus should be “its”**]** manufacture.

Carotenoids are taken in supplements to either increase their intake or obtain specific compounds that are not usually found in the diet, such as *meso*-zeaxanthin (Bernstein et al. 2014, Phelan et al. 2017). Carotenoids in supplements are used to promote health or for cosmetic purposes (Meléndez-Martínez et al. 2018).

Botanicals and Related Products

The definition of botanical also lacks consensus. It normally refers to plants or parts of plants that are used for their medicinal properties, flavor, or scent. Other related terms such as phytomedicines and herbal and botanical products refer to products obtained from botanicals aimed at maintaining or enhancing health, whereas botanical drug products usually refer to products used as drugs and containing plant, algae, or fungi materials or combinations of them (Koch et al. 2014).

Botanicals are widely available in the form of food supplements and usually labeled as natural foods that provide diverse health benefits. Although many have a long tradition of safe use, in some cases there are concerns about their safety and quality, hence the need to establish appropriate frameworks for their evaluation (Galli et al. 2019).

Novel Foods

The term novel food is defined by Regulation (EU) of the European Parliament and of the Council (2015) as any food that was not used for human consumption to a significant degree within the EU before May 15, 1997, and falls under at least one of the categories listed in the Regulation (e.g., food consisting of or isolated from microorganisms, fungi, or algae, food consisting of engineered nanomaterials, etc.).

Examples of novel foods are lycopene from *Blakeslea trispora* (Commission Decision, 2009b) and synthetic lycopene produced by Wittig condensation (Commission Decision, 2009). Another example is lycopene oleoresin obtained by solvent extraction of ripe tomatoes (Commission Decision, 2009a). Synthetic zeaxanthin was approved as novel food ingredient in food supplements in 2013 (Commission Implementing Decision, 2013), and the deletion of the term synthetic from the novel food has been recently approved [Commission Implementing

Regulation (EU), 2018].

CONSIDERATIONS ABOUT THE FORMULATION OF CAROTENOIDS

Carotenoids are easily oxidized, above all when extracted from their natural locations in cells, hence the need for developing efficient formulations to increase their stability and dispersion in water and/or modulate their bioavailability when used as ingredients of designed products (Boon et al. 2010, Mun et al. 2015). The topic of carotenoid formulation deserved much attention, as commercially available carotenoid-containing products may actually contain very low bioavailable carotenoid contents due to improper formulation and storage, as recently pointed out in tablets especially (Hynstova et al. 2018). Within this context, the principle of delivery by design as a rational approximation to produce systems that can be commercially viable has been recently reviewed (McClements 2018).

Carotenoid Inclusion Complexes

Several studies on carotenoid inclusion complexation have been carried out using cyclodextrins**[**AU: Reviewer Comment: is cyclodextrin a food ingredient? Or food processing aid?**]** (CDs) as a host molecule (**Table 2**). CDs have a high level of biocompatibility and are generally recognized as safe (GRAS) for several food uses. Some chemically modified CDs such as the hydroxypropyl derivatives are approved as drug excipients but not for food application (Fenyvesi et al. 2016, Yuan et al. 2012). Recently, an effective encapsulation technology based on an amylose inclusion complex with an amphiphilic compound was proposed and used for the incorporation of β-carotene (Kong et al. 2018). The encapsulation of β-carotene within apoferritin nanocages improved its thermal stability and solubility in water (Chen et al. 2014).

Other Encapsulation Systems

Nanodispersions (Anarjan & Tan 2013, Anarjan et al. 2014, Shariffa et al. 2017) and nanoparticles based on chitosan/alginate (Rahaiee et al. 2015), chitosan/poly-γ-glutamic acid (Lee & Lee 2016), chitosan/casein (Koo et al. 2016), and zein (Chuacharoen & Sabliov 2016) have also been explored for carotenoid formulation. Alginate-based beads for the encapsulation of β-carotene (Zhang et al. 2016) and lycopene (Aguirre Calvo & Santagapita 2017) have also been produced.

Emulsions

Emulsion-based systems, i.e., oil-in-water, conventional, and nano/microemulsions, are widely investigated systems for carotenoid encapsulation. Emulsion systems intended for the delivery of carotenoids must be carefully designed so the particle size of the emulsion favors bioavailability and does not lead to important carotenoid losses. A higher specific surface area of an active ingredient generally leads to a higher dissolution rate and, as a consequence, to higher bioavailability. However, the stability of β-carotene in the nanodispersions decreases with a decrease in the mean particle diameter (in the range of 60 to 130 nm). This effect was attributed to both the wider contact surface between β-carotene particles and the aqueous environment and the more intense generation of free radicals during the homogenization process (Tan & Nakajima 2005). Therefore, the physical and chemical stability of emulsions to environmental temperature, pH, and ionic strength should be optimized by varying the formulation ingredients (Luo et al. 2017; Mao et al. 2009, 2010).

Table 3 summarizes materials and methods used for the preparation of carotenoid-enriched emulsions. Guan et al. (2016) showed that eugenol improved the stability of droplet dimension during storage and reduced the degradation of β-carotene caused by temperature and UV radiation. The composition and structure of the interfacial layer coating the lipid droplets also influence the properties of emulsions (Mao et al. 2013). To satisfy consumer demand for clean labels, there is a tendency to use natural food-grade emulsifiers such as proteins, polysaccharides, phospholipids, and saponins (Ozturk & McClements 2016). In emulsions designed to stabilize β-carotene, sodium caseinate showed a better protection efficacy compared to whey protein isolate. Although whey protein isolate forms a multilayer at the oil/water **[**AU: Define at first use**]** interface, sodium caseinate has a higher thickness. Moreover, their different amino acid compositions can result in a different scavenging effect and stability (Cornacchia & Roos 2011).

To preserve the biological activity of β-carotene, organogel-based nanoemulsions (Fan et al. 2017) and emulsion gels were proposed. Emulsion gels were formed via ionotropic gelation of oil-in-water emulsion using sodium alginate (Soukoulis et al. 2016) or κ-carrageenan (Soukoulis et al. 2017) as gelling agents.

Dried emulsions.

Emulsion-based delivery system can be dried, usually by spray-drying, to extend their shelf life and facilitate their use. Drying parameters, carrier materials, and scaling-up conditions have been recently summarized in detail (Janiszewska-Turak 2017). A drawback to spray-drying is that the high temperatures can degrade carotenoids. Thus, related techniques such as emulsion electrospraying are emerging, and β-carotene and lycopene have been encapsulated within protein matrices by this technique (Gómez-Mascaraque et al. 2017, López-Rubio & Lagaron 2012).

Dehydrated emulsions are solid materials in an amorphous state, as they lack molecular order in the structure. Hence, they exhibit a change between a very viscous solid-like glassy state and a liquid-like rubbery state over the glass transition temperature (T_g). Carotenoids are more stable when the matrix is in the rubbery state, as observed for β-carotene (Prado et al. 2006) and lycopene (Lavelli et al. 2013). It has been hypothesized that the glassy systems are more porous then rubbery systems and allow easier diffusion of oxygen (Harnkarnsujarit et al. 2012). Harnkarnsujarit et al. (2012) studied the microstructural formations of maltodextrin and sugar matrices in freeze-drying and demonstrated that the presence of sugars (glucose, fructose, and sucrose) results in smaller pore sizes in the freeze-dried solids. As sugars cause a decrease in freezing temperature, melting of ice crystals can occur during freeze-drying; this leads to structural collapse and causes the formation of small pores in the dried matrices. As for the liquid matrices, the composition of the interface in dried emulsions is relevant for carotenoid stability. Lim et al. (2016) found that layer-by-layer spray-dried emulsions made with trehalose (18%), whey protein isolate (9%), and arabic gum (0.27%) were more efficient than single-layer emulsions not containing gum arabic to stabilize lutein and all-*trans*-β-carotene upon storage. Alternatively, Chiu et al. (2007) achieved lycopene stabilization by using an emulsion system consisting of 4.5% gelatin and 10% poly-γ-glutamic acid.

Nano/microemulsions.

Solid lipid nanoparticles (SLNPs) and nanostructured lipid carriers (NLCs) have also been developed for carotenoid delivery and fortification. In SLNPs, the oil is fully crystallized and has a highly ordered crystalline structure. NLCs are modified SLNPs in which the lipid phase consists of a mixture of solid and liquid lipids. NLCs have a less-ordered crystalline structure (Müller et al. 2002). β-Carotene-loaded SLNPs were produced using tripalmitin as a lipid carrier and different water-soluble surfactants (Helgason et al. 2009). However, SLNP aggregation and carotenoid exclusion from the solid matrix to the surface of the SLNPs limited their application

(Qian et al. 2013). For the production of β-carotene-loaded SLNPs, a combination of palmitic acid and corn oil was used, and the probability of carotenoid exclusion was decreased. To improve the colloidal stability of SLNPs, wheat protein isolate was chosen instead of synthetic surfactants such as Tweens (Mehrad et al. 2018). The potential of NLCs as carriers for lutein was demonstrated (Lacatusu et al. 2013, Liu & Wu 2010). Formulating of astaxanthin in NLCs revealed that solid lipid type has a major effect on the physical stability of NLCs, and a mixture of glyceryl behenate and oleic acid was found to be the most appropriate choice (Tamjidi et al. 2014).

Liposomes

Liposomes encapsulating β-carotene (Moraes et al. 2013, Tan et al. 2014), lutein (Tan et al. 2013), astaxanthin (Peng et al. 2010), and lycopene (Tan et al. 2014a) were produced. For carotenoid-loaded liposome preparation, egg yolk phosphatidylcholine (EYPC) is commonly used. However, liposomes composed of mixed lipids (EYPC and Tween 80) exhibited higher rigidity strength and steric stability (Tan et al. 2014a). The interaction of carotenoids with the lipid bilayer, the effect of carotenoid chemical structure on the physical properties of liposomal membranes, and the influence of liposome encapsulation on the antioxidant activity of carotenoid were investigated (Tan et al. 2014, Xia et al. 2015).

Toniazzo et al. (2014) showed that liposome dispersions can be stabilized by the addition of a mixture of xanthan and guar gums as thickeners. The modification of the liposomal membrane surface by biopolymer coating is another stabilization approach. Tan et al. (2016) developed chitosan-coated liposomes (chitosomes) as carriers for carotenoids.

SAFETY OF CAROTENOIDS

[AU: Reviewer Comment: Need a subtitle for high-doses section**]**

Beyond the rare exception due to continued excessive intake of carotenoids commented bellow, normal intake of these compounds is considered safe. The safety evaluation of some carotenoids has been performed by organizations such as the European Food Safety Authority (EFSA) and the Joint Food and Agriculture Organization of the United Nations (FAO)/ World Health Organization (WHO) Expert Committee on Food Additives (JECFA).

As can be observed in **Table 4**, the acceptable daily intakes (ADIs) of carotenoids are much higher than the normal intakes achieved by dietary means tabulated elsewhere (Rodriguez-Concepcion et al. 2018). For instance, the ADI of lutein from *Tagetes erecta* used as an additive is 1 mg/kg body weight/day (that is, 70 mg for a person weighing 70 kg) and the ADI of zeaxanthin from the same source is 0.75 mg/kg body weight/day, whereas the daily intakes of lutein + zeaxanthin reported in several studies oscillate between 0.83 and 4.11 mg (Rodriguez-Concepcion et al. 2018). Furthermore, there are several products rich in carotenoids (including α- and β-carotene, lutein, zeaxanthin, lycopene, phytoene, and phytofluene) that are considered GRASby the US Food and Drug Administration (FDA) (Meléndez-Martínez 2019). Detailed information of toxicological studies involving carotenoids can be found in a recent revision (Vargas-Murga 2017).

Safety of high doses of carotenoids over long periods

Two studies, the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study and the β-Carotene and Retinol Efficacy Trial (CARET), raised awareness about the possible negative effects of daily supplementation of β-carotene at high doses (20 mg and 30 mg/day, respectively) as it may increase the risk of developing lung cancer in individuals highly susceptible to develop such malignancy (smokers, ex-smokers, and workers exposed to asbestos) (Eggersdorfer & Wyss 2018, Meléndez-Martínez 2019). These results contrasted with those of studies involving nonsmokers receiving supplemental β-carotene, namely the Physicians' Health Study (supplementation with 50 mg β-carotene every other day) or the Chinese Linxian intervention trial (receiving 15 mg β-carotene/day), where not only was an adverse effect not observed but associations with beneficial effects were observed (Eggersdorfer & Wyss 2018, Meléndez-Martínez 2019). Currently, it is accepted that β-carotene is usually associated with beneficial effects, and the detrimental effects observed in the CARET and ATBC trials could be attributed to the excessive pharmacological doses of highly bioavailable β-carotene supplements and the oxidant-rich and antioxidant-poor environment of smoker's lungs, which favor the formation of high levels of β-carotene oxidative derivatives (Veeramachaneni & Wang 2009).

Two nonsevere conditions associated to excessive intake of carotenoids are carotenodermia and canthaxanthin retinopathy, which disappear upon cessation of the excessive consumption. Carotenodermia (xanthosis, xanthoderma, or pseudoicterus) is a benign and reversible yellowish-orange coloration of the skin associated with high blood carotenoid levels (N300 µg carotenoids/dL) and features elevated carotenoid levels mainly in the stratum corneum, sweat, and sebum (Granado-Lorencio et al. 2017, Meléndez-Martínez et al. 2019)

The excessive use of high doses of canthaxanthin over time (from 30 mg/day) could lead to the formation of crystals of this carotenoid in the eye, which disappear when the intake of canthaxanthin was discontinued. Canthaxanthin retinopathy can occur in subjects taking tanning pills, which may lead to longstanding visual changes, including significant visual loss. Symptomatic visual loss correlates with total dosage and possibly patient age. Referring to the authors, even with profound visual loss, prognosis for improvement is very good with recognition and discontinuation of the drug (Beaulieu et al. 2013, Meléndez-Martínez et al. 2019).Drug Interactions Involving Carotenoids[AU: If using subheadings in a section, there need to be at least two, per house style. Please either add another subheading to the section or remove this one here.**]**

Many interactions are related to processes related to absorption such as micellarization or uptake by the enterocyte. Thus, the bioavailability of carotenoids is known to be affected by typical dietary components (fiber, fat, minerals, phytosterols) that can also be found in the diverse types of products dealt with in this work (see the section titled Functional Foods, Nutraceuticals, Nutricosmetics, Supplements, Botanicals, And Novel Foods), which should be taken into account for their rational design (Cervantes-Paz et al. 2017, Corte-Real & Bohn 2018, Mapelli-Brahm et al. 2018, Meléndez-Martínez et al. 2017).

The absorption of lycopene may be decreased by statins, cholesterol-lowering drugs (Selvan et al. 2011). β-Carotene supplements can interact with certain drugs, including statins, orlistat (a drug for weight control), and mineral oils (used to treat constipation). The effectiveness of simvastatin and niacin may be decreased if the patient is taking β-carotene with selenium and vitamins E and C. Cholestyramine, used to lower cholesterol, can reduce blood levels of dietary β-carotene by 30–40%. Colestipol, a drug similar to cholestyramine, may also reduce β-carotene levels. Orlistat can reduce the absorption of β-carotene by up to 30%. Mineral oil may lower blood concentrations of β-carotene, and ongoing use of alcohol may interact with β-carotene, increasing the likelihood of liver damage (Nordqvist 2017).

CHALLENGES IN THE PRESENT AND FUTURE OF CAROTENOID RESEARCH

There is an urgent global need to transform production systems to produce enough food for all mankind in a sustainable manner while contributing to the reduction of diseases related to nutrition. A circular economy, in which resources are re-used to contribute to sustainability, is becoming a priority in the political agenda. Apart from the pressure that the population growth rate is putting on a planet with finite respurces, climate change is another key phenomenom that needs to be tackled, as it also has an impact on the agro-food sector production. Sustainability has become a priority, especially in food production, which has an important negative impact in the environment (Willett et al. 2019). Research on carotenoids is very important **[**AU: As written, research on carotenoids is critical to contribute to these challenges. Please revise.**]** to tackle these challenges.

Sustainability, a Circular Economy, and Climate Change

"Sustainable development meets the needs of the present without compromising the ability of future generations to meet their own needs" (U.N. World Comm. Environ. Dev. 1987, p. 24)**[**AU: Please provide page number of quote**]**. Specifically, there is an urgent need to optimize the usage of water and reduce the levels of greenhouse gases, as these are contributing to the climate change, which in turn poses risks for food security (Vermeulen et al. 2012). The new EU strategy, the European Green Deal, emphasizes the need for immediate action to make Europe a climate-neutral region by 2050. This will be achieved by reducing pollution and supporting clean innovative products and technologies (European Commission, 2019)**[**AU: Is this a citation? If so, it is not in the Literature Cited**]**). The classical linear economy model, based on the take-make-consume-and-dispose model, needs to be replaced with a circular economy model that keeps the added value in products for as long as possible and eliminates waste.

Sustainability has become a priority, hence the increasing need of conducting life-cycle assessments (LCAs) to evaluate the impact (Djekic et al. 2019). It is expected that in the near future, obtaining certifications to highlight the environmentally friendly and socially conscious practices of the agro-food industry will become commonplace.

Sustainable diets are "diets with low environmental impacts which contribute to food and nutrition security and to healthy life for present and future generations. Sustainable diets are protective and respectful of biodiversity and ecosystems, culturally acceptable, accessible, economically fair and affordable; nutritionally adequate, safe and healthy; while optimizing natural and human resources." (Burlingame & Dernini 2012, p. 7**[**AU: Please provide page number of quote**]**). Among the United Nation's 17 Goals to Transform Our World included in the 2030 Agenda for Sustainable Development, several are related to food production systems. Among the main challenges that need to be tackled are to end hunger (Goal 2**[**AU: ?**]**), poor health (Goal 3**[**AU: ?**]**), and environmental degradation (Goals 13, 14, 15**[**AU: ?**]**) (U.N. 2019). According to the recent report of the EAT**[**AU: Define at first use**]**–Lancet Commission, food production is the largest cause of human-made pressure on Earth systems. For example, 40% of global land is occupied by agriculture, up to 30% of global greenhouse gas emissions, and 70% of freshwater use are related to food productions system. Paradoxically, 820 million people have insufficient food while a larger number consume unhealthy diets that contribute to the risk of developing diseases and premature death. The prevalent unhealthy diets along with the growing world population (it is estimated that the global population will be 10 billion by 2050) exacerbate risks to people and planet (Willett et al. 2019). It is estimated that approximately 80% of chronic disease and premature death could be prevented by healthy patterns such as not smoking, being physically active, and following healthy diets (Katz et al. 2018).

Within this demanding scenario, the future production of carotenoid-containing products needs to contemplate sustainability, circularity, and environmental respect as priorities. In recent years, works of different nature aligned with these requirements have appeared, such that the future of carotenoid production can be seen with optimism.

Research on Carotenoids in the New Agro-Food Scenario

Recent research on carotenoids toward tackling challenges related to sustainability, a circular economy, and climate change are summarized below.

Sustainable sources.

Important advances have been made in the bioprospection of endemic vegetable species for rich sources of carotenoids, above all in Latin America. As just an example of the sustainable application of genetic engineering in agriculture, the innovative production of ketocarotenoids in tomato plants by the genetic crossing of two tomato lines, one of which overexpressed bacterial carotenogenic genes, has been recently described (Nogueira et al. 2017). However, algae and microbes are highlighted in the EAT–Lancet Commission report as matrices that can be further harnessed to produce innovations in the context of healthy diets from sustainable food systems (Willett et al. 2019). Microalgae has received much interest as a biofuel feedstock in response to the uprising energy crisis, climate change, and the depletion of natural sources. Concomitantly, high-value coproducts, including carotenoids, have been produced by biorefinery, the process of obtaining biofuels, energy, and diverse high value products through biomass transformation and process equipment (Sosa-Hernández et al. 2019). The advantages of using microalgae biomass as a feedstock compared to higher plants are several: higher growth and productivities due to their all-year production capability; growth under stress conditions and lower nutritional and water requirements; no requirements of herbicides or pesticides; contribution to CO_2 sequestration and wastewater bioremediation; and easier modulation of the biosynthesis of valuable coproducts by modifying growth conditions (Caporgno & Mathys 2018). Bacteria share their biotechnological and sustainability advantages with microalgae. Indeed, they are important for alleviation of the greenhouse effect, as they can also assimilate CO_2 (Mohan et al. 2016), and for the production of typical food/feed carotenoids, including canthaxanthin, astaxanthin, lycopene, and zeaxanthin (Dufossé 2006, Galasso et al. 2017, Wang et al. 2012).

The ability of both microalgae and bacteria to grow using diverse products **[**AU: for growing what? Please revise**]** (ranging from organic wastes to flue gases) makes them very attractive in the context of waste management and a circular economy (Gupta & Goel 2019, Rodríguez López et al. 2019, Sarsaiya et al. 2019, Tao et al. 2020).

Sustainable cultivation practices.

In the current scenario of climate change and drought, the harnessing of saline water and the reduction of irrigation are especially important for the production of foods. Controlled salinity stress has been shown to lead to a two- to threefold increase in the lycopene content of some tomato genotypes (Borghesi et al. 2011) and has also proved useful in increasing the carotenoid levels in photosynthetic bacteria (Wang et al. 2017). Interestingly, some studies indicate that regulated deficit irrigation can be successfully used in certain tomato varieties without significantly reducing their commercial quality or carotenoid levels; indeed, some increases of the latter were reported (Coyago-Cruz et al. 2017, 2018).

Sustainable processing.

Currently, there is a trend in the implementation of cost-reducing and environmentally friendly processing technologies, such as nonthermal food preservation methodologies (e.g., HP processing or pulsed electric fields) (Toepfl et al. 2006). The use of HPs in carotenoid-containing products deserves further study. HP has been long known to increase the extractability of carotenoids and lead to higher retentions compared to thermal treatments (Sánchez-Moreno et al. 2003, 2005) and could be therefore harnessed to increase their bioavailability, as recently shown in citrus juices (Sentandreu et al. 2020). HP **[**AU: What does "they" refer to?**]** can be potentially modulated to optimize carotenoid retention as well as microbial and enzyme inactivation, according to the results of a recent study on carrot juices (Stinco et al. 2019).

Concerning sustainable extraction techniques such as microwave, ultrasound, HP, high voltage, pulsed electric fields, supercritical fluids, and others are aligned with the green concept, as they can be harnessed to reduce energy and solvent expenditures (Putnik et al. 2018). Carotenoids are more difficult to extract compared to other compounds due to their instability, lipophilicity, and accumulation in plastids. Ultrasound-assisted extraction (UAE) can increase their extraction yield and reduce time and the consumption of solvents due to the mechanical effect caused by cavitation. This improves the penetration of the solvent into the matrix and the release of cellular components. Thus, UAE has been recently used to optimize the extraction of carotenoids from diverse sources (microalgae, crustaceans, fruits, vegetables, food by-products, and waste) (Benmeziane et al. 2018, Campoli et al. 2018, Goula et al. 2017, Ordóñez-Santos et al. 2015, Saini & Keum 2018)

The use of innovative green solvents for the efficient and sustainable use of carotenoids, such as ionic liquids (ILs) or natural deep eutectic solvents (NDESs) is also an expanding research field. NDESs are a system composed of at least two natural components that interact to form a mixture that usually has a melting point of 100°C or below. NDESs are inexpensive, easily prepared, exhibit low vapor pressure, and can dissolve a wide variety of compounds. They are highly biodegradable and their toxicity is low or they are not toxic.. **[**AU: As written, NDESs have an interest in green chemistry. Please revise**]** NDESs have been recently used to extract carotenoids from apricots and shrimp wastes (Koutsoukos et al. 2019). ILs are thought to be useful in green extractions and circular economy because of their possible increased extraction efficiency, biocompatibility, and recyclability. They have been successfully applied in the extraction of carotenoids from *Bactris gasipaes* fruits, and a reduction of the carbon footprint by 50% compared to a conventional extraction with acetone has been reported (De Souza Mesquita et al. 2019).

CONCLUSIONS

Carotenoids are versatile isoprenoids of great importance for the sustainable provision of healthy foods in alignment with the current sustainability challenges. They are consistently present in our diets, fluids, and tissues from the time we are breastfed and even beyond the role of some of them as precursors of vitamin A, they are attracting much attention as possible health-promoting compounds. Their importance in public health to combat vitamin A deficiency is undeniable, although evidence is accumulating that they can contribute to reducing the risk of developing several types of cancers, cardiovascular diseases, and bone, skin, and eye conditions as well as neurological and metabolic disorders. In this regard, the need to establish RDIs/nutritional reference values is advocated. However, the outright demonstration of health benefits of carotenoids, which have always been present in the daily diet of humans (both as species and individuals) is much more challenging compared to other compounds whose intake and presence in humans is not so constant.

The typical individual carotenoid intakes are below 10 mg/day, although, due to their safety, the ADIs established for some of them exceed that amount several-fold. Beyond intakes, their bioavailability needs to be considered when designing products for health promotion, as this depends on diverse factors (including the carotenoid type or deposition form) and can be modified by formulation or industrial or cooking practices. Formulation is especially important for the development of supplements and related products, as it can also improve carotenoid stability.

Given their importance in ensuring food security and health promotion, research in carotenoids needs to be aligned with current sustainability and climatic challenges. In this sense, efforts need to be directed to aspects such as (non-exhaustive list):

the circular exploitation of sustainable sources,

innovation in cultivation practices as well as

methodologies and solvents for the green extraction of carotenoids, and

replacement of thermal technologies with cost-reducing and environmentally friendly nonthermal processing technologies for preservation, e.g., HP processing or pulsed electric fields.

SUMMARY POINTS

1. Carotenoids are natural, versatile isoprenoids essential to ensure food security.
2. Their importance in public health for combatting vitamin A deficiency is undeniable, and evidence is accumulating that they can contribute to reducing the risk of developing several kinds of diseases.
3. They are very important in products intended for health promotion, including functional foods, nutraceuticals, nutricosmetics, supplements, botanicals, and even novel foods.
4. Formulation is especially important in the development of some of these products to optimize the stability and bioavailability of carotenoids.
5. The outright demonstration of health benefits of carotenoids is much more challenging compared to other compounds whose intake and presence in humans is not so constant.
6. The typical individual carotenoid intakes are below 10 mg/day, although due to their safety, the ADIs established for some of them exceed that amount several-fold.
7. Given their importance in agro-food, health research in carotenoids needs to be aligned with current sustainability and climatic challenges.
8. Diverse approaches to obtaining sustainable carotenoid-rich products, including the circular exploitation of resources, innovation in cultivation practices, green extraction, and the implementation of cost-reducing and environmentally friendly emerging processing technologies, are underway.

DISCLOSURE STATEMENT

Antonio J. Meléndez-Martínez is a member of the advisory board of IBR—Israeli Biotechnology Research, Ltd., Yavne, Israel. The authors are not aware of any other affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTIONS STATEMENT

This article was designed, coordinated, revised, and edited by Antonio Meléndez-Martínez, Nora O’Brien, and Anamarija Mandić, who also contributed to the writing of the Introduction and text throughout the manuscript. The sections of the article were written mainly by Adela Pintea (Dietary Sources and Considerations Regarding Intakes); Paula Mapelli Brahm (Location and

Deposition Forms of Carotenoids in Foods); María Pilar Cano, Volker Böhm and Grethe Iren Borge (Considerations Regarding Bioavailability); Liliana Vargas-Murga and Antonio Meléndez-Martínez (Health-Promoting Biological Actions of Carotenoids: Mechanisms for and Contributions to Reduced Risk of Diseases **[**AU: As written, this reads as "Reduced Risk of Health Claims." OK?**]**); Antonio Meléndez-Martínez, Aleksandra Mišan, Jelena Vulić, Martina Fikselová, and Monica Rosa Loizzo (Functional Foods, Nutraceuticals, Nutricosmetics, Supplements, Botanicals, and Novel Foods); Jolanta Sereikaitė, Ruta Gruskiene ,and Vera Lavelli (Considerations about the Formulation of Carotenoids); Liliana Vargas-Murga and Sanja Vlaisavljević (Safety of Carotenoids); Liliana Vargas-Murga (Drug interactions Involving Carotenoids); and Antonio Meléndez-Martínez and Adela Pintea (Carotenoids in the Context of Sustainability, Circular Economy and Climate Change).

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EUROCAROTEN informative videos about the importance of carotenoids.
https://www.youtube.com/channel/UChq4_AE2vUiEArSt4SZQNjw

Free e-book in Spanish about the importance of carotenoids in agro-food and health.
hxttps://idus.us.es/xmlui/handle/11441/68953

International Carotenoid Society, http://www.carotenoidsociety.org/

Table 1 Carotenoids (α-carotene, β-carotene, lutein, zeaxanthin, lycopene, β-cryptoxanthin, phytoene, phytofluene) in fruits, vegetables, and aromatic plants[a] expressed on fresh weight basis.

Name	Scientific name	Processing	SAP Y/N	α-Carotene (µg/100 g)	β-Carotene (µg/100 g)	Lutein (µg/100 g)	Zeaxanthin (µg/100 g)	Lycopene (µg/100 g)	β-Cryptoxanthin (µg/100 g)	Phytoene (µg/100 g)	Phytofluene (µg/100 g)	Other carotenoids (µg/100 g)
Broccoli	*Brassica oleracea* L.	Raw	Y	NA	NA	140	NA	NA	NA	NA	NA	Neoxantin (695–740), violaxantin (455–600)
			N	NA	414–779	1,108–2445^{+}	NA	NA	NA	NA	NA	
		Cooked/fried/boiled	Y	24	1,575–3,300	3,275–9,000^{+}	NA	NA	NA	NA	NA	
			N	NA	450–1,890	1,043–3,460	NA	NA	NA	NA	NA	
Kale	*Brassica oleracea* L.	Raw	N	NA	3,070–9,226	4,440–39,500^{+}	200–300	NA	NA	NA	NA	Neoxantin (490–1,900), violaxantin (280–2,050)
		Cooked/fried	Y	NA	2,240–2,400	2,860–3,500	NA	NA	NA	NA	NA	
			N	NA	6202	15,798^{+}	NA	NA	NA	NA	NA	
Pepper	*Capsicum annuum* L.	Raw	Y	NA	192–5,357	220–1,409	440–9,996	NA	3,559–7,672	NA	NA	α-Cryptoxanthin, capsanthin, capsanthin 5,6-
		Dried	Y	302–598	938–1,527	32.6	130	NA	233–729	NA	NA	
			N	NA	14,500 –	NA	31,000–	NA	11,900 –	NA	NA	

					22,300		40,000		20,600			epoxide, neoxanthin, violaxanthin, antheraxanthin, capsorubin, cucurbitaxanthin A and B, latoxanthin, ζ-carotene, capsolutein, cryptocapsin, cryptoflavin, cycloviolaxanthin, luteoxanthin, mutatoxanthin, mutatoxanthin 1 and 2
		Lyophilized	Y	NA	1,701–73,669	0–14,837	0–165,010	NA	0–95,977	NA	NA	
Pumpkin/ squash	*Curcubita pepo* L., *Cucurbita maxima*, *Cucurbita*	Raw	Y	31–53	22–692	104–8,170	190	NA	3	NA	NA	NA
			N	24–7,003	186–4,226	38–2,125^{+}	NA	NA	NA	NA	NA	
		Cooked	Y	96.7	26–246	118–902	NA	32.3	0–6	NA	NA	
			N	1,130	4,570	NA	NA	NA	NA	NA	NA	

	moschata											
Tomato	*Lycopersicon esculentum* Mill., *Solanum lycopersicum* Mill.	Raw	Y	NA	280	131$^+$	NA	2,410	NA	489–9,130	370	NA
			N	NA	225–1,000	77.1–100	NA	2,300–16,315	NA	NA	NA	
		Juice/puree/paste	N	29	202–1,242	90$^+$–170$^+$	NA	360–29,330	NA	NA	510–17,940	
Watermelon	*Citrullus lamatus*, *Citrullus vulgaris*	Raw	Y	NA	43.7–77.1	39.8	NA	1,600–2,454	62.3	1,150	NA	NA
			N	NA	62.6	35.3	NA	2,489	63.2		NA	NA
Lettuce	*Lactuca sativa* L.	Raw	Y	NA	345	200–2,520$^+$	10–70	24.1	NA	NA	NA	Neoxanthin, lactucaxanthin, violaxanthin
			N	NA	172–3,490	780–2,635$^+$	NA	NA	NA	NA	NA	
Spinach	*Spinacea juncea*, *Spinacia oleraceae* L., *Tetragonia tetragonioides*, *Tetragonia expansa*	Raw	Y	NA	NA	4,370	70	NA	NA	NA	NA	Neoxanthin, violaxanthin
			N	NA	3,825–5,300	4,810–11,938$^+$	331	7,000	NA	NA	NA	
		Cooked	Y	NA	1,301	4,100$^+$	NA	NA	NA	NA	NA	
Carrot	*Daucus*	Raw	Y	3,860	14,020	157$^+$–360	NA	295	NA	NA	NA	NA

	carota L.		N	3,500–10,650	6,150–18,250	510	23	NA	NA	1,769	NA	NA
		Cooked	Y	2,390	8,813	2,970^{+}	NA	171.8	NA	NA	NA	NA
			N	4,109	8,015	358^{+}	NA	NA	NA	NA	NA	NA
Guava	*Psidium guajava* L.	Raw	N	NA	366.3–378.6	7	NA	2,316–6,999.3	NA	NA	NA	NA
Loquat	*Eriobotrya japonica* Lindl.	Raw	Y	NA	80.6–1,492.9	3.9–106	NA	NA	28.3–735.3	32,4–56,7	NA	Neoxanthin, violaxanthin
Mango	*Mangifera indica* L.	Raw	Y	19.4	152–1,510	60	40–80	25.8–27.1	12.4–30	NA	NA	Neoxanthin (30–1,681), violaxanthin (1,500–3,197), auroxanthin
			N	NA	1,557–3,558	NA	NA	77.2–75.8	11	NA	NA	
Papaya	*Carica papaya* L.	Raw	Y	NA	50–598	NA	NA	1,040–4,460	310–4,097.3	NA	NA	Luteoxanthin, cryptoflavin, cucurbitaxanthin A (1,040)
Sweet potato	*Ipomoea batatas* Lam.	Raw	Y	NA	93,300–143,900 ^{dw}	100–400 ^{dw}	100–200 ^{dw}	NA	NA	NA	NA	β-Carotene-5,6-epoxide (3,800–13,100^{dw})
		Boiled/roaste	Y	NA	74,600	100–1,100	100–400	NA	NA	NA	NA	

		d/steamed			–147,900 ^{dw}	^{dw}	^{dw}					
		Flour	Y	NA	50,100–86,500 ^{dw}	100–300 ^{dw}	100–200 ^{dw}	NA	NA	NA	NA	
Saffron	*Crocus sativus* L.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Crocetin ester (g/kg): 135 *trans*-4-GG 71.8 *trans*-3-Gg 7.2 *cis*-4-GG 4.5 *cis*-3-Gg
Celery	*Apium graveolens* L.	Raw	Y	168	150–16,200	232^{+}–26,400^{+}	NA	NA	226	NA	NA	NA
			N	NA	65–570	163–860	NA	NA	NA	NA	NA	
Coriander	*Coriandrum sativum*	Raw	Y	NA	2,100	3,780^{+}	NA	NA	1,630	NA	NA	Neoxanthin (2,800), violaxanthin (3,800)
			N	7,100	6,600	10,400	NA	NA	NA	NA	NA	
Parsley	*Petroselinum hortense*	Raw	N	NA	7,200	8,700	NA	NA	NA	NA	NA	Neoxanthin (2,500), violaxanthin (5,300)

[a] Data taken from Dias et al. (2018) and Holden et al. (1999).

Abbreviations: +, value includes zeaxanthin; *cis*-3-Gg, *cis*-crocetin(β-D-glucosil)-(β-D-gentiobiosil) ester; *cis*-4-GG, *cis*-crocetin di-(β-D-gentiobiosil) ester; dw, dry-weight basis; N, no; NA, not available; SAP, saponification; *trans*-3-Gg; *trans*-crocetin (β-D-glucosil)-(β-D-gentiobiosil) ester; *trans*-4-GG, *trans*-crocetin di-(β-D-gentiobiosil) ester; Y, yes

Table 2 Carotenoid inclusion complexes with cyclodextrins (CDs)

Carotenoid	**Cyclodextrin**	**Impact on carotenoid properties**	**References**
β-Carotene	β-CD, γ-CD γ-CD	Pink-orange colored, opalescent water solutions Increase in water solubility	Mele et al. 1998 Zaibunnisa et al. 2011
Lycopene	α-CD, β-CD, γ-CD β-CD	Water-soluble complexes Stable complexes at least 6 months	Mele et al. 2002 Blanch et al. 2007
Astaxanthin	β-CD Hydroxypropyl-β-CD	Increase in water solubility (<0.5mg/mL), increase in temperature and light stability Increase in water solubility (> 1.0 mg/mL), enhanced stability against light and oxygen	Chen et al. 2007 Yuan et al. 2008
Bixin	α-CD	Improved water solubility, increased resistance to the damage caused by light and air	Lyng et al. 2005
Red bell pepper pigments	β-CD Hydroxypropyl--β-CD	Enhanced color stability Enhanced solubility in water	Gomes et al. 2014 De Lima Petito et al. 2016

Table 3 Emulsion-based carotenoid delivery systems

Carotenoid	**Carrier**	**Emulsifier**	**Emulsification method**	**References**
Lutein	Medium-chain triglycerides	Tween 80	Spontaneous emulsification	Surh et al. 2017
	Corn oil	Sodium caseinate	High-pressure microfluidization	Davidov-Pardo et al. 2016
β-Carotene	Vegetable oil	Sodium casein	Microfluidization	Chen et al. 2017
	Corn oil	Whey protein isolate, quillaja saponin	High-pressure dual-channel microfluidization	Luo et al. 2017
	Corn oil	Sodium caseinate	Microfluidization	Yi et al. 2014
	Orange oil, long-chain triglycerides, medium-chain triglycerides	Tween 20	High-pressure microfluidization	Qian et al. 2012b
	Corn oil	Tween 20, β-lactoglobulin	High-pressure microfluidization	Qian et al. 2012a
Astaxanthin	Medium-chain triglycerides	Sodium dodecyl sulfate, decaglycerol monolaurate, decaglycerol monooleate, sodium caseinate, modified lecithin	Microchannel emulsification	Khalid et al. 2017b
	Soybean oil	Sodium caseinate, modified lecithin	High-pressure homogenization	Khalid et al. 2017a
Carotenoid extract from *Archaea*	Limonene	Triton X-100/Tween 80 (3:1)	High-pressure homogenization	Chaari et al. 2018

Table 4 Acceptable daily intake (ADI) of main carotenoids

Carotenoid	**Origin**	**ADI**	**Use**	**Reference [**AU: The below references need to be in the Literature Cited**]**
Astaxanthin	Bacterium (*Paracoccus carotinifaciens*) Yeast (*Phaffia rhodozyma*) Synthetic Astaxanthin-dimethyldisuccinate	0.2 mg/kg bw/day	Feed additive (E161j)	EFSA Panel on Additives and Products or Substances used in Animal Feed (2019).
β-carotene	Carrots (*Daucus carota*) Fungus (*Blakeslea trispora*) Microalgae (*Dunaliella salina*) Microalgae (*Dunaliella bardawil*) Palm fruit oil (*Elaeis guineensis*) Synthetic	0–5 mg/kg bw/day (<15 mg/day, recommended)[a]	Food additive (E160a)	EFSA Panel on Food Additives and Nutrient Sources added to Food (2012, 2012a)
Bixin	Annatto seed extracts (*Bixa orellana*)	6 mg/kg bw/day	Food additive (E160b)	EFSA Panel on Food Additives and Nutrient Sources added to Food (2016)
Canthaxanthin	Synthetic	0.03 mg/kg bw/day	Feed additive (E161g)	EFSA Panel on Additives and Products or Substances used in Animal Feed (2014)
Capsanthin/capsorubin	Paprika fruit extracts (*Capsicum*)	1.7 mg/kg bw/day	Food additive (E160c)	EFSA Panel on Food Additives and Nutrient Sources added to

				Food (2015)
Lutein	*Tagetes erecta* flowers	1 mg/kg bw/day	Food additive (E161b)	EFSA Panel on Additives and Products or Substances used in Animal Feed (2019a)
Lycopene	Fungus (*Blakeslea trispora*) Tomatoes (*Lycopersicon lycopersicum* L.) Synthetic	0.5 mg/kg bw/day	Food color (E160d)	EFSA Panel on Dietetic Products, Nutrition and Allergies (2008)
Norbixin	Annatto seed extracts (*B. orellana*)	0.3 mg/kg bw/day	Food additive [E160 b (ii)]	EFSA Panel on Food Additives and Nutrient Sources added to Food (2016)
Zeaxanthin	*T. erecta* flowers Synthetic	0.75 mg/kg bw/day	Food additive (161h)	EFSA Panel on Additives and Products or Substances used in Animal Feed (2019a);EFSA Panel on Dietetic Products, Nutrition and Allergies (2012)

Abbreviation: bw, body weight.

[a] The Joint FAO/WHO/Expert Committee on Food Additives (JECFA) and the EU Scientific Committee for Food (SCF) established an ADI of 0–5 mg/kg bw/day. EFSA’s Panel on Food Additives and Nutrient Sources added to Food (ANS) concluded in 2012 that no ADIs for mixed carotenes [E160a (i)] and β-carotene [E160a (ii)] can be established at present and that “the use of (synthetic) β-carotene and mixed β-carotenes obtained from palm fruit oil, carrots and algae as food color is not of safety concern, provided the intake from this use as a food additive and as food supplement is not more than the amount likely to be ingested from the regular consumption of the foods in which they occur naturally (5–10 mg/day). This would ascertain that the exposure to β-carotene from these uses would remain below 15 mg/day, the level of supplemental intake of β-carotene for which epidemiological studies did not reveal any increased cancer risk.” (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2012). Later in 2012,

EFSA’s ANS panel concluded that “exposure to β-carotene from its use as food additive and as food supplement at a level below 15 mg/day do not give rise to concerns about adverse health effects in the general population, including heavy smokers.” (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2012a)