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Carotenoids: Overview of Nomenclature, Structures, Occurrence, and Functions

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Nature is painting for us, day after day, pictures of infinite beauty if only we have the eyes to see them.

John Ruskin (1819–1900)

1.1 Introduction

The beauty of nature never ceases to surprise: the countless number of shapes and forms, a large diversity of fragrances and sounds, the unlimited palette of colors. Every day, we perceive through the senses her breathtaking majesty. The reality seen with the eyes is a mixture, the collage of rays of visible light reflected by the objects. This incredible composition comes onto the retina where, thanks to the light-sensitive cells called *cones*, the perception of the color is achieved. After the numerous physical and biochemical processes that convert a light stimulus into nervous stimulus, an image of the world creates itself in the brain. However, the leaves on the trees would never be green and the ripe tomatoes would not be red without the presence of natural pigments. Plants are equipped with sophisticated chemical compounds that absorb a part of the vital sunlight energy for use in photosynthesis and to give them color. One of them, carotenoids, are the second most abundant (after chlorophylls) pigments in nature, currently comprising over 700 specimens [1, 2]. They are responsible for the yellow, orange, and red color of fruits [3], flowers [4], seeds [5], flamingos [6–8], shrimp [9], and various other higher animals [7, 10, 11]. The deep color of these pigments is also characteristic for various simple organisms, such as yeast [12, 13], fungi [14, 15], and algae [16, 17], being natural carotenoid producers.

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Carotenoids generally cannot be synthesized by animals, but they are necessary in their diets and involved in many purposes, for example, lutein and zeaxanthin accumulate in the human eye and serve as photoprotectants against damaging effects of free radicals [18, 19]. So, without these pigments, we cannot see the beauty painted by them. Carotenoids are ubiquitous in all kingdoms of living organisms and provide various pivotal functions resulting from their structural diversity.

This opening chapter is addressed to gathering the fundamental knowledge of carotenoids, concerning their nomenclature, structure with stereochemical features, occurrence, and functions. Throughout this introductory chapter, references are made to the topics that are discussed in this book in detail.

1.2 Nomenclature and structures

Carotenoids owe their name to carrots (*Daucus carota*) due to the fact that they constitute the major pigments in the carrot root [20]. According to the International Union of Pure and Applied Chemistry (IUPAC) definition [21], carotenoids belong to the class of organic, lipid-soluble compounds, tetraterpenoids, which are composed of eight isoprenoid units joined together in the polyene chain. The structure of isoprene and an example of carotenoid with marked segments are presented in Figure 1.1. The arrangement of units is not obvious. From the center of the molecule, they are reversed, and hence two central side-chain methyl groups are in the 1,6 positional relationship while the remaining nonterminal groups are in the 1,5 relative positions. All carotenoids are derivatives of lycopene (ψ,ψ -carotene), which is represented by the formula $C_{40}H_{56}$, having a long central chain of 11 conjugated double bonds in the E (*trans*) configuration. This base acyclic structure can be chemically altered by cyclization, hydrogenation and dehydrogenation, oxidation, or any combination of these processes, making a vast range of possible carotenoids and their derivatives [22].

The specific structure of the carotenoid backbone originates from its biosynthetic pathway [2, 23]. Carotenoids are synthesized by a large variety of phototrophic and non-phototrophic organisms, including fungi, bacteria, and algae. In higher plants, the first step of the synthesis is the condensation of two geranylgeranyl diphosphate molecules forming a linkage of two C_{20} hydrocarbon fragments. This tail-to-tail enzymatic reaction is catalyzed by the phytoene synthase. The resulting compound, 15-*cis*-phytoene, is the first carotenoid having three conjugated double bonds. In further steps, a series of desaturation reactions,

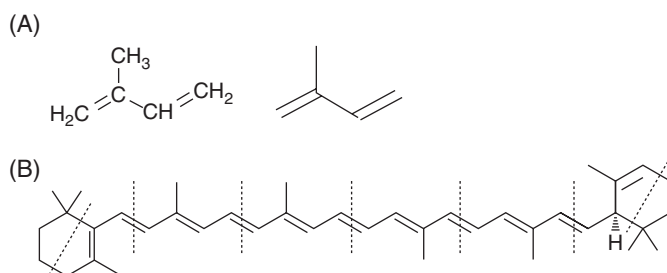


Figure 1.1 (A) The structure of isoprene; and (B) the arrangement of isoprenoid units in an exemplary carotenoid: α -carotene.

carried out by appropriate enzymes in the presence of light, introduce alternating double bonds in the 40-carbon basic skeleton leading to the lycopene structure. Thus, lycopene is the branching point of this pathway and starting point for synthesis of all other carotenoids. More information on the carotenoid biosynthesis and its regulation in plants is given in Chapter 10.

Carotenoids possess distinctive chemical reactivity and light-absorbing characteristics. One of their most remarkable features is the system of subsequent double and single bonds in the central part of the molecule. Due to the overlap of p-orbitals between adjacent carbon atoms, the delocalization of π -electrons over the entire length of the polyene chain occurs. The excited state of the molecule is accordingly of low energy, thus in general, absorption of the visible light is enough to give rise to the electronic transitions from π to π^* orbitals [24, 25]. Carotenoids possess 3–13 conjugated double bonds. Its number determines the color of the pigment from pale yellow (i.e., for ζ -carotene with 7 double bonds); through bright orange, characteristic for β -carotene (9 double bonds); to intense, deep red color (i.e., for canthaxanthin with 13 double bonds) [25]. Moreover, each double bond may exist in two configurations: as geometric isomers *Z* (*cis*) or *E* (*trans*), with *cis*-isomers being thermodynamically less stable, resulting in the all-*trans* isomers of carotenoids that are predominantly found in nature [24].

Carotenoids can be divided into two subgroups of hydrocarbons: carotens, composed only of carbon and hydrogen atoms (e.g., β -carotene), and their oxygen-containing derivatives, xanthophylls. In the latter, the additional oxygen atoms are found in various functional groups (i.e., hydroxy-, keto-, carboxy-, carbomethoxy-, epoxy-, and lactone), comprising a wide range of possible structures. Furthermore, the hydroxyl groups may also be esterified or glycosylated. Examples of some popular and structurally interesting carotenoids are shown in Figure 1.2.

To better understand the nature of studied compounds, it is essential to follow the nomenclature rules. Three naming conventions exist for carotenoids. The first one, the systematic nomenclature, is based strictly on the organic chemistry nomenclature. This method is not preferred for higher terpenoids and complex structures because their systematic names are long and awkward. The second naming system uses trivial names referring to plants or organisms from which they were originally extracted or to Latin words related to their properties. This approach is widely applied to natural products, but it can introduce ambiguity, as in the case of α -carotene that does not possess two α -ionone rings at the end of polyene chain but one α - and one β -ionone ring. Therefore, the IUPAC Commission on Nomenclature of Organic Chemistry and the IUPAC-IUB (International Union of Biochemistry) Commission on Biochemical Nomenclature have issued the *semi-systematic names*, based on both organic chemistry nomenclature and biological origin, to define precisely the structure of carotenoids [21]. A considerable advantage of this approach is the simplification in data searching in the literature and facilitation of communication between scientists from different science branches. Differences in the naming systems are presented in Figure 1.3 for lutein.

As was mentioned in this chapter, carotenoids' names originate from lycopene. Its hydrocarbon skeleton is a basic structure from which other names arise. The nomenclature consistent with the semisystematic rules starts from the correct numbering of the carbon atoms. The system is shown in Figure 1.4. However, the choice of locants of methyl groups at C1 atoms depends on the stereochemistry [21]. In acyclic terminal groups with a double bond between one and two carbon atoms (1' and 2' on the second end of the molecule), that methyl group is numbered as 1,6 which is in *trans* conformation to the main polyene chain. In β , γ , ϵ , and κ end groups, the 16 and 17 (16' and 17') are distinguished by the position of the R substituent denoting the rest of the molecule. If this moiety is on the right

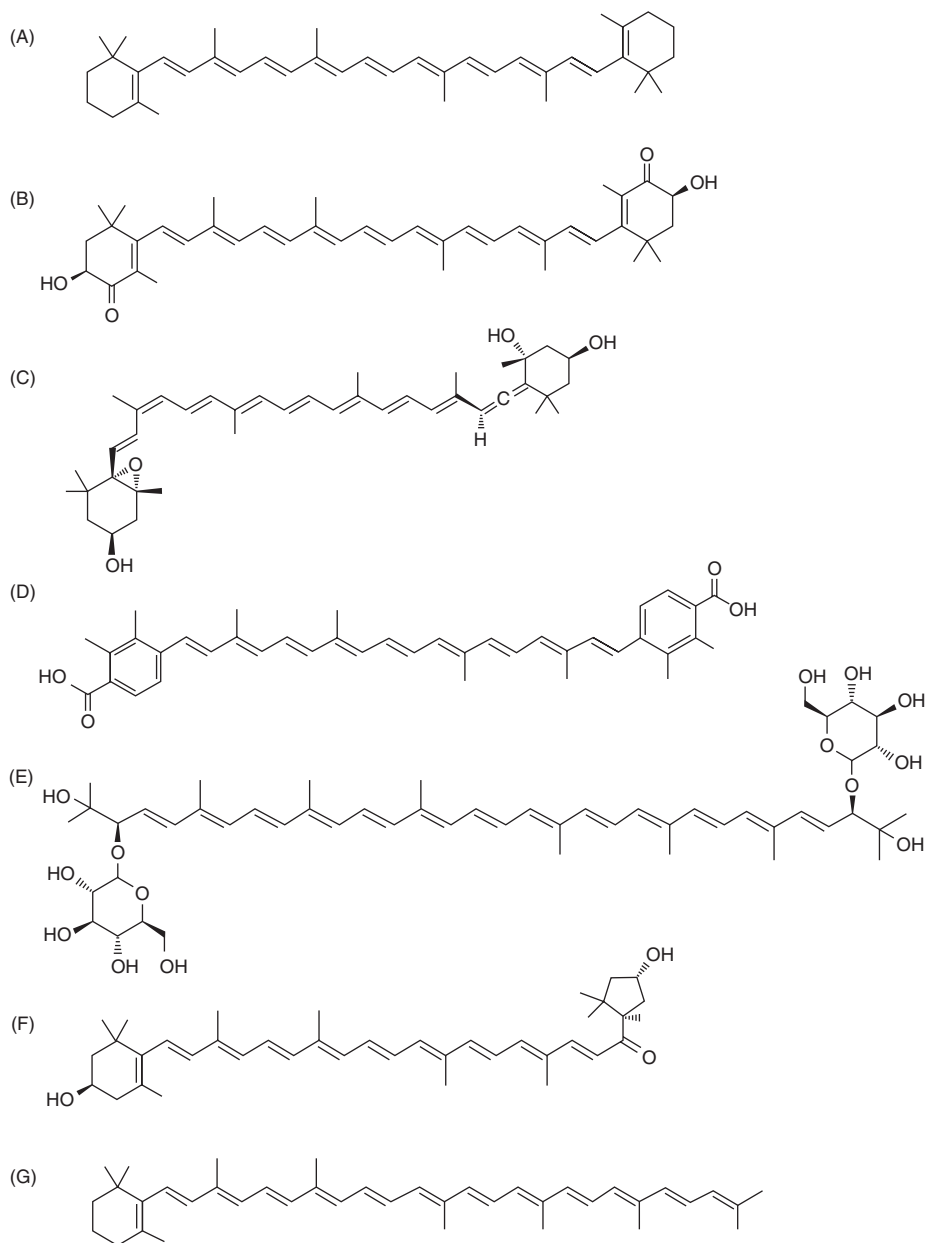
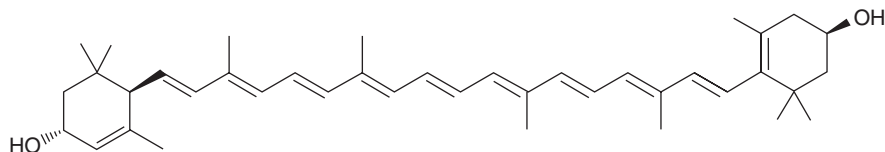


Figure 1.2 Examples of structures of carotenes and xanthophylls; a common natural source of the pigment is given in parentheses. (A) β -carotene (carrot *Daucus carota*); (B) astaxanthin (alga *Haematococcus pluvialis*); (C) neoxanthin (green leafy vegetables, i.e., spinach *Spinacia*); (D) synechoxanthin (cyanobacterium *Synechococcus*); (E) oscillaxanthin (cyanobacterium *Oscillatoria*); (F) capsanthin (paprika *Capsicum annum*); and (G) torulene (yeast *Rhodotorula* spp.).



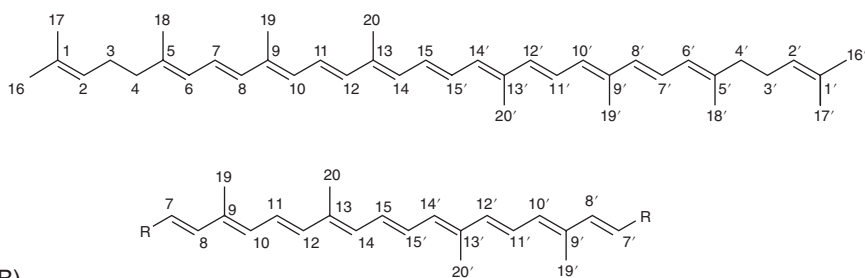
Systematic name: (1R,4R)-4-[[[(1E,3E,5E,7E,9E,11E,13E,15E,17E)-18-[(4R)-4-hydroxy-2,6,6-trimethylcyclohexen-1-yl]-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethylcyclohex-2-en-1-ol]

Trivial name: lutein (from Latin *luteus*—yellow)

Semi-systematic name: (3R,3'R,6'R)- β,ϵ -carotene-3,3'-diol

Figure 1.3 The structure of lutein and its names in three naming systems: systematic, trivial, and semisystematic.

(A)



(B)

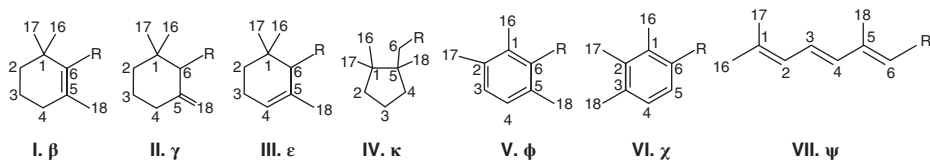


Figure 1.4 (A) The structure of lycopene compared with the structure of the carotenoid polyene chain; and (B) possible end groups found in nature (with prefixes). The numbering scheme for all structures is included.

from the C1 carbon atom, they are marked as below and above the ring plane, respectively. However, when the R group is on the left, that numbering is reversed.

Carotenoid molecules are composed of a hydrocarbon chain core (Fig. 1.4A) and two end groups attached to its opposite edges (Fig. 1.4B). Each terminal group has nine carbon atoms arranged in different structures (e.g., cyclohexene, cyclohexane, and cyclopentane) and is described by Greek-letter prefixes. All names are based on the stem name “carotene” preceded by the prefixes related to both groups occurring in the molecule. The letters should be cited in alphabetical order and doubled if they are identical. Thus, β -carotene is correctly written as β,β -carotene, α -carotene as β,ϵ -carotene, and so on. If the end groups are dissimilar, the unprimed numbers of carbon atoms are given from the end of the molecule associated with the first Greek letter appearing in the name.

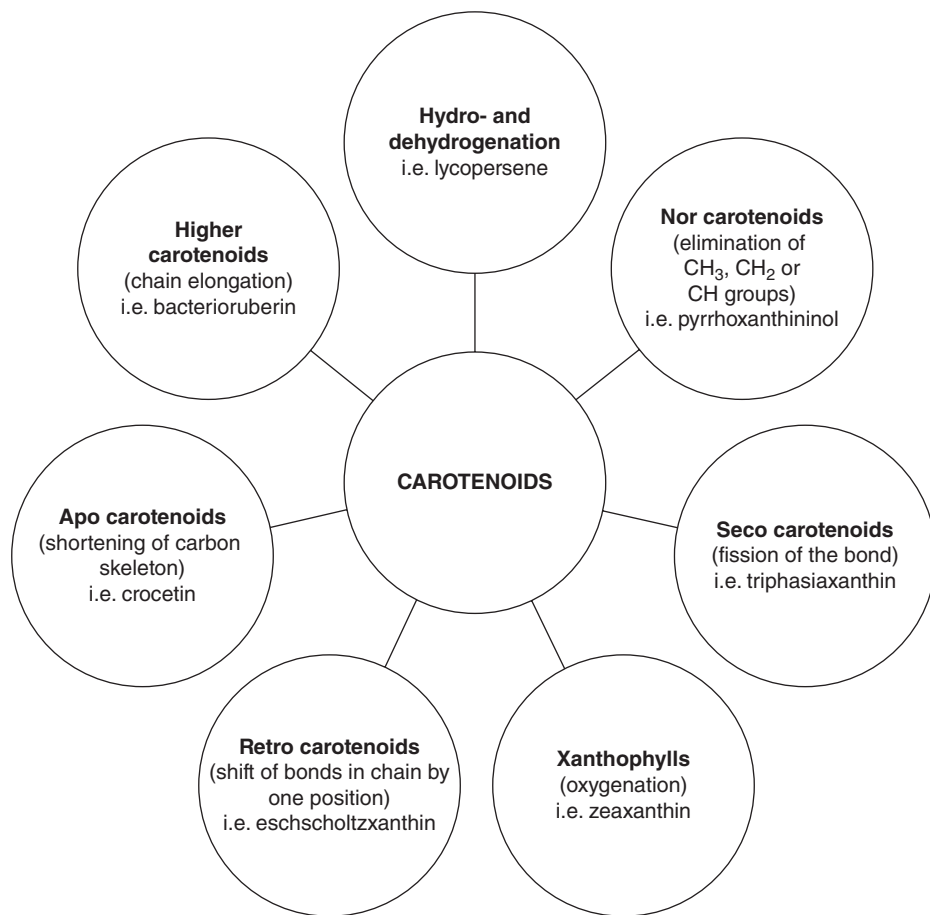


Figure 1.5 Various groups of carotenoid derivatives.

Modifications to both the chain and end groups introduce further rules in the nomenclature of carotenoids. Possible derivatives of carotenoids are presented in Figure 1.5, and the names are explained below:

- For hydrogenated and dehydrogenated derivatives, it is necessary to attach the prefixes “dehydro” and “hydro” when hydrogen atoms are removed or added, respectively, with the locants of the carbon atoms where they occurred. Additional prefixes denoting the number of modifications are used according to the standard organic chemistry principles.
- If one or more CH₃, CH₂, or CH groups has been eliminated from a carotenoid, the prefix “nor” with the locants of removed carbon atoms must be incorporated. In nor carotenoids, the numbering of the remaining carbon atoms is preserved as in the original molecules.
- Seco carotenoids are a subgroup wherein at least one band in the terminal rings has been ruptured. Thus, the name is supplemented by the prefix “seco” and numbers of carbon atoms where a gap occurs.

- Xanthophylls nomenclature follows the rules of the general organic chemistry nomenclature. For alcohols, carboxylic acids, esters of carotenoid alcohols and acids, aldehydes, and ketones, the oxygen-containing group serves as a principal group and is introduced by the use of a proper suffix. Xanthophylls classified as ethers are named in two manners depending on the type of oxygen binding. The non-bridging ethers bring to the name the appropriate “alkoxy” or “aryloxy” prefix, whereas oxygen bridges are introduced by the prefix “epoxy.” In both cases, the point of attachment of the oxygen atoms in the molecule must be specified. The numbering in xanthophylls is the same as in other carotenoids only if the two end groups are dissimilar. Otherwise, the unprimed locants are assigned to carbon atoms according to the order of importance: firstly to principal groups, cited as the suffix, then in such a manner to obtain the lowest locants’ numbers.
- If all conjugated double bonds are shifted by one position, the prefix “retro” should be included in the name with appropriate locants. The first and second numbers indicate carbon atoms from which protons were removed and added, respectively.
- Apo carotenoids are derivatives in which a carbon skeleton has been shortened by removal of a part of the molecule from one or both ends. The prefix “apo” is introduced with locants indicating that the fragment beyond this carbon atom has been replaced by hydrogen atoms. However, the side-chain methyl groups are not considered to be “beyond” the carbon atom to which it is attached. Additionally, in the case when the locants preceding the “apo” prefix are greater than 5, there is no need to give the Greek letters in the stem name.
- In contrast to apo carotenoids, there are subgroup of higher carotenoids composed of more than eight isoprenoid units. Their names follow the general principle for organic molecules and retain the numbering of the normal carotenoid.

The last step in the procedure of carotenoid naming involves the stereochemistry. The absolute configuration should be determined for each chiral center in the molecule using the R/S convention. Additionally, if any Z (*cis*)-configuration of double bonds is present in the structure, it should be denoted classically. The stem “carotene” indicates a molecule that possesses all C=C bonds in the E (*trans*) configuration.

1.3 Occurrence and functions

The diversity of functions in which carotenoids partake, in both human beings and other organisms, is enormous. Therefore, it is not particularly surprising that the number of literature reports on this topic is rather substantial and well summarized in several review articles published during the last three years (2012–2014) [16, 26–43].

1.3.1 Functions in plants

About 50 carotenoids are fundamental components of the light-harvesting antenna complexes (LHCs) of photosynthetic organisms. The main roles of pigments in LHCs are capturing light, transferring electronic excitations to the acceptor chlorophyll molecules, as well as photoprotection based on regulating the energy flow [43]. Carotenoids also play a role in stabilization of biomembranes and membrane-bound pigment–protein complexes. The function of carotenoids in pigment–protein complexes in relation to their structure is the topic of Chapter 9 of this book.

1.3.2 Antioxidants in humans

Several carotenoids act as potent antioxidants in humans. The omnipotent free-radical scavenger is astaxanthin, which has about 10-fold higher antioxidant activity compared to zeaxanthin, lutein, cantaxanthin, and β -carotene and 100-fold higher activity than α -tocopherol [44]. The antioxidant properties are the basis of preventive function toward many chronic diseases, including *neurodegenerative diseases*: stroke (lutein and astaxanthin), Alzheimer's disease (astaxanthin and β -carotene), and Parkinson's disease (β -carotene); *cardiovascular diseases*: atherosclerosis (lutein, astaxanthin, α -carotene, and crocin) and hypertension (astaxanthin, α -carotene, crocin, and lycopene); *diabetes* (lutein, zeaxanthin, astaxanthin, α -carotene, and lycopene); *cancer* (fucoxanthin, astaxanthin, α -carotene, crocin, and lycopene); and *osteoporosis* (β -cryptoxanthin and crocin) [28, 34, 35 and references cited therein, 37, 38, 45–46]. Moreover, several carotenoids are suggested to have a beneficial influence on the immunological system, decrease drug-withdrawal syndrome, show neuroprotective effect, and possess anti-inflammatory properties [28, 34, 35, 44].

It has been indicated that carotenoids can be used as biomarkers to distinguish between cancerous/malignant and healthy cells and tissues, with practical potential in medical diagnostics [47–49]. This subject is further developed in Chapter 2. Mechanisms of radiation and photoprotection of dietary carotenoids are characterized in Chapter 3.

1.3.3 Role in visual and cognitive function

One of the most important and well-described functions of carotenoids is the pro-vitamin A activity (i.e., their ability to convert into retinol) [43, 50]. Vitamin A is a compound of the key importance for child health and survival, and its deficiency result in disturbances in vision and a number of diverse other pathologies [51].

Two isomeric xanthophylls, lutein and zeaxanthin, play a key role in vision health [33 and references cited therein, 43 and references cited therein]. These pigments, in the forms of lutein, zeaxanthin, and mezo-zeaxanthin, formed metabolically from lutein in the human body, are concentrated in the central region of the retina, called the *macula lutea*. Macular carotenoids prevent damage leading to age-related macular degeneration, visual impairment, and cataracts [33 and references cited therein, 43 and references cited therein]. Lutein was also suggested to influence early visual development [52]. This pigment is also a major carotenoid of the human brain, involved in a number of cognitive processes such as learning, memory, language, and executive functions [32 and references cited therein, 33 and references cited therein]. The influence of macular carotenoids on human health is considered in Chapter 4.

1.3.4 Carotenoids in human skin

Skin coloration appears to play an important role in facial attractiveness, with skin yellowness being a desirable feature. Overall, it was suggested that skin coloration is a part of the carotenoid-linked health-signaling system that is of considerable meaning in mate choice [53].

Human skin contains various carotenoids, mainly α -carotene, γ -carotene, β -carotene, lutein, zeaxanthin, lycopene, and their isomers, that serve the living cells as a protection against oxidation [54]. A diet rich in carotenoids prevents cell damage, premature skin

aging, skin cancer, and other skin-related diseases as the increase of carotenoid level increases the radical-scavenging activity of the skin and provides a significant protection against stress-induced radical formation [55]. Moreover, the carotenoid level in the skin, which is quite easy to measure with the help of Raman spectroscopy, reflects the antioxidant status [56]. This topic is further developed in this chapter.

1.3.5 Signaling function

Carotenoids are responsible for the color of fruits, vegetables, and flowers, increasing their attractiveness for pollination, seed dispersal, and sexual attraction. Apo carotenoids contribute to the aroma of flowers, fruits, and vegetables. Carotenoid cleavage products are phytohormones and essential signaling molecules [43].

1.3.6 Industrial applications

Astaxanthin, next to β -carotene, is one of the most important carotenoids for industrial applications. Astaxanthin and (to a much lower extent) cantaxanthin, obtained from *de novo* manufacturers, play a crucial function as food colorants in salmonid and crustacean cultures [44]. Algal and yeast cultures are not only feed but also more and more often exploited sources of dietary carotenoids [16 and references cited therein]. Numerous factors influencing carotenoids' synthesis by microorganisms and various tactics that serve optimizing technological processes of carotenoid production are characterized in Chapters 12 and 13. Such microbial cultures are not only environmentally friendly but also, in the future, can function also as "recycling trash-cans" for agro-industrial wastes. Successful carotenoid production by microbial sources cultivated in industrial residues has been already reported [57–59].

Both microorganism-derived and synthetic carotenoids are used commonly as dietary supplements as well as pigments in food and beverages, for instance in fruit juices, soft drinks, and dairy products [16 and references cited therein]. Additionally, they are applied as animal feed and used in the pharmaceutical and cosmetic industries. There are often differences between synthetic and biomanufactured carotenoids in the sense of structures, and therefore their bioavailability. This point is referred to in Chapter 13. A general review of the recent spectroscopic studies regarding structures of carotenoids in *de novo* manufacturers, plants, and animals, also *in situ*, is discussed in Chapters 6–8. Topics related to carotenoids bioavailability from the food matrix and optimization of extraction procedures are included in Chapter 11. Various functions of carotenoids are summarized in Figure 1.6.

1.3.7 Carotenoids of specified properties

Industry is searching for carotenoids of modified properties both for better functionality and for new applications of carotenoids and their derivatives. Particularly, the pharmaceutical industry is interested in more hydrophilic carotenoids, with Cardax™ being an example of this. This disodium disuccinate derivative of astaxanthin is an efficient cardioprotective drug of increased solubility as compared with the original xanthophyll [60].

Various carotenoid-based compounds are synthesized and tested toward many specific applications, with carotenoid-porphyrin-fullerene derivatives being probably one of the most exotic carotenoid derivatives synthesized up to now [61]. Recent achievements, challenges, and perspectives of syntheses with carotenoids are described in Chapter 14.

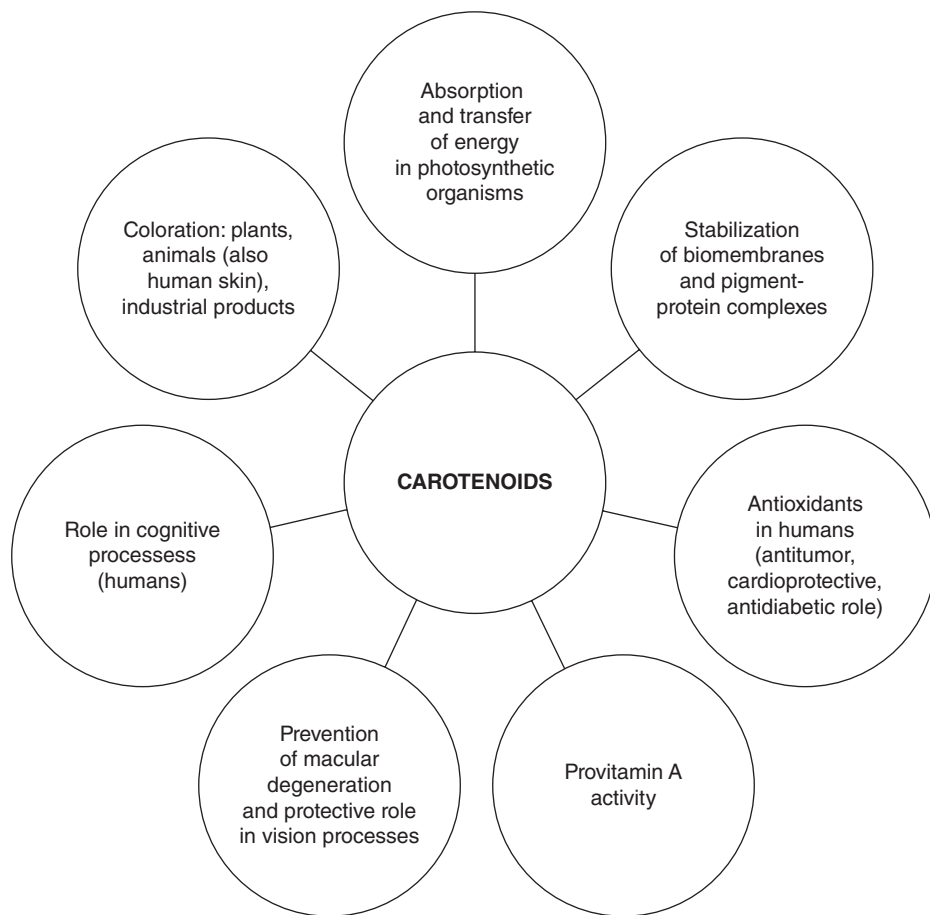


Figure 1.6 Diverse functions of carotenoids.

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