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Chapter 1

Carotenoids: A Brief Overview on Its Structure, Biosynthesis, Synthesis, and Applications

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Additional information is available at the end of the chapter

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Abstract

Currently, 1178 natural carotenoids have been properly characterized and reported in the literature, which present a huge structural diversity and physicochemical properties. This number comprises a wide distribution of these biomolecules in approximately 700 source organisms including plants, bacteria, fungi, and algae. Besides having a wide applicability as natural dyes, some carotenoids such as β-carotene already have another well-established application such as provitamin A activity. However, due to the structural diversity of these molecules, there are still numerous biochemical and physiological functions to be associated with this class of compounds. Accordingly, these characteristics enable a wide applicability, what drives the global carotenoid market. Thus, with the primary objective of addressing aspects regarding to basic science and applied carotenoid technology, a comprehensive description of the biology, biochemistry, and chemistry of these compounds will be described in this chapter.

Keywords: carotenoid, structure, synthesis, biosynthesis, industrial application

1. Historical aspects of carotenoids

It is often stated that without carotenoids, life in an oxygenic atmosphere would not be possible, and we would not exist. Thereby, over millions of years, the living organism chloroplasts maintained collections of carotenoids to protect the intricate and delicate photosynthetic apparatus against destruction by photooxidation [1, 2].

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According to Britton et al. [1], it can be considered that the study of carotenoids exceeds 200 years of history. Was Braconnot in 1817 carried out the first investigation in paprika? The following year, Aschoff isolated from the saffron, the "crocin," apocarotenoid which we now know as bixin. In 1823, Goebel's research on crab (*Brachyura*) suggested for the first time the presence of these isoprenoids in animals. Later, after investigations with carrots (*Daucus carota* L.), from which the term carotenoids derives, Wackenroder in 1831 isolated and described for the first time carotene with structure C40, now β-carotene. Shortly thereafter in 1837, Berzelius introduced the term xanthophyll due to its presence in autumn leaves. After, Kraus and Millardet in 1843 made the first investigation of carotenoids into cyanobacteria. Only 30 years later, lycopene was isolated for the first time from fruits of *Tamus communis* by Hartsen.

However, it was in the early twentieth century that a milestone occurred in the history of carotenoids. The Russian botanist Tswett in 1906 took the first step in the chromatographic technique of separation of these pigments, which together with the introduction of mass spectrometry (MS) in 1965 and high-performance liquid chromatography (HPLC) in 1971 provided a great advance in research [1, 3]. From this and with the advent of chromatographic methods and refinements in spectroscopy, the isolation and identification of carotenoids expanded greatly.

According to the last compilation, approximately 1178 naturally occurring carotenoids have been reported with 700 source organisms [4].

2. Structure, biosynthesis, synthesis, and application

In fact, it is well known that carotenoids are naturally synthesized by all photosynthetic organisms and nonphotosynthetic some, like bacteria, archaea, and fungi, which exhibit a complex carotenogenic metabolism [5].

They are classified according to the number of carbons that constitute their structure into carotenoids C30, C40, C45 and C50, but only the C40 carotenoids are those found in nature more abundantly and consequently, are those more approached in the literature. Moreover, C40 carotenoids are biosynthesized by organism eukaryotes, archaea, and bacteria, and their chemical structures are constituted by a diverse range of terminal groups [6].

Conversely, C30 and C50 carotenoids are biosynthesized by archaea and bacteria and only contain 6 and 10 C5 isoprenoid units, respectively. By contrast, only the bacteria are responsible for synthesizing C45 carotenoids composed of nine isoprenoid units [3, 6].

More than 100 naturally occurring apocarotenoids with diverse structural and functional properties have been reported. An apocarotenoid is a carotenoid in which the normal C40 structure has been shortened by the removal of fragments from one or both ends [7, 8]. Natural examples are bixin (C25 compound), the major pigment of the food colorant annatto, and crocetin (C20 compound), the main yellow coloring component of saffron [9, 10]. Lycopene, β-carotene, and zeaxanthin are the precursors of the main apocarotenoids described to date, which include bixin, crocetin, abscisic acid, strigolactone, and mycorradicin [10]. Vitamin A

is also considered an example of apocarotenoid, because it is the product of the symmetrical oxidative cleavage of β-carotene [7].

The formation of these carotenoid derivatives occurs via enzymatic and nonenzymatic oxidative cleavage of carotenoids [11, 12]. Carotenoid cleavage dioxygenases (CCDs) catalyze carotenoid cleavage at specific double bonds, typical act by incorporating oxygen atoms into adjacent carbon atoms along the conjugated carotenoid backbone. Some CCD cleavage reactions require isomerization to form substrate isomers favorable for cleavage [13]. On the other hand, nonenzymatic apocarotenoid formation can occur via singlet oxygen attack, primarily on β-carotene [14]. In addition, peroxidases and lipoxygenases are also reported to form apocarotenoids [15].

Regardless of metabolic origin, apocarotenoids present important biological functions, such as plant-environment interactions such as the attraction of pollinators and the defense against pathogens and herbivores. Also, include volatile aromatic compounds that act as repellents, chemoattractants, growth stimulators, and inhibitors, as well as the phytohormones abscisic acid and strigolactones [16]. Moreover, these isoprenoids are associated with other processes positively affecting human health were identified as responsible for inhibiting the lipid peroxidation and prevention of cancer and other degenerative diseases [14, 17, 18].

Nonapocarotenoid carotenoid cleavage products include norcarotenoids, which lack one, two or three carbon atoms in the central hydrocarbons skeleton (C40) [3]. The primary determinant is the number of carbon atoms formally lost from the C40 carotenoid skeleton [5]. An example is the peridinin, is one of the most complex carotenoids, a C37-norcarotenoid possessing (Z)-γ-ylidenebutenolide and allene functions. In addition, it has five chiral centers, including an epoxide ring [19].

Another subclass is that of secocarotenoids, in which a bond between two adjacent carbon atoms except between C(I) and C(6) in a ring has been broken [3, 5]. The semi-β-carotenone ($C_{40}H_{56}O_6$) is an example identified as the product of β-carotene ($C_{40}H_{56}$) oxidation in permanganate solutions [20].

In addition, isoprenoid structures with more than 40 carbon atoms are also reported. The rare C50 carotenoids are synthesized by the addition of two dimethylallyl pyrophosphate (DMAPP) molecules to C(2) and C(2′) of the respective C40 carotenoid [21]. These compounds have been mainly isolated from *Halobacteria, Halococcus*, and *Pseudomonas strain* and *Actinomycetales* [22]. The first C50 carotenoid discovered, decaprenoxanthin, was isolated from *Flavobacterium dehydrogenans* [23].

As shown in **Figure 1**, structurally, carotenoids have different terminal groups, of which there are seven: ψ, β, γ, ε, ϕ, χ, and κ, which may constitute the ends of the principal polyene chain of the structure of these molecules. In general terms, the terminal rings β, γ, and ε rings are formed from ψ ends, whereas ϕ, χ, and κ rings are formed from β end groups [6, 24].

Lycopene is the common precursor structure for the synthesis of cyclic and bicyclic carotenoids. Cyclization of this molecule is a branching point in carotenoid biosynthesis, where β-, γ- and ε-end groups are formed by proton loss from alternative positions in the

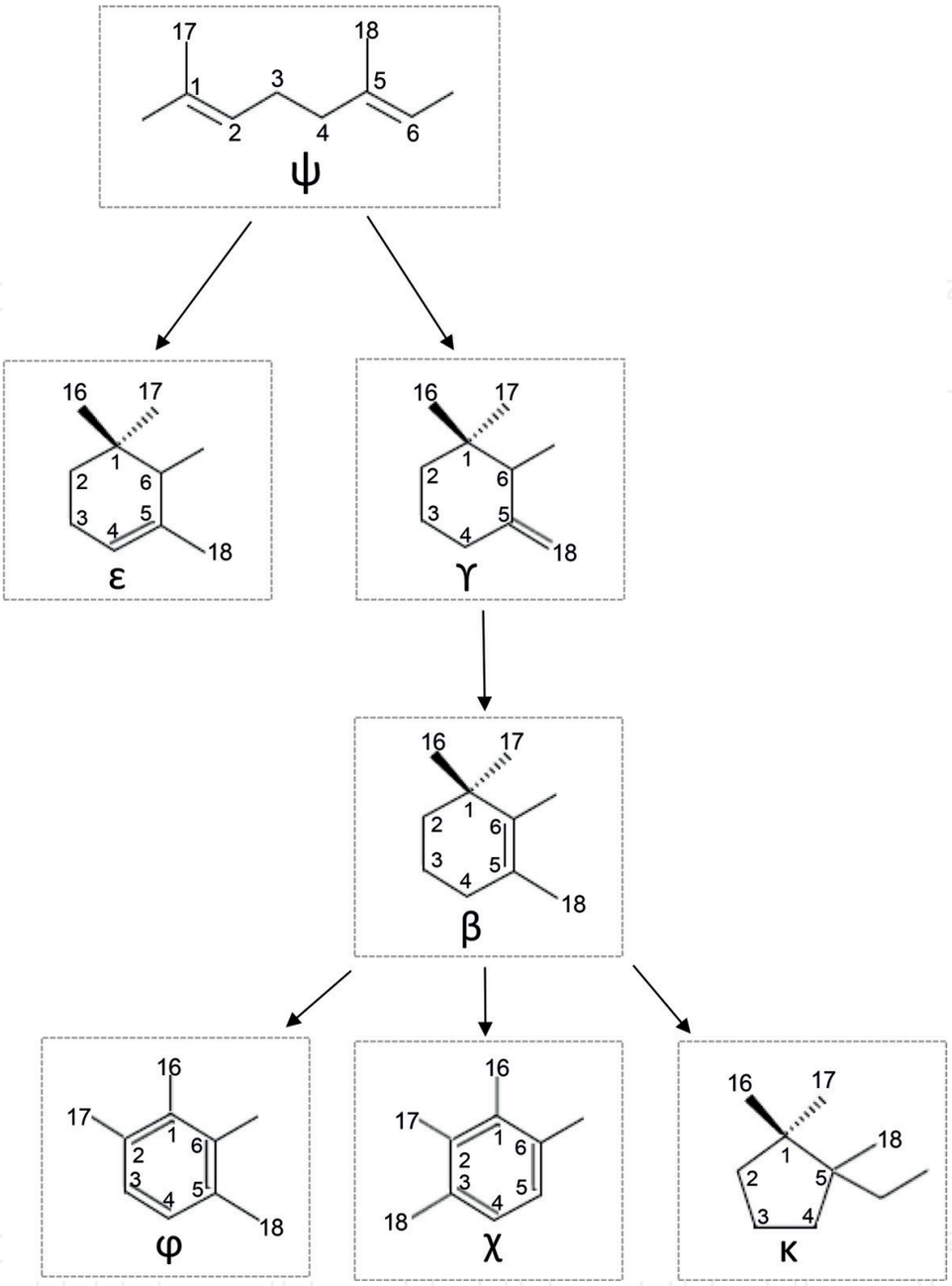


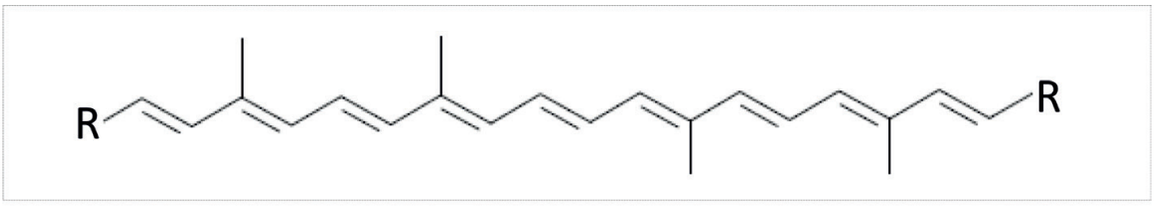
Figure 1. Different terminal rings of carotenoids.

same transient carbon ion intermediate. This cyclization process is catalyzed by the action of the enzymes lycopene cyclases [6]. The most prominent carotenoids with the ψ-, β-, γ- and ε-ends groups are licopene, β-carotene, γ,γ-carotene, and ε,ε-carotene, respectively (**Figure 2**).

The biosynthetic process of rings ϕ and χ (from ring β) occurs by the migration of methyl groups from C1 to C2 and dehydrogenation. In addition, migration of the methyl group from C5 to C3 occurs in the ring χ. Isorenieratene and renierapurpurin are representative carotenoids with the ϕ and χ end groups [24].

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In addition, carotenoids with κ terminal group are biosynthesized from 3-hydroxy-5,6-epoxy-β rings found in violaxanthin and antheraxanthin. This terminal group is characteristic of capsorubin, capsanthin, and cryptocapsin, isolated from paprika (*Capsicum annuum*) [24].



Type	End group (R)	Carotenoid
Acyclic	ψ	Lycopene
Cyclohexene	β	β-Carotene
Cyclohexene	ε	ε,ε-Carotene
Methylenecyclohexane	γ	γ,γ- Carotene
Cyclopentane	κ	Capsorubin
Aryl	χ	Renierapurpurin
Aryl	ϕ	Isorenieratene

Figure 2. Carotenoids with different terminal groups.

However, even after decades of studies with carotenoids, the studies that report on the enzymatic and chemical mechanisms responsible for the constitution of the terminal moieties of these molecules are limited, despite its relevance to the full meaning of a biosynthesis of carotenoids [24].

Considering the chemical elements present in the structure of carotenoids, they can be classified into carotenes and xanthophylls as shown in **Figure 3**. The carotenes are compounds which contain only hydrocarbons in its structure (e.g., β-carotene and lycopene). On the other hand, the xanthophylls are oxygenated carotenoids, which contain different functional groups such as an epoxy (violaxanthin, neoxanthin, and fucoxanthin), hydroxy (lutein and zeaxanthin), keto (astaxanthin and canthaxanthin), and methoxy (spirilloxanthin) functional groups. In turn, xanthophylls are among the main carotenoids in photosynthetic tissues [3, 25].

According to these modifications, these functional groups containing oxygen affect the biological functions and the solubility of carotenoids, making xanthophylls more polar than carotenes, thus allowing their separation using many types of chromatographs [7].

The formation of functional groups of the xanthophylls occurs naturally by an enzymatic reaction. The hydroxy group formation occurs through ring-specific hydroxylation reactions and is normally catalyzed by carotene β-hydroxylase enzymes of the nonheme di-iron (BCH) type. In the case of β-carotene, two sequential hydroxylations of the β rings produce first β-cryptoxanthin and then zeaxanthin. The same enzymes can also participate in the synthesis of lutein [26, 27].

Zeaxanthin epoxidase (ZEP) introduces epoxy groups in the rings of zeaxanthin, resulting in the formation of violaxanthin, which undergoes the introduction of a double allenic bond in the molecule producing neoxanthin in one step catalyzed by neoxanthin synthase (NSY) [3, 26].

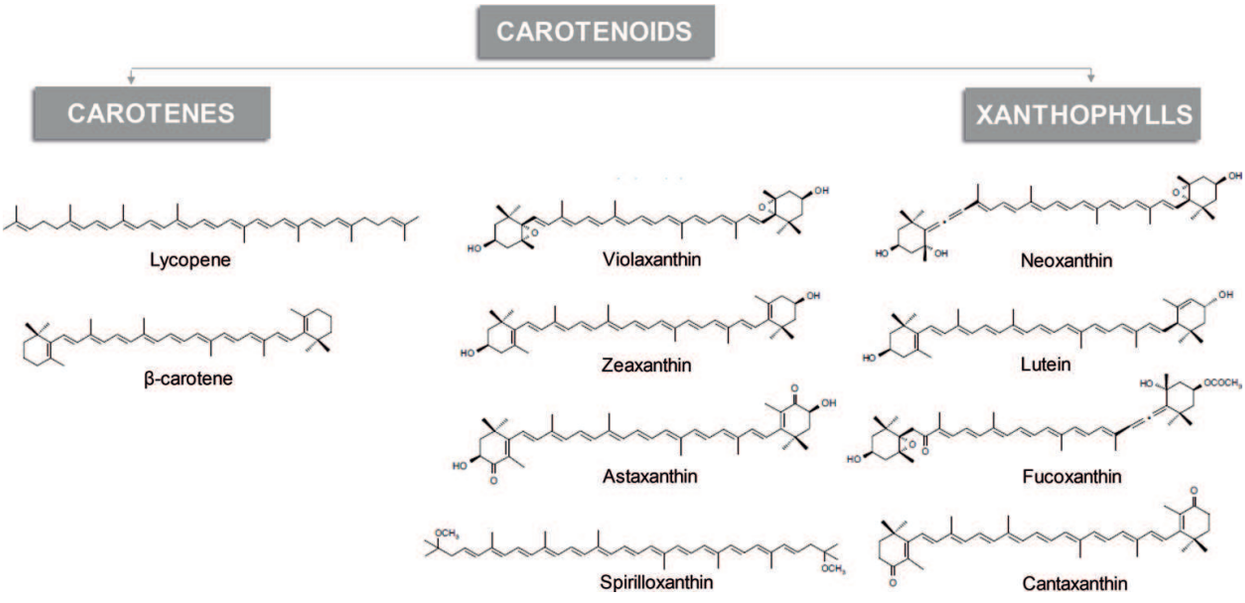


Figure 3. Examples of carotenes and xanthophylls.

Epoxy carotenoids comprise a large group of xanthophylls and are widely encountered in foods [28].

On the other hand, there are the ketocarotenoids that are produced by some algae and cyanobacteria, and are rare in plants [29]. These compounds have the ketone group inserted into the molecule by the enzyme beta-caroteneketolase. Ketocarotenoids, echinenone, and astaxanthin are the examples. Referring to astaxanthin, it still suffers action from beta-carotene hydrolase, since its structure is composed of two hydroxyls [30]. Ketocarotenoids are strong antioxidants that are chemically synthesized and used as dietary supplements and pigments in the aquaculture and nutraceutical industry [31].

Methoxy-carotenoids are previously synthesized from bacteria via enzymatic methoxylation [32], and the spirilloxanthin is an example [33]. Though the 3-methoxy-zeaxanthin has been reported in the human macula, your metabolic origins are unknown. It is suggested that methoxy xanthophyll originates from they do make metabolic changes to carotenoids acquired of the diets [32].

Besides with all the distinct conformations of carotenoids described above, these pigments may be associated to other molecules, including fatty acids (carotenoid esters), sugars (glycosylated carotenoids) or even proteins (carotenoproteins).

Carotenoids are naturally found in both free forms and esterified with fatty acids in many fruits, flowers, animals, microorganisms, and algae. For an ester to be formed, the carotenoid must have at least one hydroxyl group, since the ester linkage is formed when a carboxylic acid (fatty acid) reacts with an alcohol group (hydroxylated xanthophyll), with the elimination of a water molecule [34]. This process increases the lipophilicity of the molecule. During carotenoid biosynthesis to suggest that the xanthophyll esterification with fatty acids, it is most likely to be catalyzed by esterases or xanthophyll acyl transferases [35].

In many fruits, some plant organs, and tubers, the xanthophylls are typically found esterified with fatty acids [34, 36]. Similarly, there are carotenoids associated with sugar moieties, as it is the case of crocetin. On the other hand, some carotenoids can form complexes with proteins (carotenoproteins) that are water soluble and appear to stabilize carotenoids, as occurs with some crustaceans (astaxanthin-crustacyanine complex) [37].

Still referring to the patterns of chemical modifications, there are allene carotenoid and acetylene carotenoid structures (see **Figure 4**). In some important examples of naturally occurring carotenoids, the polyene chain is modified by the presence of one or two acetylenic (—C≡C—) or allenic (—C≡C—) groups, what is common in many marine organisms. The marine, allenic carotenoid peridinin from phytoplankton and fucoxanthin from macroalgae and phytoplankton are the carotenoids produced in largest quantity in nature [38]. Acetylenic carotenoids are synthesized de novo only in microalgae; crocoxanthin and diatoxanthin are examples of these structures [39, 40].

Given the presence of double bonds in carotenoid molecules, multiple geometrical (*cis*/*trans* or *Z*/*E*) isomers could be formed, which differ considerably in their chemical shape. However, most carotenoids found in nature are primarily in the more stable all-*trans* configurations; a small proportion of *cis* isomers is encountered [5, 12].

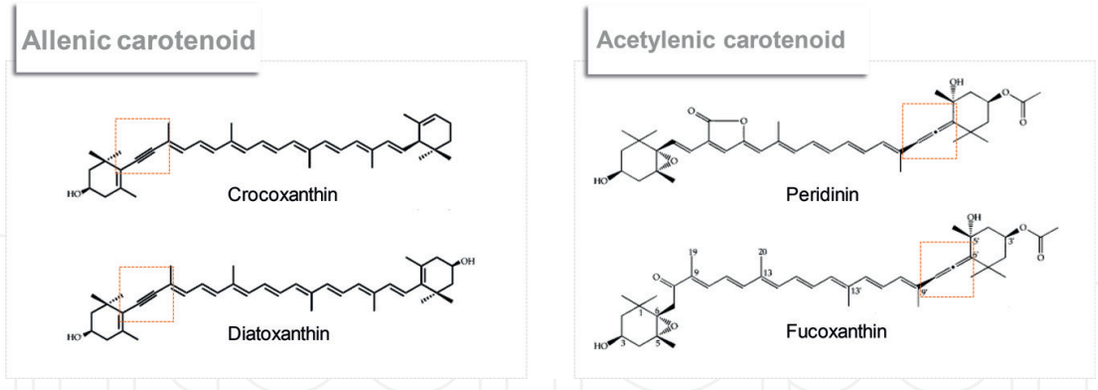


Figure 4. Carotenoids with acetylenic and allenic structure.

Theoretically, each carbon-carbon double bond in the polyene chain of carotenoids may exhibit E-Z isomerization. However, some double links like C-7,8, C-11,12, C-7′,8′, and C-11′,12′ are prevented from undergoing isomerization Z due to a steric hindrance between a hydrogen atom and a methyl group [28]. Thus, the Z-isomers of symmetrical β-carotene and zeaxanthin commonly found are the 9-*Z*-, 13-*Z*-, and the 15-*Z*-isomers, the formation of which has relatively little hindrance as it comes from two hydrogen atoms [28].

However, the C-5,6 double bond in the acyclic lycopene is unhindered, and 5-*Z*-lycopene is increasingly detected, along with the 9-*Z*-, 13-*Z*-, and the 15-*Z*-isomers [41].

Although the presence of *cis* isomers is recognized due to the isomerization caused by heat or light sources, there are some carotenoids that can occur naturally. Interestingly, they have different biological potency than their trans counterparts (e.g., lower pro vitamin A activity) [3]. Phytoene and phytofluene, which have the 15-*Z* configuration in most natural sources, are examples of carotenoids less thermodynamically stable [42]. Another example is bixin (see **Figure 5**), an apocarotenoid which occurs naturally in the *Z* form [43].

By contrast, the presence of one or more centers or axes of chirality in their molecules, some carotenoids can undergo geometric isomerization, which evidence the formation of optical (*R*/*S*) isomers. Zeaxanthin and astaxanthin are typical examples of carotenoids, in which this isomerization may occur.

Two optical isomers (3*R*-3′*R*)-zeaxanthin and (3*R*-3′*S*)-zeaxanthin, commonly referred to as *meso*-zeaxanthin and (3*S*, 3′*S*)-zeaxanthin are found in the macula lutea of the human retina [5]. Conversely, optical isomers different from astaxanthin, 3*S*, 3′*S*, 3*R*, 3′*S* (*meso*), and 3*R*, 3′*R*, in varying proportions are found in marine organisms (see **Figure 6**) [5].

At the biosynthetic level, more than 95% of all known carotenoids are formed using the same C5 building block, the isoprene (C5H8) unit, from which isopentenyl pyrophosphate (IPP) and its allylic isomer dimethylallyl pyrophosphate (DMAPP) are produced. Thus, in the route of the synthesis of isoprenoids, three molecules of IPP are sequentially added to DMAPP by prenyl transferase enzymes to yield geranylgeranyl-pyrophosphate (GGPP, C20). From this stage, the specific carotenoid biosynthetic pathway starts with condensation occurs of two molecules of GGPP, by phytoene synthase (PSY) to produce the first colorless carotenoid

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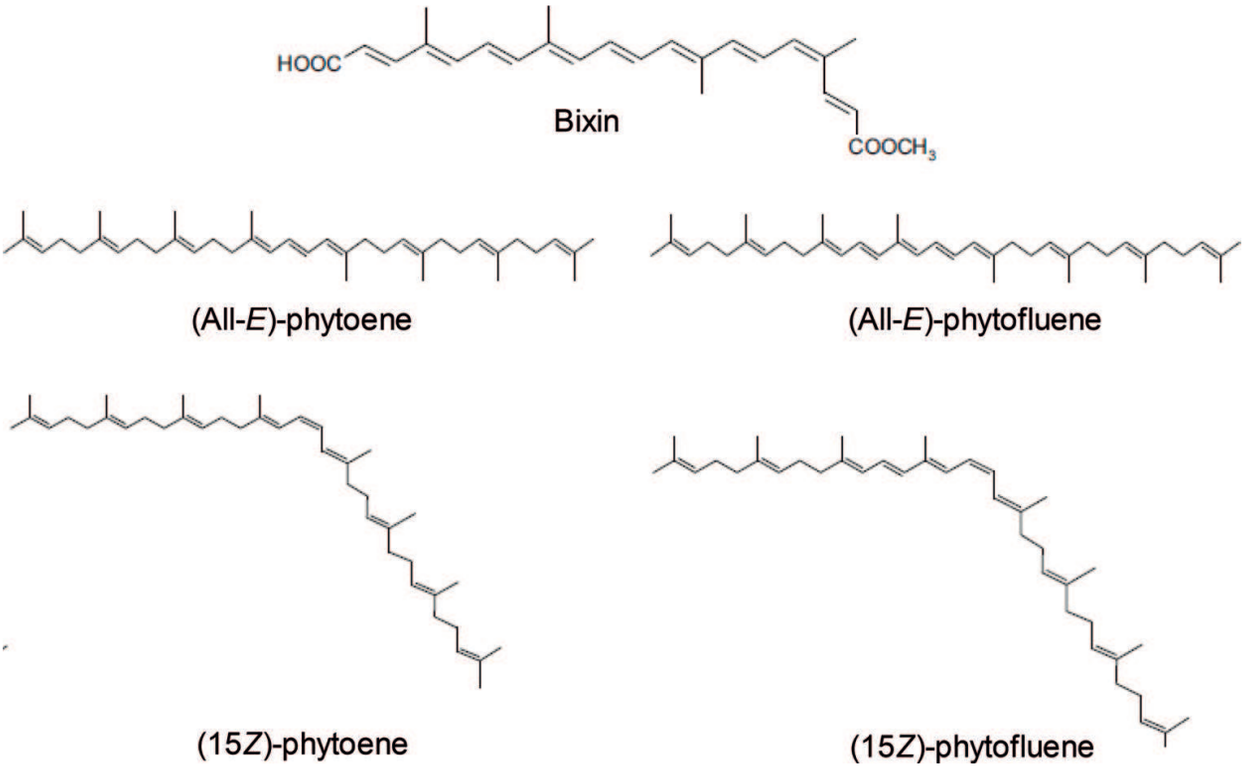


Figure 5. Geometrical isomers.

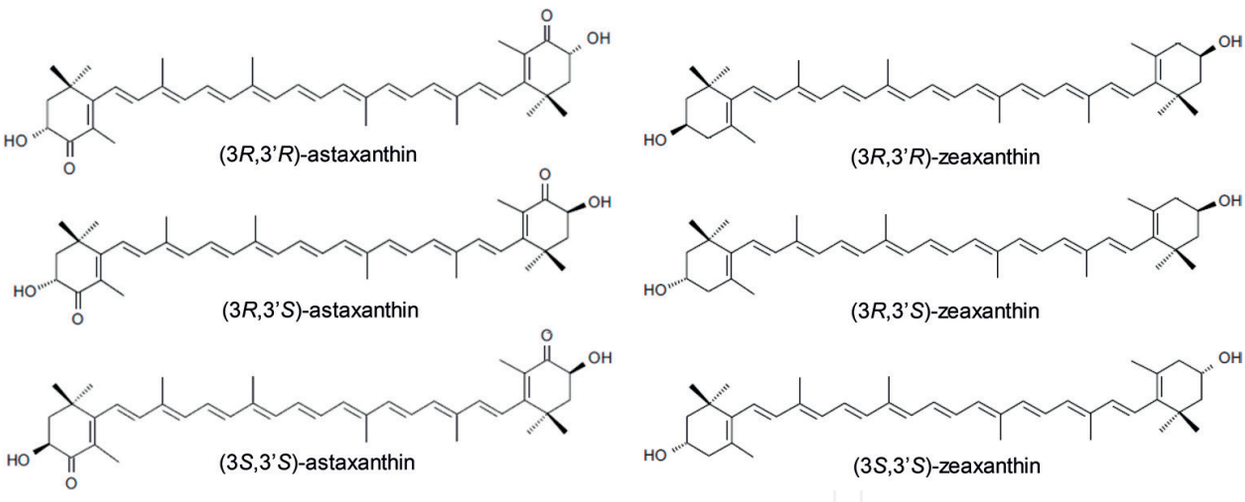


Figure 6. Optical isomers.

15-*cis*-phytoene (C40). These precursors are produced by two independent pathways in photosynthetic beings: the mevalonate (MVA) pathway and the methylerythritol 4-phosphate (MEP) pathway [3].

In contrast, approximately 5% of the biosynthesis of the other carotenoids (C30) occurs from farnesyl pyrophosphate (FPP), an intermediate precursor of geranylgeranyl-pyrophosphate (GGPP) or by the oxidative cleavage process of C40 carotenoids [21, 44].

Additionally, the carotenoids biosynthesized by different organisms are derived through a series of chemical and enzymatic modifications from the phytoene, such as reactions of desaturations, cyclizations, hydroxylations, glycosylation, oxidization, dehydrogenation, migration of double bonds, rearrangement, and epoxidations, as exemplified above [45]. These modifications are catalyzed by a number of enzymes which fall into few classes based on the type of transformation they catalyze such as geranylgeranyl pyrophosphate synthase, phytoene synthase, carotene desaturase, and lycopene cyclase. Modification of carotenes is further catalyzed by β-carotene ketolase and β-carotene hydrolase to generate various C40 carotenoids. Thus, all of these modifications contribute to yield a family of more than 1178 compounds widely distributed in nature [4, 46].

Of the total number of naturally occurring carotenoids, only eight are produced synthetically at industrial level. Between them C40 carotenoids: lycopene, β, β-carotene, (3R,3′R)-zeaxanthin, canthaxanthin, and astaxanthin; and three apocarotenoids: ß-apo-8′-carotenal, ethyl ß-apo-8′-carotenoate, and citranaxanthin [47]. For the chemical synthesis, several building concepts are possible. However, on industrial scale, only few of them have been applied successfully. The reactions of Grignard elaborated by Hoffman-La Roche in 1954 and reactions of Wittig developed by Badische Anilin- & Soda-Fabrik (BASF) in 1960, were the main reactions of syntheses employed on an industrial scale; however, Wittig reaction dominates the market currently [24, 48].

All chemically synthesized C40 carotenoids have symmetric structures, and this is explained by the fact that all structures have identical end groups at their ends. Due to these characteristics, they are efficiently produced by double Wittig condensation of a symmetrical C10-dialdehyde as the central C10-building block with two equivalents of an appropriate C15-phosphonium salt. In addition to these synthetic steps, these mixtures of isomers are thermally isomerized, in heptane or ethanol, for the full formation of all-trans/E configurations, since during the process, certain amounts of cis/Z stereoisomers are formed [24, 48]. Additionally, to use Grignard compounds, it is necessary to combine one diketone molecule and two methanol molecules, thereafter compound containing 40 carbon atoms is obtained [49].

Other methods of the synthesis of carotenoids include the hydroxylation of canthaxanthin, a C10 + C20 + C10 synthesis via dienolether condensation, and the isomerization of a lutein extracted from marigold to zeaxanthin and then oxidation to astaxanthin [48].

Apart from β, β-carotene, the other synthetically produced carotenoids are manufactured mostly by the companies Hoffmann-La Roche and BASF [47].

Furthermore, to synthetically traded carotenoids, a portion of these pigments are obtained from natural sources such as lutein (marigold flowers), β-carotene (*Dunaliella salina*), astaxanthin (*Haematococcus* spp.), and Capsorubin (*Capsicum annuum*) (see **Table** 1) [1, 50]. β-carotene followed by lutein and astaxanthin lead the carotenoid market, which is projected to reach USD 1.53 Billion until 2021 [51].

In more recent times, the major commercial use of carotenoids has been as food and feed additives for coloration. They have also found some use in cosmetics and pharmaceutical products, but the most rapidly growing market now is health supplements, which in turn, provides a stimulus growing from production [1].

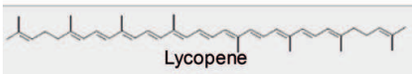
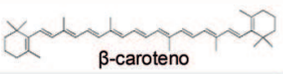
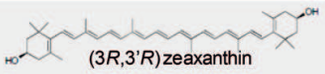
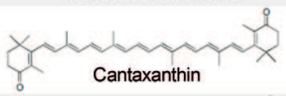
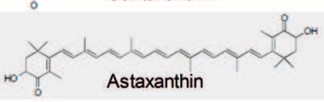
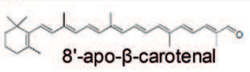
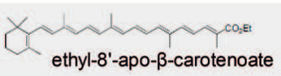
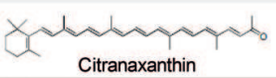
Carotenoid	Applications	Production Technology
 Lycopene	food coloration, nutritional supplement	chemical synthesis, biotechnology (Blakeslea trispora), isolation from tomato
 β-caroteno	food coloration (margarine, juice), nutritional supplement, feed additive (fertility, cattle)	chemical synthesis, biotechnology (*Dunaliella salina*)
 (3*R*,3'*R*) zeaxanthin	nutritional supplement (eye health)	chemical synthesis, isolation from natural sources
 Cantaxanthin	poultry (egg yolk and broiler pigmentation), aquaculture	chemical synthesis
 Astaxanthin	aquaculture (salmon pigmentation), dietary supplement, food coloration	chemical synthesis, biotechnology (*Haematococcus pluvialis*)
 8'-apo-β-carotenal	food coloration (cheese, dressings)	chemical synthesis
 ethyl-8'-apo-β-carotenoate	feed additive (egg yolk and broiler pigmentation)	chemical synthesis
 Citranaxanthin	feed additive (egg yolk and broiler pigmentation)	chemical synthesis

Table 1. Carotenoids industrial applications.

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