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# The Biochemistry and Antioxidant Properties of Carotenoids

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Additional information is available at the end of the chapter

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## Abstract

Carotenoids are one of the most widespread pigment groups distributed in nature, and more than 700 natural carotenoids have been described so far, and new carotenoids are introduced each year. Carotenoids are derived from 4 terpenes, including totally 40 carbon atoms. Carotenoids are naturally synthesized by cyanobacteria, algae, plants, some fungi, and some bacteria, but not made by mammals. Lately, the beneficial properties of  $\alpha$ -carotene,  $\beta$ -carotene,  $\gamma$ -carotene, lycopene, phytoene, phytofluene, lutein, zeaxanthin,  $\beta$ -cryptoxanthin, astaxanthin, and fucoxanthin carotenoids in prevention of various diseases, such as tumor formation, cardiovascular, and vision, have been documented due to their roles as antioxidants, activation in certain gene expression associated with cell-to-cell communication, provitamin A activity, modulation of lipoxygenase activity, and immune response. In this chapter, in addition to biochemical properties of carotenoids, how the structure of these molecules influences the oxidative stress in health and reducing the risk of formation of various diseases will be described.

**Keywords:** carotenoids, antioxidants, biochemistry, health, toxicity

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## 1. Introduction

Overproduction of reactive oxygen and nitrogen species, such as superoxide and peroxide radicals, plays important roles in the formation of breast, cervical, ovarian, and colorectal cancer in addition to some other malignancies in the cardiovascular system and eye. The antioxidant property of carotenoids may result from its double carbon-carbon bonds interacting with each other via conjugation and causing electrons in the molecule to move freely across these areas of the molecule. Carotenoid intake from food sources reduces the risk of breast, lung, head and neck, cervical, ovarian, colorectal, and prostate cancers and cardiovascular

or eye diseases due to their roles as antioxidants. It has been reported that carotenoids can directly interact with some free radical species.

## 2. The biochemistry and metabolism of main carotenoids

### 2.1. Terpenes

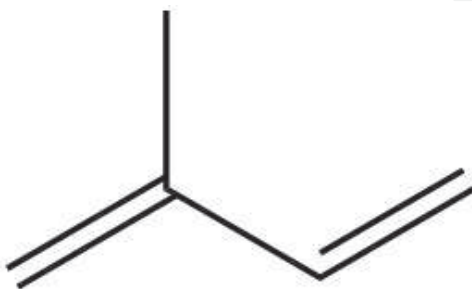
Terpenes are structures derived from isoprene chains. The chemical formula of the isoprene molecule is  $\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$  (2-methyl-1,3-butadiene) [1, 2]. There are two double bonds in the molecule and these bonds are conjugated (**Figure 1**). When 5-carbon containing isoprene molecules are polymerized, compounds called terpenes are formed [3]. This group includes biologically very important molecules. Some among these are lycopene,  $\beta$ -carotene, vitamin A, and squalene [4].

Terpenes are biosynthetically derived from isoprene units, the chemical formula of this unit is  $\text{C}_5\text{H}_8$ , and the basic molecular formulas of terpenes are multiplied, that is,  $(\text{C}_5\text{H}_8)_n$  ( $n$  is the number of joined isoprene units). The isoprene units can be connected from head to tail to form straight chains or rings. The isoprene unit is a building brick that is widely used in nature [5, 6].

Terpenes can be classified according to the number of isoprene units used, such as hemiterpenes (prenol and isovaleric acid); one isoprene unit (5C), monoterpenes (geraniol and limonene); two isoprene units (10C), sesquiterpenes (farnesol); three isoprene units (15C), diterpenes (quinagolides, sembren, and taxadiene); four isoprene units (20C), sesterterpenes; five isoprene units (25C), triterpenes (squalene); six isoprene units (30C), tetraterpenes (carotenoids); and eight isoprene units (40C), politerpenes, which include great number of isoprene units (natural rubber) [6–9].

Monoterpenes, sesquiterpenes, diterpenes, and sesterterpenes are formed by head-to-tail association of isoprene units, and triterpenes and tetraterpenes (carotenoids) are formed by head-to-head association [9].

The most important group of terpenes is carotenoids with the  $\text{C}_{40}\text{H}_{64}$  molecular formula which is formed by a tetraterpene containing eight isoprene units [8]. Carotenoids are terpene



**Figure 1.** Chemical formula for isoprene.

group materials which are formed by binding of 5-carbon-containing isoprene molecules, and they have straight chain structure formed by the condensation of isoprene molecules [1]. Carotenoids which colors vary from light yellow to dark red stemming from the double bonds are soluble in organic solvents and oils like other lipids [10].

## 2.2. Biosynthesis of terpenes and carotenoids

Carotenoids which are tetraterpenes and biological pigments including eight isoprene units are found in plants and some other photosynthetic microorganisms (naturally occurring cyanobacteria, algae, plants, some fungi, and some bacteria) [11].

Acetyl CoA, which is synthesized directly from free acetate as well as the oxidation of sugars and condensation of pyruvic acid or fatty acids, is used as a precursor in the synthesis of mevalonic acid in addition to synthesis of many natural compounds [9, 12]. First, two acetyl CoA molecules enter the reaction to give acetoacetyl-CoA, and then  $\beta$ -hydroxy- $\beta$ -methylglutaryl-CoA (HMG-CoA) is obtained via HMG-CoA synthase with another acetyl CoA. The reduction of the ester group in HMG-CoA by NADPH and HMG-CoA reductase (the pathway's rate limiting enzyme) results in mevalonic acid formation. Mevalonic acid later forms mevalonate 5-phosphate using a total of two molecules of ATP by mevalonate kinase, and then mevalonate 5-phosphate forms mevalonate 5-diphosphate by phosphomevalonate kinase (mevalonate phosphate kinase). Isopentenyl diphosphate (IPP) building blocks from decarboxylation of mevalonate diphosphate via mevalonate diphosphate carboxylase produce isoprene chains. IPP:dimethylallyl-PP isomerase converts IPP to dimethylallyl diphosphate (DMAPP) which is an acceptor by successive transfer of isopentenyl residues [9, 13]. After the release of the diphosphate, the hemiterpenes are produced from DMAPP. Upon condensation of DMAPP and IPP via geranyl-PP synthase (dimethylallyl transferase), geranyl-PP forms. Monoterpenes are produced by geranyl-PP, which is the precursor of volatile oils. Likewise, farnesyl-PP is formed by condensation of geranyl-PP with IPP via farnesyl-PP synthase (geranyl transferase). Sesquiterpenes are produced by condensation of farnesyl-PP. In addition, two molecules of farnesyl-PP give rise to triterpenes [13, 14]. Squalene, a triterpenic compound, is the precursor of sterols that participate in membrane structure. Geranylgeranyl-PP is formed from head-to-tail condensation of farnesyl-PP and IPP by geranylgeranyl-PP synthase (farnesyl transferase). Geranylgeranyl-PP also causes the formation of diterpenes (**Figure 2**) [9].

Tetraterpenes (carotenoids) are formed by the condensation of two molecules of geranylgeranyl-PP [9, 15]. The first carotenoid formed by prephytoene diphosphate in this step is phytoene which is found in green plants in association with chlorophyll. This first stable carotenoid synthesis takes place via the phytoene synthase. The second product of carotenoid biosynthesis, phytofluene, forms as a result of desaturation (catalyzed by the enzyme phytoene desaturase), which leads to the formation of saturated double bonds. Phytofluene, after having a series of dehydrogenation reactions, forms a symmetric molecule, lycopene, containing 11 double bonds. The next step,  $\alpha$ -carotene,  $\beta$ -carotene, and  $\gamma$ -carotene are produced from lycopene via ring formation in the end groups by lycopene cyclase.  $\alpha$ - and  $\beta$ -carotenes are the xanthophylls as a result of hydroxylation by  $\beta$ -carotene hydroxylase (**Figure 2**) [16, 17].

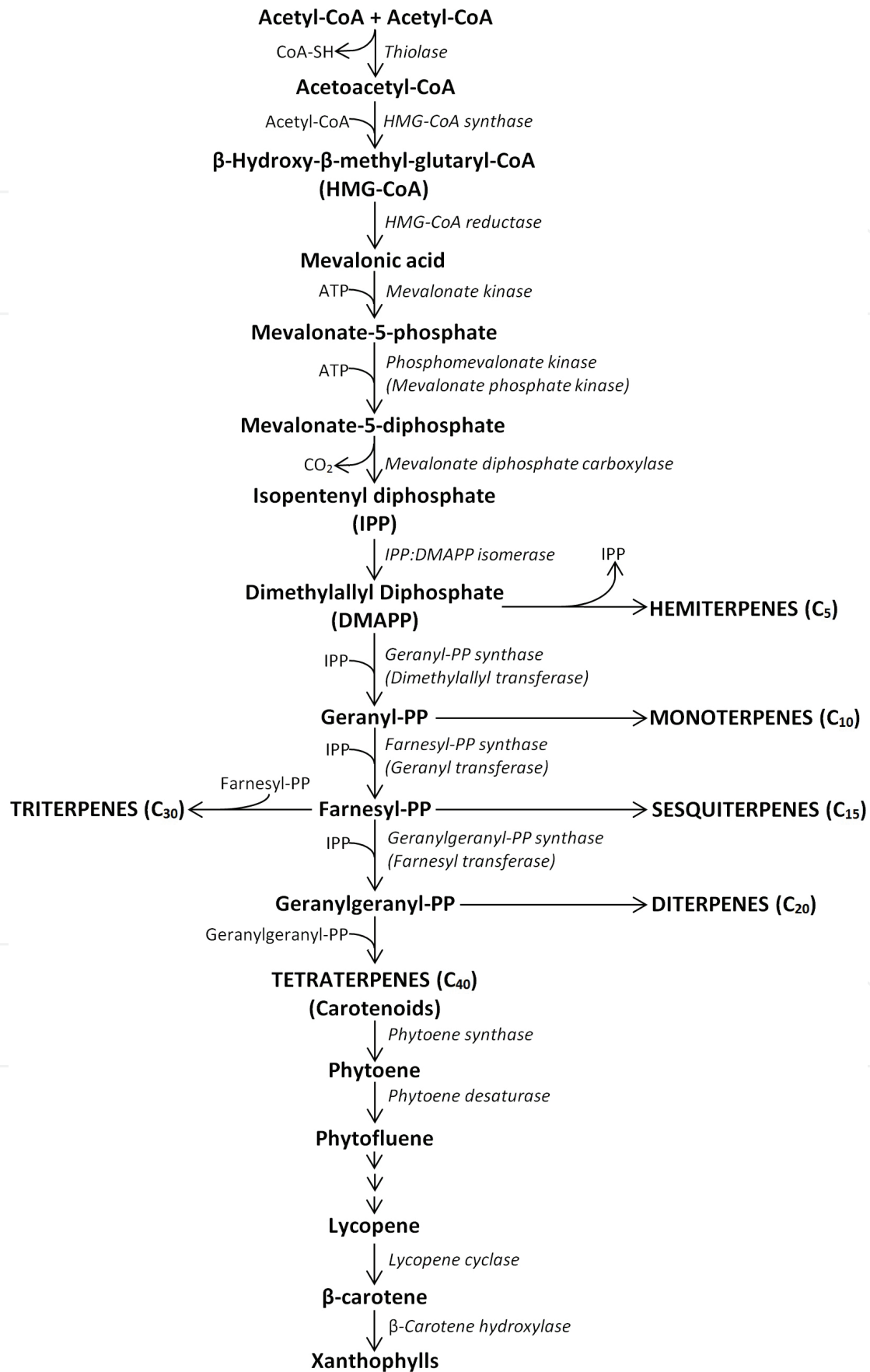


Figure 2. Biosynthesis of terpenes and carotenoids.

## 2.3. Carotenoids

More than 700 natural carotenoids have been identified, and new carotenoids have been added to this number every year [18–20]. Carotenoids are found in red-, yellow-, and orange-colored fruits and vegetables as well as in all green leafy vegetables [10].

Carotenoids are found in plant tissues as free forms (crystalline or amorphous) are dissolved form in an oily solvent. They may also be esterified with fatty acids or complexed with sugars and proteins [17]. The conjugate double-bond structure found in carotenoids also determines biological functions, such as absorption of light during photosynthesis, energy transfer, and protection from harmful effects of light on the cells during the photosynthesis. The presence of carotenoids also determines the characteristic color of these compounds [21].

Carotenoids are present in large quantities in the Leydig cells, which produce steroid hormones, and in the outer layer of the adrenal gland [22]. Carotenoids are also found in fresh broccoli, vegetables, butter, egg yolks, and animal-based foods [23].

## 2.4. Classification of carotenoids according to their structures

According to structures of carotenoids, two classes are distinguished as hydrocarbon carotenoids and xanthophylls (**Figure 3**) [24]. The apolar characteristics of hydrocarbon carotenoids are also called carotenes which include  $\alpha$ -carotene,  $\beta$ -carotene,  $\gamma$ -carotene, lycopene, phytoene, and phytofluene. Xanthophylls are more polar and contain oxygen in the form of methoxy, hydroxy, keto, carboxy, and epoxy positions. Examples of xanthophylls include lutein, zeaxanthin,  $\beta$ -cryptoxanthin, astaxanthin, and fucoxanthin [25, 26]. Carotenoids are also grouped as carotenoids with or without ring groups at the ends of the chain [26].

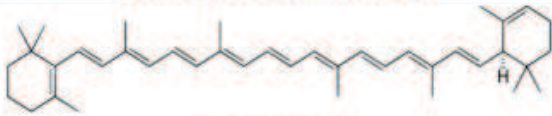
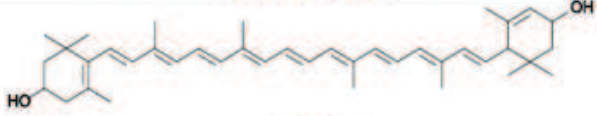
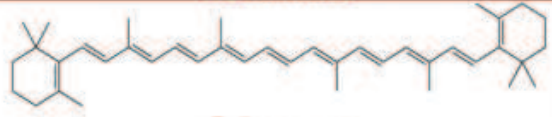
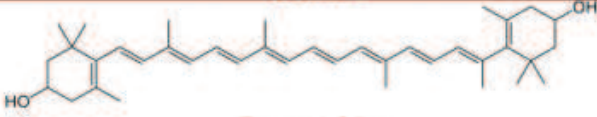
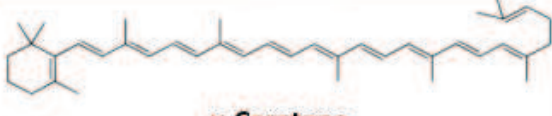
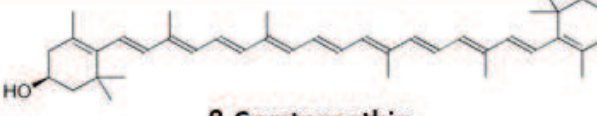

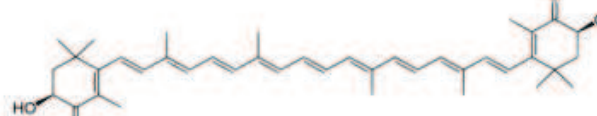
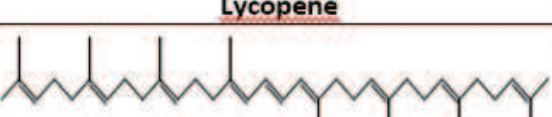
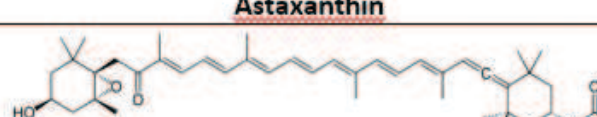
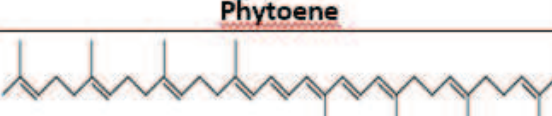
### 2.4.1. Hydrocarbon carotenoids

Carotenoids with hydroaromatic rings are called carotenes [23]. These rings are located at the both ends of the four isoprene molecules. Thus, there are two hydroaromatic rings in each carotene molecule. These hydrocarbons are called ionospheric rings and have three ionone rings. These are  $\alpha$ -,  $\beta$ -, and pseudo-ionone rings.  $\alpha$ - and  $\beta$ -ionone rings are closed rings and include one double bond. The position of the double bond  $\alpha$  is different in the  $\beta$ -ionone rings and pseudo rings. The pseudo-ionone ring includes two double bonds [3].

Carotene is a biochemically synthesized terpene from eight isoprene units [4, 8]. There are three main types,  $\alpha$ -carotene,  $\beta$ -carotene, and  $\gamma$ -carotene. The carotenoids are precursors of vitamin A and converted into vitamin A in the body. From  $\alpha$ -carotene and  $\gamma$ -carotene, one molecule of vitamin A while from  $\beta$ -carotene two molecules of vitamin A are synthesized [27–29].

$\alpha$ -Carotene molecule has  $\beta$ -ionone ring at one end and  $\alpha$ -ionone ring at the other end. There are four molecules of polymerized isoprene molecules between them. The structure of vitamin A is like half of an  $\alpha$ -carotene. Vitamin A has a  $\beta$ -ionone ring at one end and two isoprene molecules attached to it [27]. The second most common form of carotene,  $\alpha$ -carotene, is found mostly in carrots, sweet potatoes, squash, tomatoes, red peppers [30], and dark green vegetables [26].



Hydrocarbon Carotenoids	Xanthophylls
 <b>α-Carotene</b>	 <b>Lutein</b>
 <b>β-Carotene</b>	 <b>Zeaxanthin</b>
 <b>γ-Carotene</b>	 <b>β-Cryptoxanthin</b>
 <b>Lycopene</b>	 <b>Astaxanthin</b>
 <b>Phytoene</b>	 <b>Fucoxanthin</b>
 <b>Phytofluene</b>	

**Figure 3.** Classification of carotenoids according to their structures.

β-Carotene is a fat-soluble provitamin. Its active form is vitamin A [31]. The difference of β from α is that it carries the β-ionone ring at both ends. When β-carotene is divided into two molecules, vitamin A is synthesized [29]. It is found in fruits, cereals, vegetables (carrots, green plants, pumpkin, spinach), and oils [32].

γ-Carotene includes β-ionone ring at one end and the pseudo-ionone ring at the other end, and when the molecule is split, one molecule of vitamin A is synthesized [3].

Lycopene is an aliphatic carotenoid [33]. Lycopene is found among tomatoes, watermelons, pink grapefruit, and rosehip. Since lycopene dissolves in the oil, the presence of oils greatly increases its absorption by the digestive system [34].

Phytoene is a 40-carbon intermediate in the biosynthesis of phytoene carotenoids. Phytoene is a symmetric molecule containing three conjugated double bonds [35].

Phytofluene is an orange-colored carotenoid pigment found naturally in tomatoes and other vegetables [36].

#### 2.4.2. Xanthophylls

Xanthophylls contain oxygen atoms and are yellow pigments commonly found in nature [37].

Lutein is a dihydroxy-carotene formed from carotenoids with an alcohol group containing hydroaromatic  $\alpha$  structure [38]. Its both ionone rings carry hydroxyl groups [39]. Lutein is a substance that gives color to chicken fat, egg yolk, and chicken feathers [40]. That yellow-colored lutein found in plants is an organic colorant on leaves of green vegetables, such as spinach and black pepper. It is generally found in covalent interactions within fatty acids [20].

The chemical formulas of lutein and zeaxanthin are the same; in other words, they are isomers, but they are not stereoisomers. The difference between the two is the position of a double bond in the end ring [17, 39].

Zeaxanthin is one of the most common carotenoid alcohols found in the nature. It is a pigment that gives its color to maize, saffron, and many other plants. When the zeaxanthin breaks down, picrocrocin, which is responsible for the taste and aroma of the saffron, forms [41].

$\beta$ -Cryptoxanthin carotenoid has an alcohol group having a hydroaromatic structure including an OH group in one of its ionic rings. Since the other ring is the  $\beta$ -ionone ring, one molecule of vitamin A can be synthesized from it [27].

$\beta$ -Cryptoxanthin is a natural carotenoid pigment.  $\beta$ -Cryptoxanthin is found in fruits and vegetables, such as mandarin, red pepper, and zucchini, and has important functions for human health.  $\beta$ -Cryptoxanthin is closely related to  $\beta$ -carotene. Only one OH group was added to  $\beta$ -cryptoxanthin. Although  $\beta$ -carotene is present in large quantities in a large number of fruits and vegetables,  $\beta$ -cryptoxanthin is present in small number of food sources but at high concentrations [42].

Astaxanthin is a keto-carotenoid and is a zeaxanthin metabolite, containing both hydroxyl and ketone functional groups [17, 43]. Astaxanthin is found in microalgae, yeast, salmon, trout, shrimp, shellfish, and some birds' feathers [44].

Fucoxanthin, found in the chloroplasts of algae and mosses, gives them their brown or olive green color [45].

### 3. Antioxidant functions of carotenoids at molecular level for health and toxicity

The interest in carotenoids found in plants over the last years is not only due to their A provitamin activity but also due to their reduction of oxidative stress in the organism by capturing oxygen radicals, that is, their antioxidant effects [46]. Free oxygen radicals play an important role in the stress-related tissue damage and pathogenesis of inflammation. The imbalance between protective and damaging mechanisms results in acute inflammation accompanied by neutrophil infiltration [47, 48]. Superoxide radicals formed by neutrophils react with lipids and cause lipid peroxidation [49–51]. Carotenoids can inhibit active radicals by transferring electrons, giving hydrogen atoms to radicals or attaching to radicals [16].



The number of conjugate double bonds in their structure is closely related to the superoxide inhibitory effect of carotenoids [52, 53]. Carotenoids could remove singlet oxygen and peroxy radicals from reaction medium and also prevent their formation [53–55]. It is stated that carotenoids can inhibit cell renewal and transformation and regulate gene expression that plays a role in the formation of certain types of cancer. On the other hand, in some studies it has been shown that carotenoids could stimulate cancer in some cases. For example, it has been reported that in smokers, synthetic  $\beta$ -carotene does not create protective activity against lung cancer and cardiovascular diseases and even it fastens the progression of an aforementioned diseases [56–58].

The activity of carotenoids as antioxidants also depends on their interaction with other antioxidants, such as vitamins E and C [58]. In addition, some carotenoids and their metabolites activate the nuclear factor-erythroid 2-related factor-2 (Nrf2) transcription factor, which triggers antioxidant gene expression in certain cells and tissues [58, 59]. Thus, a number of chronic diseases characterized by oxidative stress, inflammation, and impaired mitochondrial function have been reported to reduce Nrf2 expression in some animal models. Elevation of Nrf2 has been shown to be effective in the prevention and treatment of many chronic inflammatory diseases, including various cardiovascular, renal, or pulmonary diseases; toxic liver damage; metabolic syndrome; sepsis; autoimmune disorders; inflammatory bowel disease; and HIV infection [58]. Prevention of low-density lipoproteins (LDL) oxidation by carotenoids has been suggested to be the basis of carotenoids' protective activity against coronary vascular disease [26].

The signaling pathways and molecules influenced by carotenoids to prevent various diseases, such as cancer and cardiovascular diseases, involve growth factor signaling members, cell cycle-associated proteins, differentiation-related proteins, retinoid-like receptors, antioxidant response element, nuclear receptors, AP-1 transcriptional complex, the Wnt/ $\beta$ -catenin pathway, angiogenic proteins, and inflammatory cytokines. During the treatment of cardiovascular and eye diseases and cancer, the dose and the exposure time of  $\beta$ -carotene, lycopene, lutein, and zeaxanthin have been reported to be crucial [37].

$\alpha$ -Carotene intake might decrease the development of non-Hodgkin lymphoma [60].  $\alpha$ -Carotene concentration in the blood may be associated with the development of various cancers [30].

$\beta$ -Carotene, which is accepted as a provitamin of vitamin A (retinol) which is required for the fulfillment of visual functions [61], effects the oxidative damage that formed on cellular lipids, proteins, and DNA as a result of sunlight and causes the formation of erythema, premature aging of the skin, development of photodermatitis, and skin cancer.  $\beta$ -Carotene protects the skin from harmful effects of UV light by its prevention of reactive oxygen species formation and anti-inflammatory properties [62, 63].

Studies have shown that  $\beta$ -carotene's provitaminase activity or antioxidant properties prevent diseases, such as atherosclerosis, cataracts, multiple sclerosis, and some types of cancers [64]. Moreover in recent studies,  $\beta$ -carotene has been proposed to decrease cell proliferation and induce apoptosis of various cancer cell lines by inhibiting calcium-/calmodulin-dependent

protein kinase IV [65]. In another study,  $\beta$ -carotene has been reported to have anticancer stem cell actions on neuroblastoma, and this anticancer action is enhanced by retinoic acid receptor  $\beta$  [66].

Lycopene, synthesized by many plants and microorganisms, is an antioxidant that cannot be synthesized by animals and humans [67]. Conjugated dienes are active in creating antioxidant activity [46], and lycopene is reported to have a higher antioxidant capacity than other carotenoids, and in particular among carotenoids, lycopene inhibits the risk of prostate cancer [52, 68].

The use of lycopene can reduce the risk of cardiovascular disease, diabetes, osteoporosis, and prostate, esophagus, colorectal, and mouth cancer risk. Recent studies indicate that lycopene intake has protective functions against cardiovascular diseases by lowering high-density lipoprotein (HDL)-associated inflammation [69]. It was proposed that there is an inverse association between the occurrence of pancreatic cancer and dietary lycopene intake together with vitamin A and  $\beta$ -carotene [70].  $\beta$ -Carotene 9',10'-oxygenase which is a key enzyme for the metabolism of lycopene has been proposed to have an important roles to prevent prostate cancer progression by inhibiting NF- $\kappa$ B signaling [71].

In neurodegenerative diseases, lycopene has been reported to increase permeability of blood-brain barrier, and a significant reduction in lycopene levels in diseases, such as Parkinson's disease and vascular dementia, has been observed. It has also been suggested that lycopene bestow protection against amyotrophic lateral sclerosis (ALS) impairment in humans [67].

The phytoene and phytofluene found in the diet accumulate in the human skin [72]. The dehydration of these carotenoids has a protective effect on the skin due to its UV absorber, antioxidant, and anti-inflammatory properties [73].

Zeaxanthin is one of two carotenoids found in the retina. Zeaxanthin mostly found at the center of the macula and lutein mostly found at the peripheral retina [39, 74]. Lutein and zeaxanthin are responsible for the formation of yellow pigment in the retina. Yellow pigments play an active role in protecting the eye from light and can prevent retinal damage [56].

$\beta$ -Cryptoxanthin acts as a chemopreventive agent against lung cancer.  $\beta$ -Cryptoxanthin has been reported to decrease lung cancer through downregulating neuronal nicotinic acetylcholine receptor  $\alpha 7$ /PI3K signaling pathway [75]. In addition to lung cancer,  $\beta$ -cryptoxanthin enhances the action of a chemotherapeutic agent, oxaliplatin, to treat colon cancer [76]. Moreover, high lycopene and  $\beta$ -cryptoxanthin including diet might protect against aggressive prostate cancer [77].

Astaxanthin has an important role in the treatment and prevention of certain diseases by its antitumor properties and protection against free radicals, oxidation of basic polyunsaturated fatty acids, and UV light effect on cell membranes [20, 78]. For example, high concentrations of astaxanthin may suppress mammary carcinoma [79]. In addition, astaxanthin has beneficial health effects against the formation of prostate carcinogenesis and tumor progression by reactivating the expression of Nrf2 and Nrf2-target genes through epigenetic modification and chromatin remodeling [80]. Astaxanthin has been shown to have antitumorigenic and anti-inflammatory effects on human lung cancer cell lines by inhibiting ERK1/2 activity [81].

In vitro studies indicate that fucoxanthin stimulates apoptosis and decreases proliferation and migration in glioma cancer cell lines U87 and U251 through Akt/mTOR and p38 pathway inhibition [82]. Fucoxanthin intake may have health benefits for the treatment of Alzheimer's disease by inhibiting acetylcholinesterase and enhancing brain-derived neurotrophic factor expression [83].

Supplementation of carotenoids by humans may have some beneficial biological actions against the formation of numerous diseases, such as cancer, cardiovascular diseases, or their skin. In addition to nutrient supplements in humans, carotenoids have applications in animal feed. Optimal health promoting actions of carotenoids depend on their proper doses, lengths of treatment, and combinations of carotenoids to maximize their effects. In this book chapter, latest findings on the biochemical and antioxidant activities of main carotenoids and their possible mechanisms of action will be presented.

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