



Role of Carotenoids in Preventing Oxidative Stress–Induced Cancer 18

Edakkadath Raghavan Sindhu, Antholi Keloth Kavya, and Ponnamparambil Purushothaman Binitha

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E. R. Sindhu (✉)

Division of Biochemistry, Malabar Cancer Centre, Kannur, Kerala, India

A. K. Kavya

Department of Biochemistry, Co operative Institute of Health Sciences, Kannur, Kerala, India

P. P. Binitha

Royal Dental College, Palakkad District, Kerala, India

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Abstract

Oxidative stress is the disproportion between the creation and balance of reactive oxygen species. Numerous recurrent ailments are described by high levels of inflammation and oxidative stress. Chemically, carotenoids are tetraterpenoids (C40 compounds), contain 8 isoprenoid residues, are mostly lipophilic in nature, and are synthesized by plants and few microorganisms; however, animals must take them through diet or food supplements. Carotenoids are classified into two basic groups – carotenes and xanthophylls. Lycopene, α -carotene and beta-carotene, comes under carotenes having hydrocarbon chain, while xanthophylls including lutein, zeaxanthin, beta-cryptoxanthin, and astaxanthin are oxidized derivatives of carotenes. Additionally, in the human body vitamin A (provitamin A carotenoids) is derived from dietary carotenoids.

There is actually a huge number of exploration considers that have researched the part of carotenoids in human health, beginning in the 1800s. A large number of studies have shown that carotenoids are related to antioxidant properties, immune modulators, reduced risk of various types of cancers, coronary artery diseases, and some eye disorders. This chapter discusses the types, sources, synthesis, uses, and protective efficacy of various types of carotenoids. Moreover, this chapter highlights the antioxidant properties of carotenoids, reflecting a wide range of key functional roles in biology.

Keywords

Free radical · Oxidative stress · Antioxidants · Carotenoids · Isoprenoids · Cancer

Introduction

The most common oxidants in biological systems are free radicals. Free radicals are explained as atoms or molecules or ions with unpaired electrons in their outer most part of the cells. Although free radical is highly reactive, for making stability it reacts with other electrons present in the living cells causing a chain reaction leading to the damage of the living cells.

Reactive oxygen-derived free radicals are frequently generated in the cell from oxygen, nitrogen, and sulfur molecules, and they are called reactive oxygen (ROS), nitrogen (RNS), and sulfur (RSS) species. Since ROS are unstable species, they may disintegrate the cell structure and lose the stability. They are capable to interact with lipids, proteins, and nucleic acids and thereby damaging cell membrane. At higher concentrations, these free radicals may exert oxidative stress, ultimately leading to cell damage (Uttara et al. 2009).

Main class of free radicals produced in living things were obtained from oxygen, such as superoxide, hydroxyl, peroxy ($RO_2\bullet$), alkoxy ($RO\bullet$), and hydroperoxy ($HO_2\bullet$) radicals (Valiko et al. 2007; Fang et al. 2002). RNS are borrowed from nitric

oxide through the response with $O_2 \cdot$ to make ONOO. RSS are easily formed from thiols by reaction with ROS (Giles and Jacob 2002).

Oxidative Stress

Oxidative stress is the reason for the development and advancement of nearly all types of ailments. Administration of exogenous antioxidants or improvement of endogenous antioxidants is an encouraging way in order to fight against free radicals that in turn leads to oxidative damage. Oxidative damage of macromolecules is caused by disproportion of free radicals and antioxidants (Prior and Cao 1999; Azab et al. 2017). ROS were produced by either adjunct of various cellular functions or by blood cells like neutrophils and macrophages (Lambeth 2004). Current research on oxidative stress is chiefly focusing on the advantages of cancer prevention agents, which are generally utilized by the cell to diminish ROS, and setting off apoptosis in tumors through improved oxidative stress conditions. Although oxygen is a vital element for living organisms, free radicals are produced by the body using oxygen in order to meet cellular respiration in mitochondria (Tiwari 2004). In our body, both types of reactive oxygen/nitrogen species (ROS/RNS) are the causative agents for different types of diseases like malignant growth, diabetes, cardiovascular issues, neurodegenerative ailments, inflammation, cataract, and osteoporosis (Loperena and Harrison 2017). The final result of this mechanism is aging which takes place through organelle damage and changes in gene expression promoted by signal transduction (Pandey and Rizvi 2010).

Antioxidants

Antioxidants are particles that repress or quench free radical responses and postpone or restrain cellular damage. Recently, studies showed that the identification of free radicals in small amount related to main functions in living organisms as well as endogenous antioxidants working opposing to this. The antioxidants in the body are used to curb oxidation process, and it consists of two main categories. Superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) belong to an enzymatic group. The nonenzymatic group contains albumin, bilirubin, glutathione, uric acid, ceruloplasmin, transferrin, and coenzyme Q10. Generally, natural and synthetic antioxidants are types of antioxidants which are developed to treat many diseases (Fig. 1).

Endogenous antioxidant enzymes like SOD, GPX, CAT, Glutathione reductase (GR), and glutathione thiotransferase (GST) are protecting the body from free radical-mediated oxidative stress. SOD, one of the best antioxidants among the endogenous antioxidant enzyme, converts the superoxide anion (O_2^-) into hydrogen peroxide, and thereby detoxified by CAT and glutathione peroxidase (GPx), and

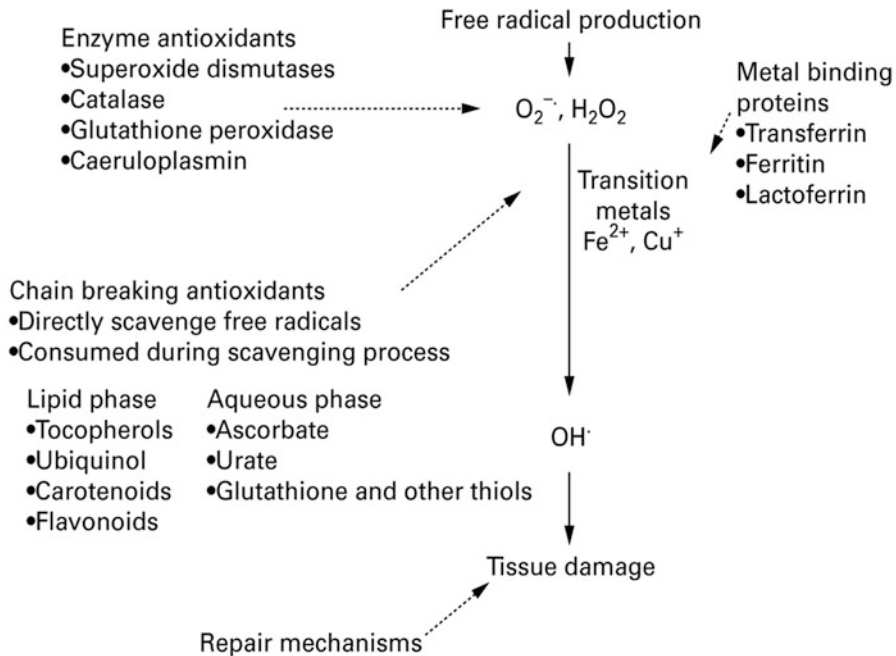


Fig. 1 Antioxidant defense against free radical attack

forms water molecule as the end product. Gpx catalyzes the reaction between reduced form of glutathione (GSH) and hydrogen peroxide, which is in turn operated by the elimination of hydrogen peroxide or lipid peroxides. The catalase enzyme acts on two hydrogen peroxide molecules and forms one molecule of oxygen and two molecules of water and hence protects the cell from damage (Von Ossowski et al. 1993).

GSH behaves as an antioxidant as well as a fundamental factor for GPX (Sastre et al. 1996). Upto a certain extent, ROS can be considered as protective molecules since it has a role in inflammation. When an organism is exposed to a high concentration of ROS, the endogenous antioxidant system may be incapable to ensure complete protection of the organism from the free radical-mediated damage. In order to overcome this deficit of antioxidants, the body can use exogenous antioxidant molecules. These antioxidant molecules may be obtained through a balanced diet that consists of all the essential nutrients thereby protecting the body from free radicals-mediated cell damage. Among all the available exogenous antioxidants, most important molecules are the carotenoids, vitamin C, and some minerals such as selenium and zinc, etc. Carotenoids are plant derivatives with strong antioxidant property. There is a balance between the ROS production and free radical scavenging activity by the antioxidant system in the body to prevent the free radical mediated cell damage and thereby effectively reducing degenerative diseases. Evidences from various studies suggest that the cellular effects of natural antioxidants

may be mediated by their interactions with specific proteins central to intracellular signaling cascades and protect the cell from ROS-mediated cell damage.

Carotenoids

They are found in many fruits, vegetables, plants, algae, and photosynthetic bacteria. They provided the distinctive yellow, orange, and red shades to leaves, fruits, vegetables, and flowers. All photosynthetic organisms, aphids, some bacteria, and fungi synthesized carotenoids. Moreover, this component is required for photosynthesis and production of carotenoid-derived phytohormones in plants (Mortensen 2006). Mammals including humans cannot synthesize carotenoids and must be obtained from the diet. Dietary intake of carotenoids in humans varies across individuals and cultures (Hammond and Renzi 2013). The marine sources of carotenoids include microalgae and marine animals.

Carotenoids are a distinctive group of over 750 pigments in nature. The predominant ones in plasma are beta-carotene, lycopene, lutein, beta-cryptoxanthin, and α -carotene (Fiedor and Burda 2014). Carotenoids can be categorized as: vitamin A precursors that do not pigment (e.g., beta-carotene); pigments with partial vitamin A activity (e.g., cryptoxanthin); nonvitamin A precursors that poorly or do not pigment (e.g., violaxanthin); and nonvitamin A precursors that pigment (e.g., lutein) (Takuji et al. 2012). Carotenes are hydrocarbons and include β -carotene and lycopene. They do not possess any substituent in their structure. Xanthophylls in addition to hydrogen and carbon have at least one oxygen atom in their structure (Hammond and Renzi 2013). Lutein and zeaxanthin are those xanthophylls with $-\text{OH}$ groups; canthaxanthin contains $=\text{O}$ groups; astaxanthin has $-\text{OH}$ and $=\text{O}$ groups; violaxanthin contains epoxy groups; and fucoxanthin has acetyl groups. Lutein and zeaxanthin are the examples for hydroxyl carotenoids, and astaxanthin and canthaxanthin are examples for keto carotenoids, based on if oxygen-containing substituent is a hydroxyl or ketone, respectively (Rodriguez 2009). The chemical group present in carotenoids is called isoprenoid polyenes, the group which is mainly focusing the pigmenting properties and various antioxidant functions.

Polarity can be modified depending on the polar functional groups present. Their structure causes them to absorb short wavelengths of light, and emergent light is of complementary color. Carotenoids play crucial role in biological systems. Studies have focused on few dietary compounds that are involved in aspects of human health or in photosynthetic processes. Epidemiological studies showed strong association between diet rich in fruits and vegetables and reductions in certain diseases, including cancer and heart disease.

Fat and bile acids are responsible for the solubilization of carotenoids present in the foods which takes place in the intestinal tract. Carotenoids interact with their own receptors and are transported to extrahepatic tissues, where they are degraded by lipoprotein lipase (Takuji et al. 2012). Violaxanthin is an example of epoxy xanthophylls, which are abundant in plants, cannot be incorporated and utilized by humans.

Sources of Carotenoids

Lycopene, β -carotene, astaxanthin, lutein, and zeaxanthin are some carotenoids synthesized by microorganisms (Bhosale et al. 2004), β -cryptoxanthin and canthaxanthin. In human plasma, the carotenoids which are seen most abundantly are lycopene, α -carotene, β carotene, lutein, zeaxanthin, and β -cryptoxanthin (Aizawa and Inakuma 2007). Microorganisms seen in marine environment can synthesize huge amount of carotenoids which had significant research applications in biology. A characteristic array of carotenoid pigments is produced by few filamentous fungi and yeasts. Fruits and flowers having their own characteristic colors are given by carotenoids and, moreover, play significant metabolic and physiological functions, particularly applicable in photosynthesis. However, the functions of carotenoids in nonphotosynthetic microorganisms are not clear; they have an important role as photo-protective as well as indispensable components in photosynthesis (Walter and Strack 2011). The bright orange color of carrots is given by the most popular carotenoid, carotene.

The principal carotenoid present in fruits is xanthophyll, whereas in tomato the major pigment is lycopene. β -cryptoxanthin and zeaxanthin are the chief pigments in mango; β -carotene in carrots; β -cryptoxanthin, lutein, antheraxanthin, violaxanthin, and traces of their carotene precursors in oranges; and lutein is present in dark green leafy vegetables. Certain carotenoids are typically found in single species. Capsanthin and capsorubin are responsible for the attractive colors of ripe fruits of the genus *Capsicum*. Even though carotenoids have important function in human health, they are not considered as essential nutrients, and so carotenoids do not have a dietary reference intake (DRI) value (Rao and Rao 2007).

More than 250 carotenoids are of marine origin with structural diversity. For example, allenic carotenoids except for neoxanthin and its derivatives (e.g., fucoxanthin) and all acetylenic carotenoids (e.g., alloxanthin) are originated from marine algae and animals. All marine animals except autotrophic marine organisms can either directly accumulate carotenoids from food or modify them through metabolic mechanisms by oxidation, reduction, etc. Major carotenoids in sponges are aryl carotenoids (e.g., isorenieratene); astaxanthin was found in some jelly fish. Lutein, zeaxanthin, and fucoxanthin are found in chitons. The principal carotenoid in crustaceans is astaxanthin and exhibits pink, red, blue, and yellow colors. Many fishes accumulate carotenoids in their integuments and gonads. Astaxanthin is widely distributed in fishes.

Carotenoid Biosynthesis

Plants and numerous microorganisms can produce carotenoids in nature. All types of photosynthetic organisms like cyanobacteria, algae, and plants can synthesize carotenoids, whereas certain bacteria and fungi which do not have the capacity to do

photosynthesis cannot. The carotenoid biosynthetic pathway has been broadly concentrated in higher plants (Cunningham and Gantt 1998). Animals are not possible to produce carotenoids but can be used in a proper way. Carotenoid belongs to isoprenoid family, and eight isoprene units are condensed to produce tetraterpenoids (C₄₀). Linkage order is reversed at the center of molecule, so the molecule as a whole is symmetrical. Carotenoids are synthesized from basic terpenoid precursor, isopentyl pyrophosphate, and then converted to geranyl geranyl pyrophosphate whose dimerization and successive reactions lead to synthesis of lycopene and carotene.

Here, Geranyl geranyl pyrophosphate is formed by condensation reaction, which is the first step in this pathway. Isopentenyl pyrophosphate (IPP) reacts with dimethylallyl pyrophosphate (DMAPP) to form geranylgeranyl pyrophosphate in the presence of enzyme geranylgeranyl pyrophosphate synthase, which is a key intermediate in the synthesis of carotenoids. Geranyl geranyl pyrophosphate also serves as precursor for chlorophyll, phyloquinones, tocopherols, gibberellin, etc., and therefore, its synthesis is subjected to complex regulation (Bartley and Scolnik 1995).

Through methyl erythritol 4-phosphate (MEP) pathway, IPP is synthesized. Various steps are then required to form IPP and DMAPP (Penna and Pogson 2006). Two Geranyl geranyl diphosphate molecules are again condensed and form 15-Z-phytoene by phytoene synthase. Four double bonds are formed through dehydrogenation reactions catalyzed by the enzymes Phytoene- and zeta-carotene desaturases. Isomerases include carotenoid isomerase and zeta-carotene isomerase. The next step is the key branch-point in pathway; lycopene ϵ -cyclases and lycopene β -cyclases were utilized for the cyclization of lycopene to form δ -carotene and β -carotene, respectively. In one branch, β -ionone ring is introduced at both ends of lycopene by lycopene β -cyclases to form β -carotene, whereas the next branch, which ends for the synthesis of lutein, utilizes two enzymes both lycopene ϵ -cyclases and lycopene β -cyclases to introduce one β - and one ϵ -ionone ring into lycopene to form α -carotene. β -ionone ring is essential for the activity of provitamin A. Thus, lycopene lacks provitamin A activity. β -ring hydroxylase converted α -carotene into zeinoxanthin, which is hydroxylated by ϵ -ring hydroxylase to produce lutein. Zeaxanthin is synthesized from β -carotene in the presence of enzyme β -carotene hydroxylase. Epoxidation of zeaxanthin leads to antheraxanthin and violaxanthin catalyzed by zeaxanthin and antheraxanthin epoxidases, respectively. In the presence of neoxanthin synthase, neoxanthin is formed from Violaxanthin (Saini et al. 2015).

After biosynthesis, they accumulate in plastids, chromoplasts, chloroplasts, or leucoplasts. Most prevalent carotenoids in chromoplasts are xanthophylls. However, there exist unique biosynthetic routes for synthesis of some carotenoids in some other plants and algae. Bright red color of red pepper is due to the presence of keto-xanthophylls, capsanthin, and capsorubin which are formed by the conversion of antheraxanthin and violaxanthin, catalyzed by enzyme, capsanthin-capsorubin synthase (Saini et al. 2015).

Structural Features of Carotenoids

Carotenoids are pigments with charming structural peculiarities. The presence of conjugating double bonds imparts them with exclusive colors and is responsible for excellent antioxidant properties. Their polarity depends on polar functional groups. Carotenoids are typically located within the biological membranes and may affect various membrane features like rigidity and thickness and are confined to hydrophobic compartment. But when they get associated with proteins, they attain accessibility to aqueous environment. Carotenes scavenge radicals in the lipid phase; xanthophylls scavenge lipid phase and aqueous phase radicals.

Both beta and alpha carotene have two isomers existing, *trans/cis*. Among these two isomers, *trans* form is more common is *trans* form; but also isomerizes to a mixture of mono- and poly-*cis*-isomers. When compared to all *trans* isomers, *cis*-isomers have higher solubility and so are more readily absorbed and transported (Stahl and Sies 2003) (Fig. 2).

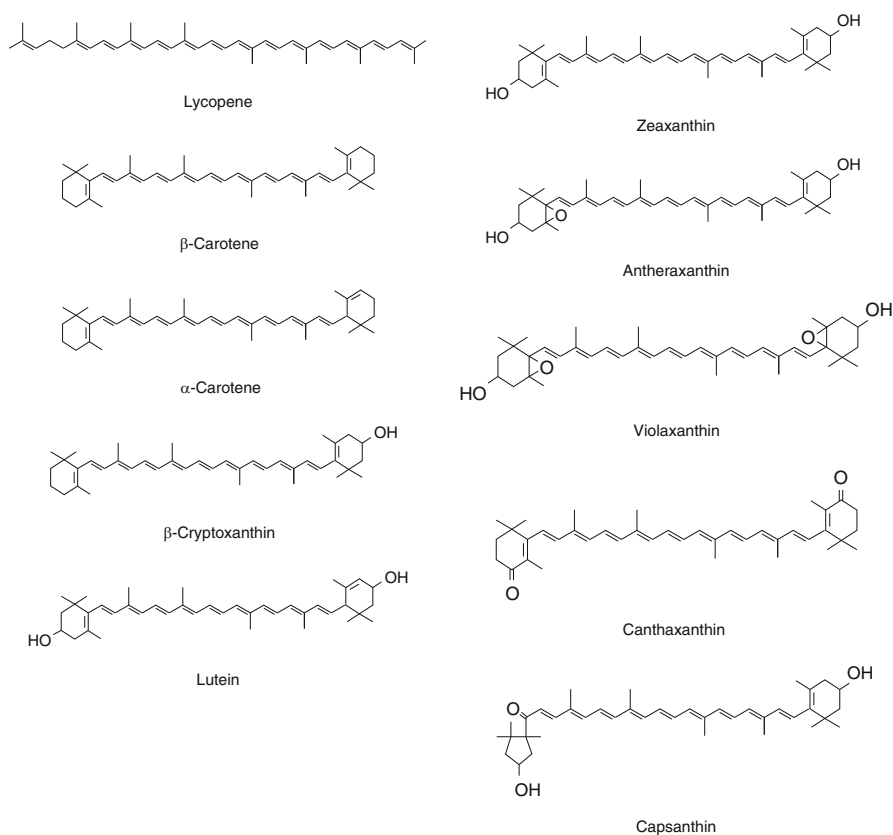


Fig. 2 Chemical structures of several all-*trans* carotenoids (Oliver and Palou 2000)

Chloroplast contains carotenoids that are involved in light harvesting and play an important role in photo-oxidative damage (Olson 1994) (Di Pietro et al. 2016). Usually compounds are seen in red, orange, or yellow due to carotenoids absorbing wavelengths between 400 and 550 nanometers (Gauger et al. 2015).

Lutein, zeaxanthin, β -cryptoxanthin, alpha-carotene, β -carotene, lycopene, phytoene, and phytofluene, the principal carotenoids in human fluids and tissues, are the most bioavailable dietary carotenoids (Mel'endez-Mart'inez et al. 2017). Two main forms of carotenoids can be identified: carotenes-pure hydrocarbons, whereas xanthophylls are derivatives containing one or more functions of oxygen.

Carotenoid's health-related role has had an impact on human nutrition such as antioxidant functions and has been reported to combat noncommunicable diseases (Siepelmeyer et al. 2016). It is suspected that the antioxidant properties of β -carotene and the properties of immunomodulation play a significant role in preventing initiation and progression of the disease. β -carotene, which is found in food-containing carotenoids, can avoid macular degeneration and cataracts (Agte and Tarwadi 2010). In an effort to prevent carcinogenesis caused by UV light, chemical carcinogens, or a combination of both, carotenoids have been added to the diets of laboratory animals (Epstein 1977; Mathews-Roth and Krinsky 1985). With the discovery of new apocarotenoid phytohormones called strigolactones, new roles for carotenoids have recently appeared in plants (Xie et al. 2010).

General Functions of Carotenoids

Functions depend on peculiarities of their structure. In plants, they are accessory pigments for photosynthesis, protection against photo-oxidation, etc.; in humans, they provide health-promoting functions. ROS generated during metabolic processes can damage DNA and cause detrimental effects. Carotenoids are biological antioxidants. Their functions are mainly attributed to antioxidant property (Di Mascio et al. 1991).

Carotenoids also exhibit important role in prevention of various cancers by inhibiting cell proliferation, induction of apoptosis, as well as by modulating gene expression. They have protective role against tumor initiation and progression. Capsanthin and related carotenoids possess antitumor-promoting activity. Dietary carotenoids can prevent oxidative stress and photo aging of skin which might be induced upon chronic exposure to sunlight and confer protection to skin by preventing formation of ROS, thereby they can protect against skin cancer (Terao et al. 2010). Antioxidant activity of β -carotene helps in reduction of cardiovascular diseases (Voutilainen et al. 2006). Antioxidant role of lutein and zeaxanthin helps to prevent the photo oxidation of lens protein that can lead to its aggregation and precipitation and result in age-related macular degeneration (AMD) and cataract (Mayne 1996). The overall mechanism of action takes place by carotenoids to protect the free radicals-induced organelle damage, and how they impart changes in gene expression by various signal transduction mechanisms is explained in the diagram (Fig. 3) (Pandey and Rizvi 2010).

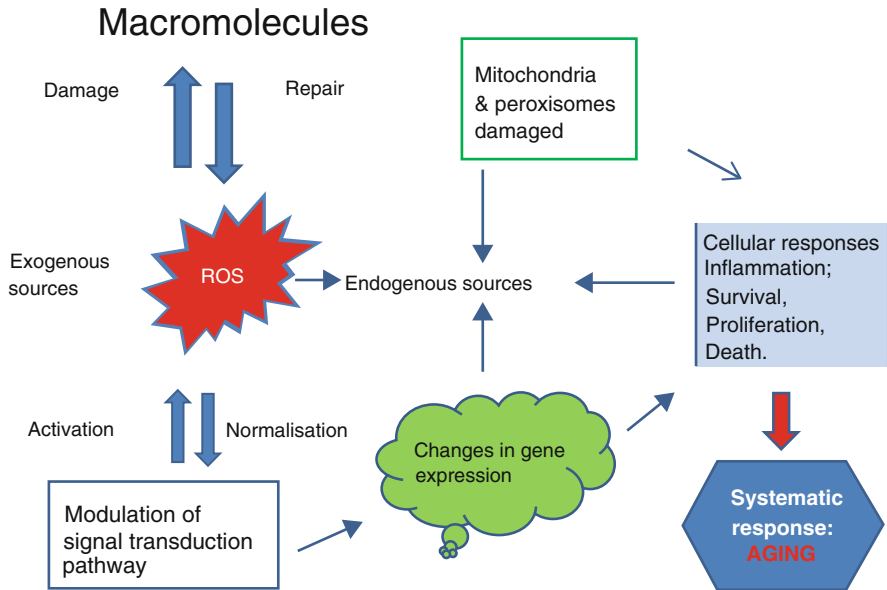


Fig. 3 ROS modulate the signal transduction pathways, which result in organelle damage, and changes in gene expression followed by altered responses of the cells, which finally results into aging. (Adapted from Pandey and Rizvi 2010)

β -Carotene

It is a provitamin A carotenoid. It is the only natural compound that protects photosynthetic reaction center complexes from damage and also provides effective treatment for erythropoietic protoporphyria. Carotene also intensifies gap-junction communications of cell membranes by increased expression of junctional protein.

Lycopene

Although lycopene does not have provitamin A activity, aging and cardiovascular diseases can be prevented by its administration. It provides immunity and inhibits lipid peroxidation through scavenging of ROS.

Lutein

Lutein is a dietary oxygenated carotenoid that is predominant in human retina. It prevents lipid peroxidation and is also protective against AMD and cataract. Lutein has a strong anti-inflammatory and ROS-scavenger capacity. It exerts cardioprotective effect by decreasing oxidative stress and myocyte apoptosis and protecting myocardium from ischemia or injury (Gammone et al. 2015).

Zeaxanthin

Zeaxanthin is an oxygenated non-provitamin A carotenoid. Its increased consumption is correlated with increased macular pigment density, and decreased rate of AMD. It also prevents oxidative damage of DNA and is also beneficial to arterial health (Gammone et al. 2015).

β-Cryptoxanthin

β-cryptoxanthin is a xanthophyll with provitamin A activity and has protective health benefits. It can ameliorate respiratory function and reduce rate of lung carcinomas and coronary artery diseases. It also has stimulatory effect on bone formation and an inhibitory effect on bone resorption (Gammone et al. 2015).

Astaxanthin

Astaxanthin is a xanthophyll abundant in marine world. It is responsible for typical coloration of salmon and crustaceans. Humans cannot synthesize and should be consumed through diet.

Canthaxanthin

Canthaxanthin may have negative effects on human health. Canthaxanthin retinopathy is a condition of accumulation of crystals in retina and leads to destruction of the blood vessels. Canthaxanthin may also have anticarcinogenic, immune-enhancing, antioxidative activities (Takuji et al. 2012).

Fucoxanthin

Fucoxanthin is one of the most abundant xanthophyll without provitamin A activity. It acts on the reduction of major cardiovascular risk factors, such as obesity, diabetes, high blood pressure, etc.

Future Perspectives of Carotenoids

Oxidative stress, which is caused by an overproduction of free radicals (FR), poses a high risk to human health. Thus, research field of current interest is to discover successful methods for scavenging FR. A specific ratio of antioxidants and ROS is maintained by each body type, and the imbalance induces oxidative stress.

Therefore, in diets for the preservation of good health and the prevention of various pathological diseases, antioxidants are widely supplemented.

A large amount of experimental data showed that carotenoids have important activity, and numerous of them are biologically active substances. Currently, researchers focused on compounds which efficiently reduce oxidative stress induced by free radicals that can cause several health-related problems.

In order to document changes in carotenoid structure and antioxidant properties in pathological conditions, additional studies, especially *in vivo*, are required. To explain the molecular processes and signaling pathways involved in carotenoid behavior, further studies are still required. Carotenoids used as a therapeutic agent in several oxidative stress induced by free radical and related studies are not adequate and are still being explored. Additional research is needed; carotenoids therapeutic usefulness against cancer still has many open fronts that should be investigated in the future. To validate the findings, higher quality studies with larger samples should be conducted. In addition, on this topic, further studies are required.

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