Preventive Role of Carotenoids in Oxidative Stress-Induced Cancer

139

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

Contents

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), consisting of 8 isoprenoid residues, mostly lipophilic in

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, Challissery, Kerala, India

S. Chakraborti et al. (eds.), *Handbook of Oxidative Stress in Cancer: Mechanistic Aspects*, https://doi.org/10.1007/978-981-15-9411-3_168

nature, and 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 come 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 have been a huge number of explorations that considered and have researched the part of carotenoids in human health, beginning during the 1800s. A large number of studies have shown that carotenoids are related to antioxidant properties, immune modulators, and 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 the outermost 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.

In the science framework, the free radicals are frequently copied from oxygen, nitrogen, and sulfur molecules. These free radicals are portions of groups of molecules called reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS). ROS are unstable species that pair up their odd free electrons by attacking healthy cells, causing a loss of cell structure and/or function (Uttara et al. 2009).

The main class of free radicals produced in living things were gotten from oxygen, such as superoxide, hydroxyl, peroxyl (RO2•), alkoxyl (RO•), and hydroperoxyl (HO2•) radicals (Valko et al. 2007; Fang et al. 2002). RNS are borrowed from nitric oxide through the response with O2 • 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 are 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 such as 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 such as malignant growth, diabetes, cardiovascular issues, neurodegenerative ailments, inflammation, cataract, and osteoporosis (Loperena and Harrison 2017). 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. Recent studies have shown that the identification of free radicals in small amount related to main functions in living organisms and the endogenous antioxidants working opposing toward this. Antioxidants are the substances which are used to curb oxidation process. The antioxidants in the body consist of two main categories. Superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase belong to enzymatic group, and nonenzymatic group contains albumin, bilirubin, glutathione, uric acid, ceruloplasmin, transferrin, and coenzyme Q10; the compounds differ in their target molecules. Generally, natural and synthetic antioxidants are types of antioxidants which are developed to treat many diseases (Fig. 1).

Endogenous antioxidant enzymes are SOD, GPX, CAT, GSH reductase (GR), and glutathione thiotransferase (GST). The main element of the enzymatic system of antioxidant protection is superoxide dismutase (SOD), which converts the superoxide anion ($O2-$) into hydrogen peroxide, which is ultimately detoxified by catalase (CAT) and glutathione peroxidase (GPx), with the water molecule as the end product (Yang and Lee 2015).

Glutathione peroxidase 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. Catalase breaks down two hydrogen peroxide molecules into one molecule of oxygen and two molecules of water in a two-step reaction (Von Ossowski et al. 1993).

GSH behaves as an antioxidant as well as a fundamental factor for glutathione peroxidase (GPX) (Sastre et al. 1996). When an organism is exposed to a high concentration of ROS, the endogenous antioxidant system is compromised, and consequently it fails to guarantee complete protection of the organism. To compensate this deficit of antioxidants, the body can use exogenous antioxidants supplied

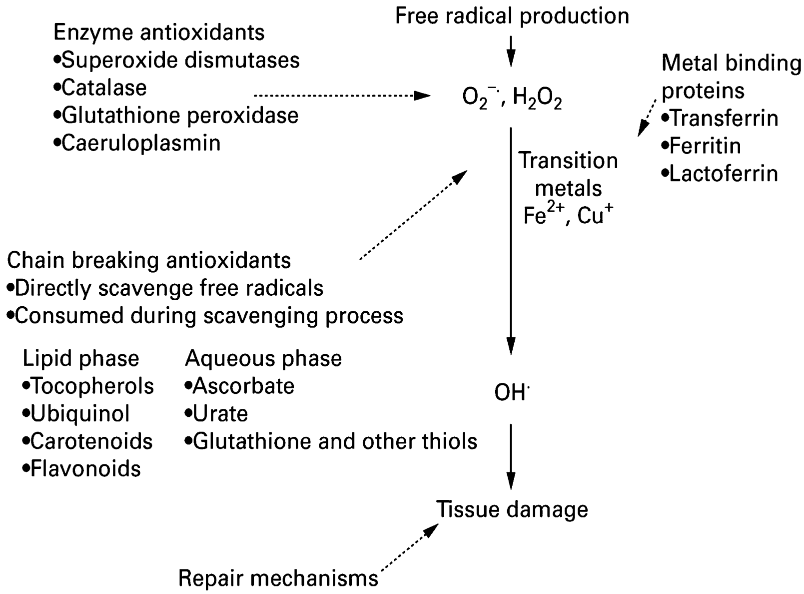

Fig. 1 Antioxidant defense against free radical attack

through food, nutritional supplements, or pharmaceuticals. Among the most important exogenous antioxidants are the phenolic compounds, carotenoids, and vitamin C and some minerals such as selenium and zinc. Accumulating evidence suggests that the cellular effects of natural antioxidants may also be mediated by their interactions with specific proteins central to intracellular signaling cascades.

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 the 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 (Maoka 2011).

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 follows: vitamin A precursors that do not pigment (e.g., beta-carotene), pigments with partial vitamin A activity (e.g., cryptoxanthin), non-vitamin A precursors that poorly or do not pigment (e.g., violaxanthin), and non-vitamin 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 –OH groups; canthaxanthin contains =O groups; astaxanthin has –OH and =O groups; violaxanthin contains epoxy groups; and fucoxanthin has acetyl groups. Lutein and zeaxanthin are examples of hydroxyl carotenoids, and astaxanthin and canthaxanthin are examples of keto-carotenoids, based on if an 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 on the pigmenting properties and various antioxidant functions (Oliver and Palou 2000).

Polarity can be modified, depending on the polar functional groups present. Their structure causes them to absorb short wavelengths of light, and the emergent light is of complementary color (Jomova and Valko 2013). Carotenoids play a 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 has taken 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 are utilized by humans.

Sources of Carotenoids

Apart from plant sources, lycopene, β-carotene, astaxanthin, lutein, zeaxanthin, β-cryptoxanthin, and canthaxanthin are some carotenoids synthesized by microorganisms (Bhosale et al. 2004; Bhosale and Bernstein 2005). In human plasma the carotenoids which are seen most abundant are lycopene, α-carotene, βcarotene, 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. Characteristic arrays of carotenoid pigments are produced by few filamentous fungi and yeasts. Fruits and flowers having their own characteristic colors are given by carotenoids, which moreover play significant metabolic and physiological functions, particularly applicable in photosynthesis. However, the functions of carotenoids in non-photosynthetic microorganisms are not clear; they have an important role as photoprotective as well as indispensable components in photosynthesis (Walter and Strack 2011; Sui et al. 2013). 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 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* (Milani et al. 2017). Even though carotenoids have an 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 jellyfish. 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, such as 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 use 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 the molecule; so the molecule as a whole is symmetrical. Carotenoids are synthesized from a basic terpenoid precursor, isopentenyl pyrophosphate, and then converted to geranylgeranyl pyrophosphate, whose dimerization and successive reactions lead to synthesis of lycopene and carotene (Kiokias et al. 2016).

Here, geranylgeranyl 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. Geranylgeranyl pyrophosphate also serves as precursor for chlorophyll, phylloquinones, tocopherols, gibberellin, etc., and therefore, its synthesis is subjected to complex regulation (Bartley and Scolnik 1995).

Through methylerythritol 4-phosphate (MEP) pathway, IPP is synthesized. Various steps are then required to form IPP and DMAPP (Penna and Pogson 2006). Two geranylgeranyl 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 the 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, introduction of β-ionone ring at both ends of lycopene by lycopene β-cyclases and forms β-carotene. Whereas in the next branch, that 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. The most prevalent carotenoids in chromoplasts are xanthophylls. However, there exist unique biosynthetic routes for synthesis of some carotenoids in some other plants and algae. The 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 the 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 such as 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 (Kaulmann 2014).

Both beta- and alpha-carotene have two isomers existing, trans and cis. Among them, the most common isomer is trans form; but it 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).

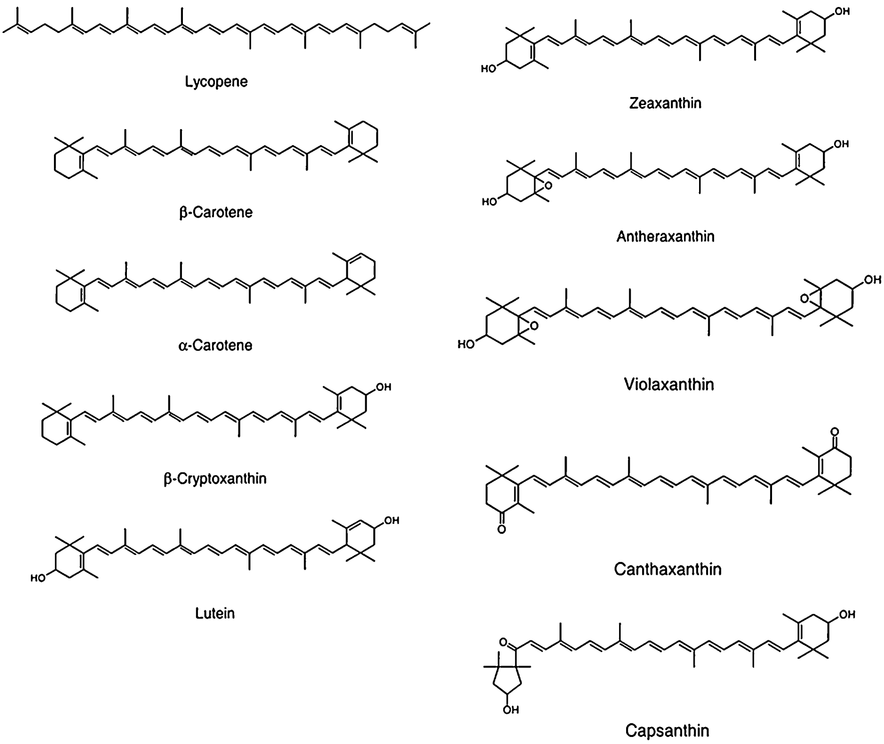

Fig. 2 Chemical structures of several all-trans carotenoids (Oliver and Palou 2000)

Chloroplast contains carotenoids that are involved in light harvesting and play an important role in photooxidative damage (Olson 1994; Di Pietro et al. 2016). Usually compounds are seen in red, orange, or yellow due to carotenoids, which absorb 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 (Meléndez Martínez et al. 2017). Two main forms of carotenoids can be identified: carotenes are pure hydrocarbons, whereas xanthophylls are derivatives containing one or more functions of oxygen (Bramley 1997).

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; Bernstein et al. 2016). It is suspected that the antioxidant properties of β-carotene and the properties of immunomodulation play a significant role in preventing the 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 (Yoneyama et al. 2019; Xie et al. 2010).

General Functions of Carotenoids

Functions of carotenoids depend on the peculiarities of their structure. In plants, they are accessory pigments for photosynthesis, protection against photooxidation, 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 modulating gene expression. They have protective role against tumor initiation and progression. Capsanthin and related carotenoids possess antitumor-promoting activity (Perera and Yen 2007). Dietary carotenoids can prevent oxidative stress and photoaging 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 the reduction of cardiovascular diseases (Voutilainen et al. 2006). Antioxidant role of lutein and zeaxanthin helps to prevent the photooxidation 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 general expression by various signal transduction mechanisms is explained in the diagram (Fig. 3) (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 (Perera and Yen 2007).

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.

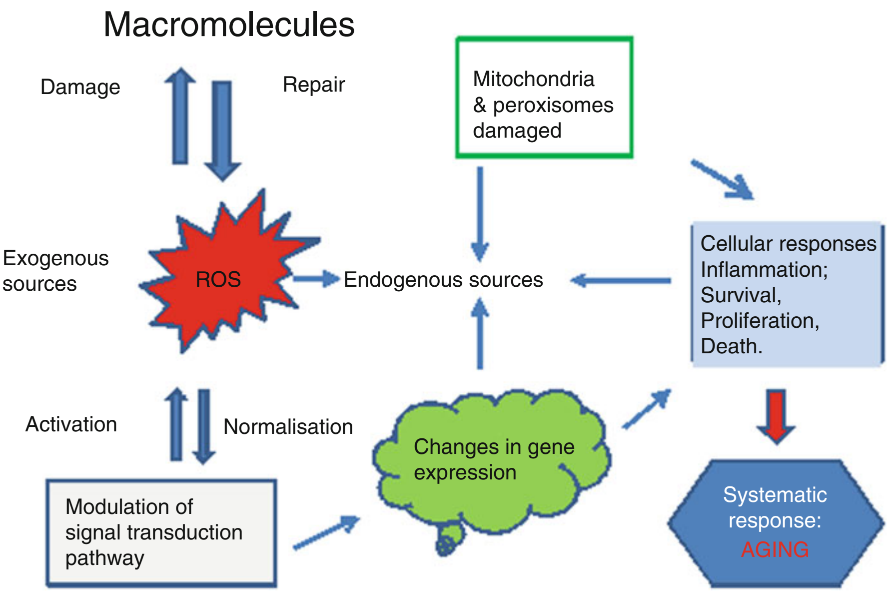

Fig. 3 ROS modulate the signal transduction pathways, which result in organelle damage, and changes in gene expression followed by altered responses of the cells, which finally result into aging. (Adapted from Pandey and Rizvi 2010)

Lutein

Lutein is a dietary oxygenated carotenoid that is predominant in the 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 the 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 it and should be consumed through diet.

Canthaxanthin

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

Fucoxanthin

A number of studies were conducted on carotenoids to find out its efficacy as a therapeutic agent against free radical induces oxidative stress. However these studies were not being well explored its complete mechanisms of action.

Conclusion

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. Related studies on carotenoids used as a therapeutic agent in several oxidative stresses induced by free radicals are not adequate and still being explored. Additional research is needed; carotenoid's 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.

References

Agte V, Tarwadi K (2010) The importance of nutrition in the prevention of ocular disease with special reference to cataract. Ophthalmic Res 44:166–172

Aizawa K, Inakuma T (2007) Quantitation of carotenoids in commonly consumed vegetables in Japan. Food Sci Technol Res 13:247–252

Azab AE, Albasha MO, Elsayed ASI (2017) Prevention of nephropathy by some natural sources of antioxidants. Yangtze Med 1:235–266

Bartley GE, Scolnik PA (1995) Plant carotenoids: pigments for photo-protection, visual attraction and human health. Plant Cell 7:1027–1038

Bernstein PS, Li B, Vachali PP, Gorusupudi A, Shyam R, Henriksen BS, Nolan JM (2016) Lutein, zeaxanthin, and meso-zeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. Prog Retin Eye Res 50:34–66

Bhosale P, Bernstein PS (2005) Microbial xanthophylls. Appl Microbial Xanthophylls 68:445–455

Bhosale P, Larson AJ, Bernstein PS (2004) Factorial analysis of tricarboxylic acid cycle intermediates for optimization of zeaxanthin production from Flavobacterium multivorum. J Appl Microbiol 96:623–629

Bramley PM (1997) 11-lsoprenoid metabolism, Plant Biochemistry Academic Press, New York

Cunningham FX, Gantt E (1998) Genes and enzymes of carotenoid biosynthesis in plants. Annu Rev Plant Physiol Plant Mol Biol 49:557–583

Di Mascio P, Murphy ME, Sies H (1991) Antioxidant defence systems; the role of carotenoids, tocopherols and thiols. Am J Clin Nutr 53:194–120

Di Pietro N, Di Tomo P, Pandolfi A (2016) Carotenoids in cardiovascular disease prevention. JSM Atheroscler 1:1–13

Epstein JH (1977) Effects of β-carotene on ultraviolet induced cancer formation in the hairless mouse skin. Photochem Photobiol 25:211–213

Fang YZ, Yang S, Wu G (2002) Free radicals, antioxidants, and nutrition. Nutrition 18:872–879

Fiedor J, Burda K (2014) Potential role of carotenoids as antioxidants in human health and disease. Nutrients 6:466–488. https://doi.org/10.3390/nu6020466Z

Gammone MA, Riccioni G, D'Orazio N (2015) Carotenoids: potential allies of cardiovascular health? Food Nutr Res 59:26762. https://doi.org/10.3402/fnr.v59.26762

Gauger T, Konhauser K, Kappler A (2015) Protection of phototrophic iron (II)-oxidizing bacteria from UV irradiation by biogenic iron (III) minerals: implications for early Archean banded iron formation. Geology 43:1067–1070

Giles GI, Jacob C (2002) Reactive sulfur species: an emerging concept in oxidative stress. Biol Chem 383:375–388

Hammond BR, Renzi LM (2013) Carotenoids. Adv Nutr 4:474–476. https://doi.org/10.3945/an.113.004028

Jomova KA, Valko M (2013) Health protective effects of carotenoids and their interactions with other biological antioxidants. Eur J Med Chem 70:102–110. https://doi.org/10.1016/j.ejmech.2013.09.054

Kiokias, Proestos, Varzakas (2016) A review of the structure, biosynthesis, absorption of Carotenoids-analysis and properties of their common natural extracts. Curr Res Nutr Food Sci 4:25–37. https://doi.org/10.12944/CRNFSJ.4

Lambeth JD (2004) Nox enzymes and the biology of reactive oxygen. Nat Rev Immunol 4:181–189

Loperena R, Harrison DG (2017) Oxidative stress and hypertensive diseases. Med Clin North Am 101:169–193

Maoka T (2011) Carotenoids in marine animals. Mar Drugs 9:278–293. https://doi.org/10.3390/md9020278

Mathews-Roth MM, Krinsky NI (1985) Carotenoid dose level and protection against UV-B induced skin tumors. Photochem Photobiol 42:35–38

Mayne ST (1996) Beta carotene, carotenoids and disease prevention in humans. FASEB J 10: 690–791

Meléndez Martínez AJ, Pérez-Gálvez A, Roca M, Estévez Santiago R, Olmedilla-Alonso B, Mercadante AZ, Ornelas Paz J d J (2017) Carotenoides En Agroalimentacion y Salud (Ed: Meléndez Marténez AJ). Editorial Terracota, Ciudad de México, pp 574–608

Milani A, Basirnejad M, Shahbazi S, Bolhassani (2017) Carotenoids: biochemistry, pharmacology and treatment. Br J Pharmacol 174:1290–1324. https://doi.org/10.1111/bph.13625

Mortensen A (2006) Carotenoids and other pigments as natural colorants. Pure Appl Chem 78(8): 1477–1491. https://doi.org/10.1351/pac200678081477

Oliver J, Palou A (2000) Chromatographic determination of carotenoids in foods. J Chromatogra A 881:543–555

Olson JA (1994) Absorption, transport, and metabolism of carotenoids in humans. Pure Appl Chem 66:1011–1016

Pandey KB, Rizvi SI (2010) Markers of oxidative stress in erythrocytes and plasma during aging in humans. Oxidative Med Cell Longev 3:2–12

Penna D, Pogson BJ (2006) Vitamin synthesis in plants: tocopherols and carotenoids. Annu Rev Plant Biol 57:711–738. https://doi.org/10.1146/annurev.arplant.56.032604.144301

Perera CO, Yen GM (2007) Functional properties of carotenoids in human health. Int J Food Prop 10:201–230. https://doi.org/10.1080/10942910601045271

Prior R, Cao G (1999) Antioxidant capacity and polyphone compounds of teas. PSEBM 220: 255–261

Rao AV, Rao LG (2007) Carotenoids and human health. Pharmacol Res 55:207–216. https://doi.org/10.1016/j.phrs.2007.01.012

Rodriguez LP (2009) Carotenoids in evolutionary ecology: re-evaluating the antioxidant role. Bio Essays 31:1116–1126. https://doi.org/10.1002/bies.200900070

Saini RK, Nile SH, Park SW (2015) Carotenoids from fruits and vegetables: chemistry, analysis, occurrence, bioavailability and biological activities. Food Res Int 76:735–750

Sastre J, Pallardo FV, Vina J (1996) Glutathione, oxidative stress and aging. Age 19:129–139

Siepelmeyer A, Micka A, Simm B (2016) Chapter 8 – nutritional biomarkers of aging. In: Molecular basis of nutrition and aging. Elsevier, pp 109–120

Stahl W, Sies H (2003) Antioxidant activity of carotenoids. Mol Asp Med 24:345–351. https://doi.org/10.1016/S0098-2997(03)00030-X

Sui X, Kiser PD, Lintig JV, Palczewski K (2013) Structural basis of carotenoid cleavage: from bacteria to mammals. Arch Biochem Biophys 539:1–22. https://doi.org/10.1016/j.abb.2013.06.012

Takuji T, Masahito S, Hisataka M (2012) Cancer chemoprevention by Carotenoids. Molecules 17:3202–3242. https://doi.org/10.3390/molecules17033202

Terao J, Minami Y, Bando N (2010) Singlet molecular oxygen quenching activity of carotenoids: relevance to protection of skin from photoaging. J Clin Biochem Nutr 48:57–62. https://doi.org/10.3164/jcbn.11-008FR

Tiwari AK (2004) Antioxidants: new- generation therapeutic base for treatment of polygenic disorders. Curr Sci 86:1092–1102

Uttara B, Singh AV, Zamboni P, Mahajan RT (2009) Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol 7:65–74

Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell B 39:44–84

Von Ossowski I, Hausner G, Loewen P (1993) Molecular evolutionary analysis based on the amino acid sequence of catalase. J Mol Evol 37:71–76

Voutilainen S, Nurmi T, Mursu J, Rissanen TH (2006) Carotenoids and cardiovascular health. Am J Clin Nutr 83:1265–1271

Walter MH, Strack D (2011) Carotenoids and their cleavage products: biosynthesis and functions. Nat Prod 28:663–692. https://doi.org/10.1039/c0np00036a

Xie X, Yoneyama K, Yoneyama K (2010) The strigolactone story. Annu Rev Phytopathol 48: 93–117

Yang HY, Lee TH (2015) Antioxidant enzymes as redox-based biomarkers: a brief review. BMB Rep 48:200–208

Yoneyama K, Xie X, Yoneyama K, Nomura T, Takahashi I, Asami T (2019) Regulation of biosynthesis, perception, and functions of strigolactones for promoting arbuscular mycorrhizal symbiosis and managing root parasitic weeds. Pest Manag Sci 75:2353–2339. https://doi.org/10.1002/ps.5401