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CAROTENOID CHEMISTRY AND ITS HEALTH PROMOTING EFFECTS: A REVIEW

Dr. Bhavna Chaudhary*

ABSTRACT

Carotenoids are one of the essential phytochemicals with remarkable biological properties. These compounds play a different role in the development of plants and animals. This article reviewsthe structural and functional properties of carotenoids. The review deals with carotenoid chemistry (structure, general properties, etc.), biosynthesis, sources as well as bioactive properties of carotenoids. The article also discusses the role of these constitutive metabolites in radical scavenging and combating various health conditions and chronic diseases.

Keywords: *Carotenoids, Antioxidant, Phytochemical, Metabolite, Biosynthesis, Cataract, Free Radical*.

Introduction

Phytochemicals are constitutive metabolites of plant origin. These metabolites help the organisms to overcome various threats that are a part of their environment and also control various essential and non-essential functions.[1] One phytochemical among many of them is Carotenoids. This review deals with the structural and biological function of carotenoids briefly.

It is very well known that these compounds are found in plants as well as many other photosynthetic and non-photosynthetic organisms that exhibit carotenogenic metabolism.[2] These are one of the most distributed groups of pigment imparting compounds and more than 600 of them have been identified.[3]

Chemistry and Sources of Carotenoids

Carotenoids belong to the group isoprenoids which intervene in various functions ranging from gene expression regulation to photoprotection and light collection. They can act as substances with aromas or vitamin activity by converting into other derivatives enzymatically or chemically. Therefore, apart from imparting color mainly red, yellow, or orange, they serve many other roles.[4]

All the compounds in this group possess a poly-isoprenoid structural framework with a long chain of the double bond and bilateral symmetry around the double bond present in the center. Carotenes are classified based on carbon numbers that are present in the skeletal structure of the compound into C_{30}, $C_{40,}$ $C_{45,}$ and C_{50} out of which C_{40} is most commonly available naturally. These carotenoids are also synthesized by various classes of bacteria and their structural framework is made up of a wide range of terminal groups.[2] Typically naturally occurring carotenoid is a tetraterpenoid structure containing a total of 8 isoprenoid rings i.e. 40 atoms of C. Now absence or presence of these isoprenoid rings determines whether a carotenoid would be of acyclic or cyclic form. The acyclic form is designated as psi form denoted by ψ symbol while cyclohexane form is of two types β, ε; cyclopentane form is denoted by κ (kappa) while aryl form is again of two types φ, χ (phi and chi) and lastly methylenecyclohexane is denoted by γ (gamma)[4].

Another categorization of these compounds is based onthe presence or absence of oxygen in their molecules. Carotenoids containing only H and C are termed as carotenes while oxygen-containing compounds are termed as xanthophyll. α-carotene, β-carotene, γ-carotene, ζ-carotene, lycopene, neurosporene are the type of carotenes. On the other hand, xanthophylls include compounds like zeaxanthin, lutein, etc.[4]

[6] Associate professor, Department of Chemistry, Smt. Pana Devi Morijawala Government Girls College, Kotputli, Rajasthan, India.

Major dietary contributors to various types of carotenoids are present in various types of pigmented fruits and vegetables. Apricot, carrots, cooked spinach, broccoli, tomatoes are rich sources of β-Carotene while cooked carrots are rich sources of α-carotene. Similarly, a huge amount of acyclic carotene which is lycopene is present in tomatoes. Lutein which is a type of xanthophyll is present in Spinach, green collard, cooked green peas, broccoli, etc in large quantities.[5]

Apocarotenoid is a type of carotenoid that has a normal C_{40} structure but is subjected to shortening by removal of fragments from either one or both the ends. Naturally, there are more than 100 different types of apocarotenoids present, but the most common ones include bixin, crocetin as well as vitamin A as it is also the product of symmetrical oxidative cleavage of β-carotene.[6]

Mostly these compounds are found in their trans or linear configuration. Isomerization from its trans to cis isomer takes place on exposure to either light or heat. It has been closely observed that the structures and stereochemistry of these compounds are closely related to their properties as well as biological activities. [7]

Biosynthesis of Carotenoids

When it comes to the synthesis of carotenoids, it is known that about 95% of all the carotenoids are synthesized from the same isoprene subunit, the same from which isopentenyl pyrophosphate which is abbreviated as IPP, and dimethylallyl pyrophosphate abbreviated as DMAPP which it the former's allylic isomerare biosynthesized. Hence while the synthesis of isoprenoids 3 molecules of IPP are added to DMAPP with the help of transferase which forms a 20-carbon atom-containing compound GGPP or geranylgeranyl pyrophosphate. After which two GGPP units condense enzymatically with the help of phytoene synthase to produce a 40-carbon containing carotenoid which is 15-cis-phyotene which is colorless. In photosynthetic organisms, these precursors are formed by two independently functioning pathways namely the methylerythritol 4-phosphate (MEP) and mevalonate pathway (MVA).[8]

Apart from this 5%of, the naturally occurring carotenoids containing 30- carbon atoms are biosynthesized from FPP (farnesyl pyrophosphate) which is the precursor of previously discussed GGPP or else by oxidative cleavage of C_{40} carotenoids.[9]

Apart from the above-discussed processes, carotenoids in other organisms are also derived through a series of enzyme involving or chemical modifications from phytoene such as glycosylation, desaturations, oxidization, dehydrogenation, epoxidation, and many others.[10] These reactions are catalyzed by enzymes such as GGOO pyrophosphate, lycopene cyclase, carotene desaturase, etc. Further modifications are brought about by β-carotene hydrolase and ketolase into other 40-carbon carotenoids.[2]

Synthetically derived carotenoids at the industrial level include astaxanthin, lycopene, canthaxanthin, citranaxanthin. Out of all the carotenoids synthesized industrially, C_{40} carotenoids have identical end groups at their ends. And due to this reason,a 10-carbon atom containing dialdehyde and two units of 15-carbon containing phosphonium salts are produced efficiently via double Wittig condensation. These mixtures of isomers are then thermally isomerized to get an all-trans configuration as there is a certain number of cis stereoisomers also formed.[2,11]

Biosynthesis of Carotenoids by Micro-Organisms

Despite the widespread distribution of these carotenoids in nature, their cellular concentration is extremely low. On the same grounds, industrially synthesized carotenoids despite being less expensive have been reported to hazardous impact on human health. Therefore, currently, commercial carotenoids derived from microbes that have not undergone genetic engineer but in some cases underwent mutagenesis are used after screening for better production characteristics. Microbial strains of *E. coli* have been shown to produce lycopene, phytoene, β- carotene, astaxanthin. Similarly, the literature reveals that strains of *S. cerevisiae*, *C. glutamicium, Y*. *lipolytica, K. marxianus,* etc. are capable of producing xanthophylls like astaxanthin and zeaxanthin as well. All these microbial species can be used to produce carotenoids industrially in large quantities.[12]

Interaction of Carotenoids with other Biomolecules

The Association of carotenoids with other molecules can lead to some variation in properties when compared to freely found carotenoids. This phytochemical is found to be associated with several proteins, sugar as well as fatty acids. They form glycosides when they are linked to some sugar moieties like gentiobiose. A carotenoid glycoside found in saffron and gardenia fruits namely crocin is formed as a result of glycosylation between crocetin and sugar moieties. Some of these can also be derived from micro-organisms like *A. aurantiacum* or *Arthrobacter spp.*[4]

Carotenoids complexing with some proteins form carotenoproteins which are generally prolific in invertebrates. In certain species of fishes astaxanthin and canthaxanthin bind to actomyosin complex via non-specific hydrophobic bonds after absorption. These conjugated carotenoproteins are also reported in carrots apart from birds, crustaceans, and microbes.[4]

Carotenoid sulfates are found in bacterial species like *Erythrobacter longus* and various animals like sponges and starfish. Similarly, Carotenoid acyl ester or xanthophyll esters are derived by acylation performed over a hydroxyl group. These esters are quite widespread and can be derived from various plants, animals, and other organisms like algae.[4]

Properties of Carotenoids

A key contributor to the general properties of carotenoids like color, reactivity, shape, etc. is the long system of conjugated double bonds.

- **Size and Shape:** the greater no. of conjugated double bonds is a characteristic that is responsible for rigidity which leads to a rod-like shape in case carotenoids are in all E-configuration while the Z-form is angular in shape. Because of which Z forms are lesser susceptible to aggregation which has an impact on bioavailability as well solubility.[13,4]
- **Solubility:** Except for some exceptions carotenoids are hydrophobic compounds. Because of this reason extraction requires organic solvents like acetone, hexane, ether, etc. In biological scenarios, they are found in a lipidic environment like as membranes, mixed micelles, lipoproteins, etc. [4]
- **Absorption of Light and Transfer of Energy:**The ability of carotenoids to absorb light is very well known. It involves the formation of a singlet form of the compound and subsequently transfers this excitation energy to chlorophyll to initiate the photosynthesis. The relevant transition in energy level, in this case, is π-π^* transition. The electron is delocalized and the energy of the excited state is quite low, therefore the amount of energy required to bring about this is small and corresponds to light in the wavelength of 400-500 nm and so these compounds are intensely pigmented as yellow, orange or red. Apart from pigmentation, these compounds have various other photochemical properties.
- **Chemical Properties:** Carotenoid radicals are formed as a result of free radical oxidation reaction and are short-lived. They possess an unpaired highly delocalized electron over the chromophore which has a stabilizing effect, therefore allowing some other reactions.[15]

Carotenoids are subjected to autoxidation by reacting with atmospheric oxidation. It has been recorded that oxidation of β-carotene in benzene at 30°C under dark conditions finally forms radicals. Similarly, thermal degradation in presence of oxygen leads to the formation of volatile and large non-volatile components. Thermal treatment of β-carotene produces products like beta-apo-13-carotenone, beta-carotene-5,6-epoxide,13-cis-beta-carotene,aurochrome,mutatochrome, etc.[14]

Photodegradation leads to the degradation of the carotenoid structure. Examples include the production of radical cations or free radical adduct on photooxidation. Similar to the excitation mechanism by photodegradation, light can also excite leading to the formation of singlet oxidation which then reacts with neutral carotenoids to produce an excited state carotenoid. In the case of β-carotene, products like β-carotene-5.8-endoperoxide, β-ionone, β-carotene-5,6-epoxide. Also, carotenoids react with radicals to form adducts as well.[14]

Bioactive Properties and Health Benefits: Carotenoids have gained much more importance in research that natural pigment because of its ability to affect human health positively.

- **Antioxidant Activity**

Carotenoids acts as antioxidants i.e. it scavenges free radical by donating an electron to minimize damage to the cells. The presence of free radicals in the body damages DNA, RNA several enzymes, cell membranes, etc. This type of damage to genetic material can later cause medical conditions like cancer, atherosclerosis. Antioxidants also trap free radicals and lipid peroxides, therefore, delaying the process of lipid peroxidation which can negatively affect enzymes and can cause damage to connective tissues.[7]

Various in-vitro studies show that lycopene is an excellent singlet oxygen quencher.[15] It was also observed in certain studies that beta carotene upregulated the expression of heme oxygenase 1 in a dose-dependent way on exposing UVA to FEK4 human fibroblasts cell line.[5]

Some research shows that these compounds and their derivatives may be responsible for the upregulation of detoxifying enzymes by activating Nrf2 dependent pathway. Nrf-2 is a transcription factor that is found to be associated with a protein called Keap-1 in the cytoplasm. This protein is responsible for the regulation of oxidative stress. On receiving the signal of increasing oxidative stress Nrf-2 dissociates from Keap-1 and moves to the nucleus where it binds to ARE (Antioxidant response element) which upregulates the expression of enzymes. Increased expression of enzymes like glutamate-cysteine ligase, glutamate S-transferase, thioredoxin, and NQO-1 which is an oxidoreductase and heme oxygenase 1.[16] A study revealed thatan increase in the level of glutathione following lycopene mediated Nrf-2 activation leads to protection against TNFα-induced oxidative stress.[17]

- **Filtering Blue Light**

The presence of long double and single bonds present in an alternate manner allows the compound to absorb light in the visible range which in the case of carotenoids is highly beneficial for human health. This property of carotenoids has particular relevance to the eye and so these help in the absorption of blue light. Reduction in the amount of short-wavelength light protects sensitive structures of the human eye from light-induced oxidative damage. Xanthophylls like lutein and zeaxanthin protect against age-related eye problems including cataracts. They are also associated with stimulating neuronal signaling efficiency in the eye.

- **Cell Communication**

Carotenes facilitate intercellular communication by activating the synthesis of specialized proteins called connexin. These proteins form pores in membranes thereby helping cells to communicate.

- **Provitamin-A Activity**

One of the most essential functions of carotenoids is their ability to synthesize vitamin A. Alpha-carotene, beta carotene as well as cryptoxanthin serve is a potential source of vitamin A[18]. Provitamin A carotenoids are not absorbed properly when compared to vitamin A. conversion of provitamin A to retinol is important and this conversion depends on factors like absorptive capacities, digestive capacities, preparation of food, and food matrix.[19]In mammals' retinal acts as the visual chromophore and for production of this particular compound vitamin A is essential. The deficiency of this vitamin has led to various immune system-related disorders as well as nightblindness. [20]Apart from these above-stated function vitamin A also plays an important role in several functions like reproduction, bone development, etc.[7]

- **Immune Functions**

Beta carotene and some other carotenoid derivatives are proven to exhibit protective effects on the immune system by targeting different mechanisms. They are known to reduce the immunosuppressive behavior of UV light. They also provide resistance to neoplastic development as well as reduce the immune suppressive effects of aging.[21]

Certain nonprovitamin A carotenoids are known to enhance the cell-mediated and humoral immune response. According to studies, these compounds showed mitogen-induced lymphocyte proliferation as well as in vitro studies showed enhance amounts of activation markers of NK as well as Th cell in PBMC cell line.[22]

Carotenoids have also been known to play a role in tumor immunity in some of the other ways.[22]

- **Disease Prevention**

Apart from the above-mentioned biological functions, carotenoids possess other effectsthat help in combating various other diseases.

These compounds have been linked with decreased risk of various degenerative diseases like macular degeneration, cancer, cardiovascular accident, cataract formation, etc. Certain studies show that they are potent inhibitors of Alzheimer's disease as well as acts against HIV too.[23]

Lutein, zeaxanthin, and many others were observed to play a role in reducing the risk of age-related macular degeneration by protecting against oxidative damage.[24] Also, these may act by neutralizing oxidants formed in the retina. Research shows that the plasma concentration of carotenoids is inversely related to the risk of developing a cataract.[25]

Carotenes are found to protect against UV light as they accumulate in the skin and are therefore associated with skin aging.[20]

Lycopene which is an acyclic carotenoid is found to have the ability to scavenge free radicals i.e. it acts as an antioxidant. It is observed to reduce the risk of osteoporosis which is another metabolic bone disease and is linked to oxidative stress. Evidence suggests that lycopene has a stimulatory effect on cell proliferation and markers responsible for the differentiation of osteoblasts as well as an inhibitory effect on osteoclast formation. Beta carotene was also found to reduce the risk of osteoporosis.[5]

Other health benefits include: maintenance of cognitive function, reducing the risk of neurodegenerative disorders as well as diabetes, prevention of heart disease by inhibitingthe synthesis of LDL cholesterol, prevention of male infertility by protecting sperms from free radicals, cancer prevention, and other chromosomal abnormalities, etc.[7]

Conclusion

Carotenoids are one of the most ubiquitous phytochemicals and constitutive metabolites found in nature. Recent studies have proven these chemicals to be highly beneficial to human health. Dietary guidelines recommend increased consumption of carotenoid-containing food items could help in reducing the risk of various health conditions including cancer and heart diseases. To understand the bioactive properties of these compounds, detailed research as well as well-designed human intervention studies are necessary. Future investigations should deal with the interaction between carotenoids and genetics as well as the environment, so that bioactivities of these compounds can be used in the treatment of various conditions.

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