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PHARMACOLOGICAL EFFECTS OF CAROTENOIDS: A REVIEW

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ABSTRACT

Vitamin A is an essential vitamin which is required in the vision process, epithelial maintenance, mucous secretion and reproduction obtained from carotenoids. Carotenoids have been considered to provide benefits in age-related diseases, against some forms of cancer (in especial lung cancer), strokes, macular degeneration, and cataracts. Till date, more than 600 carotenoids are known and 50 of them are consumed in meals to be transformed into the essential nutrient vitamin A. After their absorption, these carotenoids are metabolized by an oxidative rupture to retinal, retinoic acid and small quantities of breakdown products and are transported by plasma lipoproteins. Carotenes are mainly associated with low-density lipoproteins, while xanthophylls show a uniform distribution between the low- and high-density lipoproteins. The present review provides an insight into the recent status of pharmacological aspects of carotenoids.

INTRODUCTION: Carotenoids are synthesized in plants but not in animals. In nature, more than 600 types of carotenoid have been determined. Carotenoids are localized in sub-cellular organelles (plastids), i.e. chloroplasts and chromoplasts. In chloroplasts, the carotenoids are chiefly associated with proteins and serve as accessory pigments in photosynthesis, whereas in chromoplasts they are deposited in crystalline form or as oily droplets [1].

Some of the carotenoids such as the xanthophylls are involved in photosynthesis by participating in energy transfer in the presence of chlorophyll in plants [2]. Studies have shown that carotenoids contribute to the yellow color found in many fruits and vegetables [3]. The colors of fruits and vegetables depend on conjugated double bonds and the various functional groups contained in the carotenoid molecule [4]. A study also reported that the greater the number of conjugated double bonds, the higher the absorption maxima (λmax) [5].

As a result, the color ranges from yellow, red to orange in many fruits and vegetables [6].

Carotenoids are fat soluble compounds that are associated with the lipid fractions. Chemically, these are long, aliphatic, conjugated double bond systems, i.e., polyenes. A part of them are hydrocarbons, are usually composed of eight isoprene units and have the molecular formula C40H56 [7]. The molecule contains four isoprene units, the central two of which are joined tail-to-tail and open chain or ring structures form the ends of this chain.

A great majority of natural carotenes have double bonds in the all- Trans position, where R is an open-chain structure or a ring system. Only a few natural carotenes exhibit a cis-trans configuration. Carotenoids

are polyisoprenoid compounds and can be divided into two main groups: (a) hydrocarbon carotenoids also known as carotenes, only composed of carbon and hydrogen atoms and (b) xanthophylls that are oxygenated hydrocarbon derivatives that contain at least one oxygen function such as hydroxyl, keto, epoxy, methoxy or carboxylic acid groups. Their structural characteristic is a conjugated double bond system, which influences their chemical, biochemical and physical properties [8].

Carotenoids are a class of yellow or red natural pigments occurs widely in nature. These occur widely in plants, animals and humans. They are synthesized in plants and in some microorganisms and are only introduced with diet into human and animal organisms, which are incapable of their de novo synthesis but sometimes capable of their structural modification. They are highly physiologically important and fulfill many tasks [9]. About one half of natural carotenoids are chiral, usually containing one to six chiral centers.

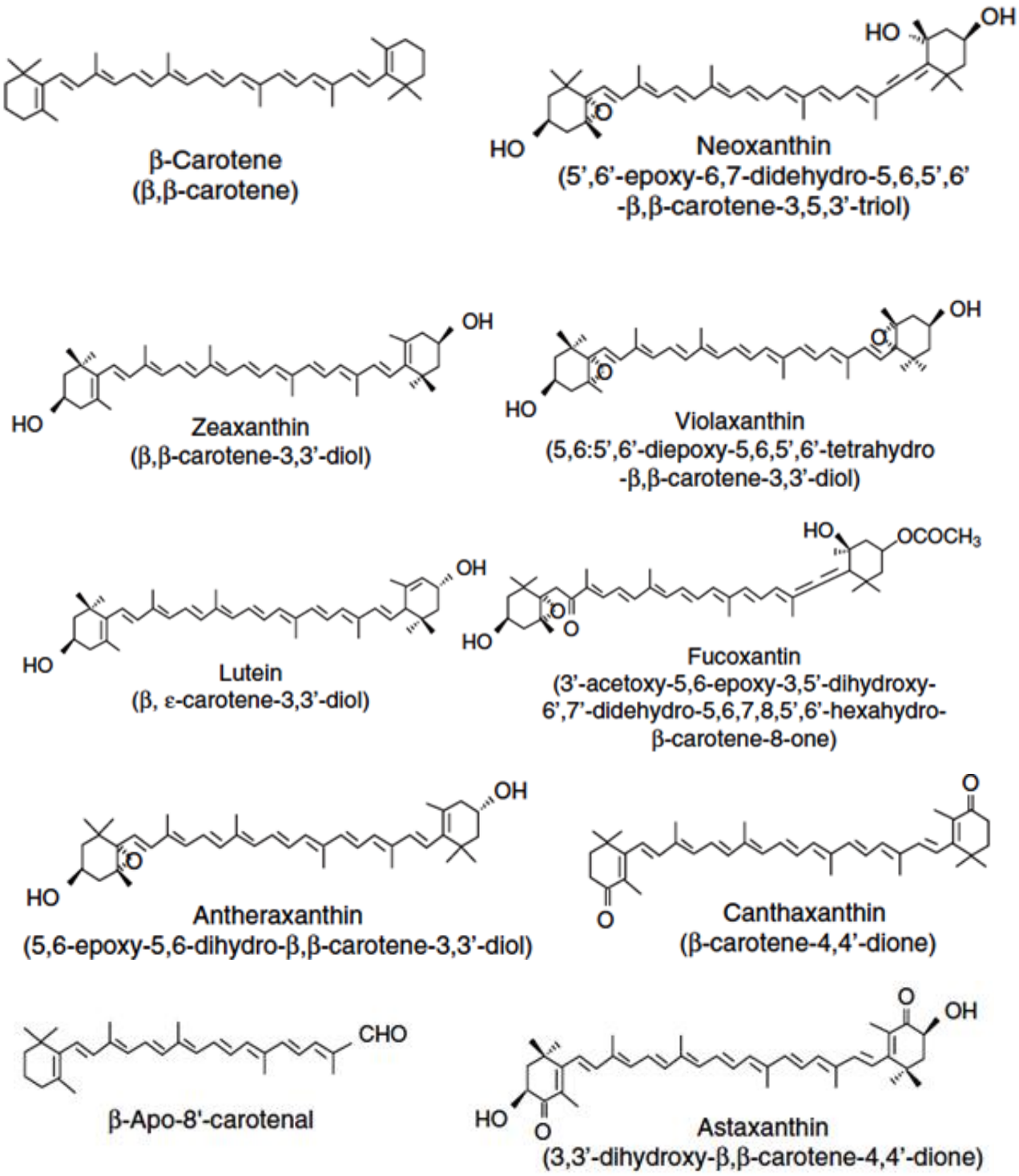
Carotenoid molecules and their products properties have profound effects on the structure and configuration by physico-chemical attacks (light, temperature, oxidants, subsistent etc.) and also on their physico-chemical properties. Trans-cis shifts have especially strong effects on shape of the molecule and thus also on its properties [4]. In general, all-trans isomers have lower energy and are more stable than cis-trans and cis isomers. These changes strongly influence spectral and chromatographic properties of carotenoids and also alter their optical activity if a chiral centre is present in the molecule, and thus may adversely affect the reliability of analytical measurements.

Up to now, more than 600 carotenoids have so far been isolated from natural sources. However, only about 40 are present in a typical human diet. About 20 carotenoids have been identified in human blood and tissues [10].

Fruits and vegetables containing vitamin C, vitamin E (tocopherols) and carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin and lycopene) have been suggested as a natural source of antioxidants. Antioxidant functions are associated with decreased DNA damage, diminished lipid peroxidation, maintained immune function and inhibited malignant transformation or proliferation in vitro that are thought to prevent the development of some diseases [11, 12].

Also, α-carotene, β-carotene and β-cryptoxanthin are considered as pro-vitamin- A carotenoids [13]. Moreover, it is generally accepted that the significance of vegetable consumption can play an important role in maintaining health and reducing the risk of illness [14]. In particular, increased vegetable consumption helps reduce the risk of cancer [15]. That is why vegetables as well as fruits are widely recommended as healthy food [16]. Vegetables are also a valuable part of the diet owing to their nutritive values [17]. They are low in energy containing limited amounts of carbohydrates and fats and high in dietary fiber, minerals and vitamins.

Carotenoids, pro-vitamins A or not, have been credited with other beneficial effects to human health: enhancement of the immune response and reduction of the risk of degenerative diseases such as cancer, cardiovascular diseases, cataract and muscular degeneration [18, 19]. The carotenoids, action against diseases is due to antioxidant activity, especially to quench oxygen [20]. However, other mechanisms have been reported such as modulation of carcinogen metabolism, regulation of cell growth, inhibition of cell proliferation, enhancement of cell differentiation, stimulation of cell-to-cell gap junction communication, retinoid-dependent signaling and filtering of blue light [21, 22].



CHEMICAL STRUCTURE OF SOME COMMON CAROTENOIDS [22]

Pharmacological Effects: Many diseases, such as cancer and strokes, involve oxidative processes mediated by free radicals. Carotenoids, by their antioxidant effect, can show benefits in such diseases; however, this function is not completely demonstrated *in vivo* [23]. Carotenoids are an integral part of membranes. Carotenes are immersed in membranes, but xanthophylls showed a variable membrane position, polar groups in xanthophylls affect their position and mobility. Consequently, carotenes are able to react efficiently only with radicals generated inside the membrane. While zeaxanthin, with their polar groups aqueous exposed, is able to react with radicals produced in that zone.

Additionally, it has been suggested that carotenoids influence the strength and fluidity of membranes, thus affecting its permeability to oxygen and other

molecules. It has been also determined that carotenoids have a remarkable effect in the immune response and in intercellular communication [24-27]. β-Carotene, canthaxanthin, 4-hydroxy-β-carotene, and the synthetic retro-dehydro-β-carotene show an efficient induction of the gap junctional communication (GJC) in murine fibroblasts.

The GJC stimulation was more than five times, depending on the carotenoid. β-Carotene and retro hydro-β-carotene were the most efficient inducers of GJC, indicating that the presence of a six-member ring is important in the GJC induction; carotenoids with five-member rings showed little activity.

Interestingly, the induction of GJC did not show correlation with the quenching of singlet oxygen. Thus, it was suggested that GJC and antioxidant activities in cancer prevention operate independently of each other [28].

The importance of carotenoids with rings of six members was emphasized by the isolation of a carotenoid-binding protein (CCBP) of 67 kDa from ferret liver. Carotenoids with substituted β-ionone rings, without β-rings, or with an intact β-ring with a shorter lineal chain were not bonded by CCBP. Consequently, it was showed that CCBP binds β-carotene mole per mole with high efficiency and specificity. Thus, CCBP may play a major role in the storage, transport, and targeting of β-carotene in mammalian systems. Additionally, it was suggested that the high affinity between CCBP and β-carotene may protect the carotenoid from degradation, and its antioxidant activity must be better [29].

There exists evidence of the effectiveness of β-carotene in the treatment of certain kinds of cancer, for example, smoking related cervical intraepithelial neoplasia and cervical and stomach cancer [30]. β -Carotene affects the immune response in rats, and by this means tumor growth is inhibited [31]. It was demonstrated that retinoic acid regulates the γ-interferon (IFN-γ) gene, which has an important role in practically all the stages of the immune and inflammatory responses [32].

In the process of senile macular degeneration, retinol is related to the induction of a gene cascade permitting the phagocytosis of damaged cell in retina; this process is critical for the photoreceptor survival [33]. Also, it has been established that retinoid affect many biological process, such as cellular proliferation, differentiation, and morphogenesis. Moreover, retinoid have been used in treatments of certain kinds of cancers and some dermatological activities. Additionally, it is mentioned that a diet with deficiencies in vitamin A or supplemented with an excess of retinoic acid could induce teratogenesis [34].

Differentiation is a complex process, during development of the monoblastic cell line U-937, the activation of both the retinoic acid receptor (RAR) and the 9-*cis*-RA receptor (RXR) are required. Thus, it was suggested that different combinations of retinoids produced different pharmacological responses in the specificity and potency in cancer therapy [35-37]. Another found that retinoic acid induces the response of proteins associated with damage by ultraviolet light in F9 and NIH3T3 cells.

Another research showed that retinoic acid conduces to differentiation of F9 cells by an increment of cellular communication. It was suggested that this process is mediated by the protein connexin 43 that induces the expression of important molecules for cellular adhesion [38].

Ang studied mice embryogenesis and found that retinoic acid has an important role during the gastrula ion process [39]. In that stage, alcohol dehydrogenate class IV was identified, and it was proposed that negative effects of alcohol consumption during fetus development could be caused by the inhibition in retinoic acid synthesis, catalyzed by alcohol dehydrogenate, which conduces to a failure in function of retinoic acid receptor (necessary for normal development).

Retinoic acid (RA) has also been related to the aging process. RA affects the gene expression levels through its interaction with triiodothyronine receptor (TR) and RAR. Interestingly, when the TR and RAR mRNA levels were analyzed in the brain of young, adult, or aged rats, lower values were found. Additionally, it was showed that RA supplementation increased the TR and RAR mRNA levels. Also, the transglutaminase activity was reduced in aged rats and recovered after RA

treatment. Transglutaminase has involved the memory process [40].

Prostaglandins are substances that have been involved in several physiological processes, and in particular prostaglandin D2 has been involved in the endogenous sleep promotion, modulation of several central actions (regulation of body temperature, release of the luteinizing hormone), etc. Recently, it was shown that prostaglandin D (PGD) synthase binds retinoic acid and retinol. In addition, it was demonstrated that *all-trans*-retinoic acid inhibits its enzymatic action but not retinol.

With the generated information, it was suggested that retinoids may regulate the synthesis of PGD2, and that PGD synthase may be a transporter of retinoids to the place where they are required. Thus, it was suggested that PGD synthase plays a critical role in regulating the development of neurons by the regulation of the transfer of all-*trans* or 9-*cis*-retinoic acid to RAR or RXR in the immature nerve cell.

Additionally, it has been mentioned that the over expression of the cyclooxygenase gene (a key enzyme in the formation of prostaglandins) is an early and central event in colon carcinogenesis [23].

Carpenter observed that mixtures of canthaxanthin with low-density lipoproteins (LDL) inhibited macrophage formation from human monocytes. However, if canthaxanthin and LDL were added simultaneously (but without previous mixture) to cellular medium, it was not observed to any effect. The same was noted with β-carotene, but with zeaxanthin the opposite was found [40]. It was explained that all evaluated carotenoids show good antioxidant activity, and observed differences are caused because they act at different levels: zeaxanthin can quench radicals in the aqueous phase, while β-carotene inhibits lipid peroxidation; on the other hand canthaxanthin was the most potent agent in the inhibition of methyl linoleate, and it was concluded that antioxidant activity depends on the particular system: radical, carotenoid, microenvironment, etc.

Thus, diets with carotenoid mixtures are recommended instead of having just one particular carotenoid, because in vivo a great variability of radicals and microenvironments take place. Additionally, in some studies β-carotene was supplied to smokers, and it was found that cancer mortality indexes were higher in smokers than in their respective controls [42-44]. It has been signaled that a combined supply of β-carotene, α-tocopherol, and selenium reduces stomach cancer mortality, and it was pointed out that the consumption of marine algae (especially Phaeophyta) diminished the risks of being affected by certain types of cancer.

Also, it was established that the main antitumor agent is not β-carotene, but other components (carotenoids) that are present in algae. In this sense, mixtures of carotenoids α-carotene, fucoxanthin, and halocintiaxanthin) have shown a higher inhibitory activity than β-carotene in proliferation of human neuroblastoma cells. In addition, α-carotene showed higher antitumorigenic activity than β-carotene in rat cancer induced by glycerol, and it was mentioned that carotenoids with a ε-ring (absent in β-carotene) have higher inhibitory activity [45]. The antimutagenicity of carotenoids in Mexican green peppers (*Capsicum annuum*) were studied the antimutagenicity inhibition by nitroarenes was higher than 90%. Pepper carotenoids were more efficient antimutagens than pure β-carotene, suggesting that other carotenoids (e.g., lutein, zeaxanthin) in the pepper extracts showed a synergistic effect with β-carotene. Also, it was mentioned that the antimutagen activity might be from blocking the entrance of toxic compounds into the cell or by their antioxidant activity [46].

Also, the antimutagenicity activity of carotenoids of Aztec marigold (*Tagetes erecta*) was evaluated. It was concluded that lutein was the compound with a higher activity on marigold extracts, but similar to the observation mentioned for the pepper extracts, the mixture of carotenoids in the marigold extract had higher antimutagenicity activity. In addition, it was suggested that lutein and 1-nitropyrene (mutagen) formed an extra-cellular complex that limits the bioavailability of 1-nitropyrene and consequently its mutagenicity.

Böhm indicated that carotenoids, α-tocopherol radicals, and ascorbic acid develop their function by diminishing the content of harmful nitrogenous compounds. Also, a synergistic effect between β-carotene and vitamins E and Complainant was

observed in cellular protection [47]. It was explained that β-carotene not only destroys oxyradicals but repairs tocopherol radicals produced when α-tocopherol destroys oxy-radicals. Additionally, it was suggested that low antioxidant levels (e.g., ascorbic acid) in smokers, in contrast with non-smokers, could be related with an apparent failure in the recycling of α-tocopherol by β-carotene.

Carotenoids protect lab animals of UV-induced inflammation and certain type of cancers. Historically, carotenoid supplementation has been used in the treatment of diseases produced by light sensitivity, which are usually hereditary: 84% of patients with erythropoietic protoporphyria, consuming diets supplemented with β-carotene, increased by a factor of 3 their ability to resist sunlight exposition without presenting symptoms. Also, carotenoids have been used in other photosensitivity diseases: congenital porphyria, sideroblastic anemia, and have shown only a limited success in treatment of polymorphic light eruption, solar urticaria *Hydroa vacciforme*, *Porphyria variegata, Porphyria cutanea tarda,* oractinic reticuloid [47]. Lutein and zeaxanthin have been considered as protective agents against aging macular degeneration and senile cataracts [44].

Also, it has been suggested that β-carotene suppress the increment of hormones related to stress syndrome [47].

CONCLUSION: The health benefits of carotenoids in the human diet are becoming increasingly apparent in the past few years. Being potent antioxidants, thus preventing from several major health disorders, higher dietary intake of carotenoids also help to rejuvenate the body by promoting the growth of healthy cells and inhibiting the growth of unhealthy ones. Thus, greater incorporation of carotenoids in pharmaceutical, food and nutraceutical products is highly recommended for maximum health benefits.

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