Fitoterapia 109 (2016) 58–66

Contents lists available at ScienceDirect

Fitoterapia

journal homepage: www.elsevier.com/locate/fitote

Review

Zeaxanthin and ocular health, from bench to bedside

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ARTICLE INFO

Article history:
Received 17 October 2015
Received in revised form 10 December 2015
Accepted 15 December 2015
Available online 17 December 2015

Keywords:
Age-related macular degeneration
Cataract
Ocular problems
Oxidative stress
Zeaxanthin

ABSTRACT

Cataracts, glaucoma, and age-related macular degeneration are known as major ocular problems which cause blindness among the elderly population worldwide. Oxidative stress plays an important role in both the initiation and progression of ocular problems and with respect to this; dietary antioxidants can serve as a therapeutic strategy for the improvement of ocular health. Zeaxanthin is known as one of the most important and common xanthophyll carotenoids, possessing multiple therapeutic effects such as strong antioxidant and pro-oxidant behaviour as well as anti-inflammatory effects. A growing body of literature shows that zeaxanthin mitigates ocular problems and suppresses oxidative stress in the retinal tissues. This paper aims to critically review the available literature regarding the beneficial effects of zeaxanthin on ocular problems with emphasis on its chemistry, bioavailability, and sources.

Contents

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http://dx.doi.org/10.1016/j.fitote.2015.12.009
0367-326X/

1. Introduction

The term “carotenoids” refers to a class of more than 700 naturally-occurring, rich-colored, non-nitrogenous, and lipophilic pigments produced by herbal, algal and bacterial sources [1,2]. These pigments with conjugated double bounds are usually found in the chloroplasts in the cell and provide most red, orange and yellow colors in fruit and vegetables, *i.e.* corn, carrot, sweet potato, orange, papaya and other plants, algae, as well as being found in animal sources, *e.g.* eggs [3–5]. As is well-known, carotenoids may be easily transformed into vitamin A in the body, an essential vitamin that acts as a strong antioxidant. Actually, carotenoids display vital pharmacological effects desired for human health. Carotenoids can be synthesized chemically or produced through biotechnological methods, *i.e.* plant tissue culture and metabolic engineering [6]. Among them, zeaxanthin is an important xanthophyll carotenoid derivative with various bioactivities (Table 1), which is defined as a micronutrient and a valuable ingredient for cosmetic and food sectors [7]. It has been recently shown to decrease the level of lipid and oxidative stress markers in a clinical study performed on middle-aged men [8] and reduce cardiovascular and cancer risk increasing antiproliferative effects [9,10]. Since it is a lipophilic compound, zeaxanthin is also known as a strong antioxidant and pro-oxidant, acting mainly in biological membranes, and as a free radical scavenger [11–14].

On the other hand, zeaxanthin is a carotenoid derivative reputed for its positive effect on age-related macular degeneration (AMD), which negatively influences the quality of daily life by disturbing such abilities as reading, recognizing faces, and mobility, as well as causing pigmentary abnormalities in the patients [15]. It is also one of the leading causes of blindness in developed countries, particularly in individuals over the age of 55 [16]. In fact, zeaxanthin is a predominant endogen carotenoid pigment found in human retina alongside lutein. However, the amount of these chemicals has been shown to diminish during the progress of AMD. Zeaxanthin has been reported to exert protective effects against AMD via the prevention of oxidative stress-induced retinal cell damage [17] among other mechanisms, and is also effective in protection against and therapy of other ocular diseases.

In this review, our aim is to cover the health effects of zeaxanthin in detail, particularly with regard to ocular diseases, as well as addressing its chemistry, bioavailability, and sources. The literature survey has been performed through a search of major data bases, *i.e.* Scopus, Web of Science, Pubmed, and Google Scholar, using the key words “zeaxanthin and ocular health”.

Table 1
Zeaxanthin and documented health effects.

	Zeaxanthin observed effects	References
1	Lutein + zeaxanthin supplementation may decrease the risk of head and neck cancer	Leoncini et al. [86]
2	Supplemental macular carotenoids improve visual but not cognitive functioning in test human subjects	Nolan et al. [87]
3	Lutein and zeaxanthin supplementation improves visual function in patients diagnosed with AMD (meta-analysis from 18 randomized control studies)	Liu et al. [88]
4	Higher levels of plasma oxygenated carotenoids decrease risk of atherosclerosis (A cohort study of 573 normal human subjects)	Dwyer et al. [89]
5	Serum L + Z concentrations correlate inversely with prevalence of metabolic syndrome in middle and elderly Chinese population	Liu et al. [90]
6	Reduced breast cancer risk among pre-menopausal Chinese women with higher L + Z dietary intake	Wang et al. [91]
7	Lower plasma HDL (and therefore carotenoid) levels affect reverse cholesterol transport and may be associated with vascular and cognitive comorbidities	Dias et al. [92]
8	MP optical density and serum L + Z correlate positively with better cognitive function among the elderly	Vishwanathan et al. [93]
9	Dietary carotenoids reduce risk of hip fracture among middle aged Singapore-Chinese men	Dai et al. [94]

2. Chemistry

Carotenoids are an important group of yellow-red conjugated polyene pigments with widespread occurrence in nature [18]. They are primarily synthesized by photosynthetic plants and microorganisms, and have a variety of roles as biological pigments, particularly in photooxidative protection and photosynthesis, as well as vision and cellular differentiation [19,20]. They derive their name from the work of Wachenroder who isolated β-carotene from carrots in 1831 giving the extracted crystals the name ‘carotene’ [21]. Carotenoids consist of two classes of molecules; the carotenes, which are strictly hydrocarbons, and xanthophylls, or oxycarotenoids, which contain oxygen [22]. They consist of 8 isoprenoid moieties bonded in a manner which reverses the formation of isoprenoid moieties at the center of the structure, so that the 2 central methyl groups are in a 1,6-positional relationship and the other non-terminal methyl groups are in a 1,5-positional relationship [23]. All carotenoids are obtained from the acyclic $C_{40}H_{56}$ structure which contains a long central chain of conjugated double bonds [24]. Different isomers are possible with carotenoids, considering *cis*/*trans* configurations of the stereogenic center conjunction, which can lead to thousands of potential combinations; at present 700 carotenoids have been identified. It has been reported that biological requirements such as membrane positioning play an important role in restricting isomers, especially *cis*/*trans*, and *cis*-carotenoids are generally uncommon throughout biological systems. However, the proportion of *cis*-isomers may increase due to the isomerization of the *trans*-isomer of carotenoids during food processing steps such as drying, microwave heating, canning, baking, and cooking [25]. Degradation of carotenoids in fruits and vegetables is the most important topic related to carotenoid loss [26].

The biosynthetic building blocks of carotenoids are 5-carbon repeating isoprene units that combine to form geranylgeranyl pyrophosphate. Tail to tail coupling of this intermediate C20 geranylgeranyl pyrophosphate gives C40 terpenes or carotenes. Further alteration of structure, including oxidation, cyclisation and rearrangements, can lead to a diverse array of natural carotenoids [27]. The most common carotenoids, such as β-carotene, have two 6-membered cyclic structures linked by a long polyunsaturated chain (Fig. 1). If one or more oxygenated functional groups are attached to the cyclic structure, the carotenoids are called xanthophylls. The two well-known xanthophylls of biological significance are lutein and zeaxanthin (Fig. 1). The only difference between these is the location of the double bond in the end rings. This difference provides lutein with three stereocenters whereas zeaxanthin has two [28]. Zeaxanthin has three isomers. The (3*R*,3'*S*) and (3*S*,3'*R*) stereoisomers are identical due to symmetry and are called meso-zeaxanthin, while the main natural and edible form is (3*R*,3'*R*)-zeaxanthin (Fig. 1.) [29]. Non-edible stereoisomers (3*S*, 3'*S*) are produced by the chemical alteration of lutein [29].

Due to the important biological activity, olefin geometry and sensitivity of some of these compounds, the stereoselective synthesis of the polyene skeleton of carotenoids and retinoids is a challenging and stimulating mission. Recently, the search for efficient routes has led to new strategies involving the use of the Stille reaction, a versatile C-C bond forming reaction between stannanes and halides or pseudohalides. Vaz et al. reported the synthesis of β-β-carotene, (3*R*,3'*R*)-zeaxanthin, and carotenoid butenolides using this approach [30].

3. Carotenoids analysis

It is well known that chemical analysis of carotenoids and their oxidized forms is complicated due to the presence of different *cis*-*trans* isomeric forms of these compounds and their instability (especially to light, temperature, oxygen and acids), among other factors. [31]. Analytical procedures for investigating carotenoids usually include a number of steps such as (a) sampling and sample preparation, (b) extraction, (c) partition to a solvent compatible with the