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Review

Lutein and zeaxanthin: Production technology, bioavailability, mechanisms of action, visual function, and health claim status

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ABSTRACT

The xanthophylls, lutein and zeaxanthin have been demonstrated to act as protective shields against high energy blue light, key contributors to central vision as well as to high visual acuity, and antioxidants that repair photo-induced oxidative damage. Like other phytochemicals, the sundry techniques for extraction, purification, structural characterization and identification of lutein and zeaxanthin have undergone considerable refinement. Supercritical CO_2 extraction, apart from being quicker and more eco-friendly than traditional organic solvent extraction, offers the advantages of higher yield and absence of solvent residues in the extracted material. Improved industrial lutein extraction and purification procedures have translated to increased efficiency in generating lutein supplements used in large scale human clinical trials. This paper reviews recent studies on the vision-enhancing potentials of lutein, and concludes that even in the absence of health claims formally and explicitly advising the public on the benefits of diets rich in lutein and zeaxanthin, both xanthophylls have the potential to substantially contribute to eye health if regularly consumed as part of a healthy diet.

1. Introduction

The xanthophyll lutein (β,ε-carotene-3,3′-diol) generally coexists in nature with its stereoisomer zeaxanthin (β,β-carotene-3,3′-diol) (Shegokar & Mitri, 2012) and occurs in abundance in green leafy vegetables such as kale and spinach, where its yellow-orange colour is masked by the dominant green colour of chlorophyll (Reif et al., 2012; Shahidi, Chandrasekara, & Zhong, 2011). While up to 40 mg lutein + zeaxanthin can be found in 100 g of a dark, green leafy vegetable like (raw) kale where the xanthophylls mainly occur in their pure crystalline forms, only < 1 mg lutein + zeaxanthin was shown to be present in 100 g of the edible portion of cooked and raw foods with a yellow-orange colour such as baby carrots, peaches, corn, papaya, and raw oranges (Holden et al., 1999). Other fruits and vegetables with high amounts of lutein and zeaxanthin include collards, turnip greens, broccoli, Japanese persimmons, peaches and olives (Holden et al., 1999). While the amount of lutein and lutein esters in wheat and wheat products such as whole wheat bread is low (Ziegler et al., 2015) in comparison to its relative abundance in fruits and vegetables, the consumption of foods and food products made from wheat flour as a staple in many regions of the world positions this grain as an important source of carotenoids. According to data made available by the Agricultural Research Service of the US Department of Agriculture, among poultry and dairy foods and food products, the highest amounts of lutein and zeaxanthin are found in egg yolk, chicken (broilers) and cheese (USDA, 2015). Importantly, the lipid-dissolved physical state of the xanthophylls in these animal sources makes them highly bioavailable (Schweiggert & Carle, 2015). Although there is currently no recommended dietary allowance for lutein and zeaxanthin, the amounts of the xanthophylls in 100 g of the afore-mentioned foods exceed the approximate dose of 6 mg/d that has been linked with improvements in visual function (Rasmussen & Johnson, 2013).

To our knowledge, there are no data on the most abundant source of zeaxanthin alone in nature but fruits and vegetables such

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as wolfberries, collards, *Capsicum annuum*, yellow corn and spinach have been reported to contain some of the highest concentrations of the xanthophyll (Sajilata, Singhal, & Kamat, 2008). In nature, lutein is most abundant in the flower petals of yellow Marigold (*Tagetes erecta* L.) which contain lutein chemically bound to fatty acids including lauric and palmitic acids (Khalil et al., 2012). Consequently, this source is used in the commercial extraction of lutein in industries using supercritical CO_2 extraction due to its eco-friendly and time-saving advantages (Hojnik, Škerget, & Knez, 2008). For a detailed discussion of the carotenoid content of about 215 raw, cooked, boiled and/or processed foods, see the USDA-NCC Carotenoid Database (Holden et al., 1999).

Decades of research have established the role of lutein and zeaxanthin as potent filters of high energy blue light in both plants and animals – a role that results directly in their function as formidable antioxidants, which quench and scavenge photo-induced reactive oxygen species, ROS (Bian et al., 2012). Although as shown in Fig. 1, the xanthophylls play critical roles in the promotion of other aspects of health and well-being not directly related to vision, they are best known for their contribution to visual health (Alves-Rodrigues & Shao, 2004; Johnson, 2014). This is not surprising given that lutein and zeaxanthin are the only carotenoids present in both the macula and lens of the human eye (Ma & Lin, 2010), the two ocular tissues critical for vision that are among the most vulnerable to oxidative damage as a result of frequent exposure to intense light (Chalam, Khetpal, Rusovici, & Balaiya, 2011).

The most recent data available from the WHO estimate that 285 million people in the world are visually-impaired while 39 million are legally blind (Pascolini & Mariotti, 2012; WHO, 2014). Several studies have suggested that lutein and zeaxanthin play critical roles in delaying the onset and reducing the risk of cataract and age-related macular degeneration (AMD), both of which are responsible for 56% of all cases of blindness globally (Bone, Landrum, Cao, Howard, & Alvarez-Calderon, 2007; Bone & Landrum, 2010; Ma et al., 2012b; Murray et al., 2013; Pascolini & Mariotti, 2012). Since 80% of all visual impairments are avoidable or curable (WHO, 2014), it has become pertinent to undertake a comprehensive review of the contributions of dietary lutein and zeaxanthin to visual health with a view to highlighting the position of these xanthophylls as critical players in reducing the incidence of ocular abnormalities. Furthermore, given heightened consumer interest in health-promoting foods in recent years (L'Abbé, Dumais, Chao, & Junkins, 2008), and the growing number of studies linking diet and functional foods to human wellness (Aluko, 2015), the pendulum for efficient disease control and health promotion is tipped towards prevention rather than treatment. Thus nutrient-based strategies could prove useful in reducing the incidence of impaired vision considering that 90% of visually-impaired persons worldwide live in developing countries (WHO, 2014) where access to adequate healthcare is often limited.

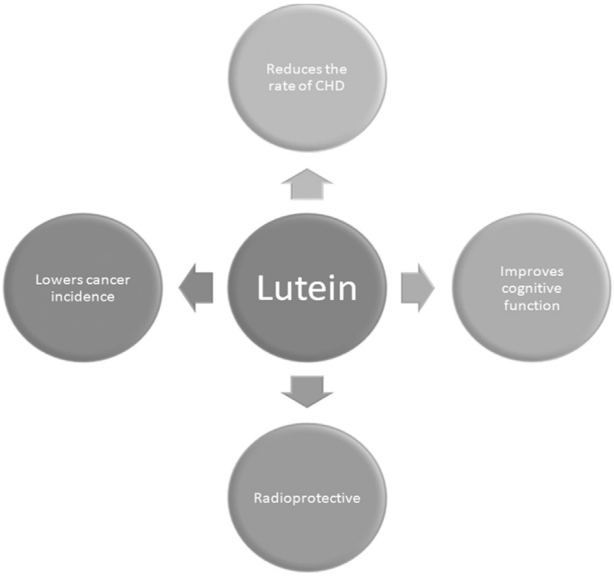

Fig. 1. Some non-vision related properties of lutein. Studies have shown that lutein which acts as an antioxidant is important for maintaining a healthy skin by protecting the skin from photo-damage and erythema caused by exposure to ultraviolet radiation (Shegokar & Mitri, 2012; Stahl & Sies, 2003). A recent study which found that dietary lutein and zeaxanthin consumption significantly reduced the rate of pancreatic cancer development in diabetics with a mean age of 65.8 and 67 (for the control and test subjects respectively) has also spawned discussions on the anticancer potentials of lutein (Jansen et al., 2013). Additionally, in a recent human intervention trial using lutein supplements, lutein was found to increase verbal fluency, memory and overall cognitive function in unimpaired subjects (Johnson et al., 2008). Finally, lutein seems to contribute to the reduction of coronary heart disease (Dwyer et al., 2001; Howard et al., 1996), and has been linked to the reduction of adhesion molecules present on the surface of endothelial cells (Alves-Rodrigues & Shao, 2004). The expression of adhesion molecules on endothelial cell surfaces is recognized as a biomarker for disease progression in atherosclerotic tissues.

2. Structure and occurrence

Named for its characteristic yellow-orange colour, pure lutein typically appears as a yellow-orange crystalline, water-insoluble, lipophilic solid with a melting point of 190 °C and a molecular mass of 568.87 g/mol (Shegokar & Mitri, 2012). Although lutein is thought to have been first isolated from the human *corpus luteum* (the Latin "*luteum*" stands for "yellow" or "egg yolk"), the oxy-carotenoid like all other carotenoids is only synthesized *de novo* by plants, certain bacteria and fungi, as well as photosynthetic microalga (Delgado-Pelayo & Hornero-Méndez, 2012). Therefore, humans and lower animals must consume plant-based diets as sources of lutein (Delgado-Pelayo & Hornero-Méndez, 2012). The ionone rings of free lutein and zeaxanthin contain a hydroxyl group, although the esterified forms contain fatty acids attached at either or both ends of their structures (Fig. 2). Lutein can exist in 8 possible stereoisomeric forms because of its 3 chiral centers. However, it naturally exists mainly in the Z (*cis*)-form (R,R,R) (Abdel-Aal, Akhtar, Zaheer, & Ali, 2013). Chemically, as shown in Fig. 2, lutein contains the basic C40 isoprenoid structure characteristic of carotenoids as well as 10 conjugated double bonds (9 conjugated double bonds in the polyene chain and a single double bond in the β-ionone ring) (Sparrow & Kim, 2010). Comparatively, in addition to its C40 isoprenoid structure, zeaxanthin contains 11 conjugated double bonds comprising of 9 conjugated double bonds in the polyene chain and 2 double bonds in the β-ionone rings (Sparrow & Kim, 2010).

3. Extraction, purification, identification and structural characterization

Supercritical carbon-dioxide (SC–CO_2) extraction, illustrated in Fig. 3, has become the method of choice for extracting biologically active materials from plant matter especially in industries because it is quicker, more efficient and more eco-friendly than traditional organic solvent processing in addition to offering higher target product yield (Careri et al., 2001). Furthermore, as a supercritical fluid, CO_2 is cheap, non-flammable, non-toxic, and readily available at high purity, while its low critical temperature and pressure make it an ideal solvent for the isolation of heat-sensitive compounds like carotenoids (Abbas, Mohamed, Abdulamir, & Abas, 2008; Brunner, 2005; Gao, Nagy, Liu, Simándi, & Wang, 2009). Although the