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REVIEW ARTICLE

Lutein and cataract: from bench to bedside

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Abstract

Cataract is one of the most important leading causes of blindness in the world. Extensive research showed that oxidative stress may play an important role in the initiation and progression of a cataract and other age-related eye diseases. Extra-generation of reactive oxygen and nitrogen species in the eye tissue has been shown as one of the most important risk factors for cataracts and other age-related eye diseases. With respect to this, it can be hypothesized that dietary antioxidants may be useful in the prevention and/or mitigation of cataract. Lutein is an important xanthophyll which is widely found in different vegetables such as spinach, kale and carrots as well as some other foods such as eggs. Lutein is concentrated in the macula and suppresses the oxidative stress in the eye tissues. A plethora of literature has shown that increased lutein consumption has a close correlation with reduction in the incidence of cataract. Despite this general information, there is a negligible number of review articles considering the beneficial effects of lutein on cataracts and age-related eye diseases. The present review is aimed at discussing the role of oxidative stress in the initiation and progression of a cataract and the possible beneficial effects of lutein in maintaining retinal health and fighting cataract. We also provide a perspective on the chemistry, sources, bioavailability and safety of lutein.

Keywords

Age-related eye diseases, antioxidant, carotenoid, lens, nutraceuticals, oxidative stress

History

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Cataract

Cataract, one of the major global health problems, is defined as opacity of the crystalline lens that may lead to blindness (Brian & Taylor, 2001). It is known to reduce vision in about 80 million people (Weikel et al., 2014) and cause blindness in about 18 million people. It is said that this number will increase due to changes in our lifestyle along with increasing numbers of old people. Although minor opacity of the crystalline lens is common and rarely affects the vision, extensive opacity of the crystalline lens may absorb and/or reflects the light rays entering the lens and generate unclear image on the retina (van Velthoven et al., 2006). The major classification of cataract includes: nuclear sclerosis, cortical and posterior subcapsular (Wong et al., 2002). Substantial proportions of cataracts are further classified as senile and mainly associated with diabetes (Pollreisz & Schmidt-Erfurth, 2010). In addition, other types of cataracts include congenital cataracts (present at birth), metabolic cataracts (associated with galactosaemia), endocrinological cataract (associated with hypothyroidism and hypercalcaemia), drug-induced cataract, traumatic cataract and some other types of cataract which are associated with certain skin diseases (atopic dermatitis, etc.) (Dawson & Schwab, 1981). Ultraviolet light, especially UV-B exposure, is another known major risk factor for cataracts (McCarty & Taylor, 2002). There is close correlation between increasing age and the prevalence of cataract in the population (Klaver et al., 1998). It has been reported that prevalence rates of cataract may double in the population every 10 years beginning from 40 years old (Brian & Taylor, 2001). Surgery is the most common and accepted treatment protocol for cataracts that can be employed at different stages of cataractogenesis. In many cases, surgical operations are performed outpatient by using local anesthesia (Campbell et al., 1993) and phacoemulsification appears to be the commonest protocol for the treatment (Hennig, et al., 2014). Extracapsular cataract extraction and intracapsular cataract extraction are other surgical protocols which are less frequently employed than phacoemulsification (Allen, 2011). It has been estimated that age-related cataracts is the leading

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cause of more than half of the blindness worldwide (Javitt et al., 1996). According to statistical reports in 2011, cataracts are responsible for disability in some 53.8 million people worldwide (over 97%) most of which are from low income countries (Waudby et al., 2011). Despite the good efficacy of surgical protocols for treating cataracts, there are limitations such as cost, time of diagnosis and inadequate service in some countries which decrease treatment outcome and leads to cataracts-induced disabilities and blindness (Miller, et al. 2005; Räsänen et al., 2006). Cataract prevention is important because the economic burden and prevalence of cataract surgery is not uniform in developing countries. Epidemiological studies have suggested that dietary modifications or antioxidant supplements can reduce the risk of cataract occurrence. However, as far as lutein is concerned, interventional studies suggest that it might be effective against nuclear cataract but no other types of cataract (Ma et al., 2014; Weikel et al., 2014).

Role of oxidative stress

A plethora of reports show the key role of oxidative stress in the pathogenesis of several diseases (Alinezhad et al., 2013; Curti et al., 2014; Nabavi et al., 2013d, 2014; Saeidnia & Abdollahi, 2013). It has been well known that oxidative stress induces biochemical changes in the constituents of the lens during cataract development (Berthoud & Beyer, 2009). Among the different layers of the lens, epithelial layers are known to be the most susceptible target for oxidative damages (Carper et al., 1999). Two mechanisms, including transcriptional and post-transcriptional regulatory mechanisms, have been suggested for oxidative damage of the epithelial layer (Spector, 1995). It has also been reported that lifelong exposure to ultra violet light radiation generates reactive oxygen species such as superoxide anion through photochemical reactions of oxygen molecules in the presence of riboflavin as electron donor and then convert it to hydrogen peroxide by ascorbic acid-mediated reduction (Vinson, 2006). Through this mechanism, hydrogen peroxide and other oxidants may build up in the aqueous humor of in the eye leading to the development of cataract and/or opacification *via* induction of oxidative damages in the protein and membrane macromolecules (Vinson, 2006). It has been reported that high levels of antioxidants, especially reduced glutathione, ameliorate the detrimental effects of hydrogen peroxide to the lens (Giblin, 2000). The oxidized glutathione byproduct is then reduced by the pentose monophosphate shunt generated glutathione reductase and reduced nicotinamide-adenine dinucleotide phosphate (Giblin et al., 1982). Reduced glutathione has also been shown to protect protein sulfhydryls, prevents protein aggregations and oxidative crosslinking, and also modifies the permeability and transport function of cell membranes (Reddy, 1990). It has also been reported that blocking the reduced glutathione recovery increases the detrimental effects of hydrogen peroxide in cultured lenses (Reddy, 1990). During aging, however, the level of reduced glutathione dramatically decreased in the lens and therefore its level in the cataractous lens is very low (Truscott, 2005). In accordance with the above-mentioned studies, numerous epidemiological reports have shown that there is a close correlation between consumption of dietary antioxidants and decreased risk of cataract cases (Brown et al., 1999; Tan et al., 2008). It can therefore be suggested that antioxidant therapy can be used for delaying in the progression of cataract and other lens opacities (Gritz et al., 2006). Since numerous adverse effects of synthetic antioxidants have been reported (Branen, 1975), much attention has been paid to natural source as rich source of antioxidants (Nabavi et al., 2012b, c, 2013b, 2013c). During the last few decades, a revolution has occurred in the field of using natural products in order to combat oxidative stress-related disorders (Nabavi et al., 2012a, 2013a, 2015; Rhone & Basu, 2008).

Why lutein?

Considerable evidence reports carotenoids' structural ability to directly react and quench highly reactive oxygenated radicals such as superoxide, peroxyl and hydroxyl not only through their electron and hydrogen donating ability but also by their radical addition activity (Rice-Evans et al., 1997; Stahl & Sies, 2003). Carotenoids donate an electron from their polyene chain undergoing oxidation process and form a radical cation which produces stabilized form of carotenoid through reacting with ascorbate (Krinsky & Yeum, 2003).

Burton & Ingold (Burton & Ingold, 1984) studied direct peroxyl radical addition pathways as another antioxidant mechanism of carotenoids. Through this reaction, a carbon centered carotenoid radical is produced and directly reacts with an oxygen molecule to produce a carotenoid peroxyl radical (Burton & Ingold, 1984). The above-mentioned phenomenon gives special oxygen-dependent characteristics to carotenoids to behave as an antioxidant or as a pro-oxidant (Palozza et al., 1997). At low oxygen concentrations, similar to the physiological condition of the retina, carotenoid can inhibit oxidation processes by consuming oxygen molecules through peroxyl radical addition pathways (Burton & Ingold, 1984). Conversely, at high oxygen pressure carotenoids show pro-oxidant behavior by excessive radicals generated through the proxyl bond cleavage and producing more radical than their consumption (Burton & Ingold, 1984).

It has been reported that lutein and zeaxanthin are present in rod outer segment membranes from both perifoveal and peripheral and Henle fiber layer of human retina (Bhosale et al., 2009). However, the amount of these carotenoids is higher in the perifoveal retina (Rapp et al., 2000). The presence of these carotenoids as antioxidants is essential for protection against oxidative degeneration (Chucair et al., 2007). Another function which is attributed to these carotenoids in the Henle fiber layer of human retina is blue light-filtering ability (Kijlstra et al., 2012). This ability helps to suppress formation of photosensitized reaction-induced oxidative stress and protect against oxidative damage (Cuthbertson et al., 2009).

It has been reported that lutein administration can restore the activities of endogenous antioxidant enzymes, inhibit caspase-3 activity and decrease the cellular reactive oxygen species level in UVB-mediated oxidative damage to retinal pigment epithelial cells (Aimjongjun et al., 2013; Arnal et al., 2009). Lutein is also known to protect the retina against blue

light damages through the inhibition of lipid peroxidation, neuronal nitric oxide synthase and c-fos protein expression in the retina (Miyake et al., 2012; Sasaki et al., 2012). It has been reported that lutein administration down-regulates expression of inducible nitric oxide synthase, inflammatory cytokines and matrix metalloproteinase-2 activity (Lo et al., 2013). It has been also reported that lutein administration leads to suppression of apoptosis, decreasing of nitrotyrosine and poly (ADP-ribose) polymerase, neuronal nitric oxide synthase in an experimental model of retinal ischemia/reperfusion (Li et al., 2009). Treatment with lutein also decreases reactive oxygen species levels in endotoxin-induced uveitis model of retinal damages (Sasaki et al., 2009).

Chucair et al. (Li et al., 2012) showed that pretreatment with lutein prevents from cytochrome *c* release and suppresses oxidative stress induced photoreceptor apoptosis, increases opsin expression and enhances the development of outer-segment (Chucair et al., 2007). Lutein treated to cultures Müller cells decreases nuclear factor kappa b, after hypoxic injuries.

Overall, lutein behaves both as an active and a passive antioxidant agent which can directly or indirectly suppresses oxidative stress, and mitigates oxidative injuries.

Chemistry of lutein

Carotenoids are lipophilic compounds of mainly a 40-carbon skeleton synthesised by plants and microorganisms. The basic structure of carotenoids, as exemplified by β-carotene, is shown in Figure 1. Biosynthetically, they are derived from the terpenoid or mevalonate group of the secondary metabolite pathway and hence composed of repeating 5-carbon backbone skeleton units called isoprenes. The 20-carbon skeleton (4 isoprene units) precursor of carotenoids is geranylgeranyl pyrophsphate (GGPP) that is also a precursor for the diterpenoids class of terpenes. When two GPPPs are joined in head to head fashion, the carotenoid skeleton is formed. For extended reviews of carotenoids formation and metabolism in living systems, readers are directed to useful articles in this field by Hirschberg (2001); Lu & Li (2008) and Shumskaya & Wurtzel (2013). The most notable feature of carotenoids is their conjugated polyene that could give rise to several possible structural diversities based on *cis* and *trans* configurations. The vast majority of carotenoids in nature, however, appear to have an all *trans* configuration. In the β-carotene skeleton, the extended polyene structure is composed of 11 double ponds (Figure 1).

Oxygenated carotenoids, as exemplified by lutein and zeaxanthine (Figure 1), are called xanthophylls, or oxycarotenoids. The structural differences between these two xanthophylls are in the position of the double bond within one of the six-member rings and stereochemistry of one of the hydroxyl (3′) groups (Figure 1). These two classical xanthophylls are major components of the macular pigment of the retina and hence often called macular pigments (Abdel-Aal et al., 2013). As with other carotenoids, these xanthophylls' physicochemical characteristics allow them to quench light and even transfer captured energy to chlorophyll for efficient harvesting of light energy. Since almost all of the light energy trapped by lutein and zeaxanthine can be transferred (Croce et al., 2001), the molecules are effectively used by almost all photosynthetic organisms for harvesting light. Both β-carotene and lutein (and zeaxanthine) are known to directly interact with reactive oxygen species in order to serve as chain-breaking antioxidant (Iannone et al., 1998). Hence, their

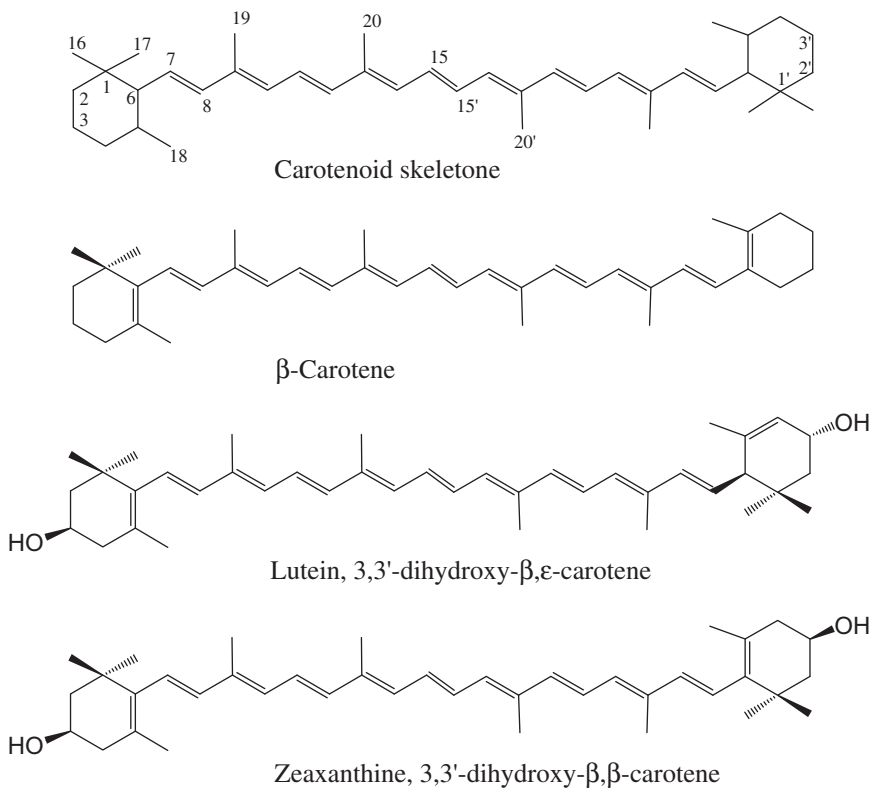

Figure 1. Structures of lutein and its closest structural xanthophylls analog, zeaxanthine. The numbering of carotenoids along with the basic carotenoid skeleton, β-carotene, is shown.

high abundance in the eye is believed to be for protection against the potential damage of the macular region of the retina (Roberts et al., 2009).

Sources

Lutein is known to be abundant in green vegetables, fruits, some seeds such as corn, peas and egg yolk. Sommerburg et al. (Sommerburg et al., 1998) have studied the lutein content of some common foods and found that the highest amount could be found in egg yolks (54 mol%) and maize/corn (60 mol%). They also reported that lutein was the major carotenoid in kiwi fruit (54 mol%), red seedless grapes (53 mol%), zucchini squash (52 mol%), pumpkin (50 mol%) and green pepper (36 mol%). Considerable amounts of lutein could also be detected in leafy vegetables such as spinach (47 mole %), stalks and celery leaves (34 mol%), Brussels sprouts (27 mol%), scallions (27 mol%), broccoli (22 mol%) and green lettuce (15 mol%). Many other studies also report similar findings (Perry et al., 2009). The major commercial source of lutein is, however, marigold (*Tagetes erecta*) petals which have been shown to contain lutein (approx. 0.03% per dry weight) (Piccaglia et al., 1998; Sowbhagya et al., 2004; Vasudevan et al., 1997; Zuorro & Lavecchia, 2010). To date, various methods of extraction, including optimized solvents and supercritical carbon dioxide systems, have been developed (Brunner, 2005; Gao et al., 2009; Hojnik et al., 2008; Navarrete-Bolaños et al., 2005). In nature, lutein is stored as a fatty ester whereby either one or two of the hydroxyl residues are bound to a fatty acid. Saponification of crude marigold (*Tagetes erecta*) extracts is therefore required to release free lutein (Hojnik et al., 2008, Piccaglia et al., 1998, Rao, 2003). Because of the long period of cultivation to the harvest cycle, coupled with the high cost of processing and extraction procedures (Siriamornpun et al., 2012), an alternative source of lutein is currently highly sought. Amongst microalgae that show promise as alternative sources of lutein are: Muriellopsis sp. (Del Campo et al., 2000), Chlorella zofingensis (Del Campo et al., 2004) and Chlorella protothecoides (Shi et al., 2000). Obviously, the use of microalgae as a commercial source of lutein over higher plants has an advantage as the efficiency of lutein production can be optimized by altering culture conditions.

Safety of lutein

Long-term human exposure to lutein from food sources have been recognized a long-time ago, but no adverse health events have been described. Studies have revealed that high consumption of lutein and zeaxanthin (up to 6 mg/day) is associated with positive health effects such as reducing the risk of age-related macular degeneration (ARMD) and cataracts (Kruger et al., 2002). Evidence demonstrates no adverse outcome on serum lipids, hematological parameters and eye examinations in humans. The evidence of safety is substantial in the hazard assessment methods such as the intake of up to 20 mg/day is an observed safe level. Furthermore, several human interventions have been conducted with different doses of lutein ranging from 20 to 40 mg/day for several months and no adverse effect was found with these high doses of lutein in extended periods (Alexandra Alves-Rodrigues, 2004; Andrew Shao, 2006; Dagnelie et al., 2000; Duncan et al., 2002). However, carotenedermia (a reversible and harmless cutaneous hyperpigmentation analogs to jaundice) is the only reported side effect associated with high intake of carotenoids and not solely lutein (Alexandra Alves-Rodrigues, 2004; Andrew Shao, 2006).

Acute toxicity

The observation during 14 days administration revealed that the oral LD_{50} of the lutein/zeaxanthin concentrate is greater than 2000 mg/kg in Wistar rats. Although, no pathological abnormalities were found at the end of the study, hyperemia of the small intestine in one rat was found in the necropsy. Therefore, the results suggested that lutein/zeaxanthin concentrate probably is not toxic (Ravikrishnan et al., 2011). In addition, oral toxicity of the crystalline lutein product (FloraGLO®) was studied in healthy female and male rats with doses of 2.6–773.2 mg/kg/day for 4 weeks. In that location, no consistent statistically significant variations were observed in hematology and clinical chemistry analyses when compared with the control. Although, histopathology findings are consistent with the expected background pattern of rats in the same age and strain, histiocyte foci in the mesenteric lymph node of some rats from high dose groups (260 and 773.2 mg/kg/day), particularly females, was reported which is regarded as the physical uptake of testing materials not organ toxicity (Kruger et al., 2002).

Sub-chronic toxicity

Body weight and feed consumption

All rats in a test, which treated with 0, 4, 40 and 400 mg/kg of the lutein/zeaxanthin concentrate for 90 sequential days, survived until scheduled necropsy. Throughout the test period, weights of female and male animals were comparable to the control group with no significant differences. Therefore, no significant effects were revealed on body weight or body weight gain, and feed consumption in female and male rats with treatment doses up to 400 mg/kg. All data suggested that administration of lutein/zeaxanthin concentrate has no adverse effects on clinical observation, body weight and quantity of feed consumption (Ravikrishnan et al., 2011). Oral toxicity of the crystalline lutein product (FloraGLO®) (2.6–260 mg/kg/day) was assessed in healthy female and male rats for 13 weeks. Administration of test materials did not affect food consumption or the body weight gain of animals. Weight gain in the low dose group (2.6 mg/kg/day) was slightly higher in female rats, while this effect was not seen in other groups. Therefore, it is assumed that this inter group variation is biologically normal (Kruger et al., 2002).

Urinalysis

A number of urinalysis parameters including volume, specific gravity, color, clarity, pH, red blood cell (RBC), white blood cell (WBC), bilirubin, ketone bodies, proteins, glucose and nitrite were analyzed in female and male rats treated with lutein/zeaxanthin concentrate with doses up to 400 mg/kg for

90 days and the results showed no changes in urine parameters (Ravikrishnan et al., 2011).

Hematology

There were no significant treatment-related changes due to oral administration of lutein/zeaxanthin concentrate with doses up to 400 mg/kg for 90 days in both female and male rats. Clotting time in males with dose levels of 4, 40 and 400 mg/kg and erythrocyte count and hemoglobin in females treated with doses of 4 and 400 mg/kg decreased significantly compared with that of control. However, these changes were in the normal range of laboratory historical data and therefore considered as biological variations and not treatment-related adverse effects (Ravikrishnan et al., 2011). Administration of the crystalline lutein product (FloraGLO®) (2.6–260 mg/kg/day) had no adverse influence in the hematology parameters in female and male rats during 13 weeks treatment. However, activated partial thromboplastin time in treated females was higher than the control, which was not associated with any pathological lesion (Kruger et al., 2002).

Clinical biochemistry

Serum chemistry properties including glucose, urea, creatinine, cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, sodium, potassium, chloride, total protein, albumin, globulin and A/G ratio were examined in female and male rats treated with doses of 0–400 mg/kg of lutein/zeaxanthin concentrate for 90 days and data suggested that the compounds did not cause significant toxic changes in the listed parameters. However, a decrease in sodium levels in males of high dose (400 mg/kg) was noted compared to the control group, which is in normal biological variation limits (Ravikrishnan et al., 2011). No significant changes occurred in clinical chemistry parameters of female and male treated animals due to the administration of crystalline lutein (FloraGLO®) (2.6–260 mg/kg/day) (Kruger et al., 2002).

Organ weight

Feeding of lutein/zeaxanthin concentrates to males and female rats with doses of 0–400 mg/kg had no adverse effects on organ weights after 90 days administration. However, statistically significant decrease in brain weight occurred in males receiving 4 and 40 mg lutein/zeaxanthin concentrate/kg/day, which were in biological limits (Ravikrishnan et al., 2011). Both mean absolute organ weights and mean relative organ weights in females and male rats were not significantly changed due to administration of crystalline lutein product (FloraGLO®) (2.6–260 mg/kg/day) for 13 weeks followed by recovery period of 4 weeks (Kruger et al., 2002).

Macroscopic and microscopic examinations

Histopathological findings of a study suggested that administration of the lutein/zeaxanthin concentrate at dose levels up to 400 mg/kg/day to rats for 90 days had no adverse macroscopic or microscopic effects. The eyes of female and male rats did not show any abnormality related to the treatment in ophthalmology examination (Ravikrishnan et al., 2011). Microscopic examination of the livers and kidneys of female rats treated with FloraGLO® crystalline lutein (260 mg/kg/day) showed apparently increase in hepatocyte vacuolation and tubular degeneration/regeneration in the liver and kidney of examining animals, respectively. This phenomenon was not observed in any male rats tested from treated or control groups. Therefore, these histopathological changes in female rats were not considered to be related to the tested material. Histopathological findings in other organs were infrequent and consistent with the expected background pattern of animals of the same age and strains (Kruger et al., 2002).

Mutagenesis

The mutagenicity of the lutein/zeaxanthin concentrate was evaluated using five strains of histidine-requiring auxotrophs of *Salmonella typhimurium* (Ames test) at a concentration of 0.031, 0.063, 0.125, 0.25 and 0.5 mg/plate. The results indicated that the compounds did not induce gene mutation by pair changes or frame shifts in the genome of the strains used (Ravikrishnan et al., 2011). The genotoxic potential of the crystalline lutein product (FloraGLO®) was verified using preincubation and a plate incorporation assay, with respective concentration range of 15.8–1580 and 15.8–5000 µg/plate. The number of mutant colonies was not increased with the tested product in both preincubation and plate incorporation assay (Kruger et al., 2002).

Bioavailability of lutein

Dietary ingestion is the only source of lutein for human consumption as it is not synthesized in the body. Therefore, there is some effort to maximize its bioavailability in order to achieve the daily requirement (Mamatha & Baskaran, 2011). Carotenoids are lipophilic molecules in the hydrophobic cores of plant membranes. Since, the presence of dietary fat is believed to be crucial for micelle formation in the small intestine, therefore dietary fat may be important for carotenoid absorption (Roodenburg et al., 2000). Additionally, bioavailability of these compounds is influenced by several other factors like structures of carotenoids, processing activities, composition and release from the food matrix, the amount of consumption and absorption by intestinal track, transportation through lipoprotein fractions, biochemical alterations, tissue specific deposition, and nutritional status and transition time by the intestine in the host (Castenmiller et al., 1999; Faulks & Southon, 2005; Kopsell & Kopsell, 2006). Oxidation, degradation, and isomerization of carotenoids through abiotic or biotic processes influenced their biochemistry as well as their bioavailability (Kopsell & Kopsell, 2006). Carotenoids are fat soluble compounds, absorbing through solubilization in bile salts and incorporation into micelles. They are released from the food matrix during processing activities, therefore, their bioavailability increased, while the thermal process may degrade their chemical structures and adversely affected bioavailability of them in some food crops. Recently, Caco-2 cell lines were applied to predict carotenoid bioavailability from both supplements and whole foods *in vitro* (Kopsell & Kopsell, 2006). Although, quantified data on lutein absorption are

Table 1. Effect of different factors on lutein bioavailability.

Tested factors	Experimental models	Results	References
Mixed micelles containing a PC or LPC	Plasma, liver and eye in rats	LPC and PC increased lutein absorption	(Lakshminarayana et al., 2006)
Mixed micelles containing a PC or LPC	Plasma and liver of mice	PC decreased and LPC enhanced accumulation of lutein	(Baskaran & Nagao 2003)
Mixed micelles with soybean oil, PC, LPC, pectin or β-carotene	Aged rats with lutein deficiency	Fat, LPC and PC increased, while pectin and β-carotene suppress lutein absorption	(Mamatha & Baskaran, 2011)
Fatty acids, PC or LPC	Caco-2 cell line	PC suppress and LPC increase lutein absorption	(Sugawara et al., 2001)
Micellar phospholipids PC or LPC	Rats	LPC increase lutein absorption more than PC	(Marisiddaiah & Baskaran, 2009)
Fiber and enzymatic disruption	Healthy women and men	Had no effect on lutein bioavailability	(Castenmiller et al., 1999)
Nanocarriers including SLN, NLC and NE	Dermis pig ear skin	No penetration even after 24 h except for NE penetrate 0.37%	(Mitri et al., 2011a)
Alcohol	Premenopausal women	Decrease in plasma lutein concentration	(Forman et al., 1995)
Nanocrystals of lutein	Fresh pig ear skin	No permeation	(Mitri et al., 2011b)
S-SNEDDS containing PC as oil phase	Rabbit	Enhance lutein bioavailability	(Shanmugam et al., 2011)

PC, phosphatidylcholine, LPC, lysophosphatidylcholine, SLN, solid–lipid nanoparticles, NLC, nanostructured lipid carriers, NE, nanoemulsion, S-SNEDDS, solid self-nano-emulsifying drug delivery system.

scarce, the results of single dose studies showed that lutein concentration peaks in the chylomicron fraction in 2 h and in serum in 16 h. The efficiency of absorption has an inverse relation with the carotenoid concentration. Depending of the level of lutein supplement, its absorption varied in the range of 28.7–43.1%. This inverse relation may be attributed to the some factors like solubility, capacity of incorporation into micelles and chylomicrons, as well as the subsequent secretion (Alexandra Alves-Rodrigues, 2004; Jenkins et al., 2000). More polar oxycarotenoids, like lutein, carried in both low density lipoproteins (LDL) and high density lipoproteins (HDL) in the human body (Yeum & Russell, 2002). Some studies indicated that concurrently consumption of carotenoids with each other may inhibit their absorption, for instance long term consumption of carotene supplement inhibit lutein absorption. However, the results depending on the model, dosage, study design and measurement method are quite variable and remains to be firmly established (Alexandra Alves-Rodrigues, 2004).

In a study, healthy men and women volunteers were participating with a mean ± standard deviation of body mass index (BMI) and age of 25.0 ± 3.2 and 46.4 ± 13.4 years, respectively. All the volunteers did not use any medication, apart from oral contraceptives, or supplements containing vitamin C, vitamin E, carotenoids, calcium, and iron and none of the woman was pregnant or lactating. They were split into two groups who consumed low and high fat spread during two 7-day experimental periods. The plasma concentration of lutein diesters (8 mg/day) after a high fat (≈36 g) meal was significantly higher than the low fat (≈3 g) meal (Roodenburg et al., 2000). Lutein esters were hydrolyzed to free lutein before or during absorption and this free form was absorbed. Esterases, and possibly lipases, mediated ester hydrolysis and the secretion of these enzymes via the pancreas is regulated by the presence of fat in the meal. The activity of the noted enzymes increased if sufficient amounts of fat are present to form lipid-aqueous interfaces in the duodenum. Therefore, it seems that low fat intake hampered release of esterases and lipases and/or formation of lipid-aqueous interfaces, resulting in the low uptake of lutein esters (Roodenburg et al., 2000). Bioavailability of lutein diester was more than unesterified lutein in the single dose study. The results of this study, in comparison with other studies with oil-solubilized, lutein suggest that formulation dissolution is a crucial factor in lutein bioavailability, while lutein diester formulation possesses no impediment in lutein bioavailability (Bowen et al., 2002). Phospholipids are known factors to modulate carotenoids absorption. There are several studies describing the influence of these lipids on lutein bioavailability. The food matrix, amongst other factors, affected the bioavailability of carotenoids, while lutein bioavailability is less affected by the food matrix (Table 1) (Castenmiller et al., 1999).

Moreover, the bioavailability of lutein was evaluated in healthy volunteers during a 4-week controlled dietary intervention and the results showed that the relative bioavailability of lutein from vegetables was 67%. Additionally, the bioavailability of β-carotene from vegetables was calculated as 14%, which suggested that bioavailability of lutein is 5 times greater than that of β-carotene. The difference in absorbability between lutein and β-carotene is regarded to β-carotene cleavage and its conversion to retinyl esters. Lutein does not have provitamin A activity, therefore this cleavage phenomenon does not occur for lutein (van het Hof et al., 1999). The bioavailability of lutein from yellow carrot was determined for lutein supplement in oil with nine healthy, nonsmoking students (five men and four women) aged 23–28 years old. The relative bioavailability of lutein from yellow carrot was calculated to be 65% of that of a lutein supplement. However, the mean serum concentration of β-carotene was stable during consumption of yellow carrots. Hence, yellow carrot has advantages over lutein supplement since in that β-carotene is also available (Molldrem et al., 2004).

Lutein and cataract

As shown in Figure 1, lutein, and its stereoisomer zeaxanthin, differs from each other only by the position of the two hydroxyl groups. Some of the dietary lutein is converted to nondietary meso-zeaxanthin. Lutein is fat-soluble and thus their absorption is regulated (Castenmiller et al., 1999). After absorption they are transported to the liver and are incorporated into lipoproteins, LDL and HDL, for transport to various tissues (Yeum & Russell, 2002). Lutein is preferentially transported to the rods of the retina and zeaxanthin to the cones of macula (Bone et al., 1988). Thus, lutein and zeaxanthin are the primary and only pigments of macular retina. The ''yellow spot'' (macula lutea) of the retina is responsible for central vision and for visual acuity. Lutein and zeaxanthin are also found in the lens of the human eye and they have two major functions there – as an antioxidant to reduce or scavenge free radicals and as a filter against high-energy and harmful blue light (Landrum & Bone, 2001). Exposure of the eye to high-energy blue light, results in free radical formation and oxidative stress (Krinsky et al., 2003). Lutein by filtering the harmful blue light reduces photo-induced oxidation of lens proteins thereby protecting against age-related eye diseases such as cataract.

Cataract is a developmental and degenerative change in the lens that leads to lens protein aggregation resulting in loss of lens transparency (Wilson, 1998). Oxidative stress is considered to be the primary driving force for a variety of factors that induce cataract (Manikandan et al., 2010; Varsha et al., 2014). Thus, the presence of lutein in lens is physiologically relevant. The role of lutein in cataract is not very clear with contradictory reports on its ability to prevent cataract, with some reports suggesting its ability to counteract only certain type of cataract. The reasons for such discrepancies are not really clear except the possibility of study limitations or the stage of cataractogenesis (Mares-Perlman et al., 2002). The chemical nature of lutein, and as also zeaxanthin, gives credence to the anti-cataract potential of this compound. Moreover, most studies on the effectiveness of lutein as an anti-cataract agent is based on human randomized trials on supplements and natural serum levels, and not much is known with regard to the mechanism of action of lutein.

Investigations into cataractous lens in order to quantify lutein have found higher levels in the epithelial layer in the cortex compared to middle portions, suggesting their importance in preventing cataract (Yeum et al., 1999). One earlier study has suggested that a differential risk for cataracts in different areas of the lens might be due to differential distribution of carotenoids in the lens (Yeum et al., 1999). The authors showed that concentrations of lutein and zeaxanthin in the epithelium cortex were threefold higher than in the nuclear epithelium, which suggests differential localization during lens development and ageing. A similar distribution was also reported by Bernstein et al. (Bernstein et al., 2001).

Apart from the antioxidant potential of lutein (Brown et al., 1999; Fernandez & Afshari, 2011; Gale et al., 2001; Krinsky et al., 2003; Moeller et al., 2000; Trevithick-Sutton et al., 2006), a few studies have demonstrated other properties for this carotenoid. In fact, one hypothesis paper (Wegner & Khoramnia, 2011) suggested that cataract formation could be a mechanism to reduce retinal oxidative stress and thus prevent the onset of ARMD. However, this remains to be experimentally verified. Chitchumroonchokchai et al. (2004) have shown that lutein inhibited ultraviolet B induced c-Jun N-terminal kinase (JNK) and p38 activation in human lens epithelial cells, suggesting that lutein may be protective against radiation cataractogenesis. Another report by Hu and Xu (2008) has shown that lutein is capable of preventing a cataract. The authors showed the ability of lutein to inhibit proliferation and migration of bovine lens epithelial cells suggesting that this could have implications for post-operative lens after phacoemulsification. This is important considering the fact that cataract surgery, though relatively safe, can still result in irreversible blindness due to fibrotic responses. Interestingly, lutein-binding protein (SR-B1) has been recently identified in retina (Sato et al., 2013) and this could affect lutein levels in an eye. In their review, Kijlstra et al. (2012) have also highlighted the potential of lutein to inhibit pro-inflammatory molecules such as NF-κB, iNOS and COX-2. This is interesting since NF-κB and iNOS are known mediators in animal models of cataracts (Manikandan et al., 2009). Even though, lutein is recognized to be a potent antioxidant, one study has shown that lutein, and its stereoisomer, zeaxanthin, are not capable of compensating for glutathione depletion (Gao et al., 2011). Thus, their effect on endogenous lens antioxidants remains to be elucidated.

The potential of lutein as an anti-cataract agent remains controversial (Mares-Perlman et al., 1995). In the Beaver Dam Eye Study (Lyle et al., 1999a) it was shown that serum vitamin E, but not carotenoids, was significantly linked to age-related nuclear cataract, which highlights on the distribution pattern of lutein in lens (Yeum et al., 1999). Another report by the same group (Lyle et al., 1999b), subsequently suggested that lutein intake could be associated with its protective function against an age-related nuclear cataract. FDA reports also have suggested lack of credible evidence for the effectiveness of lutein against cataract (Trumbo & Ellwood, 2006). Quite recently, Age-Related Eye Disease Study 2 (AREDS 2, AREDS Research Group) has also suggested the absence of significant correlations for lutein supplementation and cataract surgery. Though these studies have pointed to the lack of association between lutein supplementation and cataract, it should be remembered that cataract has a complex pathology. A wide variety of factors contribute to cataractogenesis. As far as ineffectiveness of lutein is concerned, it was previously shown that concentrations of lutein and zeaxanthin were significantly higher in Indian lenses and no significant differences exist in their concentrations in American normal and cataractous lens (Yeum et al., 1995). This suggests that lutein distribution, and probably absorption and metabolism, differs based on demography. In addition, it also appears that the anti-cataract effect of lutein may be influenced by the sex of the patient, as shown for US women (Chasan-Taber et al., 1999) versus US men (Brown et al., 1999), with men showing only modest response as far as the lutein effect on cataract extraction is concerned. This contention is also supported by one animal experiment that showed that dietary modulation of lens lutein in Japanese quail results in 5–10 times higher serum

concentrations in females compared to males (Kathleen Dorey et al., 2005). Also, there is the issue of an age-related increase in inflammation and body fat (Renzi & Johnson, 2008) that can influence lutein absorption, storage, function and metabolism. One should also be careful in noting that serum levels of lutein depend on dietary intake and thus is not a true marker of cataract risk (Olmedilla et al., 2003) as was quite often reported.

Nevertheless, there are numerous studies that have clearly and unambiguously shown the beneficial effects of lens lutein against cataract, more particularly age-related nuclear cataract (Yeum et al., 1999). A cohort study from the Nurses' Health Study has shown the relevance of lutein intake and nuclear opacification (Jacques et al., 2001). Similarly, a lot of dietary supplementation studies have clearly shown the beneficial effects of lutein against age-related cataract (Dherani et al., 2008; Jacques et al., 2001; Karppi et al., 2012; Ma et al., 2014; Weikel et al., 2014). It is to be noted that two recent meta-analysis reports have suggested that lutein intake is significantly associated with a reduced risk of nuclear cataract (Liu et al., 2014; Ma et al., 2014), with modest effects on other forms of cataract. This is interesting considering the fact that lutein concentrations are higher in the epithelial cells of the cortex when compared to the nuclear cortex (Yeum et al., 1999). This relationship has to be addressed. Moreover, a gender-dependent antioxidant response of Ocuvite + Lutein®, an antioxidant supplement, has been recently demonstrated (Hayashi et al., 2012), highlighting the probable complexity of lutein action.

Thus, a majority of the studies, both randomized trials and epidemiological, have clearly lent support to the anti-cataract potential of lutein. With zero toxicity (Alves-Rodrigues & Shao, 2004; Harikumar et al., 2008), lutein can be safely considered for potential anti-cataract applications as dietary supplements, or for possible topical uses.

Conclusion and recommendation

In the present review, we show that lutein possesses preventive and/or protective role against cataracts. We also showed that oxidative stress plays a pivotal role in the biochemical abnormalities of lens constituents during age-related cataractogenesis. It has also been reported that free radial generation during lifelong exposure to ultra violet light radiation leads to excessive production of hydrogen peroxide in the aqueous humor which plays an important role in the age-related cataratogenesis through lens opacisfication. With regard to this, it can be concluded that antioxidant therapy may be served as a novel therapeutic strategy for prevention and/or protection of ocular tissues from cataractogenesis. Numerous observational studies show a close correlation between antioxidant consumption and decreasing the risk of cataract. In this article, we show that lutein mitigates cataractogenesis through suppression of oxidative stress in the ocular tissues. A search in http://clinicaltrials.gov with a keyword ''lutein'' in 5 September 2014, showed that there are 76 ongoing and completed clinical trials to examine the clinical impacts of lutein for the treatment of different diseases. Our search showed that most of the clinical studies (29 ongoing and completed clinical trials) on the beneficial role of lutein on eye diseases especially ARMD. However, there are few studies on the promising effects of lutein on cataract. With respect to wide clinical uses of lutein and its negligible adverse effects, it can be suggested that future clinical trials should be focused on the promising role of lutein on age-related cataratogenesis. In addition, we recommend that future studies should focus on:

- Increasing the bioavailability and absorption of lutein by use of lysolecithin and lecithin, esterification, nanoparticle, etc.
- Exact molecular mechanisms and signal transductions of the beneficial role of lutein on age-related cataratogenesis.
- Finding of the most effective dose for the beneficial effects of lutein on age-related cataratogenesis.

Declaration of interest

The authors report no conflict of interest.

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