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REVIEW ARTICLE

LUTEIN AND ZEAXANTHIN – RADIO- AND CHEMOPROTECTIVE PROPERTIES. MECHANISM AND POSSIBLE USE

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ABSTRACT

Lutein and zeaxanthin are naturally occurring xanthophylls, mainly present in green, leafy vegetables and egg's yolk. Their presence is connected with blue spectrum light absorbance, including UV. This property, and fact, that these xanthophylls are accumulated by human eye's macula, leads to eye's protective functions of them including protection from age-related macular degeneration (AMD). Also, antioxidative features of lutein and zeaxanthin are boosting overall health of human body. Numerous studies proves anti-inflammatory and protective attributes of these compounds, based on many, different mechanisms. One of them is regulating redox potential in cells, and impact on expression of linked genes. In preventing of eye diseases, an important gene that is regulated by lutein and zeaxanthin is the Nrf2 gene, whose increased activity leads to optimizing the cellular response to reactive oxygen species (ROS) and preventing related diseases. Other research confirms antiproliferative properties of mentioned compounds in case of certain human cancer cell lines. There are e.g.: HepG2 (hepatitis cancer), MCF-7 (breast cancer), which treated in vitro with lutein solution showed reduction of cell growth. Lutein alone, during in vivo studies conducted on mice, exhibited also radioprotective properties, positively affecting the vitality of animals. Lutein provides also increasing of tolerance to UV radiation, reducing inflammatory processes in the skin and preventing oncogenesis. Low intake of lutein and zeaxanthin, associated with "western diet", rich in simple carbohydrates and processed food, common in developed countries, including Poland, is linked with diabetes and obesity incidence. Assuming, lutein and zeaxanthin significantly affect the well-being of the human body, and their appropriate amount in diet can help reduce risk of many diseases. For supplementation, the optimized dosage of these xanthophylls includes doses of 10 mg for lutein and 2 mg for zeaxanthin, and it is recommended to consume along with fats or meals rich in fats.

Key words: *Lutein, Zeaxanthin, antioxidants, age-related macular degeneration, AMD*

INTRODUCTION

Carotenoids are naturally occurring pigments, soluble in lipids and hydrophobic tetraterpenes, divided into two main groups: xanthophylls and carotenes. That classification is based on functional group given carotenoid structure. In xanthophylls oxygen occurs as a functional group, but carotenes do not consist of oxygen or any functional group in their molecules [31].

Carotenoids are synthesized by plants and microorganisms in order to regulate photosynthetic pathways. Consumed by human – are one of the most valuable dietary micro-compounds, leading to various health benefits and acting as free-radicals scavengers. There are over 600 naturally occurring carotenoids, but 90% of usually ingested carotenoids are limited to five (α- and β-carotene, lycopene, cryptoxanthin and lutein) [35].

Lutein and zeaxanthin belong to xanthophylls. They usually appear together and are widely spread in fruits and vegetables. Contrary to, e.g. β-carotene, they are not connected to retinol pathway, characteristic to provitamin-A carotenoids. Both pigments occur naturally as a plant metabolite and can be found in high quantities in green, leafy vegetables, such as kale and collard, spinach, broccoli, corn, lettuce, egg yolk and orange/yellow fruits (Table 1). In human and primates organisms, lutein and zeaxanthin accumulate mainly in eye's macula in retina [8, 28, 31].

Both lutein and zeaxanthin have specific molecular structure, which has impact on their functionality. Presence of hydrophilic group attached to 2 terminal β-ionone rings in one molecule provides more hydrophilic properties than in other carotenoids. This property increases their efficiency in reacting with singlet oxygen generated in water phase. The

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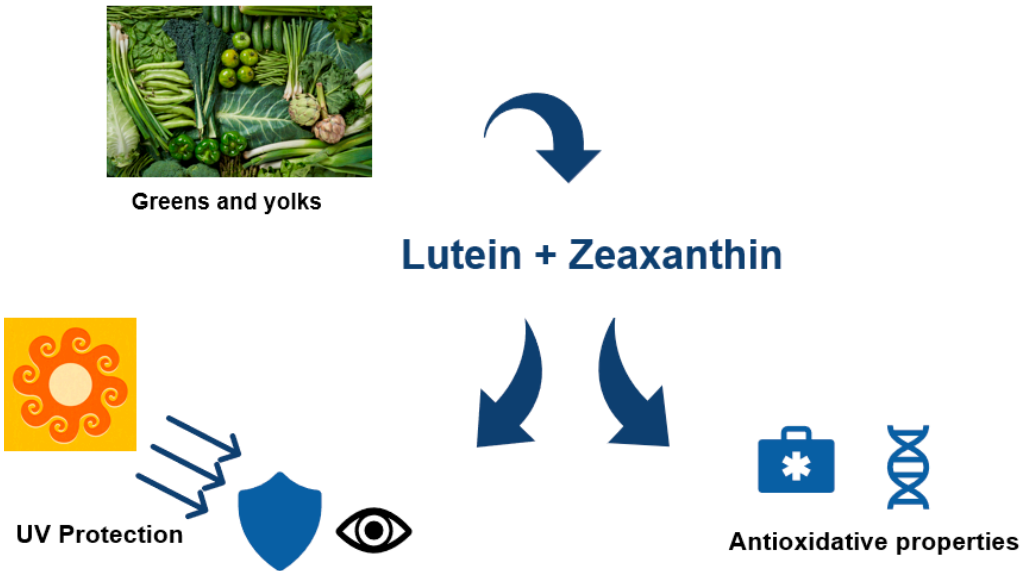

Figure 1. Schematic main functions of lutein and zeaxanthin (based on: *Aziz E.* et al.) [1]

consequence is, among others, having a potential to protect from various diseases, such as cataract, age-related macular degradation, hearth diseases and cancers (e.g. reducing activity of CYP1A2 – hepatitis enzyme responsible for activation of some cacogenesis pathways) [35, 46].

As Figure 1 shows, ingesting lutein and zeaxanthin by eating greens and egg yolks leads to raising these carotenoids levels in organism, what result better balance of ROS and protecting macula from harmful UVB and UVC radiation [3].

Bioactivity of lutein and zeaxanthin

Despite lutein and zeaxanthin concentration in foods, another important issue is bioavailability. High amount of these carotenoids is not always correlated to equally high absorption by organism. For example, corn (*Zea mays L.*) as a zeaxanthin-rich vegetable is very poor source of that xanthophyll because of only 2.4% bio-accessibility (boiled kernel, *in vitro* digestion model) but processed corn flour, eaten as tortilla contains much less zeaxanthin, but the bio-accessibility is about 8 times higher (18.4%) [20]. Main factors influencing zeaxanthin and lutein bioavailability are: form which occurs in source – solid, dissolved or crystal; place where xanthophylls are present in – e.g. chloroplasts, lipids and chemical structure and compounds which lutein or zeaxanthin are bonded with. For example, zeaxanthin mostly occurs as zeaxanthin dipalmitate. In general, occurrence of fats in high carotenoid meals, significantly boost their intestinal uptake, especially olive oil increased plasma and eye level of lutein and zeaxanthin in range of around 20% to 40% in rats after 16 days of exposure [1, 12, 20, 38].

According to Table 1, easiest way toward boosting health condition through optimized lutein and zeaxanthin ingestion is eating around 100-150 grams of kale or 200-250 grams of spinach every day, what provides generous amount of mentioned xanthophylls. Obviously, kale and spinach are not the only source of carotenoids, a balanced diet based on unprocessed products provides the body appropriate amount of

Table 1. Concentration of lutein and zeaxanthin and β-carotene in selected vegetables (based on: *Ribaya-Mercado & Blumberg*) [35]

Product	Lutein+ zeaxanthin (μg/100g)	β-carotene (μg/100g)
Kale	18246	8173
Spinach	11308	6288
Turnip greens	8440	4575
Collards	7694	4814
Mustard greens	5962	3794
Parsley, raw	5560	5050
Dandelion greens	4709	5950
Peas, green/frozen	2400	1250
Lettuce, romaine, raw	2313	3484
Squash, summer	2249	127
Beet greens	1819	4590
Lettuce, green leaf, raw	1730	4443
Broccoli	1517	1180
Squash, winter	1415	2793
Brussels, sprouts	1290	465
Onions, springs, scallions, raw	1137	598
Corn, sweet, yellow, canned	1045	33
Pumpkin	1014	2096

carotenoids [38]. Other, possible solution for surging lutein and zeaxanthin level could be eating 25 grams of goji berries daily. Study reveals that, even small (25 g) dose of this superfood is enough to lift up in-organism level of mentioned carotenoids [23].

Lutein and zeaxanthin levels and bioavailability is also connected with preparation method of food. For example, canned sweet corn have around 30% less zeaxanthin than raw sweet corn. Boiled or fried eggs have the same dependency, having between around 6% and 12% less zeaxanthin than raw. But this tendency is not principle. Pasteurized carrot and orange juices have between 40 and 50% higher carotenoids levels in comparison to unpasteurized [10, 33].

Other important factor for lutein and zeaxanthin bioavailability is composition of meals. Numerous study revealed, that meals rich in fat (especially saturated fatty acids) greatly favors assimilation of these carotenoids. Also, esterified forms of carotenoid have much higher bioavailability. For instance, zeaxanthin in esterified form – as zeaxanthin di-palmitate is characterized by greater bioavailability. This information is especially worthful for people supplementing this xanthophyll, who pay attention to practical level of zeaxanthin in their organisms [33].

There are several attempts to increase lutein and zeaxanthin bio-accessibility, and to increase the intake of this xanthophylls by common society. In recent years most significant researches on this field are accompanied by microfluidic technology and nanofluids. Example of recent study is research of *Yao* et al. [45]. Using the microfluidic technology, lutein was successfully encapsulated with safflower or olive oil as vehicles into noodle-like food, which contains lutein structurally stable for about 1 week [45].

High temperatures during cooking leads to de-esterification and isomerization of lutein molecules, what could modulate lutein bioavailability [38]. What is more, lutein extracted from marigold petals showed higher antioxidant activity than β-carotene and lycopene, and also high anti-mutagenic and anti-clustering properties [26].

Borel et al. [4] study revealed impact of single nucleotide polymorphism (SNPs) of *BCMO1* (β-carotene oxygenase 1) and *CD36* genes on plasma and retina lutein level. Research showed that different alleles of these genes are connected with lower or higher quantity of lutein despite of comparable intake of this xanthophyll [4, 17] (Table 2). Further studies about SNPs affecting the lutein bioavailability were processed [5], aiming correlation between plasma lutein level after lutein-rich meal and SNPs affecting chylomicron lutein response. Study group consisted of 39 men, and were analyzed 51 genes and 1781 SNPs. Lutein plasma chylomicron levels varied between 75% and 135% lutein concentration incensement, measured during 8 h after-meal period. Highest concentration was measured about 5 hours after meal. Concluding, effect of this research were selecting main genes (*ISX*, *ELOVL2*, *ABCG2*, *MTTP*) and their SNPs affecting intestinal lutein incorporation. Single nucleotide

Table 2. Genes affecting lutein and zeaxanthin metabolism (based on: *Mares J.*) [27]

Gene affecting lutein and zeaxanthin metabolism proteins	
Intestinal uptake	SCARB1, SCARB2, CD36, NPC1L1
Blood transport	*ABCA1, LIPC*
Straight metabolism	*BCO1*
Gene affecting lutein and zeaxanthin retina in-retina proteins	
Retinal uptake	*SCARB1, ABCA1*
Retinal transport	*CD36, ABCA1*
Retinal stabilization	*GSTP1, StARD3*
Integrity (*omega*-3 fatty acids)	*ELOVL2; 4; 5, FADS1, FADS2*
In retinopathies	*ALDH3A2, RPE, GSTM1*

Table 3. Miscellaneus effects of lutein and zeaxanthin supplementation

Minor lutein and zeaxanthin effects of supplementation		
Origin	Source	Effect
N.A.	*Elvira-Torales* et al. [8]	Potential for preventing and supporting non-alcoholics fatty liver disease treatment due to their anti-oxidative properties.
N.A.	*Mares* [27]	Potentially associated with obesity and diabetes. Low level often occurs simultaneously with these diseases.
Aztec marigold flowers extract	*Ribaya-Mescado JD., Blumberg JB* [35]	Inhibition of 1-nitropyrene and aflatoxin B1 in bacterial strain.
N.A.	*He RR*, et al. [16]	Lutein supplementation may set a new opportunities for prevention therapy lipopolysaccharide-induced uveitis and side-effects of uvea inflammation. Study reveals, that the oxidative properties of lutein reduce the disease progression through depleting levels of inflammatory mediators.

differences besides population have impact on basic lutein level and assimilating of that xanthophyll from nourishment [4, 5].

Mechanism of action of lutein and zeaxanthin

Apart from above mentioned lutein and zeaxanthin undoubted advantages for human organism, more details of the entire beneficial process will be presented below. These pigments, obtained by dietary intake or additional nutritional supplements, are incorporated into lipid micelles within the gut. Next, micelles are transported to liver and packaged into Lipoproteins – High-density lipoproteins (HDLs) and Low-density lipoproteins (LDLs) or stored. Lipoproteins leaving liver, flow with bloodstream, and are up taken through specific enzymes involved in cholesterol and/or lipid transfer. The main mechanism of mentioned xanthophyll's uptake is through scavenger receptor class B type I (SR-B1) [7]. SR-B1 receptor induces lutein and zeaxanthin uptake both in intestinal Caco-2 cells tested *in vitro* and in mice [4] and probably in other tissues, e.g. retina. Other major binding proteins involved in in-cell coming through are SR-B2, CD36, StARD3 and GSTP1 [6, 29].

These carotenoids are then cleavaged by β-carotene-15,15′-oxygenase (BCO1) and β-carotene-9′,10′-oxygenase (BCO2). BCO1 and BCO2 differ from their substrate specificity from carotenoids with their cell localization and functions. BCO2 may be considered as a little bit more significant because of cell toxic-prevention and anti-accumulative values of this enzyme [2, 6, 7].

Health benefits of lutein and zeaxanthin supplementation

In the world of progressing globalization, we can observe the propensity toward increased disease incidence. Statistics reveal that the more country is developed, the greater cancer risk is noted e.g. Australia, United States with the highest prostate and lung carcinoma rate [44].

Besides the risk factors connected with civilization development (e.g. stress and junk food), plenty of chemical and biological compounds negatively affecting the body, naturally occur, simultaneously rising up ROS production or affiliating tissue damages and inducing cancerogenesis. The examples of environmental mutagens are: Aflatoxins, sterigmatocystins and other toxins, which are food contaminants, produced mainly by *Aspergillus sp.*, *Penicillum sp.* and *Fusarium sp.* [32, 33]. Also everyday life diet brings us a lot of unconsciously ingested mutagens and carcinogens. Such diet is rich in polyunsaturated fatty acids leads to increased level of malonaldehyde in organism. Also pyrolysis of proteins rich in tryptofan (e.g. meat) or smoking tobacco (mutagenicity is correlated with nitrogen content in leaves and products of pyrolysis) accelerates mutagenesis processes in organism. One of the common carcinogens in diet is high consumption of the red meat, which contains high level of fat, generating through preservation carcinogens such as N-nitroso compounds or during high temperature processing - releasing polycyclic amines or aromatic hydrocarbons. High and constant daily consumptions of e.g. well done steaks, may increase risk of colon and prostate cancer. Other important global mutagenic and carcinogenic factors are: obesity, air and soil pollution, high alcohol consumption, sun overexposure [11].

What is more, *Azqueta* et al. [2] study reveals that increased sun exposure, smoking and age have negative impact on DNA repair and increases number of formamidopyrimidine DNA *N*-glycosylase-sensitive sites. Research also proved that alkaline comet assay is more sensitive during research on DNA damage caused by environmental mutagens than HPLC and ELISA tests [2].

Consumption of both lutein and zeaxanthin above 6 mg each day provides to serious health benefits like decreased chance for age-related macular degeneration (AMD); or above 12 mg a day for increasing cognitive functions in older people. Separately, effective intake of each xanthophyll varies between 5 and 10 mg for lutein and 1 to 2 mg for zeaxanthin. What is more, study reveals that daily intake of these xanthophylls are mostly not enough to provide desired health benefits [3, 16, 18, 21, 41]. Average consumption of carotenoids in total depends on local eating habits, season, lifestyle and other factors and ranges between 5.33 mg/day in German population, thought 3.5 mg/day in Spanish population down to around 0.9-2 mg/day in U.S.A and Australian populations [34]. In Poland, as reported in 2005's study, daily intake of lutein was estimated around 1.78 mg/day [16]. *Hamułka* et al. report that daily average intake of lutein in pregnant Polish women; was around 2.1 mg with green leafy vegetables as main source [14, 15].

Neurological and cognitive disorders

Anti-oxidative properties of lutein and zeaxanthin, especially high concentration of these xanthophylls in serum, might be helpful during *Alzheimer* disease treatment [9]. Following the *Min* and *Min* [30] research, high concentration in the serum – 1.33 – 2.08 μg/dl; preferable ≥3.06 μg/dl, significantly reduces probability of death, mostly after 100th month after diagnosis [30].

Supplementation of lutein alone (12 mg/day) or combined with DHA (docosahexaenoic acid; 800 mg/day) lead to the improvement of cognitive

functions, memory and verbal fluency. This trial has been conducted for four months, and the study group consisted of 90 elderly women [10, 18, 21]. Similar research have been done by *Lopresti* et al. [25] research group, but control group counted 19 people in age between 40 and 75. After 6-month trial of supplementation of lutein (10 mg) and zeaxanthin (2 mg), the cognitive functions of participants have been tested. Results proved that 6 months of taken supplementation slightly boosted visual learning skills and memory [25]. Meta-analysis of scientific papers from 2000 to 2020 which have been done by *Li* and *Abdel-Aal*, reveals that lutein supplementation slightly increases cognitive potential and functions, but the effects are not spectacular. According to author's research results, lutein may be more useful in preventing cognitive declines [21]. Other meta-analysis, analyzing effects of combined lutein and zeaxanthin supplementation (tested was also combination with mesoxanthin). This study indicates that combination of these carotenoids gives much better results in aspect of cognitive functions. All of the analyzed clinical trials confirm this thesis [39].

Age-related macular degeneration (AMD)

The main biological function of lutein and zeaxanthin is absorption of blue spectrum of light. These carotenoids absorb between 40% and 90% of the blue light in macula, with the highest concentration spot in outer plexiform layer in fovea. More specifically, they are located among photoreceptors and their interneurons. This placement provides retina photo-oxidative protection, as well as oxidative stress protection in lipid domains, which contains rhodopsin pigment; regulating inflammatory inducing genes [11, 24, 28, 37]. One of the most important gene regulated by lutein and zeaxanthin, but indirectly, affecting ROS balance is *Nrf2* gene which regulates cell redox homeostasis. Promoted by lutein activity of this gene might be helpful to prevent AMD and other ROS-induced eye disorders [3, 27].

Research on lutein supplementation reveals that dose of 10 mg of daily lutein supplementation may be helpful to alleviate the course of early stage of Age-related Macular Degeneration (AMD) disease. Measurement of AMD connected to inflammatory markers levels, associated with *CFH* gene (CFD, C5a, C3d), after 4-, 8-, and 12 months, showed negative correlation between lutein level and level of each marker, although depending on the period of supplementation [36]. Lutein anti-inflammatory function was unveiled to reduce level of slCAM-1 (soluble intercellular adhesion molecule-1) [39]. An extensive meta-analysis, which has been done by *Feng* et al. [10], consisted of total 855 AMD patients. Level of macular pigment optical density (MPOD) and other factors affecting visual comfort, e.g. visual acuity and contrast sensitivity, were tested. That study reveals that 10 mg/day lutein supplementation is effective after a long period of time (1 year), raising level of MPOD; although 20 mg/day lutein supplementation causes much faster results, even in a period of time shorter than half of a year. Visual acuity and contrast sensitivity also increased, after 1 year of supplementation. 20 mg a day is a maximum safe dose of lutein for a human [10].

Anti-cancer activity

Lutein provides reduction of HeLa cell culture proliferation, after 48 hours of treatment, what may be useful in new cervical cancer therapies [33].

A group of researchers tested the impact of purified lutein extract from *Medicago sativa L.* on 5 human cancer cell lines – liver HepG2, breast MCF-7, lung A549, prostate PC3, colon HCT116 and normal cell culture HFB4. In the above mentioned cultures lutein was tested as a cytotoxic agent with reference drug – doxorubicin. Effective lutein concentration was determined experimentally and ranged between 3 and 80 μg/ml. The result of this study showed a significant cytotoxic and antiproliferative effect on MCF-7 and HepG2, in comparison to doxorubicin treated cultures. Lutein did not affect proliferation of other tested cultures [34].

Kavalappa et al. [19] conducted a similar study. The aim of the research was to test the impact of lutein isolated from *Spinacia oleracea* on MCF-7 and MDA-MB-231 breast cancer cell cultures. The range of concentration of lutein was between 1 and 30 μM, in concentration gradient, depending on a given cell culture. Cultures were incubated for 24 h (37 °C, 5%CO_2; Dulbecco's modified Eagle's medium with additives). Significant cell growth and metabolic functions reduction (c.a. <50% reduction to control) was achieved in lutein concentration >5 μM for MCF-7 cells and >20 μM for MDA-MB-231 cells. Lutein in tested cells resulted with suppression of certain protein expression - Nrf2, SOD-2, HO-1, pAkt, pERK, and NF-κB. This suppressive effect leads to apoptosis based on cell ROS defense system disrupting and needs further study to implicit this data to practical application [22].

Anti-radiation functions

There are results, which showed affecting anti-irradiation function of lutein. A Group of Swiss albino mice was pre-treated with various doses of lutein, and after 15 day of supplementation the mice were irradiated by electron beam (dose – 6 Gy). Lutein

in this study turned out to be radioprotectant, with optimized dose – 250 mg/kg b. wt. Lutein pre-treated mice achieved much better results in main organs vitality (activity of major ROS-related enzymes e.g. SOD), as well as boost in hematopoietic system, which effected in greater quality and number of lymphocytes. This study is another one confirming meaningful antioxidative potential of lutein [40].

Lutein is also affecting skin in context of resistance to UV-induced mutations. Affective dosage during research was 5 mg but recommended dose of lutein is equal to 130 grams of kale (20 mg), preferable combined with other phytonutrients, as lycopene, is sufficient to reduce activity of molecular inflammatory pathways in skin cells (genes: *HO-1*, *ICAM-1*, *MMP-1*) [13]. There is also possibility to acquire beneficial effects of lutein and zeaxanthin by external usage. Hen egg yolk oil, received by cod extraction of yolk from avian eggs, due to it's rich in lipids and antioxidants composition may provide extended, external UV skin protection. Simultaneously protecting from UV and nourishing skin may be applicable in modern sun protection [17, 26].

Other effects

Low levels of lutein and zeaxanthin in serum are associated with obesity and diabetes [28]. Lutein supplementation may set a new opportunity for prevention therapy lipopolysaccharide-induced uveitis and side-effects of uvea inflammation. *He* et al. study reveals, that the anti-oxidative properties of lutein reduces the disease progression through depleting levels of inflammatory mediators [16].

CONCLUSION

Lutein and zeaxanthin are one of the most valuable gifts from nature to humankind. Lutein and zeaxanthin, which occurs mainly in green, leafy plants like kale, spinach or lettuce have a potential as therapeutic co-treatment and protective agent from various diseases. The main beneficial property of these carotenoids is scavenging of reactive oxygen species (ROS), which, generated through oxidative stress, are crucial in mutagenesis and morbific factor in mammal organisms. Numerous studies and clinical trials have confirmed exploitation of carotenoid's supplementation and established the working doses – 10-20 mg for lutein and around 2 mg for zeaxanthin. Second major aspect of lutein and zeaxanthin pro-healthfulness ability is protection from UV radiation, mainly affecting eye's macula protection from the light but also supporting skin function as organism's UV guard.

Conflict of interest

The authors declare no conflict of interest.

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