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The influence of selected active substances on the functioning of the visual system

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ABSTRACT

Age-related macular degeneration (AMD), glaucoma and cataracts are the most common eye diseases. They are predominantly caused by insufficient amounts of antioxidants in the body, which include lutein, zeaxanthin, lycopene, omega-3 fatty acids, vitamins and micronutrients. The positive properties of these biologically active substances affect the neutralization of reactive oxygen species, slow absorption of UV radiation, and improve blood supply to the structural elements of the eye. Deficiency of these substances has a negative effect on the functioning of the eye, leading to degeneration of its structures. Presently, a fully effective method of treatment has not been discovered, therefore preventative measures, especially those including a healthy diet and lifestyle, are highly important as the human body cannot synthesize these beneficial substances. This requires increasing public awareness concerning products with high nutritional value, which should be included in people's daily diet.

Keywords**:** sight, antioxidants, carotenoids, bioflavonoids, vitamins, microelements

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1. INTRODUCTION

Environment, lifestyle and diet are three main factors that can cause various adverse changes in the functioning of our eyes [15, 33]. The first symptoms of eye dysfunction are pain, tearing and burning, as well as problems with the sharpness and quality of vision. Oftentimes, adverse factors stemming from the environment cannot be avoided, however there are ways by which their negative effects can be significantly delayed or minimized [9, 16, 30]. Various micronutrients and vitamins support the body's regenerative processes and help combat oxidative stress induced by an excess of reactive oxygen species [19, 32]. Carotenoids which are present mainly in vegetables, are a structural component of the macula and retina, whereas flavone-glycosides, contained in fruits and leaves of blueberry, seem to be helpful in cataract prevention and treatment [12, 18]. The pharmaceutical market offers many drugs or dietary supplements for eye care, the appropriate dosage of which is intended to restore eye efficiency. How is the right product from such a large selection chosen? The aim of this study is to analyze literary data on the effectiveness of selected active substances contained in various pharmacological supplements. The influence of these active substances contained in foods necessary for proper functioning of the eye, based on available data is also briefly presented.

2. CAROTENOIDS

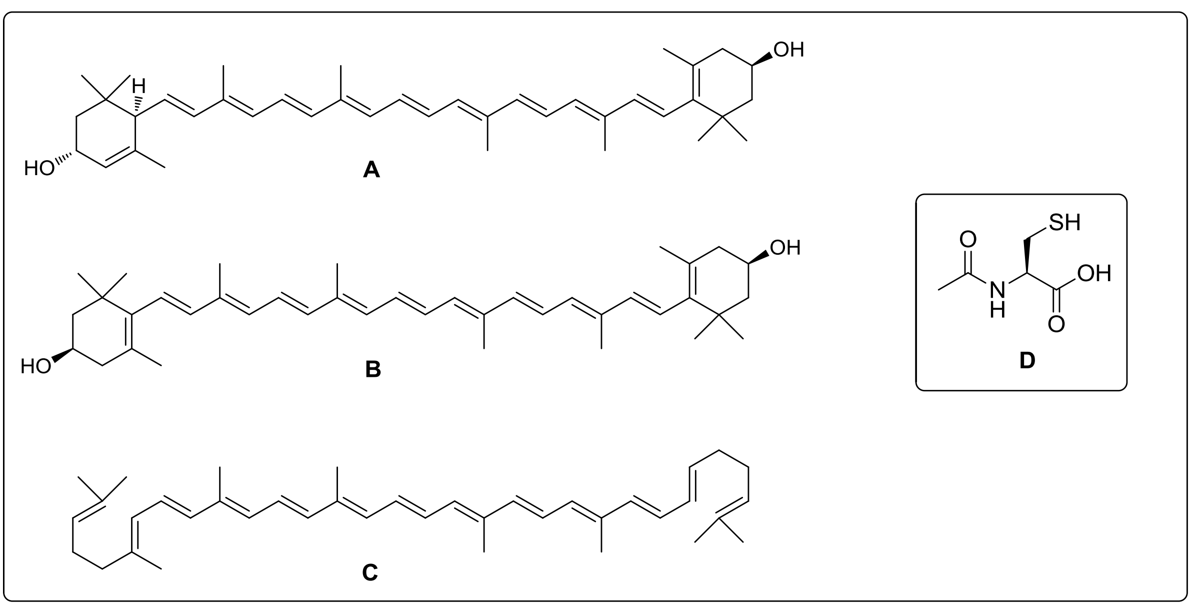

Fig. 1. Structural formulas of carotenoids: A - lutein (3,3'-dihydroxy-α-carotene), B - zeaxanthin (β, β-carotene-3,3'-diol), C - lycopene (γ, γ-carotene), D - N-acetylcysteine (N-acetyl-L-cysteine);

Carotenoids are plant dyes which accumulate in the retina of the eye. The most important carotenoids are: lutein, zeaxanthin, lycopene and β-carotene [1]. Because they are not produced by the human body, their levels depend on their supply from the diet [10, 31]. Carotenoids are transported by lipoproteins including: low-density lipoprotein (LDL, 55%), high-density lipoprotein (HDL, 33%), very low-density lipoprotein (VLDL, 10% to 19%) and others. Lutein and zeaxanthin (Figures 1A and 1B) contain nine combined double bonds in their polyene chain and constitute the protective element of the eyes which allows them to absorb high-energy phototoxic blue and ultraviolet light. Lutein and zeaxanthin are derivatives of α- and β-carotene, respectively, having two hydroxyl groups located at the ends of the β-ring of the molecule [8]. This structure makes them more polarized than other carotenoids, such as β-carotene and lycopene, which do not contain oxygen. Although lutein and zeaxanthin have identical chemical formulas and are isomers, they are not stereoisomers. The main difference between them is the placement of a double bond in the final ring, resulting in three chiral centers for lutein, and two for zeaxanthin [25]. These dyes have a positive effect on the retina due to their ability to scavenge free oxygen radicals which exert a detrimental effect on cellular elements of the eye [1, 8, 10, 25, 31].

Vitamin A

Vitamin A is defined as chemical compounds exhibiting the characteristics of provitamin A. Such substances include retinol or β-carotene, found in plant products. Some main sources of fat soluble vitamin A are foods such as pork and poultry liver, tuna, eggs, milk, carrots and red peppers as well as other readily available plant and animal products [2, 23]. β-carotene shows only half of the biological activity of vitamin A, is stored in the skin, and functions most efficiently at low oxygen partial pressures.

Among many important functions of vitamin A, its antioxidative role should be highlighted. As an antioxidant, it neutralizes reactive oxygen species, especially in tissues that are characterized by oxygen deficiency, such as in the retina, and compliments the similar effects of vitamin E [2, 23]. Vitamin A also plays a highly important role in visual processing and aids in transforming light signals into visual impulses [3]. It is also an indispensable factor in the synthesis of the viscous photosensitive dye, rhodopsin, which supports twilight vision. The photoreceptor protein converts light signals into nerve impulses.itamin A increases the production of mucus, which moisturizes the elements of the eye and counteracts the development of inflammation and so-called dry eye syndrome [2].

The first symptoms of vitamin A deficiency, observed after a few months of insufficient intake include eyelid inflammation, blurred vision, dry cornea and conjunctiva and can lead to extremely serious ocular problems such as xerophthalmia [43].

Lutein

Lutein levels are observed in the peripheral parts of the retina, mainly in the nerve fiber layer [6, 22]. The body's lutein level depends on the amount assimilated from an individual's diet. The greatest natural sources of lutein are vegetables, including cauliflower, spinach, broccoli, kale, green peppers, lettuce, peas, corn, cabbage and brussels sprouts [10, 26]. In plants, lutein is present in two forms: free form, and esterified with palmitic acid, both of which are equally absorbed by the body. The body's daily minimum requirement of this component is 6-10 mg [8, 42]. Intake of lutein either from vegetables or from dietary supplements results in its accumulation in the macula. The lutein released from food is absorbed by enterocytes, then, by simple diffusion is incorporated into chylomicrons, which arę transported to the liver [10]. Due to its high polarity, lutein is transported to the surface lipoproteins (high density lipoproteins -HDL and low-density lipoproteins - LDL). The distribution of lutein in tissues also determines its concentration in the receptors [32]. Lutein, with a maximum light absorption of 445 nm, reduces sensitivity to glare and improves visual contrast. It also increases the density of the retina pigment [8, 25] and protects the rods, which are related to the location of carotenoid in the peripheral part of the retina [10, 35].

Photoreceptor cell membranes contain polyunsaturated fatty acids that are easily oxidized under the influence of blue light. Excessive amounts of reactive oxygen species generated as a result of exposure to light are the cause of oxidative stress. The consequence of this process is the formation of peroxidation groups of lipids in the photoreceptor membranes [10]. Lutein absorbs blue light and protects against its toxic effects by reducing the number of chromosomal aberrations and, as an antioxidant, binds free radicals reducing oxidative stress [6, 8, 10, 19, 22, 29, 35].

The level of lutein in the macula is more than 1000 times higher than in other tissues. Age-related macular degeneration (AMD) is a disorder of the central part of the retina, which may develop into total blindness [1, 16, 17, 21, 24]. People between 50-60 years are most vulnerable to this disease [8, 16, 17]. Some of the most important causative factors are: chronic inflammatory processes occurring in the subretinal space, excessive exposure to ultraviolet light, oxidative stress; and a deficiency of micronutrients, such as zinc and selenium which effect the proper functioning of the antioxidant enzymes - catalase and peroxidase [1, 10, 16, 17 , 24].

Some ninety percent of AMD cases are called dry (atrophic), and do not present any clearly visible symptoms, other than a gradual loss of central vision, with the visual field becoming distorted and out of focus. The less common second form – moist (exudative), is an expression of damage to the blood vessels of the eye which can cause loss of sight quickly (in some cases several days) [9, 13, 16, 17, 19, 33, 36, 37]

The most effective ophthalmologic diagnostics for recognizing macular degeneration is ocular computed tomography (OCT), a method which allows tracing all layers of the retina and detecting the so-called druzy, or subretinal deposits in the Brucha membrane. A more recent breakthrough in the treatment of this disease is use of the 2RT laser (retinal rejuvenation therapy). This procedure's ability to stimulate and regenerate the retinal pigment epithelium it one of the innovations of laser therapy [14]. Also, lutein supplementation may increase the density of the macula pigment and decrease the degenerative changes in the macula, risk of cataracts, and even eye melanoma [10, 11, 19, 21, 22, 28].

Zeaxantin

Zeaxanthin can be found in the blood serum and macula of the eye retina and is responsible for central vision and image sharpness [8, 25]. Zeaxantin can be found naturally in foods such as broccoli, Brussels sprouts, corn, and tomatoes, however, only after thermal treatment does a loosening of the chemical skeleton of the compound take place which enables it to be absorbed into the body [26]. β-carotene resulting from the cyclization reaction of lycopene is converted into zeaxanthin by the hydroxylation process, which in turn is converted to antheraxanthin and violaxanthin, the optical and geometric forms of zeaxanthin in the epoxidase-catalyzed reaction by zeaxanthin (EC 1.14.13.90) retina (Fig. 2) [18].

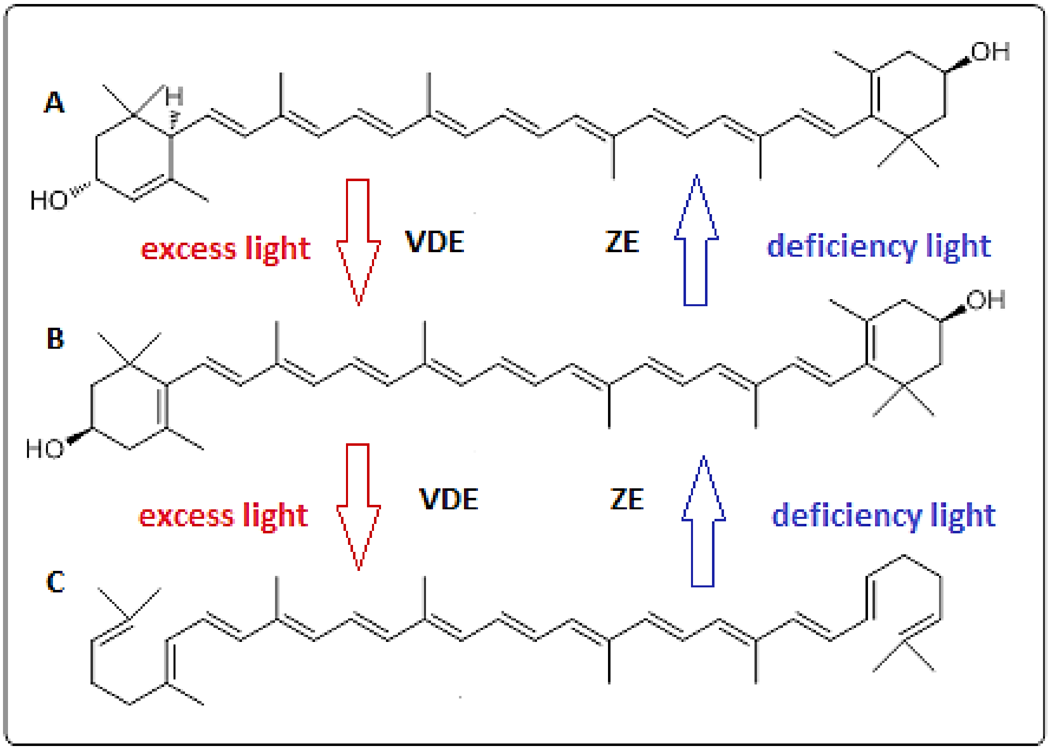

Fig. 2. The xanthophyll cycle of carotenoid biosynthesis - the conversion of violaxanthinand zeaxanthin. A - violaxanthin, B - antheraxanthin, C - zeaxanthin, VDE - violaxanthin de epoxidase (EC 1.14.15.21) (ZE - zeaxanthin epoxidase (EC 1.14.13.90).

The daily body's need for zeaxanthin is 1-2 mg. This substance protects cones and is an antioxidant that neutralizes free radicals which have a large amount of polyunsaturated fatty acids and present a great danger for photoreceptors. [7]. Together with lutein, zeaxanthin counteracts degenerative changes in the eyes by absorbing ultraviolet radiation harmful to the eye. This is why it is especially important for those exposed to constant UV radiation, such as IT specialists and drivers to use preparations containing these two components [25, 35]. Due to the aforementioned properties, zeaxanthin and lutein combined have proven effective in reducing the risk of AMD, twilight blindness, symptoms of dry eyelids, redness and lacrimation of the eyes, as well as impairment of visual acuity [1, 7, 19, 21, 33, 36, 37].

Lycopene

Lycopene is a precursor substance in the synthesis of α-carotene and β-carotene (Figure 1C), generated by the cyclization process. The body's storage site for lycopene is primarily the liver, but also the prostate gland, large intestine, lungs, adrenal glands, ovaries and skin [2, 29]. The highest source of lycopene are tomatoes and their processed products, such as tomato sauce and ketchup, which are much more easily digestible, especially when fat, such as olive oil is added to heat-treated tomatoes. Absorption, distribution, metabolism and excretion all determine the therapeutic effects of lycopene. According to studies, as much as 24% of the compound ingested accumulates in tissues, while the remaining amount is excreted in urine, bile salts and by evaporation [20]. Lycopene has numerous important functions, including neutralizing free radicals much more efficiently than β-carotene or α-tocopherol. Lycopene increases the fluidity and permeability of cell membranes, thereby activating the pathways of antioxidant response in the cells and modulates the activity of the immune system. Lycopene also increases body levels of lutein and zeaxanthin [19, 29]. This carotenoid has been shown to reduce the risk of lung, breast, prostate, liver, ovarian and gastrointestinal cancers. In the case of the eyes, lycopene reduces eye fatigue and, above all, inhibits macular degeneration. Its concentration is inversely proportional to the prevalence of AMD (which increases the risk of vision loss with age).

Vitamin E

The vitamin E family includes 8 homologous and organic chemical compounds from saturated and unsaturated α-, β-, γ-, δ-tocotrienols. Vitamin E compounds are a group of strong, natural antioxidants that protect cell membranes against the formation of toxic fatty peroxides and prevent vitamin A oxidation [18, 23]. They also enhance the absorption of β-carotene in the small intestine and the body's ability to use lutein. Deficiency or complete lack of vitamin E may result in retinopathy of preterm infants, causing an inherent defect of the retina, leading in most cases to blindness in newborns. Natural sources of vitamin E are mainly: plant-based products, fats, cereal products, olive oil, pumpkin seeds, nuts, spinach, parsley and wheat bran [2, 18].

Vitamin C

Natural sources of vitamin C in particular are: citrus fruits, such as strawberries and blackberries and vegetables, such as white cabbage, broccoli or brussels sprouts [15]. Blackcurrants are particularly rich in vitamin C and the anthocyanins present in it normalize the concentration of endothelin-1 in the blood of patients with glaucoma and contributes to regression of the disease and improves circulation in the eyeball. In addition, anthocyanins from black currant improve night vision and accelerate the regeneration of the dye - rhodopsin [12]. Vitamin C performs antioxidant functions by neutralizing free radicals, has a protective effect on cell membranes, strengthens the walls of blood vessels thereby reducing their permeability, as well as regulates the production of tear fluid [44]. By preventing oxidative stress, vitamin C reduces the risk of developing cataracts, a degenerative eye disease that usually affects people over 60 years of age [1, 18, 28]. The recommended dose of this vitamin depends on age, gender and lifestyle.

Omega-3 acids

Omega 3 acids are classified as polyunsaturated fatty acids that affect the retina, contributing to its normal development and functioning by reducing the level of drusen forming substances and C-reactive protein, which is an acute phase protein and a marker of inflammation [27, 34, 41]. The acid name is derived from the first double bond at the third carbon from the methyl end of the chain. The fat of sea fish that feed on plankton, such as salmon, herring, mackerel and trout are all especially rich in omega-3 [34]. Deficiency of omega-3 in older age may be a reason for macular degeneration. Fatty acids improve blood supply to the optic nerve, hence their highly important preventive function of protecting the visual apparatus. They also ensure the proper functioning of the retina [27]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which belong to the group of polyunsaturated fatty acids, constitute an important element in the formation of cell membranes of the central nervous system, thus, they are responsible for the functioning of the brain and the retina. DHA deficiency is particularly dangerous, as it causes the development of retinopathy in premature babies, and in the elderly, the development of AMD. The daily requirement for EPA and DHA is 200 mg [41].

N-acetylcysteine (NAC)

NAC is one of the secretolytic drugs used to remove dense secretions from the airways and rebuild the physiological layer of hydrated mucus. In recent years, another use of N-acetylcysteine (Figure 1D) and its amides (N-acetylcysteine amide, NACA) has been discovered, as these substances prevent vision loss due to the retinal degeneration processes associated with macular aging [38]. Retinal pigment epithelium cells (RPE) perform a number of beneficial functions, for example: they regulate the transport of ions and metabolites, phagocytizing photoreceptor outer segment fragments (POS) help with retinol metabolism and the formation of an external blood-retinal barrier. In connection with their functions, RPE are particularly exposed to high levels of oxidative stress resulting from lipid peroxidation. This negative impact on RPE causes high oxygen tension within the macula and exposure to light [4, 38]. The polyunsaturated fatty acids contained in the POS membrane readily oxidize by initiating the formation of a toxic reactive oxygen species (e.g., H_2O_2) and lipofuscin which induce oxidative damage within the retinal cells. NAC exhibits mucolytic properties through its sulfhydryl group. It has similar antioxidant properties to glutathione [4, 5]. N-Acetylcysteine amide has been shown to be more effective than NAC because the neutral carboxyl group of NACA penetrates the cell membrane and the blood-brain barrier much more easily. This allows the dose of medication to be reduced and thereby prevents diarrhea, which is an undesirable side effect of NAC administration.

Secondary degeneration of photoreceptors as a result of the oxidative processes, leads to the development of AMD [39]. NACA presents greater penetration capacity than other antioxidants, such as vitamin E or carotenoids [40]. NACA protects the retinal pigment epithelial cells from damage caused by oxidative stress by increasing the level of cellular glutathione and inducing selenoenzyme, which reduces peroxides using glutathione, and thus by reversing lipid peroxidation stops the production of reactive oxygen species. [38]. NACA has been shown to block apoptosis by inhibiting protein kinase (EC 2.7.11.13). Importantly, N-acetyl cysteine amide does not exhibit RPE toxicities even at high concentrations. The key importance of NACA in the treatment of retinal degeneration is the protection of RPE cells and photoreceptors against damage [38]. In addition to proven antioxidant functions, NACA also has anti-inflammatory properties. The N-acetyl cysteine applied as a 5% solution additionally exerts a mucolytic effect, cleansing the cornea [4].

Bioflavonoids

Bioflavonoids are substances present in fruits and vegetables and are responsible for their intense color. Particularly noteworthy are the fruits of the chokeberry bush. Studies have shown that bioflavonoids significantly reduce the permeability of the eye capillaries, restoring their elasticity. The most numerous group of flavonoid compounds are anthocyanins, which are characterized by antioxidant, anti-inflammatory and anti-cancer properties. These compounds have a protective effect for the blood vessels walls and counteract damage resulting from ischemia [45]. The capture of reactive oxygen species is important in the prevention of neurodegenerative diseases and inflammation of the eyeball.

The development of glaucoma leads to the formation of high intraocular pressure, which is the direct cause of progressive damage to the optic nerve. The main therapeutic effect in the treatment of this disease is normalization of pressure in the eye [30]. Bioflavonoids are the subject of many studies regarding their use as substances that inhibit ocular inflammatory diseases and diabetic retinopathy.

Micronutrients

For proper eye functioning, copper, selenium and zinc are necessary [1,7]. As enzymes with antioxidant properties, these micronutrients enhance the fight against free radicals, protecting the body against oxidative stress. For example, zinc, which is a component of peroxide dismutase (Zn-SOD), participates in the elimination of superoxide free radicals. Products rich in zinc are oysters, wheat germ, pumpkin seeds and watermelon. Zinc plays an important role in maintaining normal plasma levels of vitamin A. The most valuable sources of selenium are Brazil nuts, tuna and seafood. Copper is found in oat flakes, cocoa and sunflower seeds, and its main function is to strengthen collagen bonds, which has a positive effect on the stability of the blood vessels of the eye. These three elements also prevent the development of cataracts and macular degeneration [7, 28].

Table 1. The content of selected active ingredients affecting the functioning of the eye.

Ingredient	Content in food (per 100g)	Content in medicines and food supplements (in 1 tablet / capsule)
Lutein	0,01 - 40 mg	4,0 - 10 mg
Zeaxanthin	0,01 - 40 mg	0,5 - 2 mg
Lycopene	3 - 15 mg	0,3 - 30 mg
β-carotene	0,6 - 9,9 mg	1 - 10 mg
Vitamin A	0,3 - 21,9 mg	0,38 - 0,8 mg
Vitamin E	0,5 - 38,7 mg	5,0 - 30 mg
Vitamin C	40 - 182,6 mg	30 - 180 mg
EPA Eicosapentaenoic acid	0,5 - 1700 mg	90 - 300mg
DHA -Docosahexaenoic acid	0,5 - 1700 mg	58 - 200 mg
Selenium	0,05 - 32,2 mg	20 - 110 ug
Zinc	0,15 - 8,4 mg	2,5 - 15 mg

3. CONCLUSIONS

Lutein, zeaxanthin, lycopene, flavonoids and vitamins present in dietary products are essential for scavenging free radicals whose adverse effects lead to serious consequences, such as age-related macular degeneration, glaucoma and cataracts. There is no effective substance that can completely protect the body against eye diseases, however, the eyes can be strengthened and regenerated through adapting a balanced and varied diet, adequate supplementation, wearing glasses with UV filters and regular eye control checkups. The protective properties of carotenoids, flavonoids, fatty acids, vitamins and micronutrients are very extensive and are still the subject of many scientific studies.

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