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Potential properties of natural nutraceuticals and antioxidants in eye protection

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Abstract

Eye health is crucial and the onset of diseases can reduce vision and affect the quality of life of patients. The main causes of progressive and irreversible vision loss include various pathologies such as cataracts, ocular atrophy, corneal opacity, age-related macular degeneration, uncorrected refractive error, posterior capsular opacification, uveitis, glaucoma, diabetic retinopathy, retinal detachment, undetermined disease and other disorders involving oxidative stress and inflammation. The eyes are constantly exposed to the external environment and, for this reason, must be protected from damage from the outside. Many drugs, including corticosteroids and antinflammatory drugs have widely been used to counteract eye disorders. However, recent advances have been obtained via supplementation of patients with natural antioxidants and nutraceuticals. In particular, evidence has been accumulated that polyphenols (mostly deriving from Citrus Bergamia) represent a reliable source of antioxidants able to counteract oxidative stress accompanying early stages of eye diseases. Luteolin, in particular, has been found to protect photo-receptors thereby improving vision in many disease states. Moreover, a consistent anti-inflammatory response was found to occur when curcumin is used alone or in combination with other nutraceuticals. On the other hand, CoQ10 has been demonstrated to produce consistent effect in reducing ocular pressure thereby leading to protection in patients undergoing glaucoma. Finally, both grape seed extract rich in anthocyanosides and polyunsaturated fatty acids (PUFAs) seem to contribute in the prevention of retinal disorders. Thus, combination of nutraceuticals and anti-oxidants may represent the right solution for a multiaction activity in eye protection to be associated to current drug therapies, and this will be of potential interest in early stages of eye disorders.

Keywords: Eyes diseases; Oxidative damage; Antioxidant compounds; Vitamin A; Vitamin C; Lutein; Curcumin; Quercetin; Coenzyme Q10; PUFAs; BPF; Grape seed;

1. Introduction

To date, it is known that improving eye health is one of the objectives of the UN Summit on Sustainable Development and this can be achieved by including promotion, prevention, care and rehabilitation strategies. Improving eye health includes not only a best vision, but also reducing disability and increasing well-being [1]. Therefore, it is possible to deepen the health of the eye and solve world problems associated with it only apparently: for example, the reduction of hunger reduces the diseases of the eyes related to malnutrition, but bidirectionally, better eye health reduces poverty and thus reduces hunger [2]. Normal human eye measures approximately 22 to 27 mm in the anteroposterior diameter and possesses a circumference from 69 to 85 mm. The Human eyeball consists of three primary sections: (1) the outer layer of support of the eye, which includes clear cornea, opaque sclera, and their interdigititation, designated as limbo; (2) the central uveal layer of the eye comprising the iris, ciliary body, and choroid; (3) the inner layer of the eye, commonly referred to as the retina [3, 4]. The visual process begins with the crossing of light through the clear cornea, the pupillary opening, the crystalline lens and the retina. Finally, the visual impulse is transmitted to the brain through the optic nerve [5, 6]. Light is a form of electromagnetic energy that enters our eyes, through the pupil, and is made to converge, from the cornea and the lens, on the receptors of the retina that is located on the back wall of the eye. The pupil is surrounded by a pigmented iris that can expand or contract, making the pupil larger or smaller as the incident light level changes. Retinal receptors detect light energy and, through a transduction process, generate the action potentials that then travel along the optic nerve [7, 8]. In Figure 1 eye structure and vision mechanism are shown.

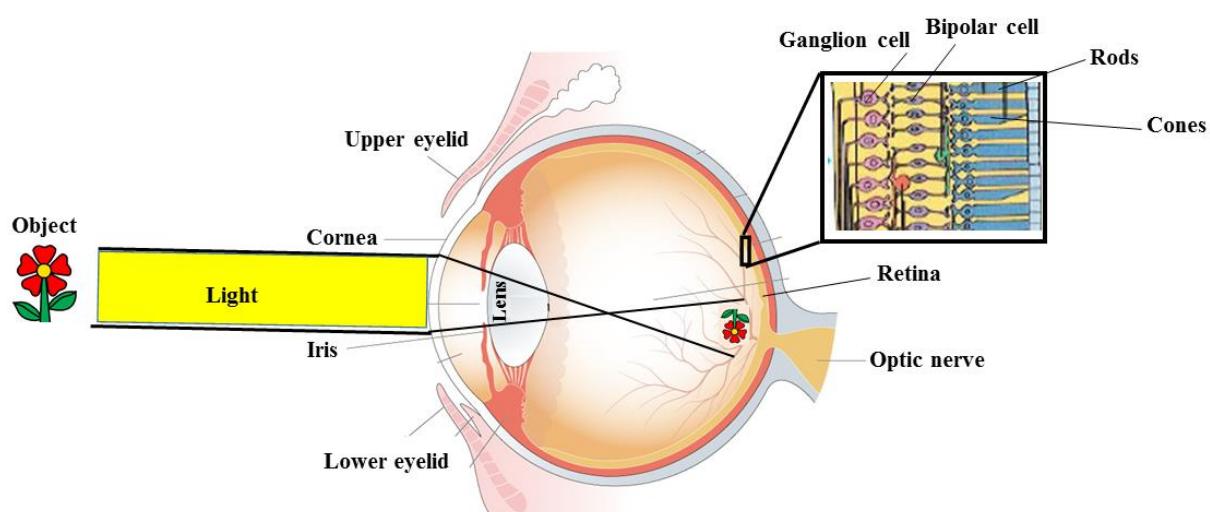


Figure 1. Eye structure and vision mechanism

The eye, regardless of its complex structure, is connected structurally and functionally with vascular, nervous, endocrine and immune tissue. Nevertheless, it is constantly exposed to the external environment and, for this reason, it must be protected from damage from the outside. A very important protection to the eye is guaranteed by the production of a tear film consisting of aqueous components, electrolytes, lipids and mucus. In this way, the lubrication is maintained and any factor that disturbs its composition is able to alter the stability of the eye, its osmolarity, its tissue structure, mechanical and inflammatory mechanisms [9-11]. Eye diseases are due to aging, the occurrence of local and specific diseases or concomitant pathologies. Impaired vision negatively affects quality of life and daily activities, increases the risk of disability and depression in older age, up to loss of independence [12-14]. Eye diseases more easily found are ocular atrophy, corneal opacity, cataract, uncorrected refractive error, posterior capsular opacification, uveitis, glaucoma, age-related macular degeneration, diabetic retinopathy, retinal detachment and undetermined disease [15, 16]. The drug therapy adopted for these pathologies, can be supported by the intake of particular foods or food supplements, which have been shown to be able to address, together with drugs, the pathophysiologic mechanisms directly involved. Numerous micronutrients and nutraceuticals products, in fact, can affect some eye components through the involvement of different metabolic pathways [17-19]. This review can be divided into three sections: in the first part, the close correlation between the main pathologies affecting the eye and oxidative damage is described; in the second part, the beneficial effects of some anti-oxidant compounds on eye health are developed; finally, the third section deals with the hypothetical development of an antioxidant mixture, motivating the choice and the age of the people who should take it.

2. Reactive oxygen species and eyes health

Oxygen (O_2) is essential for life since it is crucial for aerobic breathing of cells and tissues as well as for ensuring the energy cycle of life. Under normal conditions, aerobic metabolism predicts that O_2 undergoes a reduction reaction giving rise to water (H_2O). On the contrary, in some situations there is an incomplete reduction of O_2 , the formation of very unstable and reactive species, known as reactive oxygen species (ROS) and their accumulation [20]. In metabolic reactions, the first ROS to form is the superoxide anion ($O^{2-}\cdot$), which is the most abundant of ROS and possesses a half-life of milliseconds. Because of its very short half-life, this radical ion is not able to attack biological macromolecules, but may begin the formation of high concentrations of ROS by chain reactions. The $O^{2-}\cdot$ is also used by the immune system to kill pathogenic microorganisms: phagocytes produce $O^{2-}\cdot$ in large quantities, through the enzyme NADPH oxidase, and use it to eliminate pathogens, through an oxygen-dependent mechanism. Due to the toxicity of $O^{2-}\cdot$, all organisms have developed superoxide antagonist enzyme isoforms, superoxide dismutase (SOD), capable of catalyzes superoxide neutralization, producing the hydrogen peroxide (H_2O_2) [21]. H_2O_2 is the second most present ROS; it is a small molecule, a non-radical oxygen species, which spreads easily in biological membranes, propagating its effects even at a distance. In addition, H_2O_2 is able to generate other ROS and decompose, converting to water and oxygen through an exothermic reaction. Since the oxidation state of oxygen in H_2O_2 is -1 (intermediate between states 0 and -2), H_2O_2 can function as both oxidizing and reducing agent. Reactions in which H_2O_2 is cycled by oxidant is favored in an acidic environment, while reactions in which it behaves as a reducing agent are favored in a basic environment [22]. The hydroxyl radical ($OH\cdot$) is the most powerful and harmful of all oxygen species since, despite having a very short half-life, it shows a high reactivity. Therefore, it is a very dangerous compound for the body because cannot be

eliminated by an enzymatic reaction, and because it reacts with every oxidizable available compound. OH• can damage all kinds of biological macromolecules and the only means to protect cellular structures is the use of antioxidants or any other efficient repair system [23]. Biological macromolecules (lipids, proteins, and nucleic acids) can be damaged by ROS, although lipids are more susceptible to oxidation. There are defensive mechanisms, both exogenous and endogenous, against oxidative attack: if the production of ROS and the ability of antioxidant biological systems to counteract the effects of ROS metabolites are unbalanced, oxidative stress occurs, which produces damage and abnormalities more or less serious, in the cells [24]. Exogenous antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) [25]. Oxidative stress involves the onset of many pathologies, including cancer, neurodegenerative diseases, atherosclerosis, cardio-circulatory pathologies, asthma, infertility, aging, dermatitis, hypertension, diabetes, rheumatoid arthritis among others [26-30]. Oxidative stress is also involved in eye diseases, such as dry-eye disorder, cataracts, glaucoma, eye surface disorders, retinitis pigmentosa, diabetic retinopathy, uveitis, age-related macular degeneration and toxic neuropathies [31, 32]. The human eye is constantly exposed to sunlight, artificial light and high metabolic activity; in addition, exposure to ionizing radiation, environmental toxins, chemotherapy, contribute to oxidative damage in eye tissues, making the eye particularly susceptible to oxidative damage. Prolonged exposure to ROS, therefore, constitutes a considerable risk for the health of the eye, whose cells, following the damage of their macromolecules, highlight the impairment of metabolism, resulting in necrotic or apoptotic death [33]. Eye dryness disorder defines the dysfunction of the eye surface which consists in a deterioration of the tear film and which leads to dryness of the eyes. This disorder involves several portions of the eye including the eyelids, tear glands and various tissues of the eye surface [34]. A significant increase in oxidative activity, associated with a decrease in antioxidant defenses in the fluids and tissues of the eye, can damage the eye surface causing serious alteration to the tissues of the cornea and conjunctiva, evolving in the development of eye dryness and visual damage. In fact, in patients suffering from dry eye was detected, in addition to an imbalance in the state of the tear film, also the overexpression of the production of ROS on the eye surface [35, 36]. Retinal eye diseases are numerous and particularly linked to oxidative stress for three important reasons: 1) the retina is constantly subjected to the action of visible light that generates photooxidation; 2) The work carried out by the retina is considerable and requires a large consumption of oxygen which, during mitochondrial respiration, could favour the accumulation of ROS; 3) Polyunsaturated fatty acids (PUFA) are particularly present in the retina which is, consequently, susceptible to lipid peroxidation [37]. Diabetic retinopathy is considered, to date, the main cause of blindness in developed countries. Impaired blood glucose levels cause significant damage to vision, which is aggravated in the presence of ROS accumulation. Free radicals damage cells by acting on biological macromolecules: they disaggregate amino acids by altering the protein structure, fragment nucleic acids by damaging DNA, modify lipids and membrane structure [38]. These alterations lead, over time, to cell death by necrosis. Finally, ROS accumulation damage in diabetic patients causes systemic alterations justified by a vascular dysfunction [39, 40]. Glaucoma includes a group of disorders in which selective retinal ganglion cell (RGC) loss occurs, placed on the inner surface of the retina and connecting its axons to the optic nerve. This disease is the second cause of blindness in the world and is a progressive optic neuropathy caused, in most cases, by elevated intraocular pressure [41]. Glaucoma is closely related to oxidative stress, and evidence of this correlation has been provided by both animal and human experiments [42]. In the models used glaucoma was induced by increased intraocular pressure, optic nerve compression, axotomy, reduced blood supply to the optic nerve, and autoimmune damage. In all these induced situations, an increase in ROS, a reduction in antioxidants and an increase in retinal lipid peroxidation have always been found [43]. The mechanism of action involves ROS and biological macromolecules, proteins and nucleic acids [44, 45]. Cataracts consists in the opacification of the lens, located inside the eye that has the purpose of filtering the

light that penetrates through the pupil, directing it towards the retina [46]. The triggering causes of cataract onset are multiple, including aging, genetic inheritance, metabolic, environmental or nutritional insults; sometimes it can be a consequence of other eye diseases, (retinal degenerative, uveitis, glaucoma) or systemic diseases such as diabetes [47]. Nowadays, it is increasingly believed that cataract is caused by the presence of high molecular weight protein aggregates or by the breakdown of the microarchitecture of the lens. This hypothesis involves post-translational modifications of lens proteins that alter their conformation, leading to destabilization and eventual aggregation [48]. Membrane, luminal or secretory proteins are synthesized in the rough endoplasmic reticulum (ER) and transported into its lumen [49-51]. When internal or external factors intervene, the proteins, inside ER, conform incorrectly, becoming misfolded proteins. Poorly folded proteins in the ER trigger cataract formation processes [48]. In cells, misfolded proteins are eliminated or corrected in suitable conformations by specific pathways, including the unfolded protein response (UPR). However, chronic UPR further amplifies the degradation, modification and aggregation of the proteins of lens in the downstream cascade. UPR culminates in calcium imbalance, protein degradation, oxidative insults, redox state disturbances and loss of antioxidant defense mechanisms [52]. Recent studies have shown that ROS, in patients with cataracts, induced a reduction in DNA methylation in the *Keap1* promoter gene, activating the expression of Keap1 protein. In physiological conditions Keap1 is capable of Increase the nuclear factor erythroid 2-related factor 2 (Nrf2) proteasomal degradation. Since Nrf2 controls the basal and induced expression of a number of antioxidant response genes, it is evident that the reduction of Keap1, induced ROS, increases the degradation of Nrf2 and, as a result, reduces a cell's antioxidant control system [53-55]. The consequence is that oxidative damage increases exponentially, along with the development of cataracts of the lens. Finally, an excessive production of free radicals alters the redox state, modulating an inflammatory response, which leads to the exacerbation of oxidative damage favoring numerous pathological states [56]. The main negative function of ROS occurs on biological macromolecules, generating lipid peroxidation, DNA oxidation and protein alteration, which contribute to the damage of cell structure and function. A prolonged condition of ROS-induced cell damage results in the onset of inflammation and pathologies affecting different body districts. In figure 2 is represented how the accumulation of ROS can generate eye pathologies.

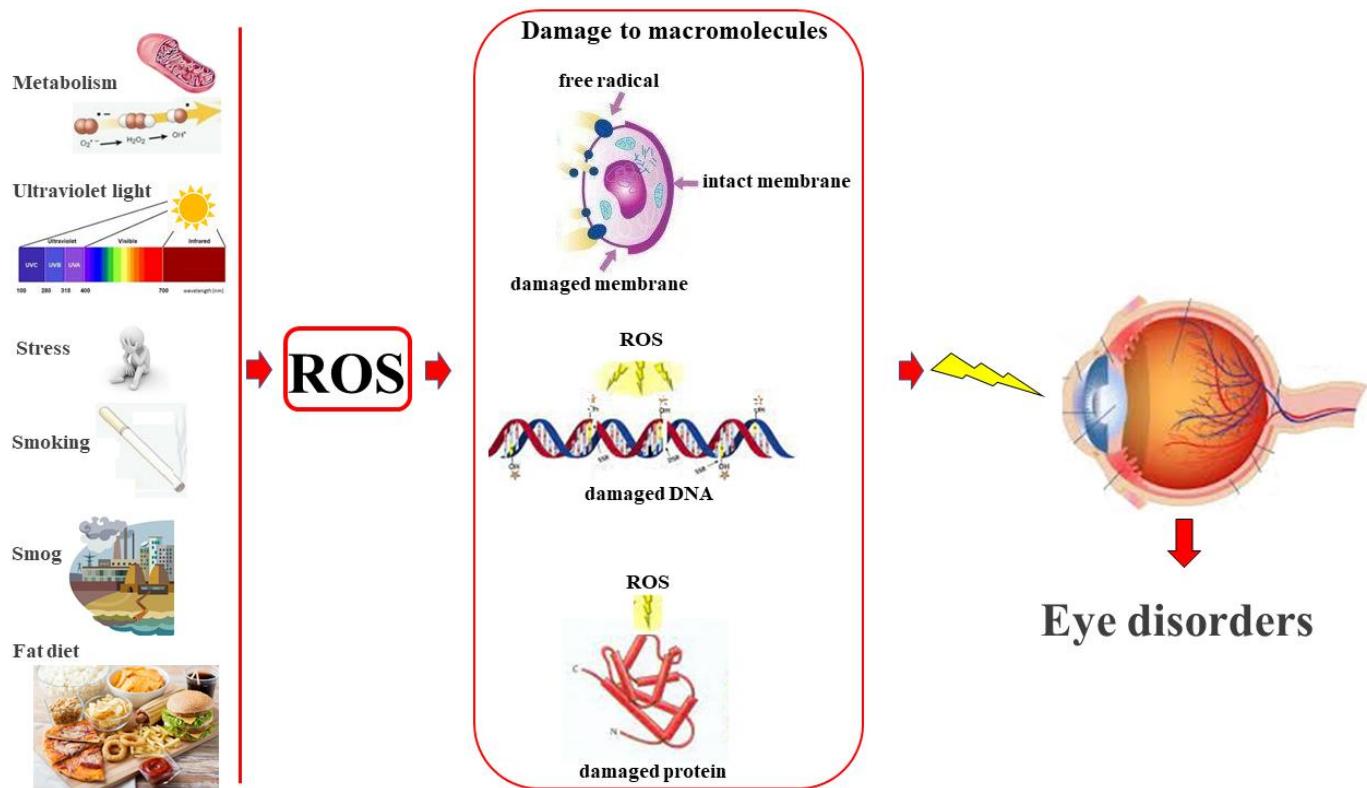


Figure 2. Prolonged damage to biological macromolecules ROS-induced favors the onset of eye diseases

3. Role of antioxidants on eye health

As oxidation leads to the onset of damage and in several districts, the role of antioxidants has become of massive interest, for doctors and patients, in treatment and prevention of diseases. An antioxidant compound can be defined as a substance that can delay or prevent oxidation [57]. The body uses different strategies against the production and accumulation of ROS: first of all, antioxidant enzymes are used, as already reported, as CAT, SOD, GSH-px and it is important to remember that some antioxidant enzymes need, to function properly of micronutrients such as zinc, selenium, copper and manganese [58]. Second of all, ROS can be reduced or neutralized by the intake of antioxidant nutrients such as vitamin E (a-tocopherol), beta-carotene, vitamin C, among others [59]. An insufficient intake of foods with antioxidant function or an unbalanced diet can alter the body's natural antioxidant system and facilitate the damage induced by ROS. Additional defense mechanisms include antioxidant compounds such as metallathionein, melanin and glutathione [60, 61]. Below will be studied the beneficial effects of some anti-oxidant compounds on eye health.

3.1 Vitamin A and lutein

Among dietary factors, vitamin intake has become increasingly positive in reducing oxidative stress and, as a result, improving the outcome of any eye pathologies. Vitamin A is a fat-soluble life-essential group of compounds characterized by an unsaturated isoprenoid chain structure. Famously vit A performs important functions including cell proliferation, reproduction, foetal growth and development, vision in darkness, corneal and conjunctiva development, immune system functioning and central nervous system formation [62]. Unlike water-soluble vitamins, vitamin A easily accumulates in the body, especially in the liver and adipose tissue. This characteristic determines the advantage of not easily developing clinical deficiency symptoms, but at the same time it has the disadvantage of being able to provide accumulation toxicity. The vitamin A can be supplied in the diet both from products of animal origin, such as retinol, and vegetable following the intake of vegetable carotenoids, such as provitamin A [63]. In the eye, the retina is responsible, as already mentioned, for visual perception that is mediated to specific structures known as cones and bastocells, fundamental for vision in light and in the dark, respectfully. Active vitamin A is associated with a protein receptor coupled to protein G, the complex known as rhodopsin, generating a chain of reactions whose last consequence is the transmission of optical perceptions to the brain via the optic nerve [62]. Vitamin A is responsible for the maintenance of homeostasis reduction-oxidation. In fact, retinol binds to different proteins, acting as a redox reagent. In addition, carotenoids such as β -carotene, α -carotene, lutein, lycopene and cryptoxanthine are well known antioxidants [64, 65]. An excessive intake of vitamin A is potentially toxic and has been associated with 100 000 RE per day (1 RE = 1 μ g retinol) in adults and 10 000 RE per day in children. In women in the first trimester of pregnancy, a dose of 3000-9000 RE day created teratogenic effects. The Group of Experts on Vitamins and Minerals have not been able to set a safe limit for Vitamin A, therefore today it is recommended as a maximum intake per day 700 lg for men and 600 lg for women [66]. Among the approximately 850 types of naturally occurring carotenoids, very few of them are present in human tissues. Among these it is important to mention lutein and its stereoisomers, zeaxanthin and meso-zeaxanthin, present in the human retina, which are present in the human retina [67]. It is a class of a carotenoid, named xanthophyll, that cannot be synthesized de novo in human body and are taken only with diet. The most xanthophyll-rich foods, including lutein and zeaxanthin, are leafy green vegetables such as cabbage, broccoli, peas, spinach, lettuce and egg yolk [68]. These compounds are hydrophobic, however, due to the presence of the hydroxyl group, lutein and zeaxanthin are relatively polar compounds. After their intake, food carotenoids are dispersed in gastric juice and incorporated into lipid droplets, transferred to micelles with food lipids and finally into the bloodstream. Therefore, fat-rich diets generally facilitate the absorption of dietary carotenoids [69]. Lutein is particularly concentrated in the central portion of the retina, where the photoreceptor cells, responsible for visual acuity and central vision, are located. In the macula of the retina are found zeaxanthin in the middle-peripheral region, meso-zeaxanthin in the epicentre and lutein concentrated in maximum quantities in the periphery. The absence of these three carotenoids is often used to predict the risk of developing macular diseases [69]. Lutein is also found in the human lens, protecting it from age-related eye diseases such as cataracts [70]. Lutein is retained in the human retina for a prolonged period of time and it has been shown that, even after three months from the interruption of lutein supplementation, the optical density of the macular pigment remains high despite its low serum concentration [71, 72]. Lutein has been shown to exert an extremely powerful antioxidant action with several mechanisms of action: 1) render the role of the oxygen singlet poorly active; 2) reduce /or eliminate free radicals; 3) filter blue light, thereby reducing phototoxic damage to photoreceptor cells; 4) reduce the expression of nitric oxide synthase inducible (iNOS) [73-75]. In addition, lutein is able to turn off the inflammatory process, inhibiting the pro-inflammatory cytokine cascade, the expression of nuclear-kB transcription factor (NF-kB) and the activation of the complement system [76-79]. Many clinical studies have attributed lutein to anti-oxidant and anti-inflammatory properties in the eye, justifying a benefit in some diseases such as age-related macular degeneration, diabetic retinopathy, cataracts, retinitis pigmentosa

and myopia [80, 81]. Lutein supplementation showed a relatively high safety profile and was classified as "gras" by the US Food and Drug Administration (FDA) [82]. Although German, Canadian and American studies have reported daily intakes of lutein of 1.9;1.4 and 2 mg respectively [83, 84], these results have been shown to be undervalued and the randomized clinical trial "Age-Related Eye Disease Study 2" (AREDS 2) showed a lutein intake of 10 mg per day persisted 5 years in over 4000 patients. Subsequently, the Council for Responsible Nutrition (CRN) stated that lutein intake is safe up to 20 mg/day [85].

3.2 Vitamin C and Coenzyme Q10

Vitamin C (ascorbic acid) is chemically a low molecular weight carbohydrate capable of donating electrons to free radicals from both the second and third carbon and quench their reactivity, acting as a reducing agent. While most vertebrates can synthesize this compound humans, together with guinea pigs, some fish, birds, and insects, rely exclusively on dietary intake to maintain the body pool of vitamin C. This is a hydrophilic vitamin and, despite its small size, does not cross the plasma membrane by passive diffusion [86]. During the detoxification reactions of ROS, vitamin C oxidizes to dehydroascorbate but this oxidized form can subsequently be reduced, to generate vitamin C again by glutathione-dependent enzymes. However, if the oxidative damage is continuous, dehydroascorbate undergoes an irreversible degradation; in the event in which vitamin C is present in excessive doses, it can act as a pro-oxidant, contributing to the formation of hydroxyl radicals and increasing oxidative damage. This means that vitamin C can pass from being an antioxidant in physiological conditions and a pro-oxidant under pathological conditions [87]. Vitamin C is particularly present in the eye, in the aqueous humor (saline fluid that is located between the cornea and the crystalline) and vitreous humor (connective tissue of gelatinous consistency occupying the eyeball cavity between the posterior surface of the lens and the retina). In particular, in these districts its concentration exceeds plasma concentrations by 20 to 70 times [88]. In the eye, vitamin C absorbs UV light, preventing the penetration of UV rays with subsequent oxidative damage photoinduced in the tissues and behaving as a physiological "sunscreen" [89]. In addition, vitamin C is able to scavenge or quench the superoxide anion radical, hydrogen peroxide, hydroxyl radical, singlet oxygen and reactive nitrogen oxide [90], protecting the cornea, the lens and other ocular tissues against oxidative damage. Finally, vitamin C has been shown to play a role in the prevention of lipid peroxidation of membrane [91]. Since it has been shown that individuals with vitamin C deficiency developed cataracts more easily than others, and that there was a close correlation between vitamin C and the health of crystalline, numerous studies have been conducted on the relationship between vitamin C and the risk of cataracts [92, 93]. The Recommended Daily Allowance (RDA based on the intake of vit C is 75 and 90 mg/day for women and men, respectively coming was established by U.S. Institute of Medicine (IOM) in 2000 [94]. Recent data suggest that the current RDA for vitamin C may be too low. Recent data suggest that the current RDA for vitamin C set by the IOM for men and women may be too low. On the basis of a comprehensive review of the scientific evidence, it was concluded that 200 mg/d is the optimum intake of vitamin C for the majority of the adult population to take also advantage of the health benefits of the eye [95]. Coenzyme Q10 (coQ10) possesses a quinone structure and, for this reason, is also known as ubiquinone. Chemical structure of coQ10 is very similar to that of vitamin K; nevertheless, this cofactor is not considered a vitamin because it is the only fat-soluble antioxidant that animal cells synthesize *de novo* in the body [96]. It is found in all cell membranes and its main function is to be a cofactor of the mitochondrial enzymes that cooperate in the formation of ATP, an energy source needed to perform the cellular

biochemical functions. In particular, this liposoluble compound works to transport the electrons in mitochondria during aerobic cellular respiration, from complex I (NAHD ubiquinone oxioreductase) and complex II (succinate ubiquinone reductase) to complex III (ubiquinone cytochrome c reductase). Another function of coQ10 is to participate in the creation of a proton gradient in the intermembrane space [97]. This compound possesses also direct and indirect antioxidant properties, in its reduced form (CoQ10H₂). The direct antioxidant property is achieved by reducing the accumulation of ROS, while the indirect action occurs with the regeneration of a form of vitamin E (α -tocopherol) [98]. CoQ10 collaborate in lowering the lysosomal pH, transporting H⁺ ions inside, in order to facilitate an acidic environment necessary to degrade cellular debris [99]. Finally, it has been recognized at coQ10 a participation in gene expression and this could explain its effects on overall tissue metabolism [100, 101]. Since the quantity of coQ10 present in the body is determined by 2 sources: biosynthesis [102, 103] and dietary supplementation, its deficiency may occur for the following reasons: 1) reduced dietary intake; 2) impaired biosynthesis; 3) increased usage by the body [104]. A shortage of coQ10 is mainly manifested by reduced energy metabolism, impaired protection from free radicals and deacidification of lysosomes [105-107]. Since the retina is the most metabolically active tissue of the body, with the highest consumption of energy (tissue/size ratio), patients with coQ10 deficiency may develop retinopathies, suggesting that coQ10 can play an important role in pathogenesis of retinal conditions [108, 109]. In addition, a study by Que et al. showed higher coQ10 concentrations in young people (30 years) compared to older human retinas (80 years), highlighting how the oxidative stress plays a key role in the pathogenesis of many age-related diseases such as atherosclerosis, cataract and Alzheimer's disease [110-112]. In this way, the accumulation of ROS in aging, results in increased cell damage that mediates the apoptotic mechanisms of cell death [113]. Age-related macular degeneration (AMD) causes loss of central vision, which has significant impacts on quality of life. Plasma coQ10 levels are substantially reduced in patients with AMD, compared to control patients and this suggests an association between coQ10 and AMD pathogenesis [114]. Since the retina and the ocular macula are exposed to light more than any organ or tissue in the body, these districts will be particularly sensitive to oxidative stress and lipid peroxidation. The result of this oxidative damage leads to apoptotic cell death [115]. Glaucoma is characterized by the loss of retinal ganglion cells (RGCs) which are fundamental in the transmission of the signal from the photoreceptors to the optic nerve. As the prevalence of glaucoma increases with age, there may be a possible correlation between RGC and coQ10 deficiency in old age [116, 117]. Experimental studies have shown that intravitreal administration of coQ10 minimizes apoptosis in RGC. This supported the neuroprotective role of coQ10 [118, 119]. The normal concentration range of coQ10 in human plasma is 0.8-1.2 mg/L and, in cases of deficiency, supplementation typically given to adults is 1.2-3 g/day [120].

3.2 Curcumin and Quercetin

Curcumin is a pigment insoluble in water extracted from the rhizome of *Curcuma longa*, a species that belongs to the Zingiberaceae family. Dust obtained contains 2-5% curcumin; curcumin is a biologically active phytochemical compound with health benefits and its extract also contains β -carotene, lycopene, epigallocatechin gallate, and quercetin [121, 122]. In recent years, several studies have confirmed the use of curcumin for prevention and treatment of many diseases, especially inflammatory and cancer [123-126]. Curcumin inhibits the production of free radicals, and so shows antioxidant properties [127]. The effect of curcumin on oxidative damage is based on its ability to scavenge ROS and reactive Nitrogen species (RNS) [128]. It is able to modulate the activity of active enzymes in neutralisation of free radicals, GSH-Px, CAT and SOD [129]. In addition, it can inhibit enzymes that generate ROS, such as lipoxygenase/cyclooxygenase and xanthine hydrogenase/oxidase. Finally, being lipophilic, curcumin is able to eliminate peroxylic

radicals, behaving like vitmin E. Antioxidant properties of curcumin cause the inhibition of oxidative stress and this reduces the risk for many lifestyle diseases [130]. In addition, curcumin exerts an anti-inflammatory effect: lowers the expression of the gene $I\kappa B\alpha$, gene cyclooxygenase-2 (COX-2), prostaglandin E-2 (PGE-2), interleukin 1-6-8 (IL-1, IL-6, IL-8) and tumor necrosis factor α (TNF- α). The anti-inflammatory effect is also exerted by the ability of curcumin to activate the proliferator-activated peroxisome receptor γ (PPAR- γ), a nuclear receptor protein that binds to the peroxisome proliferator response element (PPRE) and regulates gene transcription [125, 126]. Recently it has been highlighted that ROS are fundamental regulators of angiogenesis, the process that allows new blood vessels form within the vascular system, and that vascular function critically depends on the amount of ROS present: in fact while high doses of ROS induce oxidative stress and subsequent cell death, both conditions inhibit angiogenesis; low doses of ROS promote it through some sublethal damage of the cell membrane and subsequent release of the growth factor of fibroblasts FGF-2, directly involved in angiogenesis [131, 132]. Given the properties of curcumin, this compound could be used in the treatment of diseases related to angiogenesis including eye diseases [133, 134]. Most retinal diseases, as already mentioned, imply abundance of ROS and reduced levels of scavenger antioxidants. In particular, RGC and photoreceptors are extremely sensitive to oxidative stress damage and it is known that the accumulation of ROS is often involved in several diseases of the retina, such as uveitis, age-related macular degeneration, diabetic retinopathy, retinal tumors and proliferative vitreoretinopathy (PVR) [135]. In order to know the effect of curcumin after an oxidative stress insult, Munia et al., have shown that this nutraceutical compound was capable of protecting human retinal epithelial cells from death [136]. Dry eye disease is characterized not only by reduced secretion tears, but also rapid tear evaporation, responsible for the damage to the eye surface [137]. In this disease is included an inflammatory process involving IL-6, IL-8, IL-1 β [138]. It has been shown that curcumin could exert a protective effect through its anti-inflammatory activity, inhibiting the expression of pro-inflammatory cytokines in conjunctiva [139]. Uveitis is an inflammation of the eye that includes the iris and adjacent tissue. Lal et al. reported an improvement in patients with chronic uveitis who have been given oral capsules of curcumin (75 mg/capsule) [140]. A decrease in aqueous flare and keratic precipitates was observed after treatment. Its beneficial effects can be derived from their antioxidant, anti-inflammatory and antifibrinolytic properties [141]. Because curcumin has low oral solubility and bioavailability, its biomedical potential cannot be exploited in animals and humans [142]. The exogenous curcumin administered in humans for a period of about 8 weeks, has been shown to be able to adequately perform all the functions of this natural compound [143]. Quercetin is a member of the subclass of flavonols and is abundant in the human diet. It has received considerable attention from the scientific community in recent years thanks to numerous effects on human health, including antioxidant [144], anti-inflammatory [145], anti-cancer [146, 147], anti-aging [148], against autoimmune [149] and metabolic pathologies [150]. The eye surface serves as a protective and functional barrier for the rest of the eye. Diseases of the eye surface can affect the structure of the cornea or conjunctiva leading to corneal thinning, inflammation and visual deficits [151]. Prolonged inflammation in these districts can lead to a partial or even complete loss of vision, affecting quality of life. Unfortunately, to date, we do not possess a non-invasive treatment can preserve corneal function and surgery and corneal transplantation remain the only solution [152]. Given the problems and side effects of a corneal transplant, scientists have sought an alternative. The effectiveness of the administration of ocular drugs depends on many factors, including drug absorption, bioavailability, and retention on the front surface. Lipophilic drugs, in general, are associated with increased corneal epithelial permeability and the solubilization of these compounds in water eye drops was tested. Topical application of quercetin or other flavonoids may be more effective in treating conditions affecting the eye surface [153]. Studies have shown that a protective role is carried out by quercetin when administered

as an average daily consumption of about 16-23 mg/day in human populations [154, 155]. In Figure 3 the chemical structures of the examined compounds are represented.

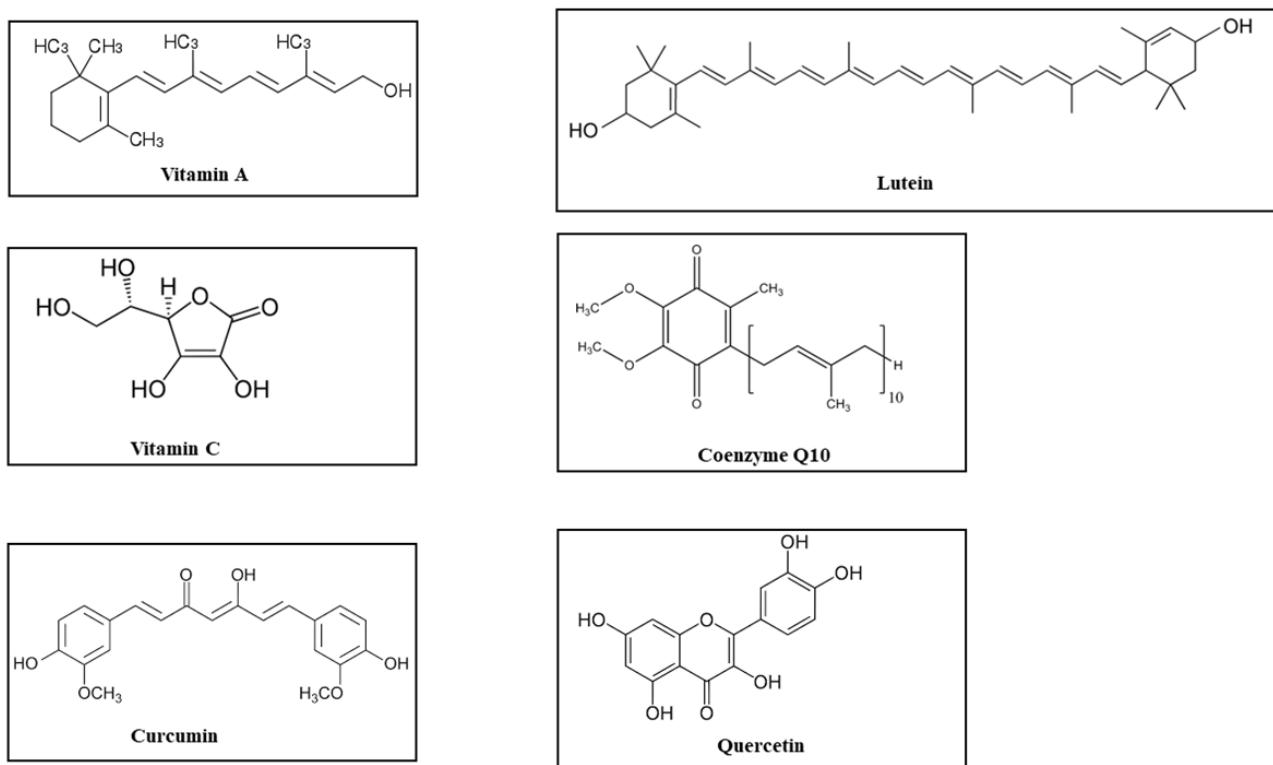


Figure 3. Chemical structures of the examined compounds

3.4 PUFAs

Polyunsaturated fatty acids (PUFAs) are lipids whose hydrocarbon chain has a polar hydrophilic end with a carboxyl group (-COOH) and another end with a non-polar hydrophobic methyl group (-CH₃). The n-3 and the n-6 represent two classes of PUFAs defined as "essential" as they must be taken with the diet because humans do not have the desaturases Δ12 and Δ15, enzymes catalyzing the formation of double bonds along the hydrocarbon chain [156]. In particular, linoleic acid (LA, 18: 2) is the n-6 PUFA from which γ-linolenic and arachidonic acid derive, while from α-linolenic acid (ALA, 18: 3) derive n-3 PUFAs such as eicosapentaenoic acid (EPA, 20: 5 n-3) and docosahexaenoic acid (DHA, 22: 6 n -3). LA is present in safflower, soy and corn oils while the vegetables that contain ALA are flaxseed, beans, nuts and the leaves of some green plants. In the liver, the amount of EPA and DHA obtained from the metabolism of ALA is very small, therefore they must be taken with the diet. Both lean and fatty marine fish, fish oil and algal-derived supplements are particularly rich in EPA and DHA, although they are present in small quantities in many foods of animal origin. For this reason, they must be present in the daily diet [156]. In particular, EPA and DHA can be present in cellular phospholipid membranes and have powerful antioxidant and anti-inflammatory effects [157]. The positive effects of taking n-3

PUFAs are well documented; in fact, the long-term effects against certain pathologies such as cardiovascular diseases, neurodegenerative diseases and osteoarthritis are known [158-160, 156]. The n-3 PUFAs are also implicated in diseases affecting the eye. In the case, for example, of neovascular eye diseases, such as retinopathy of prematurity, diabetic retinopathy, and age-related macular degeneration, current therapies have important side effects. Clinical and experimental investigations have shown that such treatments could be accompanied by a higher intake of n-3 PUFAs [161]. Despite conflicting results between fundamental and clinical research, it appears that PUFAs can act positively on the damage that determines the pathogenesis of glaucoma [162, 163]. Indeed, the effect of PUFAs can be both on intraocular pressure (IOP) and on survival of retinal ganglion cells (RGC). In the first case, endogenous prostaglandins (PGs), obtained from the metabolism of PUFAs, by activating the EP4 and FP receptors, reduce IOP. In the second case, thanks to their anti-inflammatory and antioxidant effects, n-3 PUFAs can reduce the inflammation and oxidative stress responsible for the RGC dysfunction or death [162, 163]. In particular, patients with pseudoexfoliative (PEX) glaucoma have benefited from the administration of a high-rich DHA nutraceutical formulation that reduced oxidative stress and inflammation [164]. The fact that PUFAs may have beneficial effects for glaucoma is linked to their positive action on endothelial dysfunction and atherosclerosis [165]. Regarding cataracts, a study was conducted on male Wistar rats in which it was found that the antioxidant and anti-inflammatory activity of lutein increased in the presence of EPA + DHA [166]. In particular, micellar lutein with EPA + DHA has been shown to positively regulate α -crystalline chaperone function [167]. Chang et al. demonstrated a reduction in free fatty acid levels in patients with senile cataract compared to normal controls. The levels of DHA were particularly low [168]. Studies on the molecular mechanisms responsible for aging in the eye have allowed us to define the involvement of the ELOVL2 (elongation of very-long-chain fatty acids-like 2) enzyme in the regulation of molecular aging in the retina [169]. The ELOVL2 enzyme catalyzes an elongation reaction of n-3 and n-6 PUFAs, which are essential for retinal function. In particular, DHA is the main PUFA in the retina and is involved in the photoreceptor function, in retinal development and has an antioxidant role [169]. The involvement of PUFAs in age-related macular degeneration (AMD), which is the leading cause of blindness in the elderly, has been demonstrated. In particular, the analysis of the eyes of subjects with AMD showed a reduction in PUFAs, and a direct correlation was also reported between the reduced dietary intake of n-3 PUFAs and the increased risk of AMD. Given the function of the ELOVL2 enzyme it appears that this is directly involved in the onset of AMD along with PUFAs [169]. Furthermore, it appears that DHA may reduce the risk of AMD occurrence by stimulating the synthesis of endogenous antioxidants and the selective autophagy of misfolded proteins [170]. In a study conducted on the eyes of patients with AMD, the analysis of the lipid profile of the retina reported a low ratio between n-3 and n-6 PUFAs, demonstrating the protective role of dietary n-3 PUFAs against AMD [171]. The efficacy of PUFA treatment has also been studied in patients suffering from a multifactorial inflammatory disease, such as dry eye disease (DED) [172]. The improvement, over time, of parameters such as tear breakup time (TBUT), ocular surface disease index (OSDI), osmolarity and Schirmer's test, led to the conclusion that PUFAs have an effect positive on nonspecific typical DED when administered briefly and not in combination with other eye medications [172]. Other authors acknowledge the efficacy of n-3 PUFA supplementation in managing DED even though they consider the evidence to be uncertain and inconsistent [173]. Numerous evidence indicates that PUFAs derived specialized-pro-resolving mediators (SPM) are capable of maintaining ocular surface health and immune homeostasis, thanks to the fact that SPM pathways and receptors are highly expressed in the ocular surface [174]. Here, the SPMs, produced endogenously, regulate wound healing, innate immunity and nerve regeneration. In particular, SPMs are involved in the protection of the cornea, they are present in significant quantities in healthy human tears, they guarantee an anti-inflammatory state by increasing the speed of healing of corneal wounds. SPMs reduce the risk factors for corneal transplant rejection by improving

graft viability and inhibiting the initiation of alloimmunity [174]. Furthermore, endogenous SPMs have been shown to improve nerve regeneration in the stroma and cornea, representing potential topical therapies in the case of corneal diabetic neuropathy. Some SPM appear to improve symptoms of allergic conjunctivitis such as reduced mucin secretion and total conjunctival immune cell count. They can also be used effectively as topical treatments for immune-driven DED, as well as for the reduction of ocular surface damage due to viral or bacterial infections, also caused by the use of contact lenses [174]. Furthermore, variations in the levels of very long-chain (VLC)-PUFAs and in the n-3 /n-6 ratio were studied in two different experimental models such as the spontaneously diabetic Nile rat and the Akita mouse which represents a genetic model of diabetes [175]. The evaluations were made in diabetic conditions and following the integration of n-3 PUFAs with the diet. VLC-PUFAs represent a special class of retinal lipids deriving from PUFAs. The levels of VLC-PUFAs and the n-3 /n-6 ratio were also measured in human retinal punches from diabetic and non-diabetic donors [175]. In retinal punches of diabetic and retinopathic patients the levels of VLC-PUFAs were lower than in healthy subjects of the same age. Dietary supplementation with n-3 PUFAs increased the ratio of n-3/n-6 VLC-PUFAs in both experimental models. Therefore, the authors Gorusupudi et al concluded that the enrichment of the diet with n-3 PUFAs allows to reduce the risk of diabetes onset and of the retinopathy caused by it [175]. In addition, the effect of dietary supplementation of n-3 PUFAs on myopia, a condition that is increasing worldwide, was investigated in experiments conducted on mice, in particular on a model of lens-induced myopia (LIM). The results obtained showed that EPA and its metabolites are capable of inhibiting the choroidal thinning and the myopia progression [176].

3.5 *Grape seed extract and bergamot polyphenolic fraction*

Grape seed extract has shown beneficial effects in many diseases thanks to its composition that identifies it as a flavonoid polyphenolic compound; its main components are: + catechin, - epicatechin gallate, gallate and -epigallocatechin [177, 178]. Beneficial properties of grape seed include prevention and treatment of diabetes and its complications [179], prevention of obesity and inflammatory reaction [180, 181]; the ability to modify early cerebrovascular injury caused by hypertension [182], alleviation of exercise fatigue [183] protection of the myocardium from injury [184, 185]. lowering blood lipid, regulating the metabolism and improving the intestinal flora [186, 187]. Most of these activities are carried out thanks to the antioxidant effect of grape seed extract, which makes it more powerful and effective than other plant polyphenolic compounds [188, 189]. Among the active ingredients present in grape seed extract, proanthocyanidins are responsible for the biological, therapeutic and pharmacological properties [190, 191]. Many studies have looked at the correlation between grape seed and eye disease: for example, Mani Satyam et al. showed, in an *in vivo* study in rats, that the administration of grape seed extract one day before treatment with sodium selenite, capable of inducing cataract formation in animals, was able to significantly reduce the disease and its damage [192]. Another recent study showed that treatment with grape seed extracts was able to reduce the damage of retinal degeneration, caused by aging, by attenuating the expression of some pro-inflammatory cytokines [interleukin 6 (IL-6), IL-12 and IL-1 β] or formation of their messenger RNAs [193]. The protective effects of grape seed proanthocyanidins, on retinal ganglion cells, have also been confirmed by an important study in which Li et al. demonstrated this result in several neurodegenerative disorders [194].

Bergamot belongs to the *Rutaceae* family, that are dicotyledonous angiosperm plants that include about 1600 species and that are characterized by the presence of oleiferous glands producing ethereal aromatic oils. This plant, which belongs to the citrus genus,

grows preferably in areas with tropical and subtropical climate and prefers a rocky-calcareous soil [195]. The most important citrus fruits are lemon (*Citrus limonum*), sweet orange (*Citrus sinensis*), lime (*Citrus aurantifolia*), mandarin (*Citrus reticulata*), grapefruit (*Citrus vittis*) and bergamot (*Citrus bergamia*). For this reason, bergamot is a plant endemic to the Calabria Region, in Italy, and its fruit is considered a subspecies of bitter orange or a hybrid derived from bitter orange and lemon [196]. Bergamot pulp and juice are a rich source of polyphenols including flavonoids, and are used for innumerable human health benefits such as anti-inflammatory and antiviral [197, 198], antitumor [199, 200], hypolipidaemic [201, 202], antioxidant, cardioprotective [203], antiplatelet [204] and metabolic protective [205]. In addition, bergamot is rich in vitamins, dietary fibre, minerals, secondary metabolites including polyphenols, flavonoids, carotenoids, essential oils, sugars, ascorbic acid and some trace elements [206]. Among flavonoids, the main ones are neohesperidin, naringin, neodiosmin, eriodictyol and neoerythocitrin [207, 208]. This composition makes the bergamot's flavonoid profile unique, justifying its use in many human pathologies [209]. Although specific data on the protective effects on eyes of BPF are not available in the literature, it is hypothetical that the high polyphenolic content and the strong antioxidant properties can also bring benefits in the ocular district. It would be appropriate to carry out relevant trials in order to confirm or deny the potential involvement of BPF on the ocular segment.

4. Antioxidant mixtures to protect/reduce eye disease: a hypothesis

As can be seen from the chemical structure of the compounds examined, the presence of OH groups or the catecholic group explain and justify their antioxidant properties: in fact, data available in the literature indicate that electron donors, particularly the hydroxyl group, are an essential component for performing antioxidant activity [210-213]. In the last decades, mixtures of compounds with antioxidant activity were used instead of treatment with a single compound. Obviously, this type of treatment must be subjected to preliminary scientific studies, which clearly demonstrate that among the components used there are no interference, onset of accumulation effects or competitive reactions. After having obtained these results, it is possible to proceed with the treatment of the mixture, evaluating whether the results can offer a potential antioxidant additive [214-218]. The use of a mixture of antioxidants, for senile macular degeneration, was evaluated and patients were treated with a specific combination of high doses of zinc and antioxidant vitamins [500 mg of vitamin C, 400 units (about 270 mg) of vitamin E, 15 mg of β -carotene, 80 mg of zinc and 2 mg of copper]. The treatment has proven useful. On the contrary, in healthy patients, treatment was found to be ineffective in preventing the onset of the disease [219, 220]. Lutein, a carotenoid present in the macula that forms the pigments filtering the light radiation, has also been associated in this mixture in place or together with β -carotene [164, 165]. In this review, we hypothesize, a theoretical use of a mixture that includes all compounds described; in particular, in order not to depart from the results already known, the concentrations of each component of the mixture, could be as indicated in Table 1.

COMPOUND	CONCENTRATION/DAY	REF
Vitamin A	0,5 mg	168
Vitamin C	300 mg	169
Lutein	10 mg	170
Curcumin	800 mg	171
BPF	250 mg	203

Grape seed extract	100 mg	191
Quercetin	150 mg	172
Coenzyme Q10	100 mg	173
Zinc	60 mg	174
PUFAs	1-2 mg	159

Table 1. Concentration of components in the hypothetical mixture to be administered to maintain eye health

The working hypothesis would be to use this mixture, which provides for the concentration of each constituent lower than its recommended daily intake value, so as to avoid potential antagonism or accumulation reactions. The mixture would be recommended to healthy subjects, in order to prevent the accumulation of ROS and the consequent oxidative damage; in addition, it could also be administered in conjunction with minor eye disorders in order to assess its hypothetical healing properties. The mixture could be administered from the age of 40. This choice could be explained by the need not to have already accumulated excessive amounts of ROS related to aging, not necessarily be subjected to demanding pharmacological treatments that may affect oxidative stress and have not been subjected to an excess of adverse environmental factors.

5. Discussion

The eye is an organ continuously exposed to ionizing radiation, industrial smoke, pollutants and engine exhausts, which makes the eyes extremely susceptible to oxidative attack. In addition, is highly exposed to both light and robust metabolic activity. These two conditions expose the eyes to a continuous phototoxic damage and to an increase/accumulation of oxidative damage, responsible of the principal pathologies that affect their health [221, 222, 56]. It has been widely shown that sunlight, as well as incandescent lamps, can represent a risk factor for the health of the eye and especially for the retina. To date, the replacement of incandescent light with a compact fluorescent lamps (CFLs) or light emitting diodes (leds), is particularly diffused and these low energy devices have increased the possibility of phototoxic eye damage [223, 224]. On the other hand, oxidative stress, which occurs in case of an overproduction of ROS or a failure of cellular buffering mechanisms, is able to alter the health of the eye by oxidation of biological macromolecules and an imbalance at the molecular and cellular level [225, 226]. The main ophthalmic processes, in which oxidative stress is involved, are: eye surface disorders, glaucoma, diabetic retinopathy, cataracts, toxic neuropathies, uveitis, retinitis pigmentosa, and age-related macular degeneration [227-231]. The human body has some systems of defense against oxidative stress, which are located in the cytoplasm, in the cell membrane and in the extracellular space: 1) enzyme systems, located in intracellular space, the best known are SOD, CAT and GSH-Px; these enzymes solve the formed ROS. SODs are metalloproteins that accelerate the dismutation of superoxide into hydrogen peroxide. There are two molecular types of SOD in humans: cytosolic (CuZnSOD), which contains copper and zinc, and mitochondrial (MnSOD), which contains manganese [232, 233]. CAT is found in peroxisome and mitochondria and its function is to catalyze the dismutation of hydrogen peroxide in water and molecular oxygen [234, 235]. GSH-Px is found in the cytosol and mitochondria. This is known to work by eliminating hydroperoxides, transforming them into water. This reaction is associated with the transformation of reduced glutathione into oxidized GSH [236, 237]. 2) Free radical scavengers, slow oxidation reactions or "capture" free radicals, transforming them into less aggressive compounds. They can be

water-soluble, like glutathione and vit C, or fat-soluble like vit E and carotenoids. 3) Chelating agents of transition metals, are molecules that bind iron and copper avoiding that these metals act in the reactions of Fenton and Haber-Weiss [238, 239]. The protective effects of exogenous antioxidants, taken by feeding, are added to those generated by endogenous antioxidants, just described. The integration of exogenous antioxidants could take place with the administration of vitamins A, C and E and Coenzyme Q10 [240-242]. In this review, the protective roles of some exogenous anti-oxidants (Vit A, vit C, Coenzyme Q10, lutein, quercetin, PUFAs and curcumin), against the main eye pathologies, in which oxidative damage is directly involved, have been investigated. In the last section of this review it has been suggested the use of all these described substances, combined in a mixture, in the prevention or treatment of many eye disorders. According to this ideal administration, each component would be considered in a specific concentration, so as to confirm the studies and data obtained from the use of each individual substance. In particular, the concentrations are reported in Table 1. The ideal mixture should be administered daily and the objectives would be to exert an additive antioxidant effect, without developing side effects or accumulation reactions. We imagined to administer the mixture from the age of 40 and up and this choice could be explained by the need not to have already accumulated excessive amounts of ROS related to aging, not necessarily undergo demanding pharmacological treatments that may affect oxidative stress and have not been subjected to an excess of adverse environmental factors. However, there are some limits related to the ideal administration of this mixture: first of all, not all the components are hydrophobic, and could, therefore, easily cross the biological membranes. In order to address and solve this problem, one could imagine the formation of a single liquid form, hydrophobic, through appropriate chemical reactions [243-246] and administered as eye drops [247, 248]. With this method of formulation two important limits could be avoided: the degrading action in the gastrointestinal system and the bioavailability of the compounds following digestion [249-251]. Second of all, the total antioxidant potential of the mixture should be calculated, which is not necessarily equal to the sum of that of the individual components [252-254]. Finally, specific toxicity experiments should be conducted in order to demonstrate that the mixture under consideration does not cause harm in any body district [255, 256]. After carrying out these preliminary tests, *in vitro* and *in vivo* tests could be carried out and, subsequently, clinical trials.

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