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Micronutrient supplements and eye diseases

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Abstract

Persuasive evidence has been gathered over the past few decades that the onset and evolution of eye diseases are profoundly affected by environmental and behavioral causes. The eye is highly susceptible to all kinds of atmospheric agents, such as pollutants, particulate matter, sunlight, that can severely harm its function. Several lifestyle practices and behaviors including smoking, excessive alcohol consumption, high-fat or high-sugar dietary regimens, chronic stress, long screen time, have also been clearly associated with the deterioration of vision. Clinical conditions affected by any combination of these factors comprise age-related macular degeneration, cataracts, glaucoma, diabetic retinopathy, choroid, and retinal pathologies, digital eye strain, myopia. A mechanism that appears to be central in the pathogenesis and/or progression of many eye conditions is oxidative stress due to the eye's elevated respiratory activity and its environment favoring the photochemical generation of reactive oxygen species. There is strong evidence that nutrition plays a significant role in eye diseases and that nutritional supplements, especially those with antioxidant properties, are likely to support a normal visual function. Here, we review the properties of C3G, zinc, lutein, and verbascoside, micronutrients with primarily antioxidant activity and that research has indicated as beneficial for maintaining eye health and good vision.

Keywords: Cyanidin-3-glucoside; zinc; lutein; verbascoside; micronutrients; eye disease

Introduction

Over the past few decades, solid evidence has been accumulated that environmental causes can contribute importantly both to the onset and the evolution of eye diseases. The eye, being constantly exposed to the atmosphere, is highly vulnerable and can easily be damaged due to the harmful effects of several pollutants present in the environment such as gases, particulates, chemicals, UV light, etc. Exposure to air pollutants generally causes ocular symptoms ranging from eye irritation to severe chronic discomfort, although the damage produced by long-term exposure to air pollutants has not yet been fully understood **[1–3]**. Several lifestyle practices and behaviors are also clearly associated with the deterioration of vision **[4]** and clinical conditions that may be affected by incorrect lifestyles include Age-related Macular Degeneration (AMD), cataracts, glaucoma, diabetic/hypertensive retinopathy, choroid, and retinal pathologies. Smoking triggers free radicals generation increases oxidative stress and reduces antioxidant levels in the blood eventually disturbing vision **[5,6]**, and has been consistently associated with nuclear cataracts **[7]**. Heavy alcohol consumption has been found to be associated with cataracts **[8]** and intoxication creates short-term vision problems such as night blindness, double vision, and accommodation paralysis. A high-fat diet damages vision by clogging up blood vessels in the retina and limiting the amount of oxygen as well as nutrient supply to the photoreceptors that eventually die. Dietary intake of saturated fat was found to be associated with an 80% increased risk of AMD **[9,10]**. Stress produces adrenaline which raises intraocular pressure that in turn may be a cause of glaucoma **[11]** and a high-sugar diet or unmanaged diabetes can affect vision by contributing to a number of disorders such as diabetic retinopathy, cataracts, macular edema, and glaucoma **[12–14]**. Convincing evidence from several studies has indicated that, together with genetic causes, environmental and behavioral risk factors are prominently implicated in the onset of myopia, although the relative contribution of each remains uncertain. Myopia or nearsightedness is the most widespread vision problem globally **[15,16]**. In 2016, about 1.5 billion people worldwide (nearly a quarter of the global population) were found to be nearsighted and the same study estimated that by 2050 about half of the global population will be affected by myopia **[17]**. Myopia is especially prevalent in East Asia, where 70 to 80 percent of the residents of some countries are affected **[18]**. Myopia occurs when the light comes into focus in front of the retina instead of directly on it. The most important anatomical factor underlying this disease is an excessive elongation of the eye **[19]** but it can also be caused by a cornea that is too curved for the length of the eyeball or a lens inside the eye that is too thick. Myopia obviously affects an individual's quality of life but, in addition, it has been shown to increase the risk of other severe ocular diseases such as macular degeneration, retinal detachment, cataracts, and glaucoma that can lead to blindness **[20–23]**. Genetic work carried out over the past

decade has revealed that myopia is a complex trait with many genetic variants of small effects influencing it and over 200 genetic loci associated with myopia have been discovered **[24,25]**. Although myopia has a recognized genetic basis, it has become manifest that dramatic changes in the environment across many human populations have substantially modified its prevalence over time **[26–28]**. A number of studies have documented the role of changes in socioeconomic status, time spent outdoors, education, and near-work as risk factors for myopia **[29–32]**. Myopia seems to be robustly linked to educational attainment or educational intensity **[33–35]** and a Mendelian randomization study showed that more years of schooling were statistically associated with higher severity of myopia but not *vice versa*, strongly supporting a causal role of education on myopia development **[36]**. Education is also a proxy for near-work activities and a meta-analysis corroborated that longer time spent on near-work was associated with increased odds of myopia even though extricating reading, writing, watching TV, video gaming and screen time remains difficult **[37]**.

Closely related to near-work activities is another widespread ocular condition variably known as digital eye strain (DES), computer vision syndrome (CVS), or visual fatigue (VF). DES describes a group of eye and vision-related problems resulting from prolonged use of digital devices **[38]**. The formal medical term for eye strain is asthenopia for which two distinct mechanisms and sets of symptoms have been described: external eye symptoms of burning, irritation, tearing and dryness were closely related to the dry eye syndrome, while internal symptoms of strain, ache, and headache behind the eyes were linked to accommodative and/or binocular vision stress **[39]**. Although these symptoms are typically transient, they may be frequent and persistent causing serious eye discomfort and vision difficulties and could produce an economic impact when vocational computer users are affected. Although DES affects a huge number of individuals, its precise physiological basis remains unclear. Engagement with digital devices has increased massively in recent years across all age groups in developed as well as in underdeveloped nations **[40,41]**. While there are challenges in determining the prevalence of DES due to its subjective nature and the lack of objective instruments to identify it, levels of 50% or more have been reported in numerous published studies, indicating that a large proportion of the population worldwide is at risk of developing this condition **[41]**. The current COVID-19 pandemic situation is clearly poised to severely exacerbate pathologies linked to near-work activities and education. The pandemic has drastically changed our habits and lifestyle: a large number of workers has been forced to resort to home working and nations worldwide have adopted e-learning to prevent the spread of the coronavirus among students in the classrooms. It has thus become accepted to routinely spend 8-10 hours per day in front of a digital device screen making individuals even more vulnerable or prone to the variety of eye problems described above.

A key shared mechanism thought to play a role in the pathogenesis and/or progression of many eye conditions is oxidative stress. In the eye, oxidative stress is elevated for two reasons: i) the eye's elevated metabolic and respiratory activity and ii) the transparency of its components (cornea, lens, vitreous) that favors the photochemical generation of Reactive Oxygen Species (ROS). Although the human eye has a robust antioxidant system **[42]**, conditions under which this system is weakened by increased ROS levels result in oxidative damage. The information currently available provides a strong indication that nutrition is a significant factor in eye diseases and that nutritional supplements, especially those with antioxidant properties, are likely to have a prominent function in the prevention of several eye diseases and conditions **[43–47]**. Yet, as their name suggests, dietary supplements are designed to add, not replace, nutrients obtained from a healthy diet. Here, we will review the general and eye-specific properties of a few supplement micronutrients with antioxidant activities that research has shown to be beneficial for maintaining eye health and good vision.

Cyanidin-3-glucoside

Anthocyanins probably constitute the largest and most important group of water-soluble plant pigments. They belong to the widespread flavonoid group of polyphenols, which are responsible for the blue, purple, and red color of many plant tissues. These natural compounds are commonly present in the human diet, particularly in red, blue, or purple fruits and vegetables. Anthocyanins have gained intensive research interest as a preventive and therapeutic plant agent. Historically, anthocyanin-rich food has been used as traditional medicine and anthocyanin-rich extracts are thought to have diverse health benefits, leading to their widespread use in folk medicine **[48–50]**. Pharmacologically, anthocyanins have shown a surprising pleiotropy of effects. Based on multiple studies, including animal models, cell-line work, and human clinical trials, it has been concluded that anthocyanins are likely to play a vital role in the prevention and cure of numerous pathologies through their antioxidant, anticarcinogenic, antiviral, antidiabetic, anti-inflammatory, cardioprotective, anti-apoptotic, anti- microbial and eye-protective activities **[51,52]**. Anthocyanin-rich foods are also likely to have beneficial effects against cognitive decline and age-related neurodegeneration and modulate neuronal functions **[53,54]**. Cyanidin-3-glucoside (C3G) is one of the most common anthocyanins naturally found in black rice, black bean, purple potato, and many colorful berries. This compound is especially interesting because it has been shown to have specific beneficial effects in the prevention and protection of a number of ocular system diseases and conditions. The positive properties of C3G can mostly be ascribed to its potent antioxidant activity **[52,55]**.

Indeed, when the antioxidant activity of 14 anthocyanins and their glycosylated derivatives was evaluated, C3G showed the highest oxygen radical absorbance capacity **[56]**. The retina has the highest

respiratory rate of any other mammalian tissue **[57,58]** and is, therefore, a significant source of oxidative stress. By countering this oxidative stress, C3G appears to benefit vision in several ways as shown in a number of studies. Using rat retinal degeneration models, which are widely employed as a proxy for human retinal dystrophies, it has been determined that C3G safeguards retinal structure and function, especially scotopic vision, from the injury that leads to retinal degeneration **[59]** and that anthocyanins extracted from C3G-enriched black soybean have a protective effect against methyl nitrosourea- induced retinal degeneration **[60]**. Neuroprotection by bilberry extract, whose main component is C3G, was also convincingly documented in a murine model of photo-stressed retina upon daily prophylactictreatment **[61]** and in a visible-light-induced retinal degeneration model in rabbits where the protective effects of bilberry extract were shown to be mediated by increasing the antioxidant defense mechanisms, suppressing lipid peroxidation and proinflammatory cytokines and inhibiting retinal cells apoptosis **[62]**.

Bilberry extract was demonstrated to provide protection in mice models of ocular inflammation. In one case, bilberry extract feeding improved retinal electrophysiology, preserved rhodopsin, and was less damaging to photoreceptors **(Figure 1) [63]**, and in another work, the extract showed a reduction in neurotoxic Nitric Oxide (NO) and malondialdehyde, combined with an increased neuroprotective antioxidant capacity due to elevated levels of glutathione and vitamin C as well as reduced superoxide dismutase and glutathione peroxidase activity **(Figure 2) [64]**. Furthermore, bilberry extract intake mitigated the degeneration of retinal ganglion cells *in vivo* in a mouse model of optic nerve injury and alleviated retinal ganglion cells damage *in vitro* and *in vivo* under oxidative conditions **[65]**. Black currant extract could inhibit the enlargement of globe component dimensions in a negative lens-induced chick myopia model **[66]**. Interestingly, a beneficial effect of C3G-rich bilberry extract on myopia was also revealed by clinical studies showing that such extract was effective for the improvement of subjective accommodation in myopic eyes, possibly by improving contrast sensitivity **[67,68]**. An improvement in contrast sensitivity was also associated with the daily intake for 12 months of bilberry anthocyanins in human subjects with non-proliferative diabetic retinopathy **[69]**. A polyphenol-enriched fraction of bilberry showed a preventive effect against cataract formation by inhibiting m-calpain- mediated proteolysis and oxidative stress in the lens suggesting a potential role as an anticataract agent in age-related cataracts **[70]**. It is of note for their possible function in the prevention of eye conditions that anthocyanins are selectively distributed to ocular tissues after oral, intravenous, or intraperitoneal administration in rats and rabbits as well as in pigs **[71,72]**.

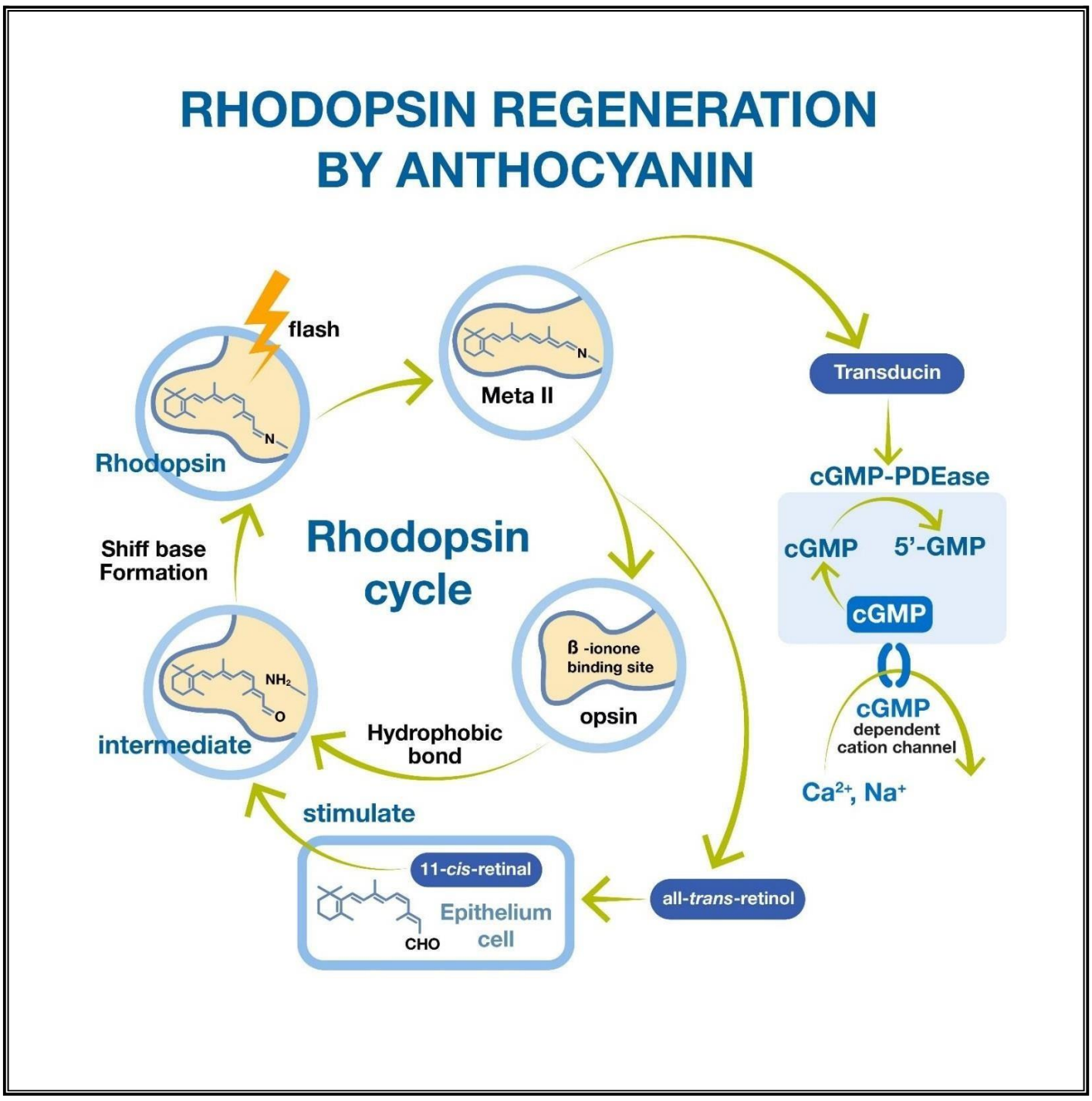

Figure 1: Rhodopsin regeneration by anthocyanin.

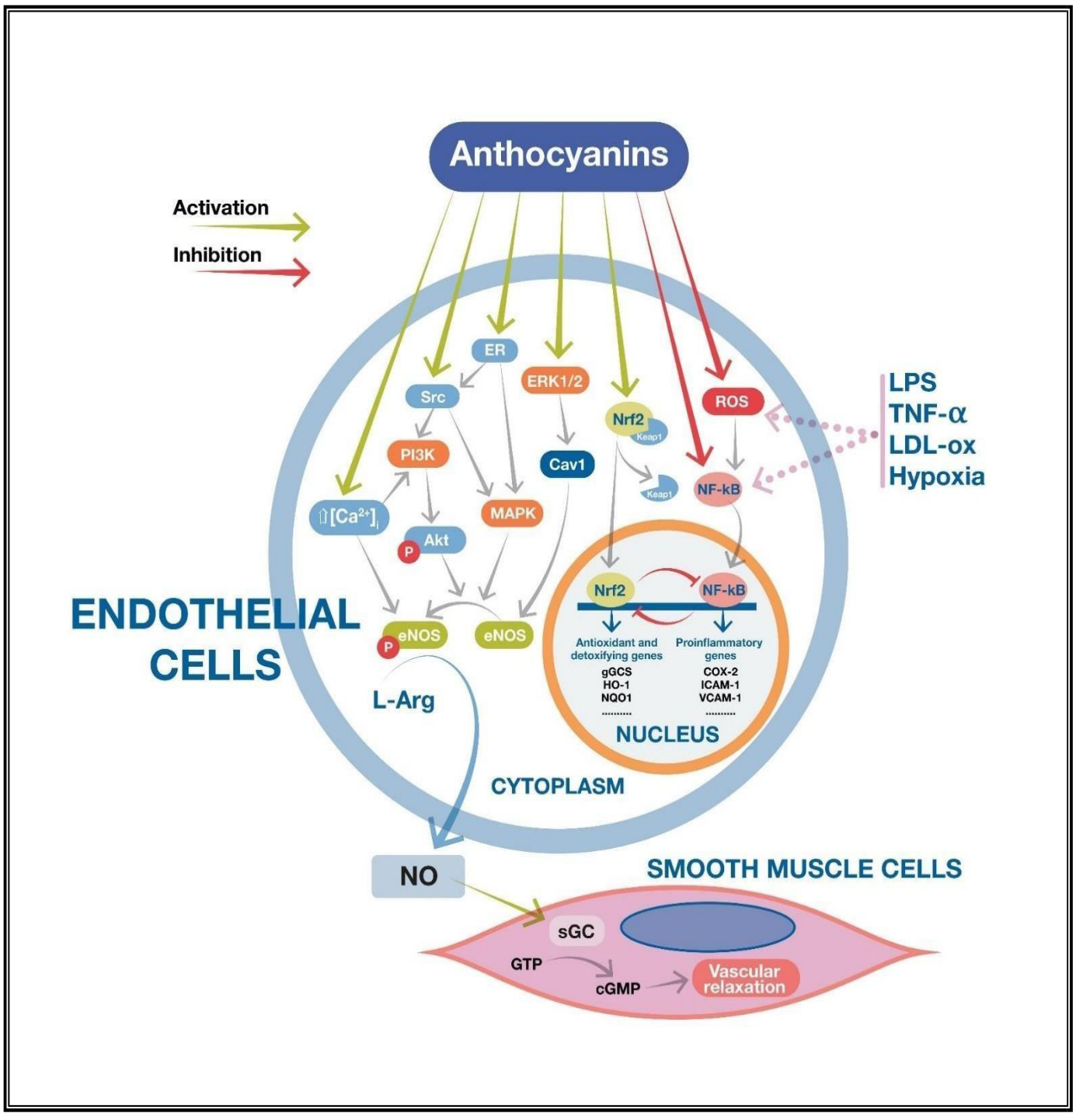

Figure 2: Anthocyanins: Mechanism of action.

Verbascoside

Phenylpropanoid glycosides are water-soluble derivatives of natural polyphenols widely distributed in the plant kingdom that have been found to play important roles in protection against oxidative stress **[73,74]**. Verbascoside (also known as acetonide) belongs to the phenylpropanoid glycoside family of compounds and is structurally characterized by caffeic acid and 4,5-hydroxyphenyl ethanol bound to a β-(D)-glucopyranoside, with rhamnose in sequence to the glucose molecule. Verbascoside is mainly present in the Verbascum species **[75]** but it has also been found in many other plant species. Several beneficial effects have been ascribed to this compound, including anti- inflammatory, antibacterial, antioxidant, neuroprotective, and photoprotective effects **(Figure 3) [76]**.

Recent mechanistic studies have discovered that verbascoside down-regulates Ca^{2+}-dependent MAPK signaling in cell models **[77]**. Furthermore, verbascoside has been shown to strongly inhibit NO, Tumor Necrosis Factor-alpha (TNF-α), and Interleukin-12 (IL-12) production **[78]**, and its anti-inflammatory and anti-irritant effects have been attributed mostly to its ability to inhibit inducible nitric oxide synthase and NO release **[79,80]**. The anti-Inducible Nitric Oxide Synthase (anti-iNOS) activity of verbascoside has been linked to the downregulation of the nuclear factor-kB (NF-kB) and Activator Protein-1 (AP-1) **[81]**, two transcription factors that were shown to represent important modulators of inflammatory processes in chronic inflammatory diseases **[82]**. In cells treated with verbascoside, an anti- inflammatory response was found to be dependent on a significant decrease of the expression and activity of iNOS, extracellular O_2 production, superoxide dismutase, catalase, and glutathione peroxidase activities at the post-translational level **[83]**. Importantly, verbascoside is particularly effective in protecting from UV irradiation **[76]**. In a model of UVC irradiation of human keratinocytes, verbascoside effectively protected cells from UVC-induced necrosis strongly suggesting that free radical scavenging plays an important role in the photo-protection process **[84,85]**. Regarding the effects of several glycosylated and non-glycosylated plant polyphenols including verbascoside, resveratrol, polydatin, rutin, and quercetin on the inflammatory, apoptotic, metabolic, and proliferative responses of cultured human epidermal keratinocytes to non-cytotoxic doses ofsolar- simulated UVA and UVB, it was found that verbascoside provided the best protection by inhibiting multiple pathways activated by UV irradiation and could, therefore, be a good candidate for skin cancer chemoprevention due to its prominent and long-lasting post-UV anti- inflammatory activity **[86]**.

Although a direct role in vision and eye health needs to be supported by more experimental evidence, verbascoside has shown botanical properties that are promising for providing therapeutic support in the management of a number of ocular system conditions whose pathogenesis has been linked to oxidative mechanisms such as glaucoma, cataract and macular degeneration **[87–89]**. The effects of a diet supplemented with verbascoside have been studied on the antioxidant capacity and oxidative state of the different eye tissues and fluids in a healthy hares model. This study demonstrated that verbascoside supplementation can protect ocular tissues and fluids from naturally occurring oxidation in a dosage-dependent manner **[90]**. Verbascoside was also reported to have an anti-apoptotic activity via the inhibition of caspase-3 **[91,92]**. In agreement with these observations, verbascoside is likely to inhibit autophagy-induced apoptosis in retinal ganglion cells through the optineurin and PI3K/AKT/mTOR pathway, potentially suggesting that glaucoma patients may benefit from such treatment **[93]**.

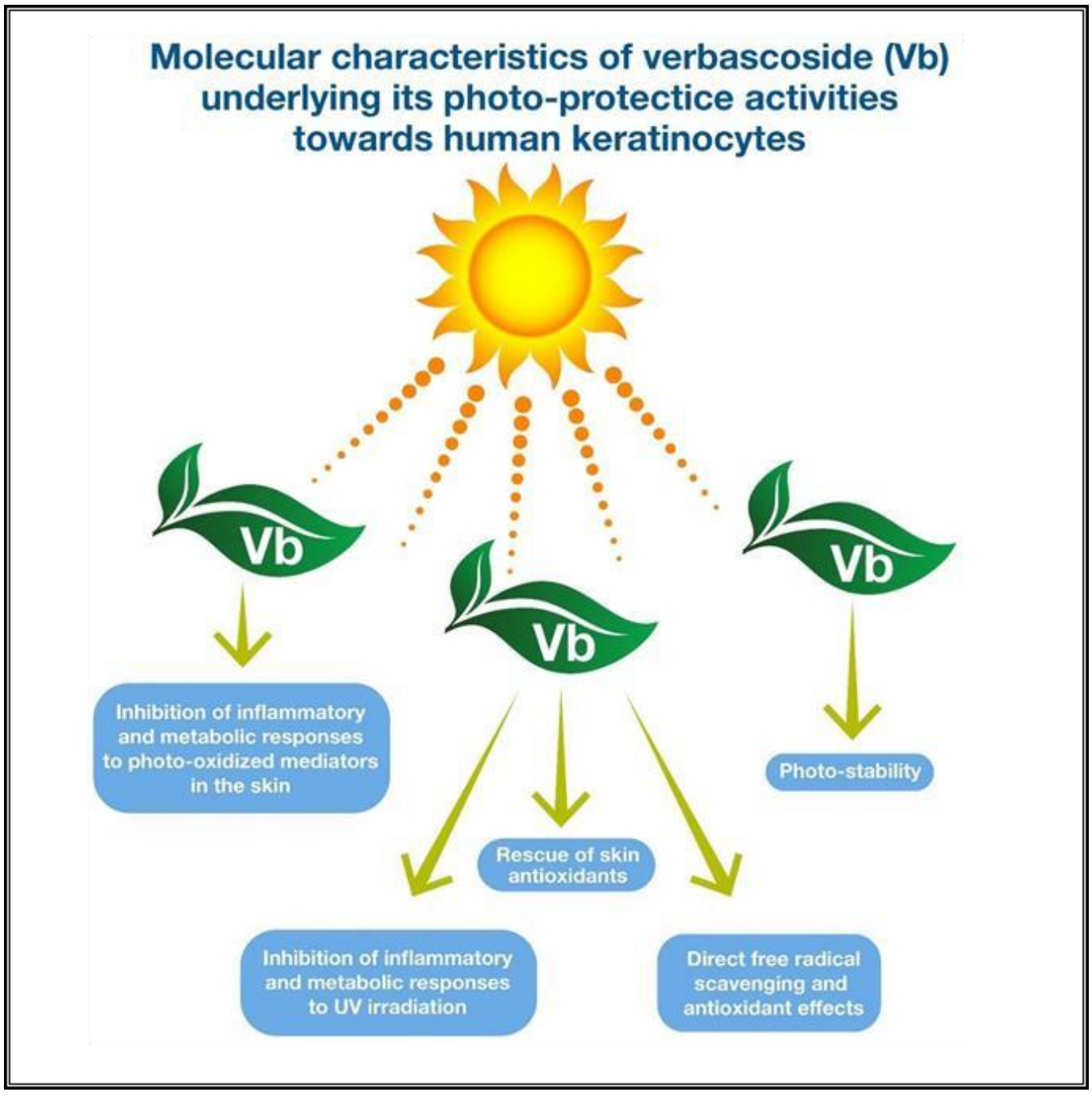

Figure 3: Verbacoside: mechanism of action and beneficial effects.

Zinc

Zinc is an essential micronutrient for all organisms **[94]**, indispensable to human health because it serves as a co-factor for a few hundred enzymes and a couple of thousand transcription factors. Zinc has a number of biological functions that bear on virtually any given biological process: it affects multiple aspects of the immune system, displays antioxidant properties, and is an anti-inflammatory agent **[95]**. Several studies have demonstrated that zinc deficiency increases the production of reactive oxygen species and oxidative damage in cell lines **[96–100]**, in experimental animals fed low zinc diets **[101–106]**, and in human subjects **[107,108]**. Because zinc is not redox-active under physiological conditions it does not function as an antioxidant per se and its antioxidant properties are the result of indirect actions. A number of possible mechanisms have been proposed to explain the increased oxidative stress under zinc-limiting conditions **[109]**. First, zinc is a structural component of superoxide dismutase an enzyme that reduces the toxicity of ROS by promoting the conversion of superoxide radicals to hydrogen peroxide and molecular oxygen, thus, its activity may be compromised under zinc deficiency. Second, Zn-metallothionein has been shown to have antioxidant activity by oxidating metal-bound cysteine ligands in the protein **[110,111]**. The expression of many Metallothioneins is induced by zinc treatment through activation of responsive Metal Transcription Factor 1 (MTF-1), a zinc-dependent transcription factor, possibly leading to an increased ability in eliminating ROS. Thus, low expression levels of metallothionein in zinc-limited cells would result in this antioxidant function being lost. Third, it has been proposed that zinc may compete with redox-active metal ions like Cu and Fe for binding to sites on proteins and other cellular macromolecules thereby

zinc may compete with redox-active metal ions like Cu and Fe for binding to sites on proteins and other cellular macromolecules thereby inhibiting the site- specific production of oxygen radicals **[112,113]**. Zinc can also neutralize free radicals either through the scavenging activity of glutathione or as a glutathione peroxidase cofactor because it is known to affect the expression of glutamate-cysteine ligase, a crucial enzyme involved in the synthesis of glutathione **[114]**. Inflammation is a response of the host to pathogens or injury whose acute phase response lowers zinc concentration in the blood that, in turn, increases the inflammatory response. Thus, zinc deficiency has a pro-inflammatory effect while optimal zinc concentrations suppress the inflammatory response. *In vitro* studies have shown that zinc decreases the transcription factor NF-κB and its target pro-inflammatory genes, such as TNF-a, IL-6, IL-8, and IL-1, and increases gene expression of A20 and PPAR-γ, two zinc finger proteins that act to inhibit NF-κB activation resulting in a strong anti-inflammatory response via a feedback loop **[115–117]**. A transcriptional target of NF-κB is the zinc transporter Zip8 which transports zinc into the cell and modulates IκB kinase reversibly to trigger an anti- inflammatory response **[118]**.

Among human organs and tissues, the eye has a very high zinc content, which is concentrated especially in the retinal pigment epithelium and the retina but present also in other ocular compartments **[119–121]**. The European Food Safety Authority (EFSA) Panel 2009 report states that a cause-and-effect relationship has been satisfactorily established between the dietary intake of zinc and maintenance of normal vision highlighting the importance of this metal in eye health **[122]**. A vast literature is available to provide evidence that zinc serves important functions in the retina. Zinc is known to be active in the process of vision and its deficiency results in impaired dark adaptation and dark blindness **[123]** which in most cases can be reversed by zinc supplementation **[124]**.

Similar clinical observations on zinc and dark adaption were made in a case series of sickle cell anemia patients **[125]** and also healthy human subjects **[126]**, which further suggested that these effects on visual function may be related to dietary zinc deficiency. It is also thought that zinc might play a role in the stabilization of rhodopsin **[127,128]** and that zinc-induced de-stabilization of rhodopsin is believed to be relevant in inherited genetic retinal diseases, such as retinitis pigmentosa **[129,130]**. An important nutritional effect of zinc has been identified in slowing the progression of AMD, one of the leading causes of visual disability worldwide. Evidence from large randomized, placebo-controlled Age- Related Eye Disease Study 1 and 2 (AREDS 1 and 2) suggested that these components may help protect against the progression to AMD and related vision impairment **[131–133]**. In particular, it was shown that retinal degeneration is suppressed by zinc supplementation in combination with the AREDS formula and other antioxidants **[134]**. In this scenario, the Rotterdam Eye Study, a population-based cohort study, suggested that zinc was associated with a 35% reduced risk of incident AMD **[135]** and the Blue Mountains Eye Study found that higher dietary zinc intake had a favorable effect on incident AMD **[136,137]**.

Lutein

Carotenoids are the most abundant pigment groups and lipid-soluble antioxidants in nature **[138,139]**. Lutein is a xanthophyll carotenoid found at elevated concentrations in the macula of the human retina. Since all mammals, including humans, are unable to synthesize carotenoids **[140]**, lutein uptake is strictly dependent on the diet. The most abundant sources of lutein are green leafy vegetables such as peas, broccoli, spinach, kale, and lettuce as well as egg yolks, durum wheat, and various types of corn **[141]**. Lutein exhibits various properties ranging from anti- inflammatory, anti-oxidative, to blue light-filtering effects that can benefit the human eye. Lutein has been demonstrated to exert an extremely potent antioxidant action by quenching singlet oxygen and effectively scavenging free radicals **[142–144]**. Another protective effect of lutein consists in the ability to filter blue light with the highest efficacy compared with other carotenoids **[145]**. As the peak wavelength of lutein absorption is around 460 nm, within the range of blue light, lutein can reduce light-induced damage by absorbing 40% to 90% of incident blue light depending on its concentration **[143]**. Because lutein is greatly enriched in the outer plexiform layer of the fovea **[146]**, where the majority of axons of rod and cone photoreceptor cells are located, it is poised to reduce phototoxic damage to these cells **[145]**. Additionally, several *in vitro* studies have observed that lutein displays anti- inflammatory properties by inhibiting both the pro-inflammatory cytokine cascade **[147,148]** and the transcription factor NF-kB **[149– 151]**. Compelling evidence has also been provided that lutein reduces the expression of iNOS **[152]**, ROS production **[150,153]**, and the activation of the complement system **[154]**. Finally, lutein could reduce the Vascular Endothelial Growth Factor (VEGF) expression, a known inducer of unregulated angiogenesis under pathological conditions **[155]**, and since inflammation and abnormal angiogenesis in retinal vasculature are believed to represent major pathogenic mechanisms underlying several eye conditions, this ability to suppress the inflammatory response and VEGF expression suggests a possible effect in reducing the severity/progression of these diseases.

Due to the combination of eye-protective attributes and its relatively high safety profile **[156]**, lutein has often been considered by many to be an adjunct agent for a number of eye diseases **[157–159]**. The role of lutein in maintaining general eye health is under active investigation but some studies have clearly highlighted the positive role of regular dietary supplementation of lutein in the improvement of macular pigment optical density levels **[160–167]**, in promoting visual acuity **[161,168–170]** and contrast sensitivity **[161,163,164,167–169,171]**. The benefits of lutein have been studied more closely for specific eye diseases, in particular AMD and diabetic retinopathy. The already mentioned AREDS and AREDS2 studies are

the most important large-scale clinical studies investigating the association between different nutrients intake and AMD progression. In the AREDS2 study, where lutein replaced beta-carotene in the original AREDS formulation, AMD progression was significantly reduced in the lutein-enriched group with the additional benefit of an improved treatment safety **[172]**. A long-term cohort study found a remarkable 40% reduced risk of advanced AMD progression for predicted plasma lutein/zeaxanthin scores suggesting that a higher intake of lutein/zeaxanthin is associated with a long-term reduced risk of advanced AMD **[173]**.

One of the key risk factors of diabetic retinopathy is elevated blood glucose level and clinical trials have shown that glycemic control is crucial in preventing or delaying the progression of diabetic retinopathy **[174,175]**. A recent retrospective study among type 2 diabetic patients showed that supplementation of lutein and zeaxanthin improves retinal thickness and function, strongly suggesting a protective effect of carotenoids on visual function at least in the diabetic state **[176]**. The results of other, though more limited, studies on the blood levels of lutein were consistent with the overall indication that lutein is beneficial by showing that higher lutein plasma levels are associated with a possible lower risk of diabetic retinopathy development or progression **[177–179]**. Although most available information concerns the protective role of lutein in AMD and diabetic retinopathy, more evidence is emerging that demonstrates the potential role of lutein in alleviating other eye diseases including myopia and cataract.

Concluding remarks

The eye is subjected to a highly oxidative environment due to its exposure to light, irritants, pollutants and its high molecular oxygen tension, and robust metabolic activity. Oxidative stress caused by the combination of these environmental and metabolic factors has been implicated in the pathogenesis of several ocular diseases, such as cataracts, glaucoma, age-related macular degeneration, diabetic retinopathy, glaucoma, retinal dystrophies. In addition, oxidative stress is thought to contribute prominently to eye conditions with robust environmental and behavioral components including digital eye strain, dry eye, and myopia as well as aging-related vision decay. For this reason, molecules whose main property is to inhibit oxidative stress such as C3G, zinc, lutein, and verbascoside, play an important role as therapeutic supports in eye diseases. A survey conducted in 2011 by the Ocular Nutrition Society found that 70% of the USA population in the age range 45–65 years ranked vision as the most important of the five senses, yet well over half of those surveyed were not aware of the importance that nutrients have in eye health. While a healthy diet is critical for obtaining all the necessary elements, nutritional supplementation under the supervision of healthcare professionals could play an important role in preventing or slowing down the progression of eye diseases, especially in the case of Digital Eye Strain, Visual Fatigue, and for elderly patients whose standard diet may not ensure an adequate daily intake of nutrients.

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