

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 prophylactic treatment [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].

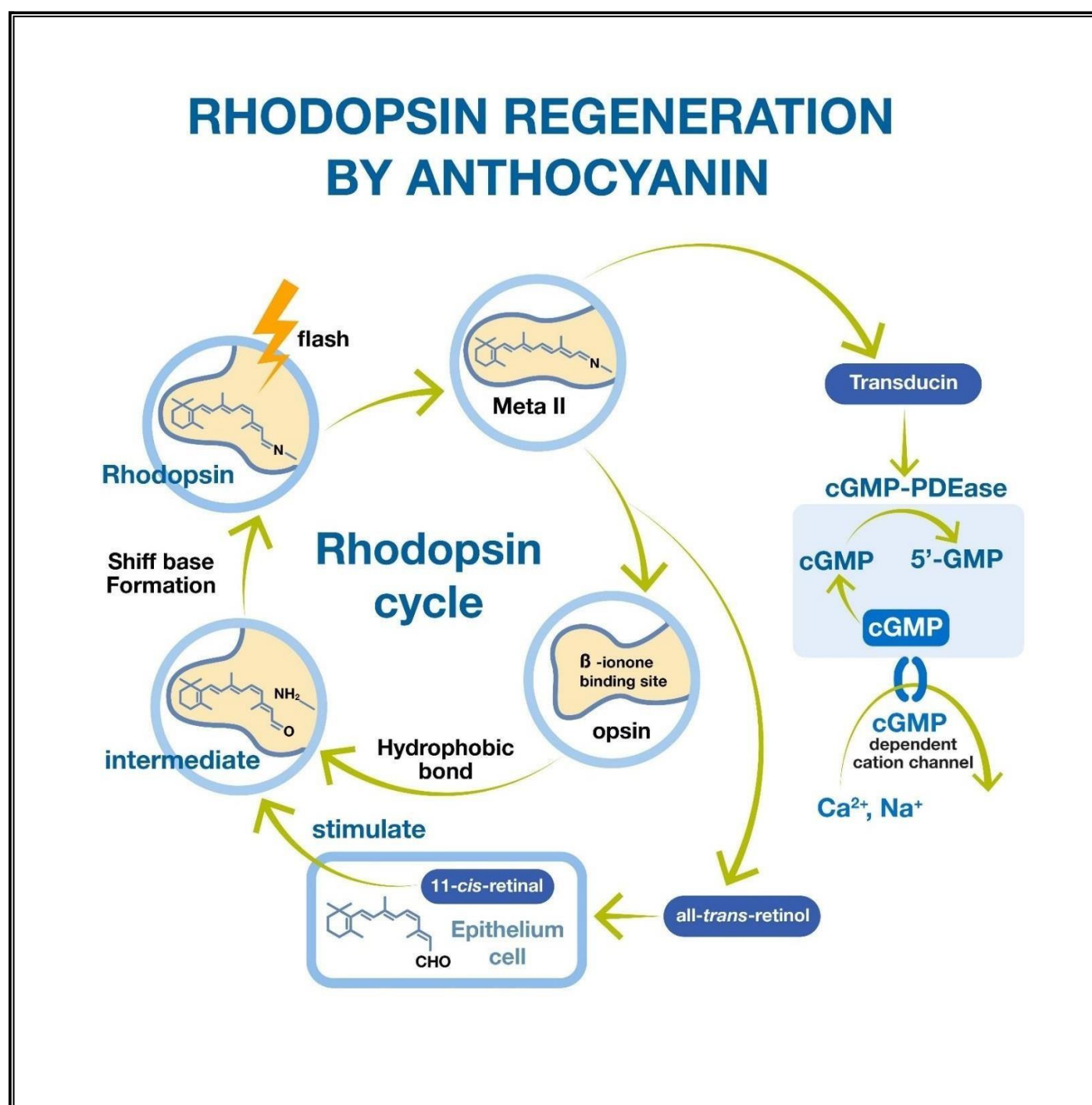


Figure 1: Rhodopsin regeneration by anthocyanin.

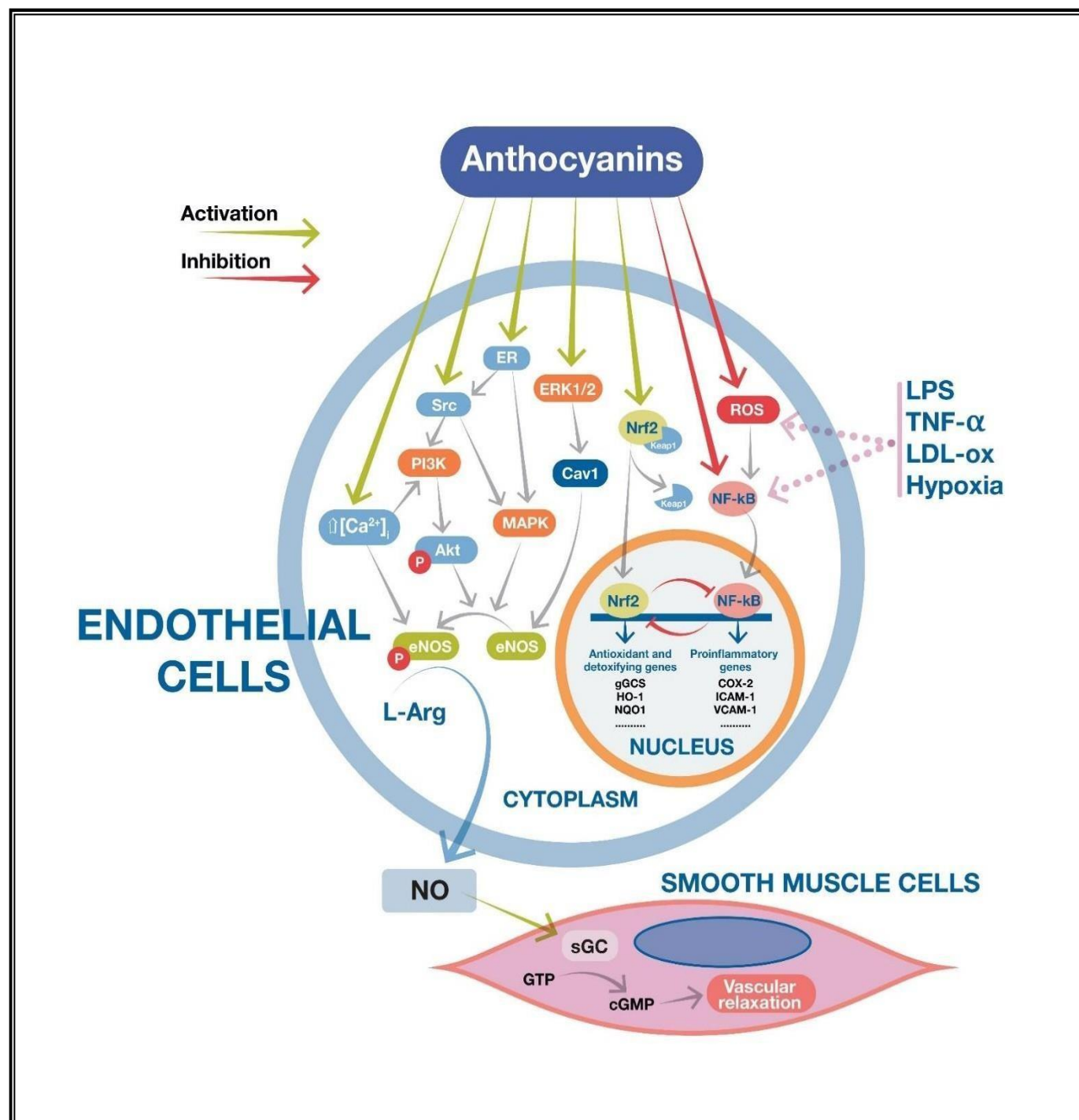


Figure 2: Anthocyanins: Mechanism of action.

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 acetoneide) 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- α (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 of solar-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].

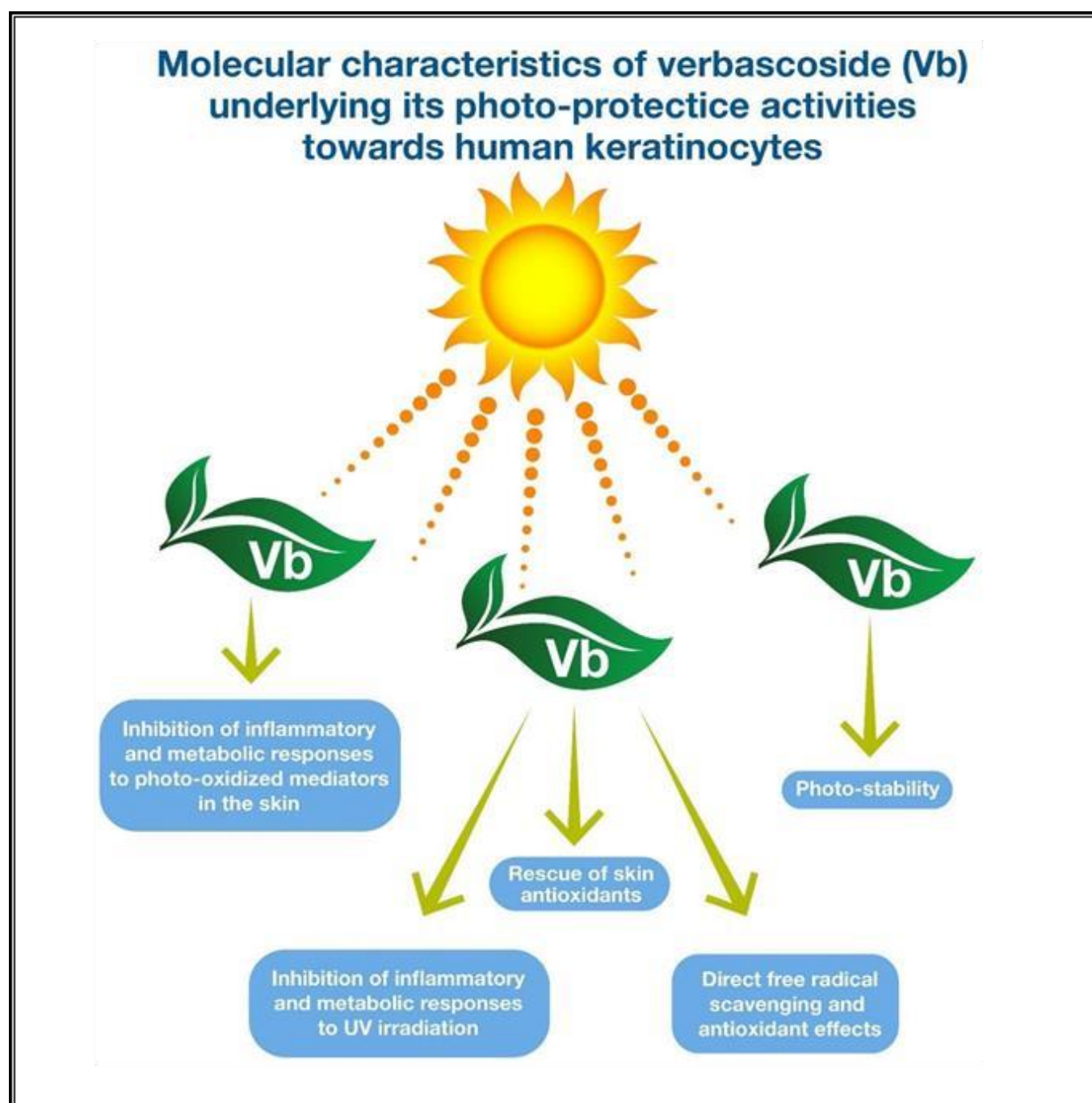


Figure 3: Verbascoside: mechanism of action and beneficial effects.

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- κ B and its target pro-inflammatory genes, such as TNF- α , 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- κ B activation resulting in a strong anti-inflammatory response via a feedback loop [115–117]. A transcriptional target of NF- κ B is the zinc transporter Zip8 which transports zinc into the cell and modulates I κ B 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 adaptation 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- κ B [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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References

1. Anderson CC, Anderson JH (1999) Sensory irritation and multiple chemical sensitivity. *Toxicol Ind Health*. 15(3-4): 339-45.
2. Waheed MA, Basu PK (1970) The effect of air pollutants on the eye. I. The effect of an organic extract on the conjunctival goblet cells. *Can J Ophthal*. 5(3): 226-230.
3. Altshuller AP (1977) Eye irritation as an effect of photochemical air pollution. *J Air Pollut Control Assoc*. 27(11): 125-1126.
4. Klein BEK, Klein R (2007) Lifestyle Exposures and Eye Diseases in Adults. *Am J Ophthalmol*. 144(6): 961-969.
5. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, et al. (2005) Smoking and age-related macular degeneration: A review of association. *Eye*. 19(9): 935-944.
6. Mitchell P, Chapman S, Smith W (1999) “Smoking is a major cause of blindness”. *Med J Aust*. 171(4): 173–174.
7. Kelly SP, Thornton J, Edwards R, Sahu A, Harrison R (2005) Smoking and cataract: review of causal association. *J Cataract Refract Surg*. 31(12): 2395-2404.
8. Hiratsuka Y, Li G (2001) Alcohol and eye diseases: A review of epidemiologic studies. *J Stud Alcohol*. 62(3): 397-402.
9. Mares-Perlman JA, Brady WE, Klein R, VandenLangenberg GM, Klein BEK, et al. (1995) Dietary Fat and Age-Related Maculopathy. *Arch Ophthalmol*. 113(6): 743–748.
10. Kishan AU, Modjtahedi BS, Martins EN, Modjtahedi SP, Morse LS (2011) Lipids and Age-related Macular Degeneration. *Surv Ophthalmol*. 56(3): 195-213.
11. Gillmann K, Hoskens K, Mansouri K (2019) Acute emotional

- stress as a trigger for intraocular pressure elevation in Glaucoma. *BMC Ophthalmol.* 19(1): 69.
12. Harding JJ, Egerton M, van Heyningen R, Harding RS (1993) Diabetes, glaucoma, sex, and cataract: analysis of combined data from two case control studies. *Br J Ophthalmol.* 77(1): 2-6.
13. Tumosa N (2008) Eye disease and the older diabetic. *Clin Geriatr Med.* 24(3): 515-527.
14. Klein R, Klein BE, Moss SE, Cruickshanks KJ (1995) The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology.* 102(1): 7-16.
15. Morgan IG, French AN, Ashby RS, Guo X, Ding X, et al. (2018) The epidemics of myopia: Aetiology and prevention. *Prog Retin Eye Res.* 62: 134-149.
16. Modjtahedi BS, Ferris FL, Hunter DG, Fong DS (2018) Public Health Burden and Potential Interventions for Myopia. *Ophthalmology.* 125(5): 628-630.
17. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, et al. (2016) Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *Ophthalmology.* 123(5): 1036-1042.
18. Xiang ZY, Zou HD (2020) Recent Epidemiology Study Data of Myopia. *J Ophthal.* 2020(7): 1-12.
19. Young TL, Metlapally R, Shay AE (2007) Complex trait genetics of refractive error. *Arch Ophthalmol.* 125(1): 38-48.
20. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P, et al. (2014) Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: An evidence-based systematic review. *Am J Ophthalmol.* 157(1): 9-25.e12.
21. Shen L, Melles RB, Metlapally R, Barcellos L, Schaefer C, et al. (2016) The Association of Refractive Error with Glaucoma in a Multiethnic Population. *Ophthalmology.* 123(1): 92-101.
22. Lin SC, Singh K, Chao DL, Lin SC (2016) Refractive error and the risk of age-related macular degeneration in the South Korean population. *Asia Pac J Ophthalmol.* 5(2): 115-121.
23. Iwase A, Araie M, Tomidokoro A, Shimizu H, Kitazawa Y, et al. (2006) Prevalence and Causes of Low Vision and Blindness in a Japanese Adult Population. The Tajimi Study. *Ophthalmology.* 113(8): 1354-1362.
24. Tedja MS, Haarman AEG, Meester-Smoor MA, Verhoeven VJM, Klaver CCW, et al. (2020) The Genetics of Myopia. In: Ang M, Wong TY (eds) *Updates on Myopia: A Clinical Perspective.* Springer Singapore, Singapore, pp 95–132.
25. Baird PN, Saw S-M, Lanca C, Guggenheim JA, Smith Lii EL, et al. (2020) Myopia. *Nat Rev Dis Primers.* 6(1): 99.
26. Williams KM, Bertelsen G, Cumberland P, Rahi J, Hammond CJ, et al. (2015) Increasing Prevalence of Myopia in Europe and the Impact of Education. *Ophthalmology.* 122(7): 1487-1497.
27. Morgan IG, Ohno-Matsui K, Saw S-M (2012) Myopia. *Lancet.* 379(9827): 1739-1748.
28. Dolgin E (2015) The myopia boom. *Nature.* 519(7543): 276–278.
29. Dirani M, Shekar SN, Baird PN (2008) The role of educational attainment in refraction: The genes in myopia (GEM) twin study. *Invest Ophthalmol Vis Sci.* 49: 534-538.
30. Foster PJ, Jiang Y (2014) Epidemiology of myopia. *Eye (Basingstoke).* 28(2): 202–208.
31. Pan CW, Ramamurthy D, Saw SM (2012) Worldwide prevalence and risk factors for myopia. *Ophthalmic Physiol Opt.* 32(1): 3-16.
32. Ramessur R, Williams KM, Hammond CJ (2015) Risk factors for myopia in a discordant monozygotic twin study. *Ophthalmic Physiol Opt.* 35(6): 643-651.
33. Wong TY, Foster PJ, Johnson GJ, Seah SKL (2002) Education, socioeconomic status, and ocular dimensions in Chinese adults: The Tanjong Pagar Survey. *Br J Ophthalmol.* 86(9): 963-968.
34. Morgan RW, Speakman JS, Grimshaw SE (1975) Inuit myopia: an environmentally induced “epidemic”? *Can Med Assoc J.* 112(5): 575-577.
35. He M, Zheng Y, Xiang F (2009) Prevalence of myopia in urban and rural children in mainland china. *Optom Vis Sci.* 86(1): 40- 44.
36. Mountjoy E, Davies NM, Plotnikov D, Smith GD, Rodriguez S, et al. (2018) Education and myopia: Assessing the direction of causality by mendelian randomisation. *BMJ (Online).* 361: k2022.
37. Huang HM, Chang DST, Wu PC (2015) The association between near work activities and myopia in children - A systematic review and meta-analysis. *PLoS ONE.* 10(10): e0140419.
38. Portello JK, Rosenfield M, Bababekova Y, Estrada JM, Leon A, et al. (2012) Computer-related visual symptoms in office workers. *Ophthalmic Physiol Opt.* 32(5): 375-382.
39. Sheedy JE, Hayes JN, Engle J (2003) Is all Asthenopia the Same? *Optom Vis Sci.* 80(11): 732-739.
40. Palaiologou I (2016) Children under five and digital technologies: implications for early years pedagogy. *European Early Childhood Education Research Journal.* 24(1): 5-24.
41. Sheppard AL, Wolffsohn JS (2018) Digital eye strain: Prevalence, measurement and amelioration. *BMJ Open Ophthalmol.* 3(1): e000146.
42. Costagliola C, Menzione M, Rinaldi E (1988) Free-radicals, visible-light and vitreous liquefaction - protection by superoxide- dismutase and catalase. *Molecular biology & medicine.* 13: 25– 31.
43. Brown NA, Bron AJ, Harding JJ, Dewar HM (1998) Nutrition supplements and the eye. *Eye.* 12(Pt 1): 127-133.

44. Smith RG (2010) Nutrition and eye diseases. *J Orthomol Med.* 25: 67-76.
45. Mares JA, Millen AE, Lawler TP, Blomme CK (2017) Chapter 19-Diet and supplements in the prevention and treatment of eye diseases. *Nutrition in the Prevention and Treatment of Disease*, 4th edn. Academic Press. pp 393-434.
46. Chew EY (2013) Nutrition effects on ocular diseases in the aging eye. *Invest Ophthalmol Vis Sci.* 54(14): ORSF42-ORSF47.
47. Grover AK, Samson SE (2014) Antioxidants and vision health: Facts and fiction. *Mol Cell Biochem.* 388(1-2): 173-183.
48. De Pascual-Teresa S, Sanchez-Ballesta MT (2008) Anthocyanins: From plant to health. *Phytochem Rev.* 7 : 281–299.
49. Wallace TC, Giusti MM (2013) Anthocyanins in health and disease. CRC Press.
50. O'Connor T (2015) Anthocyanins in Health and Disease. *Journal of Nutrition Education and Behavior.* 47(2): 193.
51. Celli GB, Tan C, Selig MJ (2018) Anthocyanidins and anthocyanins. In: Laurence Melton, Fereidoon Shahidi, Peter Varelis (eds) *Encyclopedia of Food Chemistry*, Academic Press, pp 218-223.
52. He J, Monica Giusti M (2010) Anthocyanins: Natural colorants with health-promoting properties. *Annu Rev Food Sci Technol.* 1: 163-187.
53. Tsuda T (2012) Dietary anthocyanin-rich plants: Biochemical basis and recent progress in health benefits studies. *Mol Nutr Food Res.* 56(1): 159-170.
54. Rendeiro C, Vauzour D, Kean RJ, Butler LT, Rattray M, et al. (2012) Blueberry supplementation induces spatial memory improvements and region-specific regulation of hippocampal BDNF mRNA expression in young rats. *Psychopharmacology.* 223(3): 319-330.
55. Smeriglio A, Barreca D, Bellocco E, Trombetta D (2016) Chemistry, Pharmacology and Health Benefits of Anthocyanins. *Phytother Res.* 30(8): 1265-1286.
56. Wang H, Cao G, Prior RL (1997) Oxygen Radical Absorbing Capacity of Anthocyanins. *J Agric Food Chem.* 45(2): 304–309.
57. De Gooyer TE, Stevenson KA, Humphries P, Simpson DAC, Curtis TM, et al. (2006) Rod photoreceptor loss in Rho-/- mice reduces retinal hypoxia and hypoxia-regulated gene expression. *Invest Ophthalmol Vis Sci.* 47(12): 5553-5560.
58. Arden GB, Sidman RL, Arap W, Schlingemann RO (2005) Spare the rod and spoil the eye. *Br J Ophthalmol.* 89(6): 764-769.
59. Lee SH, Jeong E, Paik SS, Jeon JH, Jung SW, et al. (2014) Cyanidin-3-glucoside extracted from mulberry fruit can reduce N- methyl-N-nitrosourea-induced retinal degeneration in rats. *Curr Eye Res.* 39(1): 79-87.
60. Paik SS, Jeong E, Jung SW, Ha TJ, Kang S, et al. (2012) Anthocyanins from the seed coat of black soybean reduce retinal degeneration induced by N-methyl-N-nitrosourea. *Exp Eye Res.* 97(1): 55-62.
61. Osada H, Okamoto T, Kawashima H, Toda E, Miyake S, et al. (2017) Neuroprotective effect of bilberry extract in a murine model of photo-stressed retina. *PLoS ONE.* 12(6): e0178627.
62. Wang Y, Zhao L, Lu F, Yang X, Deng Q, et al. (2015) Retinoprotective effects of bilberry anthocyanins via antioxidant, anti-inflammatory, and anti-apoptotic mechanisms in a visible light-induced retinal degeneration model in pigmented rabbits. *Molecules.* 20(12): 22395-22410.
63. Miyake S, Takahashi N, Sasaki M, Kobayashi S, Tsubota K, et al. (2012) Vision preservation during retinal inflammation by anthocyanin-rich bilberry extract: Cellular and molecular mechanism. *Lab Invest.* 92(2): 102-109.
64. Yao N, Lan F, He RR, Kurihara H (2010) Protective effects of bilberry (*Vaccinium myrtillus* L.) extract against endotoxin- induced uveitis in mice. *J Agr Food Chem.* 58(8): 4731–4736.
65. Matsunaga N, Imai S, Inokuchi Y, Shimazawa M, Yokota S, et al. (2009) Bilberry and its main constituents have neuroprotective effects against retinal neuronal damage in vitro and in vivo. *Mol Nutr Food Res.* 53(7): 869-877.
66. Iida H, Nakamura Y, Matsumoto H, Takeuchi Y, Harano S, et al. (2010) Effect of black-currant extract on negative lens-induced ocular growth in chicks. *Ophthalmic Res.* 44: 242–250.
67. Kamiya K, Kobashi H, Fujiwara K, Ando W, Shimizu K (2013) Effect of fermented bilberry extracts on visual outcomes in eyes with myopia: A prospective, randomized, placebo-controlled study. *J Ocul Pharmacol Therap.* 29(3): 356- 359.
68. Lee J, Lee HK, Kim CY, Hong YJ, Choe CM, et al. (2005) Purified high-dose anthocyanoside oligomer administration improves nocturnal vision and clinical symptoms in myopia subjects. *Br J Nutr.* 93(6): 895-899.
69. Kim ES, Yu SY, Kwon SJ, Kwon OW, Kim SY, et al. (2008) Clinical Evaluation of Patients with Nonproliferative Diabetic Retinopathy Following Medication of Anthocyanoside: Multicenter Study. *J Korean Ophthalmol Soc.* 49(10): 1629-1633.
70. Choi JI, Kim J, Choung SY (2019) Polyphenol-enriched fraction of *Vaccinium uliginosum* L. Protects selenite-induced cataract formation in the lens of Sprague-Dawley rat pups. *Mol Vis.* 25: 118-128.
71. Kalt W, Hanneken A, Milbury P, Tremblay F (2010) Recent research on polyphenolics in vision and eye health. *J Agr Food Chem.* 58(7): 4001–4007.

72. Matsumoto H, Nakamura Y, Iida H, Ito K, Ohguro H (2006) Comparative assessment of distribution of blackcurrant anthocyanins in rabbit and rat ocular tissues. *Exp Eye Res.* 83(2): 348-356.
73. Kurkin VA (2003) Phenylpropanoids from medicinal plants: Distribution, classification, structural analysis, and biological activity. *Chem Nat Compd.* 39(2): 123-153.
74. Korkina LG (2007) Phenylpropanoids as naturally occurring antioxidants: From plant defense to human health. *Cell Mol Biol.* 53(1): 15-25.
75. Alipieva KI, Orhan IE, Cankaya IIT, Kostadinova EP, Georgiev MI (2014) Treasure from garden: Chemical profiling, pharmacology and biotechnology of mulleins. *Phytochem Rev.* 13: 417-444.
76. Alipieva K, Korkina L, Orhan IE, Georgiev MI (2014) Verbascoside - A review of its occurrence, (bio)synthesis and pharmacological significance. *Biotechnol Adv.* 32(6): 1065-1076.
77. Motojima H, Villareal MO, Iijima R, Han J, Isoda H (2013) Acteoside inhibits type I allergy through the down-regulation of Ca/NFAT and JNK MAPK signaling pathways in basophilic cells. *J Nat Med.* 67(4): 790-798.
78. Rao YK, Fang SH, Hsieh SC, Yeh TH, Tzeng YM (2009) The constituents of *Anisomeles indica* and their anti-inflammatory activities. *J Ethnopharmacol.* 121(2): 292-296.
79. Picerno P, Autore G, Marzocco S, Meloni M, Sanogo R, et al. (2005) Anti-inflammatory activity of verminoside from *Kigelia africana* and evaluation of cutaneous irritation in cell cultures and reconstituted human epidermis. *J Nat Prod.* 68(11): 1610-1614.
80. Marzocco S, Piccinelli AL, Rastrelli L, Mazzon E, Cuzzocrea S, et al. (2007) Inhibition of inducible nitric oxide synthase in vitro and in vivo by a water-soluble extract of *Wendita calysina* leaves. *Naunyn Schmiedebergs Arch Pharmacol.* 375(6): 349-358.
81. Lee JY, Woo ER, Kang KW (2005) Inhibition of lipopolysaccharide-inducible nitric oxide synthase expression by acteoside through blocking of AP-1 activation. *J Ethnopharmacol.* 97(3): 561-566.
82. Zenz R, Eferl R, Scheinecker C, Redlich K, Smolen J, et al. (2008) Activator protein 1 (Fos/Jun) functions in inflammatory bone and skin disease. *Arthritis Res Ther.* 10(1): 201.
83. Speranza L, Franceschelli S, Pesce M, Reale M, Menghini L, et al. (2010) Antiinflammatory effects in THP-1 cells treated with verbascoside. *Phytother Res.* 24(9): 1398-1404.
84. Kostyuk V, Potapovich A, Suhan T, De Luca C, Pressi G, et al. (2008) Plant polyphenols against UV-C-induced cellular death. *Planta Med.* 74(5): 509-514.
85. Pastore S, Potapovich A, Kostyuk V, Mariani V, Lulli D, et al. (2009) Plant polyphenols effectively protect HaCaT cells from ultraviolet C-triggered necrosis and suppress inflammatory chemokine expression. In: *Annals of the New York Academy of Sciences.* 1171(1): 305-313.
86. Kostyuk VA, Potapovich AI, Lulli D, Stancato A, De Luca C, et al. (2013) Modulation of Human Keratinocyte Responses to Solar UV by Plant Polyphenols As a Basis for Chemoprevention of Non-Melanoma Skin Cancers. *Curr Med Chem.* 20(7): 869-879.
87. Zafrilla P, Losada M, Perez A, Caravaca G, Mulero J (2013) Biomarkers of oxidative stress in patients with wet age related macular degeneration. *J Nutr Health Aging.* 17(3): 219-222.
88. Costagliola C, Iuliano G, Menzione M, Nesti A, Simonelli F, et al. (1988) Systemic human diseases as oxidative risk factors in cataractogenesis. I. Diabetes. *Ophthalmic Res.* 20(5): 308-316.
89. Tanito M, Kaidzu S, Takai Y, Ohira A (2012) Status of Systemic Oxidative Stresses in Patients with Primary Open-Angle Glaucoma and Pseudoexfoliation Syndrome. *PLoS ONE.* 7(11): e49680.
90. Mosca M, Ambrosone L, Semeraro F, Casamassima D, Vizzarri F, et al. (2014) Ocular tissues and fluids oxidative stress in hares fed on verbascoside supplement. *Int J Food Sci Nutr.* 65(2): 235-240.
91. Yang J, Yan Y, Liu H, Wang J, Hu J, et al. (2015) Protective effects of acteoside against X-ray-induced damage in human skin fibroblasts. *Mol Med Rep.* 12(2): 2301-2306.
92. Peng XM, Gao L, Huo SX, Liu XM, Yan M (2015) The Mechanism of Memory Enhancement of Acteoside (Verbascoside) in the Senescent Mouse Model Induced by a Combination of d-gal and AlCl₃. *Phytother Res.* 29(8): 1137-1144.
93. Chen Q, Xi X, Zeng Y, He Z, Zhao J, et al. (2019) Acteoside inhibits autophagic apoptosis of retinal ganglion cells to rescue glaucoma-induced optic atrophy. *J Cell Biochem.* 120(8): 13133-13140.
94. Prasad AS, Miale A, Farid Z, Sandstead HH, Schulert AR (1990) Clinical and experimental. Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypogonadism. *J Lab Clin Med.* 116(5): 737-749.
95. Prasad AS (2008) Clinical, immunological, anti-inflammatory and antioxidant roles of zinc. *Exp Gerontol.* 43(5): 370-377.
96. Oteiza PI, Clegg MS, Zago MP, Keen CL (2000) Zinc deficiency induces oxidative stress and AP-1 activation in 3T3 cells. *Free Radical Bio Med.* 28(7): 1091-1099.

97. Zago MP, Mackenzie GG, Adamo AM, Keen CL, Oteiza PI (2005) Differential modulation of MAP kinases by zinc deficiency in IMR-32 cells: Role of H₂O₂. *Antioxid Redox Signaling*. 7(11- 12): 1773-1782.
98. Ho E, Ames BN (2002) Low intracellular zinc induces oxidative DNA damage, disrupts p53, NFκB, and AP1 DNA binding, and affects DNA repair in a rat glioma cell line. *PNAS*. 99(26): 16770-16775.
99. Aimo L, Cherr GN, Oteiza PI (2010) Low extracellular zinc increases neuronal oxidant production through nadph oxidase and nitric oxide synthase activation. *Free Radical Bio Med*. 48(12): 1577-1587.
100. Ho E, Courtemanche C, Ames BN (2003) Zinc deficiency induces oxidative DNA damage and increases P53 expression in human lung fibroblasts. *J Nutr*. 133(8): 2543-2548.
101. Bruno RS, Song Y, Leonard SW, Mustacich DJ, Taylor AW, et al. (2007) Dietary zinc restriction in rats alters antioxidant status and increases plasma F2 isoprostanes. *J Nutr Biochem*. 18(8): 509- 518.
102. Song Y, Leonard SW, Traber MG, Ho E (2009) Zinc deficiency affects DNA damage, oxidative stress, antioxidant defenses, and DNA repair in rats. *J Nutr*. 139(9): 1626-1631.
103. Shaheen AA, Abd El-Fattah AA (1995) Effect of dietary zinc on lipid peroxidation, glutathione, protein thiols levels and superoxide dismutase activity in rat tissues. *Int J Biochem Cell Biol*. 27(1): 89-95.
104. Hammermueller JD, Bray TM, Bettger WJ (1987) Effect of zinc and copper deficiency on microsomal NADPH-dependent active oxygen generation in rat lung and liver. *J Nutr*. 117(5): 894-901.
105. Bray TM, Kubow S, Bettger WJ (1986) Effect of dietary zinc on endogenous free radical production in rat lung microsomes. *J Nutr*. 116(6): 1054-1060.
106. Sullivan JF, Jetton MM, Hahn HKJ, Burch RE (1980) Enhanced lipid peroxidation in liver microsomes of zinc-deficient rats. *Am J Clin Nutr*. 33(1): 51-56.
107. Song Y, Chung CS, Bruno RS, Traber MG, Brown KH, et al. (2009) Dietary zinc restriction and repletion affects DNA integrity in healthy men. *Am J Clin Nutr*. 90(2): 321-328.
108. Prasad AS, Beck FWJ, Bao B, Fitzgerald JT, Snell DC, et al. (2007) Zinc supplementation decreases incidence of infections in the elderly: Effect of zinc on generation of cytokines and oxidative stress. *Am J Clin Nutr*. 85(3): 837-844.
109. Eide DJ (2011) The oxidative stress of zinc deficiency. *Metallomics*. 3(11): 1124-1129.
110. Maret W (2003) Cellular zinc and redox states converge in the metallothionein/thionein pair. *J Nutr*. 133(5): 1460S-1462S.
111. Maret W (2008) Metallothionein redox biology in the cytoprotective and cytotoxic functions of zinc. *Exp Gerontol*. 43(5): 363-369.
112. Zago MP, Oteiza PI (2001) The antioxidant properties of zinc: Interactions with iron and antioxidants. *Free Radic Biol Med*. 31(2): 266-274.
113. Zago MP, Verstraeten S V, Oteiza PI (2000) Zinc in the prevention of Fe²⁺-initiated lipid and protein oxidation. *Biol Res*. 33(2): 143- 150.
114. Ha KN, Chen Y, Cai J, Sternberg P (2006) Increased glutathione synthesis through an ARE-Nrf2-dependent pathway by zinc in the RPE: Implication for protection against oxidative stress. *Invest Ophthalmol Vis Sci*. 47(6): 2709-2715.
115. Jarosz M, Olbert M, Wyszogrodzka G, Młyniec K, Librowski T (2017) Antioxidant and anti-inflammatory effects of zinc. Zinc- dependent NF-κB signaling. *Inflammopharmacology*. 25(1): 11- 24.
116. Prasad AS, Bao B, Beck FWJ, Sarkar FH (2011) Zinc-suppressed inflammatory cytokines by induction of A20-mediated inhibition of nuclear factor-κB. *Nutr*. 22(7-8): 816-823.
117. Bao B, Prasad AS, Beck FWJ, Fitzgerald JT, Snell D, et al. (2010) Zinc decreases C-reactive protein, lipid peroxidation, and inflammatory cytokines in elderly subjects: A potential implication of zinc as an atheroprotective agent. *Am J Clin Nutr*. 91(6): 1634-1641.
118. Liu MJ, Bao S, Gálvez-Peralta M, Nebert DW, Wewers MD, et al. (2013) ZIP8 Regulates Host Defense through Zinc- Mediated Inhibition of NF-κB. *Cell Rep*. 3(2): 386-400.
119. Erie JC, Good JA, Butz JA, Pulido JS (2009) Reduced Zinc and Copper in the Retinal Pigment Epithelium and Choroid in Age- related Macular Degeneration. *Am J Ophthalmol*. 147(2): 276- 282.
120. Grahn BH, Paterson PG, Gottschall-Pass KT, Zhang Z (2001) Zinc and the eye. *J Am Coll Nutr*. 20(2): 106-118.
121. Wills NK, Sadagopa Ramanujam VM, Kalariya N, Lewis JR, van Kuijk FJGM (2008) Copper and zinc distribution in the human retina: Relationship to cadmium accumulation, age, and gender. *Exp Eye Res*. 87(2): 80-88.
122. Gilbert R, Peto T, Lengyel I, Emri E (2019) Zinc Nutrition and Inflammation in the Aging Retina. *Mol Nutr Food Res*. 63(15): e1801049.
123. Jacobson SG, Meadows NJ, Keeling PWN, Mitchell WD, Thompson RPH (1986) Rod mediated retinal dysfunction in cats with zinc depletion: Comparison with taurine depletion. *Clin Sci*. 71(5): 559-564.
124. Morrison SA, Russell RM, Carney EA, Oaks E V (1978) Zinc deficiency: a cause of abnormal dark adaptation in cirrhotics. *Am J Clin Nutr*. 31(2): 276-281.
125. Warth JA, Prasad AS, Zwas F, Frank RN (1981) Abnormal dark adaptation in sickle cell anemia. *J Lab Clin Med*. 98(2): 189-94.

126. Mahajan SK, Prasad AS, Brewer GJ, et al (1992) Effect of changes in dietary zinc intake on taste acuity and dark adaptation in normal human subjects. *J Trace Elem Exp Med* 5: 33-45.
127. Pålsgård E, Ugarte M, Rajta I, Grime GW (2001) The role of zinc in the dark-adapted retina studied directly using microPIXE. *Nuclear Instruments and Methods in Physics Research, Section B: Beam Interactions with Materials and Atoms*. 181(1-4): 489-492.
128. Gleim S, Stojanovic A, Arehart E, Byington D, Hwa J (2009) Conserved rhodopsin intradiscal structural motifs mediate stabilization: Effects of zinc. *Biochemistry*. 48(8): 1793–1800.
129. Olsson JE, Gordon JW, Pawlyk BS, Roof D, Hayes A, et al. (1992) Transgenic mice with a rhodopsin mutation (Pro23His): A mouse model of autosomal dominant retinitis pigmentosa. *Neuron*. 9(5): 815-830.
130. Silverstone BZ, Berson D, Seelenfreund MH (1981) Plasma zinc levels in high myopia and retinitis pigmentosa. *Metab Pediatr Ophthalmol*. 5(3-4): 187-190.
131. Kassoff A, Kassoff J, Buehler J, Eglow M, Kaufman F, et al. (2001) A randomized, placebo-controlled, clinical trial of high- dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 119(10): 1417-1436.
132. Chew EY, Clemons TE, Agrón E, Kurinij N, Davis MD, et al (2013) Long-term effects of vitamins C and E, β -carotene, and zinc on age-related macular degeneration: AREDS Report No. 35. *Ophthalmology*. 120(8): 1604-1611.
133. Chew EY, Clemons TE, SanGiovanni JP, et al. (2013) Lutein+ zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 309(19): 2005-2015.
134. Wong P, Markey M, Rapp CM, Darrow RM, Ziesel A, et al. (2017) Enhancing the efficacy of AREDS antioxidants in light- induced retinal degeneration. *Mol Vis*. 23: 718-739.
135. Van Leeuwen R, Boekhoorn S, Vingerling JR, Witteman JCM, Kalver CCW, et al. (2005) Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA*. 294(24):3101-3107.
136. Tan JSL, Wang JJ, Flood V, Rochtchina E, Smith W, et al. (2008) Dietary Antioxidants and the Long-term Incidence of Age-Related Macular Degeneration. The Blue Mountains Eye Study. *Ophthalmology*. 115(2): 334-341.
137. Gopinath B, Liew G, Russell J, Cosatto A, Burlutsky G, et al. (2017) Intake of key micronutrients and food groups in patients with late-stage age-related macular degeneration compared with age-sex-matched controls. *Br J Ophthalmol*. 101(8): 1027-1031.
138. Saini RK, Nile SH, Park SW (2015) Carotenoids from fruits and vegetables: Chemistry, analysis, occurrence, bioavailability and biological activities. *Food Res Int*. 76(Pt 3): 735-750.
139. Fernández-García E, Carvajal-Lérída I, Jarén-Galán M, Garrido- Fernández J, Pérez-Gálvez A, et al. (2012) Carotenoids bioavailability from foods: From plant pigments to efficient biological activities. *Food Res Int*. 46(2): 438-450.
140. Eroglu A, Harrison EH (2013) Carotenoid metabolism in mammals, including man: Formation, occurrence, and function of apocarotenoids. *J Lipid Res*. 54(7): 1719-1730.
141. Perry A, Rasmussen H, Johnson EJ (2009) Xanthophyll (lutein, zeaxanthin) content in fruits, vegetables and corn and egg products. *J Food Compos Anal*. 22(1): 9-15.
142. Kim SR, Nakanishi K, Itagaki Y, Sparrow JR (2006) Photooxidation of A2-PE, a photoreceptor outer segment fluorophore, and protection by lutein and zeaxanthin. *Exp Eye Res*. 82(5): 828-839.
143. Krinsky NI, Johnson EJ (2005) Carotenoid actions and their relation to health and disease. *Mol Aspects Med*. 22(6): 459-516.
144. Kijlstra A, Tian Y, Kelly ER, Berendschot TTJM (2012) Lutein: More than just a filter for blue light. *Prog Retin Eye Res*. 31(4): 303-315.
145. Junghans A, Sies H, Stahl W (2001) Macular pigments lutein and zeaxanthin as blue light filters studied in liposomes. *Arch Biochem Biophys*. 391(2): 160-164.
146. Snodderly DM, Auran JD, Delori FC (1984) The macular pigment.II. Spatial distribution in primate retinas. *Invest Ophthalmol Vis Sci*. 25(6): 674-685.
147. Chung RWS, Leanderson P, Lundberg AK, Jonasson L (2017) Lutein exerts anti-inflammatory effects in patients with coronary artery disease. *Atherosclerosis*. 262: 87-93.
148. Bian Q, Gao S, Zhou J, Qin J, Taylor A, et al. (2012) Lutein and zeaxanthin supplementation reduces photooxidative damage and modulates the expression of inflammation-related genes in retinal pigment epithelial cells. *Free Rad Bio Med*. 53(6): 1298-1307.
149. Muriach M, Bosch-Morell F, Arnal E, Alexander G, Blomhoff R, et al. (2008) Lutein prevents the effect of high glucose levels on immune system cells in vivo and in vitro. *J Physiol Biochem*. 64(2): 149-157.
150. Liu T, Liu W hong, Zhao J sheng, Meng FZ, Wang H (2017) Lutein protects against β -amyloid peptide-induced oxidative stress in cerebrovascular endothelial cells through modulation of Nrf- 2 and NF- κ b. *Cell Biol Toxicol*. 33(1): 57-67.
151. Chang J, Zhang Y, Li Y, Lu K, Shen Y, et al. (2018) NrF2/ARE and NF- κ B pathway regulation may be the mechanism for lutein inhibition of human breast cancer cell. *Future Oncol*. 14(8): 719- 726.
152. Rafi MM, Shafaie Y (2007) Dietary lutein modulates inducible nitric oxide synthase (iNOS) gene and protein

- expression in mouse macrophage cells (RAW 264.7). *Mol Nutr Food Res*. 51(3): 333- 340.
153. Li S, Ding Y, Niu Q, Xu S, Pang L, et al. (2015) Lutein has a protective effect on hepatotoxicity induced by arsenic via Nrf2 signaling. *BioMed Res Int*. 2015: 315205.
 154. Tian Y, Kijlstra A, Van Der Veen RLP, Makridaki M, Murray IJ, et al. (2015) Lutein supplementation leads to decreased soluble complement membrane attack complex sC5b-9 plasma levels. *Acta Ophthalmol*. 93(2): 141-145.
 155. Fernández-Robredo P, Sádaba LM, Salinas-Alamán A, Recalde S, Rodríguez JA, et al. (2013) Effect of lutein and antioxidant supplementation on VEGF expression, MMP-2 activity, and ultrastructural alterations in apolipoprotein E-deficient mouse. *Oxid Med Cell Longev*. 2013: 213505.
 156. Ranard KM, Jeon S, Mohn ES, Griffiths JC, Johnson EJ, et al. (2017) Dietary guidance for lutein: consideration for intake recommendations is scientifically supported. *Eur J Nutr*. 56(Suppl 3): 37-42.
 157. Johra FT, Bepari AK, Bristy AT, Reza HM (2020) A Mechanistic Review of β -Carotene, Lutein, and Zeaxanthin in Eye Health and Disease. *Antioxidants*. 9(11): 1046.
 158. Li LH, Lee JCY, Leung HH, Lam WC, Fu Z, et al (2020) Lutein supplementation for eye diseases. *Nutrients*. 12(6): 1721.
 159. Buscemi S, Corleo D, Di Pace F, Petroni ML, Satriano A, et al. (2018) The effect of lutein on eye and extra-eye health. *Nutrients*. 10(9): 1321.
 160. Bone RA, Landrum JT (2010) Dose-dependent response of serum lutein and macular pigment optical density to supplementation with lutein esters. *Arch Biochem Biophys*. 504(1): 50-55.
 161. Richer S, Stiles W, Statkute L, Pulido J, Frankowski J, et al. (2004) Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: The Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry*. 75(4): 216-229.
 162. Weigert G, Kaya S, Pemp B, Sacu S, Lasta M, et al (2011) Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 52(11): 8174-8178.
 163. Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, et al. (2015) Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age- related macular degeneration. *BioMed Res Int*. 2015: 564738.
 164. Ma L, Yan SF, Huang YM, Lu XR, Qian F, et al. (2012) Effect of lutein and zeaxanthin on macular pigment and visual function in patients with early age-related macular degeneration. *Ophthalmology*. 119(11): 2290-2297.
 165. Fujimura S, Ueda K, Nomura Y, Yanagi Y (2016) Preliminary analysis of the relationship between serum lutein and zeaxanthin levels and macular pigment optical density. *Clin Ophthalmol*. 2016(10): 2149-2155.
 166. Nolan JM, Loughman J, Akkali MC, Stack J, Scanlon G, et al. (2011) The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. *Vision Res*. 51(5): 459-469.
 167. Wolf-Schnurrbusch UEK, Zinkernagel MS, Munk MR, Ebnetter A, Wolf S (2015) Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. *Invest Ophthalmol Vis Sci*. 56(13): 8069-8074.
 168. Liu R, Wang T, Zhang B, Qin L, Wu C, et al. (2015) Lutein and zeaxanthin supplementation and association with visual function in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 56(1): 252-258.
 169. Richer SP, Stiles W, Graham-Hoffman K, Levin M, Ruskin D, et al. (2011) Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age- related macular degeneration: The Zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. *Optometry*. 82(11): 667-680.e6.
 170. Piermarocchi S, Saviano S, Parisi V, Tedeschi M, Panozzo G, et al. (2012) Carotenoids in Age-related maculopathy Italian study (CARMIS): Two-year results of a randomized study. *Eur J Ophthalmol*. 22(2): 216-225.
 171. Sasamoto Y, Gomi F, Sawa M, Tsujikawa M, Nishida K (2011) Effect of 1-year lutein supplementation on macular pigment optical density and visual function. *Graefes Arch Clin Exp Ophthalmol*. 249(12): 1847-1854.
 172. Chew EY, Clemons TE, SanGiovanni JP, Danis RP, Ferris FL, et al. (2014) Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression AREDS2 report no. 3. *JAMA Ophthalmol*. 132(2): 142-149.
 173. Wu J, Cho E, Willett WC, Sastry SM, Schaumberg DA (2015) Intakes of lutein, zeaxanthin, and other carotenoids and age- related macular degeneration during 2 decades of prospective follow-up. *JAMA Ophthalmol*. 133(12): 1415-1424.
 174. Turner R (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 352(9131): 854-865.
 175. Zavrelova H, Hoekstra T, Alssema M, M.C. Welschen L, Nijpels G, et al. (2011) Progression and regression: Distinct developmental patterns of diabetic retinopathy in patients with type 2 diabetes treated in the Diabetes Care System West- Friesland, the Netherlands. *Diabetes Care*. 34(4): 867-872.

176. Moschos MM, Dettoraki M, Tsatsos M, Kitsos G, Kalogeropoulos C (2017) Effect of carotenoids dietary supplementation on macular function in diabetic patients. *Eye Vis (Lond)*. 4 : 23.
177. Zhang PC, Wu CR, Wang ZL, Wang LY, Han Y, et al. (2017) Effect of lutein supplementation on visual function in nonproliferative diabetic retinopathy. *Asia Pac J Clin Nutr*. 26(3): 406-411.
178. Brazionis L, Rowley K, Itsiopoulos C, O'dea K (2009) Plasma carotenoids and diabetic retinopathy. *Br J Nutr*. 101(2): 270-277.
179. Hu BJ, Hu YN, Lin S, Ma WJ, Li XR (2011) Application of Lutein and Zeaxanthin in nonproliferative diabetic retinopathy. *Int J Ophthalmol*. 4(3): 303-306.