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Vision-Boosting Nutrition: Exploring the Benefits of Nutritional Supplements for Eye Health

Bochatay T[1], Fetian IR[1] and Mozaffarieh M[1,2]*

[1]University of Basel, Basel, Switzerland

[2]Limmat Eye Center, Zurich, Switzerland

ABSTRACT

Oxidative stress, defined by an imbalance in free radical generation and antioxidant defense, serves as a pivotal risk factor for multiple ocular pathologies, including glaucoma, cataracts, and age-related macular degeneration (AMD). Under normal physiological conditions, endogenous mechanisms adequately regulate reactive oxygen species (ROS) levels. However, excessive ROS accumulation, surpassing the body's antioxidative capacity, initiates oxidative stress, precipitating macromolecular damage and potentially accelerating disease progression in ocular tissues. This review delineates the significance of dietary antioxidants in mitigating oxidative stress specifically within the context of eye health. Focus is directed towards the bioactive compounds, polyphenolic flavonoids and anthocyanosides, prevalent in various foods such as Nigella sativa, tea, chocolate, fruits, and vegetables (polyphenolic flavonoids), as well as blueberries and bilberries (anthocyanosides). These compounds engage distinct mechanistic pathways to neutralize ROS; polyphenolic flavonoids donate electrons, whereas anthocyanosides scavenge free radicals. The current synthesis aims to elucidate the molecular interactions and therapeutic potential of these antioxidants in preserving ocular health and preventing the onset or progression of related diseases, providing a comprehensive understanding for future research and clinical applications.

***Corresponding author**

Maneli Mozaffarieh, University of Basel & Limmat Eye Center,Zurich, Hardturmstrasse 133, 8005 Zurich, Switzerland.

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Introduction

Antioxidative nutrition can have positive effects on ocular health and there is a growing interest among patients to find out more as to what they can do themselves to prevent eye disease [1]. Currently millions of people world- wide are suffering from vision loss due to diseases such as cataract, age-related macular degeneration, glaucoma or diabetic retinopathy [2]. Although the aetiology of these diseases is complex and multifactorial, oxidative stress has been implicated to play a role as a risk factor in all these conditions [3]. Our eyes are quite susceptible to oxidative stress because of high oxygen consumption and exposure to light [4]. This leads to the generation of reactive oxidative species (ROS) which as the term implies are more reactive oxygen molecules in comparison to the stable ground state oxygen molecule which is relatively inert [5]. Our body has antioxidative defence mechanisms to cope with the production of these free radicals [6]. If, however, the production of these free radicals exceeds our bodies coping capacity the resulting oxidative stress can damage macromolecules such as proteins and DNA thus resulting in an ocular disease [7].

Oxidative Stress and Eye Disease

The eye is a remarkable organ but is at the same time also quite susceptible to oxidative stress [8]. The retina is vulnerable to oxidative stress because of its high metabolic activity and high levels of oxygen consumption [9]. The photoreceptors use more than half of the oxygen consumed by the retina [10]. The oxygen supply to the retina is therefore highly regulated and any disruption as e.g., by means of reperfusion can lead to cellular damage resulting in various ocular pathologies such as age-related macular degeneration (AMD), diabetic retinopathy or glaucoma. AMD is one main cause of blindness in western countries and it is brought about by the loss of retinal pigment epithelial (RPE) cells and photoreceptors in the macula [11]. RPE is important for the health of photoreceptor cells as RPE cells phagocytose photoreceptor outer segment cells to guarantee their optimal functionality [12]. In addition, the RPE cells transport metabolic waste through Bruchs membrane to the choroid to be eliminated [13]. AMD is characterized by the presence of Drusen deposits accumulating between Bruchs membrane and the RPE [14]. Drusen deposits have advanced glycation end-products (AGEs) and carboxyethyl pyrrole adducts [15]. These are the result of oxidative modification of fatty acids in photoreceptor [16]. The presence of these molecules in the Drusen implies that oxidative stress plays a role in the pathogenesis of AMD [17]. As mentioned above oxidative stress plays a role in the development and progression of diabetic retinopathy [18]. High levels of glucose in the blood can lead to an increase in ROS which can damage cells and lead to functional and structural changes in the microvasculature of the retinal [19]. These changes include basement membrane thickening, microvascular cell loss or capillary closure [20]. These changes may lead to altered blood flow, loss of intercellular junctions, and increased vessel permeability thereby contributing to diabetic retinopathy [21].

Reperfusion phenomena lead to enhanced oxidative stress in the mitochondria [22]. The term reperfusion refers to a normalization of the blood flow after a period of impaired blood flow [23]. This phenomenon leads to an increased production of free radicals particularly the superoxide radical in the mitochondria [24]. The optic nerve of the eyes is packed densely with mitochondria as this is an area of high energy consumption and thus the optic nerve is also quite susceptible to damage by increased levels of oxidative stress and thus there is a higher chance of developing a glaucoma [25]. The retinal ganglion cells are the neuronal cells responsible for converting visual signals into neural signals and transmitting them to the brain via the optic nerve [26]. RGCs are highly metabolically active and rely on the mitochondria for energy supply and survival [27]. When they do not receive enough energy, they die leading to glaucoma. This process is also in part mediated by oxidative stress [28].

Oxidative stress is also involved in anterior ocular disease pathogenesis such as dry-eye, uveitis or cataract [29]. Dry eye is an inflammatory disease that leads to ocular dryness, pain and tear film instability [30]. ROS produced by environmental factors, such as pollution or UV promote pathogenesis of dry eye disease [31]. Studies show that molecular markers of oxidative stress have been observed in patients with dry eye. ROS can damage the tear film produced by the eye's glands [32]. The most common damaged glands are the meibomian glands, which secrete meibum that forms the lipid layer [33]. The instability of this layer is called meibomian gland dysfunction, a common cause of Dry Eye [34]. This dysfunction shows an increased level of inflammatory factors (IL-6 and TNF-a) and the infiltration of leukocytes inside the glands [35].

The lens of the eye is encapsulated and avascular, which is a protection against oxidative stress, but also has a high refractive index due to crystallin proteins [36]. These proteins must be properly folded and soluble to ensure transparency [37]. Age-related modifications unfold and destabilize the crystallin proteins that finally aggregate and cause the lens opacification [38]. Oxidative modifications predispose crystallins to aggregate and form cataract [39]. Due to the long-lived nature of crystallin proteins, the lens epithelium has a high level of Glutathion (GSH), an antioxidant that balances the lens redox state [40]. However, in the central lens nucleus, the levels of GSH are low [40]. It makes the lens nucleus vulnerable to oxidative stress and cataract formation [41]. The Flammer syndrome (FS) presents a unique challenge in determining appropriate dietary recommendations due to its association with altered vascular reactions and predisposition to certain eye and systemic diseases. While nutrition adaptation is advocated as a compromise between no treatment and pharmacological intervention, it must be personalized, considering the individual's health condition, as dietary interventions such as calorie restriction or salt reduction may have unintended consequences on FS symptoms and vascular regulation [42].

The above diseases are only a few examples of ocular pathologies for which oxidative stress plays a role. One way to reduce oxidative stress is by maintaining a healthy diet rich in antioxidants [43]. This will be discussed in more detail below.

Antioxidative Potential of Certain Foods

Most of antioxidative food and beverages contain polyphenolic flavonoids or anthocyanosides [44]. These two molecules are capable of neutralising oxygen radicals either by donating a proton to the free radical or withdrawing an electron from the free radical. Polyphenols are present in most fruits and vegetables [44]. Chemically, a phenol is an organic compound consisting of a benzene ring with a hydroxyl (OH) group attached to one of the carbon atoms in the benzene ring. Polyphenols have more than just one hydroxyl group attached to the benzene ring. These molecules were initially used to modify the food's properties like colour, bitterness or flavour [45]. Polyphenols possess colour because they absorb light between 400-700 nm. They can absorb light because of the presence of the conjugated double bonds in the benzene ring creating a delocalized electron system. The colour reflected by the polyphenols depends on the number of conjugated double bonds in the structure [46].

Anthocyanins are a subclass of the polyphenol family [47]. Depending on their pH these water-soluble molecules possess the colours red, purple, blue or black. Chemically6these molecules consist of an aromatic benzene ring bonded to a heterocyclic ring that contains appositively charged oxygen atom which is also bonded to a third aromatic ring [48]. The positively charged oxygen atom in the central ring of the anthocyanin has the capacity to scavenge a free radical [49]. presence of conjugated double bonds, creating a delocalized electron system. The colour rejected depends on the number of conjugated bonds in the structure.

Carotenoids are pigments found in fruits and vegetables or plants, responsible for the yellow, orange and red colours [50]. They are classified into carotenes and xanthophylls [51]. Carotenes, such as β-carotene, are highly soluble in organic solvents and insoluble in polar solvents. In contrast, xanthophylls, for example lutein, are soluble in polar solvents and organic solvents [50].

Carotenoids have a wide range of functions in human health, being especially an antioxidant factor [52]. Human must ingest carotenoids because they cannot synthesize them. More than 650 different types exist in nature, but only 30-40 carotenoids have been found in human blood sample, with β-carotene and lutein being the most abundant [53].

β-carotene is a pro-vitamin A molecule. A lack of vitamin A can is a major public health problem in poor countries and can cause blindness or even death. It can mainly be found in carrots and sweet potatoes [54].

Lutein constitutes a macular pigment for the eye. It absorbs blue light (high energy, short wavelength light), protecting the eye against photochemical injuries and has antioxidant properties, such as neutralizing ROS or reducing the formation of lipofuscin, an insoluble pigment [55]. Thus, lutein provides benefits for ocular function as for example reduction of the progression of age-related macular degeneration and cataract [56].

Carotenoids also improve cognitive functions, cardiovascular health and prevent cancer. Therefore, a high intake in carotenoids rich food is recommended [53].

Reduction of oxidative stress at the level of mitochondria can be achieved by gingko biloba. Polyphenolic compounds, such as tea, dark chocolate, or coffee have antioxidative properties [57].

This can be achieved by gingko; dark chocolate; polyphenolic flavonoids occurring in tea, coffee; anthocyanosides found in bilberries; as well as by ubiquinone and melatonin [58].

In the next section we will describe some of the food's rich in the antioxidative molecules described above.

Examples of Dietary Sources of Polyphenols and Anthocyanosides Tea Culture

Tea, a traditional beverage originating from China, India, and Tibetan regions, has become one of the world's most popular drinks. Initially used for medicinal purposes by boiling fresh leaves in water, tea transformed into a daily beverage around the 3rd century, leading to the development of various cultural practices and processing methods. The Chinese first cultivated tea in Taiwan, and in response to this monopoly, the Dutch and British introduced tea cultivation to India. By the 20th century, the cultivation of tea had rapidly expanded to Europe, Africa, South America, and Australia.

Over the centuries, tea has inspired poets and artists, becoming increasingly prevalent and eventually iconic. It embodies culture and tradition, symbolizing hospitality, respect, and a respite from daily life's hustle. Additionally, tea holds spiritual significance, often associated with patience and mindfulness. In Asian countries, tea ceremonies are significant cultural events where tea is prepared and presented in various traditional methods. In the United Kingdom, tea serves as a social opportunity, a time for relaxation and companionship.

Polyphenols in Tea

To understand the benefits of tea on eye health, it is important to differ between green and black tea. Green tea is made from unoxidized tea leaves, so the tea preserves its natural green colour and has a higher polyphenolic content in comparison to black tea [59]. The minimal oxidation helps to preserve the natural polyphenols present in the leaves, which are catechins. Catechins include epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate (EGCG). Black tea undergoes full oxidation before drying, which turns the leaves dark and gives black tea its distinguished taste and colour [60]. Oxidation of the leaves of black tea causes the catechin content of black tea to decline as it is transformed into other substances, such as theaflavins and the arubigins. Black tea still contains polyphenols, but the overall content decreases due to oxidation process [61].

Antioxidants present in tea, particularly the catechins, may help protect the retina and reduce the risk of AMD. Tea consumption also improves blood flow and circulation. Tea also has anti-inflammatory properties that protects the eyes [62].

Coffee from Ethiopia to Europe

Coffee's intriguing history begins in Ethiopia, where, according to folklore, a goat herder named Kaldi noticed his goats displaying unusually high energy after consuming coffee beans. Curious, Kaldi tried the beans himself and experienced a significant increase in alertness. His discovery soon spread to the Arab world, leading to the cultivation of coffee plants and the establishment of coffee houses. These establishments quickly became hubs for socializing and intellectual exchange. By the 17th century, coffee had reached Europe, becoming a trendy drink among the elite. The 18th century saw the global expansion of coffee cultivation as European colonial powers set up plantations in tropical regions. Today, coffee is a staple of daily life for millions around the globe and remains one of the world's most popular commodities.

Polyphenols in Coffee

Coffee contains over 1500 chemicals, most of them are formed during the roasting process. The usual phenols are caffeine, chlorogenic acid and trigonelline. The state concentrations depend on the type of coffee; Chlorogenic acids are the most abundant polyphenol with a concentration between 4,8% and 6.41% of dry matter, caffeine represents from 1,4% to 2,2% and trigonelline is between 0,6%-1,7%. Caffeine and chlorogenic acids also act as antioxidants [63]. These antioxidant polyphenols contribute to oxidative stress prevention and enhance the production of nitric oxide (NO) by increasing endothelial nitric oxide synthase (eNOS) expression [64]. The enzyme eNOS is found in endothelial cells and is responsible for the production of NO. Polyphenols in coffee also promote NO bioavailability by protecting NO against breakdown by free radicals. All this leads the protection of endothelial cells and prevention of hypertension [65].

After coffee consumption, an antioxidant rise in human's plasma can be observed, along with a diminution of low-density lipoprotein (LDL) [66].

Moreover, coffee contains the molecule 3-methyl-1,2-cyclopentanedione (MCP) which is a selective scavenger of peroxynitrite (ONOO-), that plays a crucial role in the pathogenesis of glaucomatous optic neuropathy [67]. MCP can convert one of its carbonyl groups into a hydroxyl group, this chemistry enables MCP to give a proton to peroxynitrite to neutralize it. It has been shown that polyphenols in coffee protects mutagenicity and inhibit lipid peroxidation [68].

Coffee is a good antioxidant substance and has also neuroprotective properties, which are two mechanisms involved in some eye's diseases. Coffee can therefore be used as natural therapy; however, more studies are needed.

Chocolate Nectar of the Deities

In the dense tropical rainforests of Mesoamerica, more than 3000 years ago, early civilizations such as the Maya, Toltec, and Aztec engaged in the advanced cultivation of the Theobroma cacao, or cacao tree. These societies developed agronomic techniques to harness the botanical properties of cacao, from which they extracted beans to produce a potent, bitter beverage. The value attributed to these cacao beans was immense, serving not only as a staple in their diet but also as a fundamental unit of economic exchange.

The chemical composition of cacao beans, rich in flavonoids and other polyphenols, likely contributed to their revered status, perceived as imparting vitality and enhanced well-being. This reverence elevated chocolate to a sacred status, dubbed "the food of the gods" in these cultures. The ritualistic use of chocolate in ceremonial practices and its inclusion in the grave goods of the elite underscore its cultural and spiritual significance. As a result, cacao did not merely sustain the body; it played a crucial role in the social and religious fabric of these ancient societies, symbolizing wealth, health, and divine connection.

It was even customary for individuals to be buried with bowls of chocolate. Spain was the first European country to encounter chocolate, although the exact details of how it arrived remain unclear. Christopher Columbus brought cocoa beans back to Spain following his fourth voyage in 1502, although they were still a rarity. Later, the Aztec ruler of Mexico introduced Hernan Cortés, a Spanish conquistador, to a drink made from cocoa beans. Cortés conceived the idea of sweetening the bitter beverage with sugar, a practice he introduced to Spain. It took several years for chocolate to spread to other countries like France and England. As it moved across Europe, chocolate was enhanced with sugar and spices, adapting to local tastes. European methods of processing and preparation evolved, leading to the invention of solid chocolate bars and candies.

Polyphenols in Chocolate

Chocolate can be categorized into different types, with dark and white chocolate representing two distinct varieties. Dark chocolate has a higher cacao content compared to other types of chocolate, which gives it a rich and intense flavour. White and milk- chocolate have a higher sugar and fat content, but the flavonoid content is lower. Cacao powder contains up to approximately 50mg of polyphenols per gram and is particularly rich in catechins (flavan-3-ols) and procyanidins [69]. According to a study carried out in 'Lancet dark chocolate contained four times as much catechin as tea. The initial levels of flavonoids in the cacao bean can change during fermentation, drying, roasting and storage conditions. Chocolate flavonoids lower blood pressure, lower, total blood cholesterol, triglycerides and LDL-cholesterol and improve endothelium vasodilator responses [70]. Antioxidant effects of cacao may influence insulin resistance and reduce risk of diabetes, protecting the eye against diabetic retinopathy [71].

Ginkgo Biloba Icons of Hope, Strength and Resilience, Revered Across Cultures

The Ginkgo Biloba tree, among the most ancient of tree species still existing, originates from Japan, China, and Korea. It is renowned for its robustness and ability to adapt, flourishing in diverse soil conditions and climates. In a remarkable display of resilience, a Ginkgo tree survived the atomic devastation of Hiroshima in 1945. Despite severe damage to its leaves and branches, it did not die but sprouted new growth in subsequent years, becoming a symbol of hope and endurance.

For thousands of years, the leaves and fruit of the Ginkgo Biloba have been utilized for both culinary and medicinal purposes. In contemporary pharmacology, Ginkgo remains highly valued; its extracts are employed in preventing age-related ailments and addressing oxidative stress. Known for boosting cognitive functions and enhancing blood flow, Ginkgo Biloba continues to be an essential component in the field of health and wellness.

Polyphenols in Ginkgo

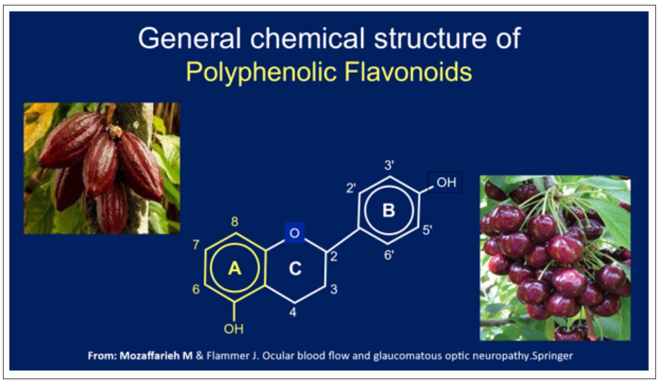
The Ginkgo Biloba Extract (GBE) consists of 60 bioactive compounds and the chemical composition can vary. Two major component groups are flavonoids (24-27%) with quercetin and kaempferol derivatives and terpenoids (5-7%) with ginkgolide [72].

The flavonoid glycosides give antioxidant properties to Ginkgo, especially at the mitochondrial level [73]. Mitochondria are particularly susceptible to oxidative stress because they are a primary source of free radical production, particularly the superoxide anion [74]. In comparison other antioxidants like Vitamin E or C, ginkgo flavonoids have the capacity to get to the inner mitochondrial membrane, making it an effective antioxidant at the mitochondrial level. The antioxidative effects of ginkgo have been shown in in- vitro where the extract was shown to reduce oxidative stress, in animal experiments where it was shown to provide a neuroprotective effect on retinal ganglion cells and in human glaucoma in which it reduced systemic oxidative stress as measured by comet assay analysis in the blood of glaucoma patients [75].

Bilberries and Blueberries the Star Berries of the Great Spirit

Along the Northeast Coast, some native American tribes believed that wild blueberries have a magical power and used these fruits for medicinal or ceremonial purposes. The tribes called blueberries ''star berries'' due to the five-pointed star shaped calyx and the fruits was known to have a deep connection with the "Great Spirit". Indeed, berries were seen as precious gifts that were sent during times of extreme need like a famine.

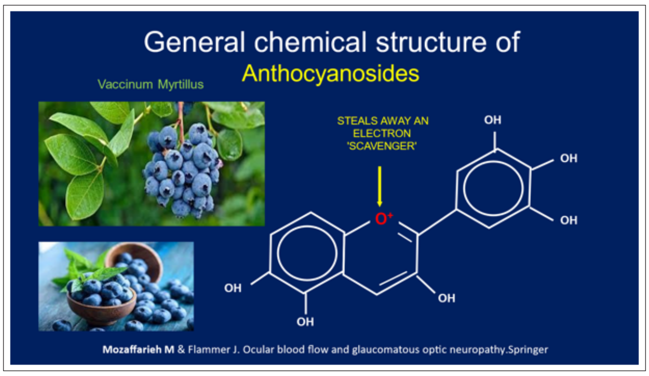
During World War 2, there was another belief about blueberries. It is said that pilots were eating a lot of blueberry jam to improve eyesight, especially night vision. Furthermore, blueberry jam played an important role in the survival kits issued to the pilots thanks to the nutritional content, the storage stability and the taste. These kits were designed to provide a mix of items that could sustain pilots until rescue or escape. In 2000, a double-blinded study found that there was no improvement in night vision between placebo and people taking bilberry extract. However, eating bilberry fruit containing a high content of anthocyanin seems to improve retina problems associated with high blood pressure or diabetes.



Anthocyanosides in Blueberries

Bilberries, as well as blueberries, are coloured foods and both are part of the genus Vaccinium. The main difference between the two is that the flesh of blueberries is green or white and the bilberries is dark red or purple [76]. As mentioned above, anthocyanins give dark red to purple colour to the fruit, and this explains why bilberries contain more anthocyanins [47]. Bilberries have 15 anthocyanins components, and this high content gives them strong free radical scavenging properties. The main anthocyanins are cyanidin and delphinidin [77].

Delphinidin may have a relaxing effect on the eye's ciliary muscle and would be useful to treat glaucoma, visual fatigue or pseudo-myopia [78]. This muscle controls lens focus, maintains ocular pressure and produces aqueous humor. Cyanidin can stimulate the rhodopsin regeneration, after being activated by the light absorption [79]. The rhodopsin triggers a cascade of biochemical reactions that lead to the generation of nerve impulses sent to the brain for visual perception [80].



Nigella Sativa

Most of the medicinal properties of Nigella sativa were explored previously as an orally provided nutritional or dietary supplement of ground seeds in tablet or capsule form, oil extract in soft gel capsules, or as an aqueous extract in different combinations of N. sativa powder or extract with other vitamins such as vitamin E, are commonly offered as black seeds extract or black cumin oil to enhance natural physiological and immunological defense [81].

Thymoquinone is a naturally occurring compound and is the major component of Nigella sativa, also known as black seed or black cumin. For centuries thymoquinone has been used especially in the Middle East traditionally to treat wounds, asthma, allergies, fever, headache, cough, hypertension, and diabetes. Studies have suggested beneficial effects of thymoquinone to be attributed to its antioxidant, antibacterial, anti-oxidative stress, anti-inflammatory, and neuroprotective properties [82]. Recently, there has been a surge of interest in thymoquinone as a treatment for neurodegeneration in the brain, such as that seen in Alzheimer's (AD) and Parkinson's diseases (PD). In vitro and in vivo studies on animal models of AD and PD suggest the main neuroprotective mechanisms are based on the ant—inflammatory and anti-oxidative properties of thymoquinone. Neurodegenerative conditions of the eye, such as Age-related Macular Degeneration (AMD) and glaucoma share at least in part similar mechanisms of neuronal cell death with those occurring in AD and PD. It has been shown a critically analyze the evidence to date of the effects and potential neuroprotective actions of thymoquinone in the eye and ocular neurodegenerations [83].

Polyphenols in Nigella Sativa

Although many studies have explored the bioactive compound content of Nigella sativa (black seed – BS) essential oil, data on the phenolic compound content in the extracts of Nigella sativa seeds gives inconclusive results [84].

In the intricate landscape of ocular health, the role of antioxidants, particularly polyphenols extracted from Nigella sativa, shines brightly as a beacon of hope. As our eyes navigate the inevitable journey of aging, they become increasingly vulnerable to oxidative stress—a process intricately linked to the onset and progression of various ocular pathologies such as glaucoma, diabetic retinopathy, and age-related macular degeneration [85].

Polyphenols, abundant in Nigella sativa, emerge as potent defenders against oxidative stress and its detrimental effects on ocular tissues. These bioactive compounds exhibit multifaceted functions, with antioxidant prowess standing at the forefront. By neutralizing harmful free radicals and reducing oxidative damage, polyphenols extracted from Nigella sativa act as guardians of ocular health, offering protection against cellular deterioration and degenerative eye conditions [86].

Furthermore, beyond their antioxidant role, polyphenols from Nigella sativa showcase immunomodulatory functions, orchestrating a harmonious balance within the immune system. This dual action—combating oxidative stress while bolstering immune defenses—positions polyphenols as formidable allies in the battle for ocular wellness.

As individuals seek proactive measures to safeguard their vision and promote eye health, knowledge of nutrients rich in antioxidants becomes paramount. Incorporating polyphenols extracted from Nigella sativa into one's diet or supplementation regimen offers a tangible pathway towards fortifying ocular defenses and mitigating the risk of sight-threatening conditions [87,81].

In essence, polyphenols from Nigella sativa stand as potent defenders of ocular vitality, harnessing the power of antioxidants and immunomodulation to nurture and protect the windows to our soul—our eyes. Embracing these natural wonders empowers individuals to take proactive steps towards preserving vision and embracing a future illuminated by the brilliance of healthy eyesight [88].

Anthocyanosides in Nigella Sativa

Although Nigella sativa may not be rich in anthocyanins, it boasts a diverse range of phytochemicals that offer substantial health benefits. Incorporating Nigella sativa into your diet or supplement routine can positively impact overall well-being and contribute to improved cardiovascular, ophthalmological, immune, and metabolic functions.

L-Methylfolate

The history of L-methylfolate and its connection to nutrition traces a fascinating journey through our evolving understanding of dietary impacts on health. Dating back to the early 20th century, scientists began to unravel the importance of folate, a B-vitamin found naturally in foods like leafy greens, legumes, and citrus fruits. Initially recognized for its role in preventing a type of anemia, folate's significance expanded as researchers delved deeper into its metabolic pathways.

In the mid-20th century, the discovery of folate's involvement in preventing neural tube defects during pregnancy marked a milestone in public health and prenatal care. This breakthrough spurred efforts to fortify foods like grains with synthetic folic acid, leading to significant reductions in birth defects worldwide.

However, it wasn't until more recent decades that scientists identified the critical role of L-methylfolate, the active form of folate, in various biochemical processes. As research advanced, it became evident that individuals with certain genetic variations had difficulty converting folic acid into its active form, L-methylfolate. This revelation prompted the development of L-methylfolate supplements, offering a more direct and effective means of ensuring folate adequacy, particularly for those with specific genetic predispositions or health conditions.

Moreover, the relationship between L-methylfolate and nutrition extends beyond basic folate metabolism.

In the realm of ocular diseases, the intricate interplay between nitric oxide (NO), homocysteine (Hcy), and endothelin assumes paramount importance. In the context of L-methylfolate, the interconnections elucidated by Park (2020) and Stanger (2003) offer insights into the intricate relationships involving nitric oxide

(NO), homocysteine (Hcy), and endothelin [89,90]. Researches have shown that these molecular players not only influence vascular function systemically but also play crucial roles in maintaining ocular health and homeostasis [91]. Studies have elucidated its influence on endothelial function and cardiovascular health, shedding light on the broader implications of folate status beyond its classical roles [92].

Additionally, Agron et al. (2021) conducted a retrospective analysis emphasizing the significance of various nutrients in age-related macular degeneration (AMD). Notably, 67% of participants in the Age-Related Eye Disease Study (AREDS) cohort were found to have consumed a multivitamin supplement containing B-vitamins, further emphasizing the relevance of B-vitamins, including L-methylfolate, in the management of AMD. This underscores the importance of comprehensive nutritional interventions, including supplementation with key nutrients such as L-methylfolate, in mitigating the risk and progression of AMD [93].

Today, L-methylfolate stands as a cornerstone in nutritional science, embodying the intricate interplay between genetics, diet, and health outcomes. Its journey from a simple vitamin to a sophisticated therapeutic tool underscores the ongoing quest to harness the power of nutrition for optimal well-being.

Final Words

Our eyes are susceptible to cellular damage induced by oxidative stress. Oxidative stress is an inevitable process within our bodies that increases as we age. An increased level of oxiditave stress is involved in the onset and progression of various ocular pathologies, including glaucoma, diabetic retinopathy or age-related macular degeneration. In general, a diet rich in antioxidants is beneficial in reducing levels of oxidative stress and reducing the risk of developing these diseases. For the most part a lot of individuals want to be able to do something positive by themselves to promote eye health and thus knowledge of nutrients rich in antioxidatns may be an efficient way for them to protect their ocular health.

References

1. Khoo HE, Suan Ng H, Yap WS, Goh HJ, Yim HS (2019) Nutrients for Prevention of Macular Degeneration and Eye-Related Diseases. Antioxidants (Basel) 8: 85.
2. Burton MJ, Ramke J, Marques AP, Bourne RRA, Congdon N, et al. (2021) The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. Lancet Glob Health 9: e489-e551.
3. Bissell M, Fetian I, Mozaffarieh M (2022) The Role of Oxidative Stress in the Pathogenesis of Eye Diseases. hb TIMES Schw Aerztej 6: 72-77.
4. Ivanov IV, Mappes T, Schaupp P, Lappe C, Wahl S (2018) Ultraviolet radiation oxidative stress affects eye health. J Biophotonics 11: e201700377.
5. Zhou Z, Song J, Nie M, Chen X (2016) Reactive oxygen species generating systems meeting challenges of photodynamic cancer therapy. Chemical Society Reviews 45: 6597-6626.
6. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O (2012) Oxidative stress and antioxidant defense. World Allergy Organ J 5: 9-19.
7. Gabriele Pizzino, Natasha Irrera, Mariapaola Cucinotta, Giovanni Pallio, Federica Mannino, et al. (2017) Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev 2017: 8416763.
8. Kruk J, Kubasik Kladna K, Aboul Enein HY (2015) The Role Oxidative Stress in the Pathogenesis of Eye Diseases: Current Status and a Dual Role of Physical Activity. Mini Rev Med Chem 16: 241-257.
9. Jun Wang, Mengling Li, Ziyue Geng, Saadullah Khattak, Xinying Ji, et al. (2022) Role of Oxidative Stress in Retinal Disease and the Early Intervention Strategies: A Review. Oxidative Medicine and Cellular Longevity 2022: 7836828.
10. Keshav Kooragayala, Norimoto Gotoh, Tiziana Cogliati, Jacob Nellissery, Talia R Kaden, et al. (2015) Quantification of Oxygen Consumption in Retina Ex Vivo Demonstrates Limited Reserve Capacity of Photoreceptor Mitochondria. Invest Ophthalmol Vis Sci 56: 8428-8436.
11. Masuda T, Shimazawa M, Hara H (2017) Retinal Diseases Associated with Oxidative Stress and the Effects of a Free Radical Scavenger (Edaravone). Oxid Med Cell Longev 2017: 9208489.
12. Mazzoni F, Safa H, Finnemann SC (2014) Understanding photoreceptor outer segment phagocytosis: use and utility of RPE cells in culture. Exp Eye Res 126: 51-60.
13. Hurley JB (2021) Retina Metabolism and Metabolism in the Pigmented Epithelium: A Busy Intersection. Annu Rev Vis Sci 7: 665-692.
14. Patrick T Johnson, Geoffrey P Lewis, Kevin C Talaga, Meghan N Brown, Peter J Kappel, et al. (2003) Drusen-Associated Degeneration in the Retina. Investigative Ophthalmology & Visual Science 44: 4481-4488.
15. John W Crabb, Masaru Miyagi, Xiaorong Gu, Karen Shadrach, Karen A West, et al. (2002) Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. Proc Natl Acad Sci USA 99: 14682-14687.
16. Zhongjie Fu, Timothy S Kern, Ann Hellström, Lois E H Smith (2021) Fatty acid oxidation and photoreceptor metabolic needs. J Lipid Res 62: 100035.
17. Armento A, Ueffing M, Clark SJ (2021) The complement system in age-related macular degeneration. Cellular and Molecular Life Sciences 78: 4487-4505.
18. Cameron D Haydinger, Genevieve F Oliver, Liam M Ashander, Justine R Smith (2023) Oxidative Stress and Its Regulation in Diabetic Retinopathy. Antioxidants (Basel) 12.
19. Carol Yimlui Cheung, M Kamran Ikram, Ronald Klein, Tien Yin Wong (2015) The clinical implications of recent studies on the structure and function of the retinal microvasculature in diabetes. Diabetologia 58: 871-885.
20. Melvin R Hayden, Ying Yang, Javad Habibi, Sarika V Bagree, James R Sowers (2010) Pericytopathy: oxidative stress and impaired cellular longevity in the pancreas and skeletal muscle in metabolic syndrome and type 2 diabetes. Oxid Med Cell Longev 3: 290-303.
21. Semeraro F, Cancarini A, dell'Omo R, Rezzola S, Romano MR, et al. (2015) Diabetic Retinopathy: Vascular and Inflammatory Disease. J Diabetes Res 582060.
22. Kalogeris T, Bao Y, Korthuis RJ (2014) Mitochondrial reactive oxygen species: a double edged sword in ischemia/reperfusion vs preconditioning. Redox Biol 2: 702-714.
23. Theodore Kalogeris, Christopher P Baines, Maike Krenz, Ronald J Korthuis (2012) Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol 298: 229-317.
24. Paweł Kowalczyk, Dorota Sulejczak, Patrycja Kleczkowska, Iwona Bukowska-Ośko, Marzena Kucia, et al. (2021) Mitochondrial Oxidative Stress-A Causative Factor and Therapeutic Target in Many Diseases. Int J Mol Sci 22: 13384.
25. Tsuji T, Murase T, Konishi Y, Inataniet M (2023) Optic Nerve Injury Enhanced Mitochondrial Fission and Increased Mitochondrial Density without Altering the Uniform Mitochondrial Distribution in the Unmyelinated Axons of

Retinal Ganglion Cells in a Mouse Model. Int J Mol Sci 24: 4356.

26. Ichinose T, S Habib (2022) ON and OFF Signaling Pathways in the Retina and the Visual System. Frontiers in ophthalmology 2: 989002.
27. Liu H, Prokosch V (2021) Energy Metabolism in the Inner Retina in Health and Glaucoma. Int J Mol Sci 2.
28. Tezel G (2006) Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. Prog Retin Eye Res 25: 490-513.
29. Dammak A, Pastrana C, Martin-Gil A, Carpena-Torres C, Cerda AP, et al. (2023) Oxidative Stress in the Anterior Ocular Diseases: Diagnostic and Treatment. Biomedicines 11: 292.
30. Hessen M, Akpek EK (2014) Dry eye: an inflammatory ocular disease. J Ophthalmic Vis Res 9: 240-250.
31. Seen S, Tong L (2018) Dry eye disease and oxidative stress. Acta Ophthalmol 96: e412-e420.
32. Shu DY, Chaudhary S, Cho KS, Lennikov A, Miller WP, et al. (2023) Role of Oxidative Stress in Ocular Diseases: A Balancing Act. Metabolites 13.
33. Chhadva P, Goldhardt R, Galor A (2017) Meibomian Gland Disease: The Role of Gland Dysfunction in Dry Eye Disease. Ophthalmology 124: S20-S26.
34. Sheppard JD, Nichols KK (2023) Dry Eye Disease Associated with Meibomian Gland Dysfunction: Focus on Tear Film Characteristics and the Therapeutic Landscape. Ophthalmol Ther 12: 1397-1418.
35. Lee J, Lee S, Zhang H, Hill MA, Zhang C, et al. (2017) Interaction of IL-6 and TNF-α contributes to endothelial dysfunction in type 2 diabetic mouse hearts. PLoS One 12: e0187189.
36. Glazier AN (2022) Proposed Role for Internal Lens Pressure as an Initiator of Age-Related Lens Protein Aggregation Diseases. Clin Ophthalmol 16: 2329-2340.
37. Sweeney P, Park H, Baumann M, Dunlop J, Frydman J, et al. (2017) Protein misfolding in neurodegenerative diseases: implications and strategies. Transl Neurodegener 6: 1-6.
38. Bloemendal H, Jong WD, Jaenicke R, Lubsen NH, Slingsby C, et al. (2004) Ageing and vision: structure, stability and function of lens crystallins. Progress in Biophysics and Molecular Biology 86: 407-485.
39. Norton-Baker B, Mehrabi P, Kwok AO, Roskamp KW, Rocha MA, et al. (2022) Deamidation of the human eye lens protein γS-crystallin accelerates oxidative aging. Structure 30: 763-776.
40. Giblin FJ (2000) Glutathione: a vital lens antioxidant. J Ocul Pharmacol Ther 16: 121-135.
41. Berthoud VM, Beyer EC (2009) Oxidative stress, lens gap junctions and cataracts. Antioxid Redox Signal 11: 339-353.
42. Vahedian Z, Ghasem Fakhraie, Jerome Bovet, Maneli Mozaffarieh (2017) Nutritional recommendations for individuals with Flammer syndrome. EPMA Journal 8: 187-195.
43. Lobo V, Patil A, Phatak A, Chandra N (2010) Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev 4: 118-126.
44. Hassanpour SH, Doroudi A (2023) Review of the antioxidant potential of flavonoids as a subgroup of polyphenols and partial substitute for synthetic antioxidants. Avicenna J Phytomed 13: 354-376.
45. Lin D, Mengshi Xiao, Jingjing Zhao, Zhuohao Li, Baoshan Xing (2016) An Overview of Plant Phenolic Compounds and Their Importance in Human Nutrition and Management of Type 2 Diabetes. Molecules 21: 1374.
46. Liu Y, Phil Kilby, Terry J Frankcombe, Timothy W Schmidt (2020) The electronic structure of benzene from a tiling of the correlated 126-dimensional wavefunction. Nat Commun 11: 1210.
47. Mattioli R, Antonio Francioso, Luciana Mosca, Paula Silva (2020) Anthocyanins: A Comprehensive Review of Their Chemical Properties and Health Effects on Cardiovascular and Neurodegenerative Diseases. Molecules 25: 3809.
48. Liu Y, Jiake Fan, Zhongqing Xue, Yajing Lu, Jinan Zhao (2022) Crystal Structure and Noncovalent Interactions of Heterocyclic Energetic Molecules. Molecules 27: 4969.
49. Mattioli R, Antonio Francioso, Luciana Mosca, Paula Silva (2020) Anthocyanins: A Comprehensive Review of Their Chemical Properties and Health Effects on Cardiovascular and Neurodegenerative Diseases. Molecules 25: 3809.
50. González Peña MA, Ana Eugenia Ortega-Regules, Cecilia Anaya de Parrodi, José Daniel Lozada-Ramírez (2023) Chemistry, Occurrence, Properties, Applications and Encapsulation of Carotenoids-A Review. Plants 12: 313.
51. Thomas SE, Johnson EJ (2018) Xanthophylls. Adv Nutr 9: 160-162.
52. Eggersdorfer M, Wyss A (2018) Carotenoids in human nutrition and health. Arch Biochem Biophys 652: 18-26.
53. Elvira Torales LI, García Alonso J, Periago Castón MJ (2019) Nutritional Importance of Carotenoids and Their Effect on Liver Health: A Review. Antioxidants (Basel) 8: 229.
54. Goodman DS (1984) Vitamin A and retinoids in health and disease. N Engl J Med 310: 1023-1031.
55. Koushan K, Raluca Rusovici, Wenhua Li, Lee R Ferguson, Kakarla V Chalam (2013) The role of lutein in eye-related disease. Nutrients 5: 1823-1839.
56. Buscemi S, Davide Corleo, Francesco Di Pace, Maria Letizia Petroni, Angela Satriano (2018) The Effect of Lutein on Eye and Extra-Eye Health. Nutrients 10: 1321.
57. Mozaffarieh M, Grieshaber MC, Orgül S, Flammer J (2008) The potential value of natural antioxidative treatment in glaucoma. Surv Ophthalmol 53: 479-505.
58. Mozaffarieh M, Flammer J (2007) Is there more to glaucoma treatment than lowering IOP? Surv Ophthalmol 52: 174-179.
59. Chacko SM, Priya T Thambi, Ramadasan Kuttan, Ikuo Nishigaki (2010) Beneficial effects of green tea: A literature review. Chinese Medicine 5: 13.
60. Farhan M (2022) Green Tea Catechins: Nature's Way of Preventing and Treating Cancer. Int J Mol Sci 23: 10713.
61. Buhailiqiemu Abudureheman, Xiaochun Yu, Dandan Fang, Henghui Zhang (2022) Enzymatic Oxidation of Tea Catechins and Its Mechanism. Molecules 27: 942.
62. Tsz Kin Ng, Kai on Chu, Chi Chiu Wang, Chi Pui Pang (2023) Green Tea Catechins as Therapeutic Antioxidants for Glaucoma Treatment. Antioxidants (Basel) 12.
63. Yamagata K (2018) Do Coffee Polyphenols Have a Preventive Action on Metabolic Syndrome Associated Endothelial Dysfunctions? An Assessment of the Current Evidence. Antioxidants 7: 26.
64. Serreli G, Deiana M (2023) Role of Dietary Polyphenols in the Activity and Expression of Nitric Oxide Synthases: A Review. Antioxidants (Basel) 12.
65. Li Q, Youn JY, Cai H (2015) Mechanisms and consequences of endothelial nitric oxide synthase dysfunction in hypertension. J Hypertens 33: 1128-1136.
66. Daniela Martini, Cristian Del Bo, Michele Tassotti, Patrizia Riso, Daniele Del Rio, et al. (2016) Coffee Consumption and Oxidative Stress: A Review of Human Intervention Studies. Molecules 21: 979.

67. Ae Ra Kim, Yani Zou, Hyung Suk Kim, Jae Sue Choi, Gregory Youngnam Chang, et al. (2002) Selective peroxynitrite scavenging activity of 3-methyl-1,2-cyclopentanedione from coffee extract. J Pharm Pharmacol 54: 1385-1392.
68. Roman Sirota, Shlomit Gorelik, Raviv Harris, Ron Kohen, Joseph Kanner (2013) Coffee polyphenols protect human plasma from postprandial carbonyl modifications. Mol Nutr Food Res 57: 916-919.
69. Katz DL, Doughty K, Ali A (2011) Cocoa and chocolate in human health and disease. Antioxid Redox Signal 15: 2779-2811.
70. Arts IC, Hollman PC, Kromhout D (1999) Chocolate as a source of tea flavonoids. Lancet 354: 488.
71. Ramos S, Martín MA, Goya L (2017) Effects of Cocoa Antioxidants in Type 2 Diabetes Mellitus. Antioxidants (Basel) 6.
72. Noor E Tabassum, Rajib Das, Mashia Subha Lami, Arka Jyoti Chakraborty, Saikat Mitra, et al. (2022) Ginkgo biloba: A Treasure of Functional Phytochemicals with Multimedicinal Applications. Evid Based Complement Alternat Med 2022: 8288818.
73. Priyanka Sati, Praveen Dhyani, Indra Dutt Bhatt, Anita Pandey (2019) Ginkgo biloba flavonoid glycosides in antimicrobial perspective with reference to extraction method. J Tradit Complement Med 9: 15-23.
74. Cui H, Kong Y, Zhang H (2012) Oxidative stress, mitochondrial dysfunction, and aging. J Signal Transduct 2012: 646354.
75. Pingal Pritam, Rahul Deka, Anuradha Bhardwaj, Rashi Srivastava,Dhruv Kumar, et al. (2022) Antioxidants in Alzheimer's Disease: Current Therapeutic Significance and Future Prospects. Biology 11: 212.
76. Tânia C S P Pires, Cristina Caleja, Celestino Santos-Buelga, Lillian Barros, Isabel C F R Ferreira (2020) Vaccinium myrtillus L. Fruits as a Novel Source of Phenolic Compounds with Health Benefits and Industrial Applications - A Review. Curr Pharm Des 26: 1917-1928.
77. Anja K Lätti, Laura Jaakola, Kaisu R Riihinen, Pirjo S Kainulainen (2010) Anthocyanin and flavonol variation in bog bilberries (Vaccinium uliginosum L.) in Finland. J Agric Food Chem 58: 427-433.
78. Nomi Y, Iwasaki Kurashige K, Matsumoto H (2019) Therapeutic Effects of Anthocyanins for Vision and Eye Health. Molecules 24.
79. Kiel JW, Hollingsworth M, Rao R, Chen M, Reitsamer HA (2011) Ciliary blood flow and aqueous humor production. Prog Retin Eye Res 30: 1-17.
80. Molday RS, Moritz OL (2015) Photoreceptors at a glance. J Cell Sci 128: 4039-4045.
81. Issa Rasheed Fetian, Issa D Fitian, Lukas Villiger, Maged Darwish (2021) Response to Nigella sativa in Patients with Confirmed and Suspected COVID-19. healthbook TIMES Das Schweizer Ärztejournal Journal des Médecins Suisses 1: 66-75.
82. Nur Musfirah Mahmud, Luminita Paraoan, Nurliza Khaliddin, Tengku Ain Kamalden (2022) Thymoquinone in Ocular Neurodegeneration: Modulation of Pathological Mechanisms via Multiple Pathways. Front Cell Neurosci 16: 786926.
83. Anela Topcagic, Sanja Cavar Zeljkovic, Erna Karalija, Semira Galijasevic, Emin Sofic (2017) Evaluation of phenolic profile, enzyme inhibitory and antimicrobial activities of Nigella sativa L. seed extracts. Bosn J Basic Med Sci 17: 286-294.
84. Faruque Ahmad, Fakhruddin Ali Ahmad, Syed Amir Ashraf, Hisham H Saad, Shadma Wahab, et al. (2021) An updated knowledge of Black seed (Nigella sativa Linn.): Review of phytochemical constituents and pharmacological properties. J Herb Med 25: 100404.
85. Mithun Rudrapal, Shubham J Khairnar, Johra Khan, Abdulaziz Bin Dukhyil, Mohammad Azam Ansari, et al. (2022) Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action. Front Pharmacol 13: 806470.
86. Klaudia Ciesielska Figlon, Karolina Wojciechowicz, Anna Wardowska, Katarzyna Aleksandra Lisowska (2023) The Immunomodulatory Effect of Nigella sativa. Antioxidants (Basel) 12: 1340.
87. Issa Rasheed Fetian, Issa D Fitian, Lukas Villiger, Maged Darwish (2020) Nigella Sativa Immunomodulatory Activity as a Potential Treatment of Novel Coronavirus (2019-nCoV) - A Review of Current Literature. TIMES Schw Aerztej 1: 58-65.
88. Burits M, Bucar F (2000) Antioxidant activity of Nigella sativa essential oil. Phytother Res 14: 323-328.
89. Ji Won Park, Barbora Piknova, Audrey Jenkins, David Hellinga, Leonard M Parver, et al. (2020) Potential roles of nitrate and nitrite in nitric oxide metabolism in the eye. Scientific Reports 10: 13166.
90. Stanger Olaf, Martin Weger (2003) Interactions of homocysteine, nitric oxide, folate and radicals in the progressively damaged endothelium. PMID 41: 1444-1454.
91. Brinks J, Dijk EHC van, Klaassen I, Schlingemann RO, Kielbasa SM, et al. (2022) Exploring the choroidal vascular labyrinth and its molecular and structural roles in health and disease. Progress in retinal and eye research 87: 100994.
92. Stanhewicz Anna E, Larry Kenney W (2017) Role of folic acid in nitric oxide bioavailability and vascular endothelial function. Nutrition reviews 75: 61-70.
93. Elvira Agrón, Julie Mares, Traci E Clemons, Anand Swaroop, Emily Y Chew, et al. Dietary nutrient intake and progression to late age-related macular degeneration in the age-related eye disease studies 1 and 2. Ophthalmology 128: 425-442.