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The Synergistic Role of Tea and Nigella Sativa in Ocular Health: Antioxidant Strategies Against Oxidative Stress

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ABSTRACT

Oxidative stress plays a pivotal role in the development and progression of major ocular diseases such as glaucoma, cataracts, and age-related macular degeneration (AMD), all of which contribute significantly to vision loss and blindness among the elderly. Addressing this pathogenic mechanism is critical for advancing preventive and therapeutic strategies. Among the array of natural antioxidants, tea (with a particular emphasis on green tea) and *Nigella sativa* (black seed) have emerged as highly promising due to their unique biochemical profiles and potent biological activities.

Green tea is especially noted for its rich content of polyphenolic flavonoids—including catechins such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin-3-Gallate (ECG), and Epigallocatechin-3-Gallate (EGCG). These bioactive molecules, preserved in high concentrations by the minimal oxidation processing of green tea, have demonstrated powerful antioxidant activity. The mechanisms by which these catechins combat oxidative stress are relevant for mitigating cellular and tissue damage within the ocular system.

Similarly, *Nigella sativa* is renowned for its major constituent, thymoquinone, which has been demonstrated to exert robust antioxidant, anti-inflammatory, and neuroprotective effects. These properties are particularly valuable in reducing ocular tissue injury and slowing the progression of degenerative eye diseases.

The significance of focusing on tea and *Nigella sativa* as antioxidant sources lies in their complementary mechanisms of action and their proven efficacy in reducing oxidative damage in various models. Together, these natural compounds present a synergistic and accessible dietary intervention for the prevention and management of vision-threatening ocular diseases linked to oxidative stress.

This review underscores the importance of leveraging the complementary mechanisms of tea and *Nigella sativa* in mitigating oxidative stress-related ocular pathologies and advocates for further research to explore their combined therapeutic efficacy.

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Introduction

The eyes, due to their constant exposure to light and high metabolic activity, are particularly susceptible to oxidative stress [1]. This oxidative burden plays a significant role in the pathogenesis of various ocular diseases, including glaucoma, diabetic retinopathy, and AMD [2]. Antioxidants, both endogenous and exogenous, are crucial in mitigating oxidative damage and slowing the progression of these diseases.

Tea, a widely consumed beverage, is rich in antioxidants, particularly polyphenols, which are found in abundance in coloured foods such as fruits and vegetables [3,4]. Tea contains three main classes of flavonoids: catechins (e.g., epigallocatechin-3-gallate, EGCG), oligomeric flavonoids, and flavonols [5]. These compounds exert protective effects by reducing oxidative stress, improving endothelial function and nitric oxide homeostasis, modulating inflammatory pathways, and enhancing ocular blood flow [6-10].

In addition to tea, *Nigella sativa* (black seed) has emerged as a potent natural antioxidant with significant ocular protective effects. Its bioactive compounds, including Thymoquinone (TQ), flavonoids, and saponins, exhibit strong anti-inflammatory, antioxidative, and neuroprotective properties [11]. Studies suggest that thymoquinone can mitigate retinal damage induced by oxidative stress, protect against vascular dysfunction in diabetic retinopathy, and reduce intraocular pressure in glaucoma by modulating oxidative stress markers and inflammatory pathways [12-14]. Furthermore, *Nigella sativa* has been shown to enhance retinal blood flow and improve endothelial function, which is crucial for maintaining healthy vision [15-17].

This review summarizes the beneficial effects of tea and *Nigella Sativa* consumption for ocular health, highlighting their potential synergistic role in reducing oxidative stress and slowing the progression of degenerative eye diseases.

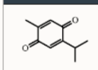
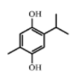
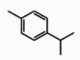
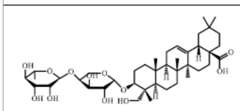
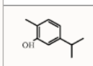
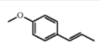
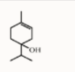
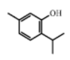
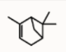
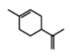
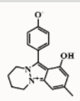
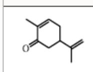
Historical Background

Tea, an ancient and fascinating beverage, has a past rich in mystery and tradition that has evolved through the centuries, from its uncertain roots in the Chinese, Tibetan, and Indian regions to becoming one of the world's most popular beverages [18]. The evolution of drinking tea started with the use of tea as a medicinal remedy up to its establishment as a national drink in China during the Tang dynasty [19]. During this same dynasty, a Buddhist monk described the types of tea, their preparation, mode of use, and benefits. The use of tea in traditional tea ceremonies also gave tea consumption a spiritual significance.

Over the centuries, tea inspired artists and poets during the Romantic Tea Era under the Song dynasty in China, while in Japan, it was introduced by Buddhist monks [20]. Matcha tea, the forerunner of the traditional Japanese tea ceremony, is the result of the method of tea preparation developed in Japan. Merchants, missionaries, and explorers between Europe and the East were the first to learn about tea traditions in China and Japan [21]. However, the marketing of tea in Europe came thanks to Dutch traders and later its adoption by the English nobility. The British East India Company played a key role in monopolizing the tea trade with China, thus helping to create the British Empire [22]. However, the fate of the company was influenced by events such as the Boston Tea Party and the tensions between the American colonies and England. India played a crucial role in changing the tea landscape, where many women workers were involved [23], following the discovery of tea plantations in Assam and Darjeeling (northeastern Indian region), which ended dependence on Chinese supplies.

Similarly, *Nigella sativa*, also known as black seed, has a long and rich history in traditional medicine and cultural practices. This plant has been used for thousands of years in ancient Egyptian, Greek, Indian, and Middle Eastern cultures as a natural remedy. Historical records indicate that *Nigella sativa* was found in the tomb of Pharaoh Tutankhamun, highlighting its medicinal value in ancient civilizations [24]. The therapeutic use of black seed oil has been documented across Persian, Indian, and Arab cultures, where it was traditionally used to support immune function, digestive health, and inflammatory conditions [25].

Table 1: Active components of Nigella sativa.

Visual	Name	Chemical formula	Exact mass	Molecular weight	m/z	Elemental Analysis
	Thymoquinone	C10H12O2	164,08	164,20	164.08 (100.0%), 165.09 (10.8%)	C, 73.15 H, 7.37 O, 19.49
	Thymohydroquinone	C10H14O2	166,10	166,22	166.10 (100.0%), 167.10 (10.8%)	C, 72.26 H, 8.49 O, 19.25
	P-Cymene	C10H14	134,11	134,22	134.11 (100.0%), 135.11 (10.8%)	C, 89.49 H, 10.51
	A-Hederin	C41H66O12	750,46	750,97	750.46 (100.0%), 751.46 (44.3%), 752.46 (9.6%), 752.46 (2.5%), 753.46 (1.1%)	C, 65.58 H, 8.86 O, 25.57
	Carvacol	C10H14O	150,10	150,22	150.10 (100.0%), 151.11 (10.8%)	C, 79.96 H, 9.39 O, 10.65
	Anethol	C10H12O	148,09	148,21	148.09 (100.0%), 149.09 (10.8%)	C, 81.04 H, 8.16 O, 10.80
	4-Terpineol	C10H18O	154,14	154,25	154.14 (100.0%), 155.14 (10.8%)	C, 77.87 H, 11.76 O, 10.37
	Thymol	C10H14O	150,10	150,22	150.10 (100.0%), 151.11 (10.8%)	C, 79.96 H, 9.39 O, 10.65
	Alpha-Pinene	C10H16	136,13	136,24	136.13 (100.0%), 137.13 (10.8%)	C, 88.16 H, 11.84
	Limonene	C10H16	136,13	136,24	136.13 (100.0%), 137.13 (10.8%)	C, 88.16 H, 11.84
	Nigellidine	C18H18N2O2	294,14	294,35	294.14 (100.0%), 295.14 (19.5%), 296.14 (1.8%)	C, 73.45 H, 6.16 N, 9.52 O, 10.87
	Carvone	C10H14O	150,10	150,22	150.10 (100.0%), 151.11 (10.8%)	C, 79.96 H, 9.39 O, 10.65

Adapted from Fetian et al. (2020) [17].

Today, both tea and *Nigella sativa* remain globally significant, valued not only for their cultural heritage but also for their health benefits. Tea is the world's most popular beverage after water, a global icon that unites cultures and traditions from every corner of the globe. Millions of people drink this beverage to mark special occasions, gather with loved ones, or demonstrate hospitality. Similarly, *Nigella sativa* is widely consumed for its medicinal properties, often incorporated into traditional diets and herbal remedies.

Drinking tea is a way to relax, unwind, and connect with others, while *Nigella sativa* is recognized for its potential health-boosting properties, particularly its antioxidative and anti-inflammatory effects. The key molecules in tea contributing to these positive effects are the so-called polyphenols, while in *Nigella sativa*, the active compound thymoquinone plays a major role. These compounds, and their benefits, will be discussed below.

Bioactive Components

Tea is a beverage rich in bioactive components that contribute significantly to its health benefits [26]. These components include polyphenols, pigments, polysaccharides, amino acids, saponins and caffeine, each of which offers different benefits for our well-being.

Polyphenols, in particular catechins such as Epicatechin (EC), Gallocatechin (GC), epigallocatechin (EGC), Epicatechin Gallate (ECG), Gallocatechin Gallate (GCG) and Epigallocatechin Gallate (EGCG) , are among the most important natural antioxidant molecules [27].

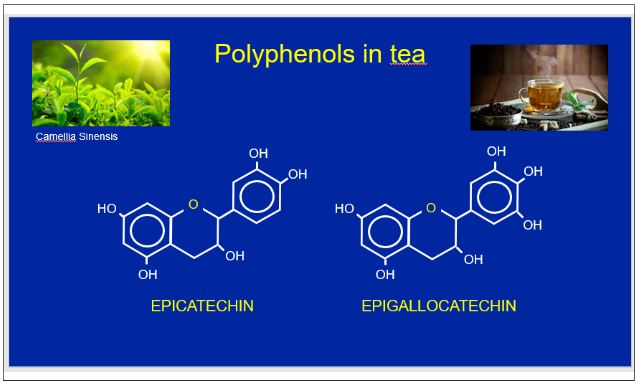


Figure 1: Polyphenols in Tea

Their antioxidant properties in the body makes them a valuable resource in preventing chronic diseases and preventing premature ageing [28]. The pigments formed during oxidation of tea are also responsible for many of the beneficial properties of this beverage. These pigments have been shown to have anti-inflammatory, anti-cancer and antioxidant effects, thus contributing to the promotion of general health.

Polysaccharides in tea can improve digestion, support the immune system and they have some antioxidant properties, while amino acids, for example L-theanine, can have a calming effect on the nervous system, improving concentration and mood [29-31]. This may explain why tea is often associated with a relaxing effect, despite also containing caffeine.

The saponins in tea have anti-inflammatory and antioxidant properties, thus contributing to the overall health of the body. Finally, caffeine is the most well-known alkaloid present in tea, albeit in smaller quantities than in coffee. Caffeine has a stimulating effect on the nervous system, increasing alertness and energy [32,33]. It is important to note that the exact content of all the above-mentioned molecules may vary between different types of tea. The bioavailability of these molecules can be influenced by several factors, including the method of tea preparation, the type of tea used and the time of day at which it is consumed [34].

Polyphenols as Antioxidants

Free radicals are autonomous molecules or ions that have one or more unpaired electrons. These molecules are formed through metabolic processes within the body's cells [35]. Biological free radicals are extremely unstable and contain electrons available to react with various organic substances such as lipids, proteins and DNA. These free radicals are responsible for a phenomenon known as oxidative stress [36], which can cause damage to cell structures and is associated with numerous degenerative diseases, ageing and even cancerous mutations. Several processes can generate free radicals, including smoking, exposure to ultraviolet radiation, stress, alcohol consumption and many others. To counteract the damaging effects of free radicals, our body has a category of molecules called antioxidants. These antioxidants can be of two types: endogenous, produced by our body, as glutathione, or exogenous, obtained through food, such as vitamins A, C and E [37]. Antioxidants can neutralize excess free radicals by donating a proton or capturing an electron.

A particularly beneficial group of natural antioxidants found in a variety of plants and fruits including tea are polyphenols. These compounds are divided into three main categories according to their structure: simple phenols, tannins and flavonoids [38]. In addition to their antioxidant action, polyphenols play important roles as anticarcinogenic, anti-inflammatory and antibacterial agents [39].

Chemically, polyphenols are molecules consisting of condensed phenolic cycles, which are organic compounds containing one or more hydroxyl (OH) groups linked to an aromatic ring. The hydroxyls group present in polyphenols can donate a proton to free radicals, thus contributing to their neutralization [35].

Differences Between Green and Black Tea

All the different qualities of tea derived from the same plant the camellia sinensis. What determines the properties such as color, flavor and other qualities of tea is the way of processing it. The different fermentation process between green and black tea significantly changes the visual appearance, chemical composition and aroma of the tea [40].

Black tea leaves must wither, roll, and completely oxidize for a long period before being dried. The result of oxidation is what makes the leaves dark and creates its characteristic flavor [29]. Instead, green tea leaves are heated to block oxidation enzymes.

After steaming, the leaves are dried and rolled, making them soft and thin.

Due to this fermentation process of green tea, in which oxidation is blocked, its antioxidant properties are maintained in comparison to black tea [41]. Green tea is kept in a low-oxidized state at high temperatures, preserving the green leaves. On the other hand, black tea undergoes a long oxidation process, which gives it its characteristic dark brown or black color [42]. This degree of oxidation also has a significant impact on flavor, with a higher degree of oxidation producing a more intense and bitter taste, while green tea retains a more natural and lighter flavor.

Fermentation of tea also plays a very important role in its chemical composition, especially in polyphenol and caffeine concentration. The greater the degree of oxidation of the leaves, the lower the polyphenol content and the higher the caffeine content [43]. A cup of green tea contains a lower amount of caffeine than black tea. These amounts can also vary depending on the brewing time of the tea bag: the longer it is left to steep, the higher the caffeine content [44]. The predominant and most active polyphenol in green tea is epigallocatechin gallate [45]. while black tea contains a higher amount of theaflavins which promote cognitive function of the brain, and give black tea a distinctive reddish color [46].

Many studies show that drinking green tea is beneficial for many diseases in which oxidative stress plays a role. Diseases in which drinking tea might be beneficial include cardiovascular diseases, inflammatory syndromes, glaucoma, diabetic retinopathy or MS [27]. This topic will be discussed in more detail below.

Oxidative Stress in Ocular Diseases

What is Oxidative Stress

Metabolic processes that generate energy at the cellular level employ oxygen as the main oxidizing agent. However, this mechanism can result in the production of reactive oxygen species (ROS). Oxidative stress is a phenomenon that occurs in the body when there is an imbalance between the generation of free radicals and the biological system's ability to counteract them through defense mechanisms, such as antioxidants [35]. An excess of oxidants, in the form of free radicals, can cause damage at the macromolecular level, involving proteins, sugars, lipids and DNA, with serious consequences for cell survival and functioning.

Examples of Ocular Diseases Associated with Oxidative Stress

The eye is an organ that is particularly exposed to oxidative stress. The cornea is a transparent layer of avascular tissue with a protective function. Corneal epithelial cells are constantly exposed to high concentrations of oxygen and UV radiation and thus exposed to higher levels of oxidative stress leading to changes in corneal optical properties [47]. Oxidative stress plays a significant role in the pathogenesis of some anterior eye diseases, such as dry eye [48]. This inflammatory condition is characterized by an altered tear film, resulting in dry eye, discomfort, pain and tear film instability. eye patients. ROS can also lead to dysfunction of the lacrimal and meibomian glands; this dysfunction is a key factor in the pathogenesis of dry eye, causing increased inflammation (IL-6 and TNF-a) and infiltration of leukocytes within the glands [49].

The eye's crystalline lens, which is transparent, encapsulated and avascular, forms a natural barrier against oxidative stress. It is composed mainly of proteins called crystallin's that have a regular, soluble arrangement, forming a transparent structure that allows light to pass through and the refractive index to increase. The crystalline contains numerous antioxidants, such as glutathione, to counterbalance the oxidizing power of certain molecules [50]. Changes related to age, radiation exposure and increased oxidative stress can alter crystalline proteins, causing them to aggregate and leading to opacification of the lens and formation of cataracts [51].

One of the most common inflammations of the eye is uveitis, which can occur with varying degrees of severity. Oxidative stress can enhance uveitis by amplifying inflammation

thereby causing clinical and histologic expression of uveitis in the form of inflammatory cell infiltration [52]. In the tissues of the anterior uvea of patients suffering from uveitis high levels of hydrogen peroxide were measured [53]. Our bodies have defense systems in the form of enzymes and non-enzymatic reactions such as catalase 2 and glutathione peroxidase in the iris and ciliary body to neutralize free radicals as hydrogen peroxide [54]. Up to some degree neutralization of free radicals occurs, however if the concentration of the oxidants overcomes the antioxidant capacity can lead to the disease uveitis. Hydrogen peroxide increases lipid peroxidation in iris epithelium cell membranes which alters release of neurotransmitters from central and peripheral nerve [55].

The retina performs a major mitochondrial function. Together with the retinal ganglion cells (RGCs) and the optic nerve, it requires a considerable supply of oxygen to support its metabolic activities. These regions are extremely sensitive to oxidative stress. RGCs are the neuronal cells responsible for the transformation of visual signals into neural signals and subsequent transmission to the brain via the optic nerve. In glaucoma patients, there is a characteristic loss of RGCs and their axons, resulting in a diminished visual field. Oxidative stress, combined with increased ocular pressure and altered trabecular network, is a major cause of RGC loss [56].

As previously mentioned, the oxygen supply to the retina is carefully regulated, with the photoreceptors using more than half of the available oxygen. The retinal microenvironment is particularly susceptible to oxidative damage due to its high oxygen consumption, exposure to visible light, and various other factors [57]. With advancing age and decreasing antioxidant capacity, a compromised retinal microenvironment develops, which can lead to age-related macular degeneration (AMD). AMD is a major cause of blindness in Western countries [58], characterized by the loss of retinal pigment epithelial (RPE) cells and photoreceptors in the macula. RPE cells are essential for photoreceptor function and are responsible for transporting waste across Bruchs' membrane to the choroid for elimination. Another feature of AMD are drusen, deposits of lipid material under the retina, which further confirms the change in oxidation, in this case, of fatty acids [59].

The progression of diabetic retinopathy can be promoted by free radicals. Hyperglycemia can cause an increase in ROS, leading to microvascular complications [60]. Furthermore, high glucose levels can activate polyol metabolism, reducing antioxidant levels [61]. These processes, together with hyperglycemia, create a proinflammatory environment. Such changes may contribute to impaired blood flow, loss of intercellular junctions, and increased vessel permeability, thus contributing to diabetic retinopathy [62,63]. The above examples of some of the main ocular diseases associated with oxidative stress.

Mechanisms of Action of Tea and *Nigella Sativa* in Ocular Health

The protective effects of tea and *Nigella sativa* in ocular health are primarily mediated through their antioxidant and anti-inflammatory properties.

Tea

- **Antioxidant Activity:** The polyphenols in tea, particularly EGCG, neutralize ROS and reduce oxidative damage to ocular tissues [6,7].
- **Anti-Inflammatory Effects:** Tea polyphenols modulate inflammatory pathways, reducing the production of pro-inflammatory cytokines and chemokines [9].
- **Neuroprotection:** EGCG has been shown to protect retinal ganglion cells from oxidative stress-induced apoptosis, which is particularly relevant in glaucoma [56].

- **Vascular Protection:** Tea improves endothelial function and nitric oxide bioavailability, enhancing ocular blood flow and reducing the risk of vascular-related eye diseases [8,10].

Nigella Sativa
- **Antioxidant Activity:** Thymoquinone, the primary bioactive compound in *Nigella sativa*, scavenges free radicals and enhances the activity of endogenous antioxidant enzymes [63].
- **Anti-Inflammatory Effects:** Thymoquinone inhibits the production of pro-inflammatory mediators, such as TNF-α and IL-6, reducing inflammation in ocular tissues [13].
- **Neuroprotection:** Thymoquinone protects retinal neurons from oxidative stress and inflammation, making it a potential therapeutic agent for neurodegenerative eye diseases [14].
- **Vascular Protection:** *Nigella sativa* improves endothelial function and reduces vascular permeability, which is beneficial in diabetic retinopathy and other vascular-related eye conditions [15-17].

Synergistic Effects of Tea and *Nigella Sativa*
The combination of tea and *Nigella sativa* offers a synergistic potential in combating oxidative stress and inflammation in ocular tissues. The complementary mechanisms of action of these natural compounds enhance their overall efficacy in protecting against oxidative stress-related eye diseases.

Enhanced Antioxidant Capacity: The polyphenols in tea and thymoquinone in *Nigella sativa* work together to neutralize a broader spectrum of free radicals, providing comprehensive protection against oxidative damage.

Reduced Inflammation: The anti-inflammatory properties of both compounds synergistically reduce the production of pro-inflammatory cytokines and chemokines, mitigating inflammation in ocular tissues.

Improved Neuroprotection: The neuroprotective effects of EGCG and thymoquinone complement each other, providing enhanced protection for retinal neurons and optic nerve cells.

Vascular Support: The combined effects of tea and *Nigella sativa* on endothelial function and nitric oxide bioavailability improve ocular blood flow, reducing the risk of vascular-related eye diseases.

Clinical Implications and Future Directions
The findings of this review have significant clinical implications for the prevention and management of oxidative stress-related ocular diseases. The incorporation of tea and *Nigella sativa* into the diet may serve as a cost-effective and accessible strategy to promote ocular health and reduce the risk of vision loss.

However, further research is needed to fully elucidate the therapeutic potential of these natural compounds. Future studies should focus on:
- **Clinical Trials:** Conducting randomized controlled trials to evaluate the efficacy of tea and *Nigella sativa* in preventing and treating ocular diseases.
- **Mechanistic Studies:** Investigating the molecular mechanisms underlying the synergistic effects of tea and *Nigella sativa* in ocular tissues.
- **Dosage and Formulation:** Optimizing the dosage and formulation of tea and *Nigella sativa* for maximum therapeutic benefit.
- **Long-Term Effects:** Assessing the long-term effects of tea and *Nigella sativa* consumption on ocular health and disease progression.

Conclusion
This review highlights the potential benefits of green tea and *Nigella sativa* in promoting ocular health by combating oxidative stress. Green tea, with its high polyphenolic content, offers potent antioxidant properties that can mitigate cellular damage in the eye. Similarly, *Nigella sativa* and its bioactive compound thymoquinone exhibit strong antioxidative, anti-inflammatory, and neuroprotective effects.

The synergistic potential of these natural compounds presents a promising dietary strategy for the prevention and management of oxidative stress-related ocular diseases, such as glaucoma, cataracts, and AMD. However, further research is needed to fully elucidate their combined therapeutic efficacy and optimize their use in clinical settings.

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IRB approval is not required for review articles. The authors confirm that any aspect of the work covered in this manuscript was performed in accordance with the Declaration of Helsinki.

Informed Consent Statement
Not applicable.

Data Availability Statement
The data supporting the findings of this study are openly available in the Supplementary Material.

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Conflicts of Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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