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IP International Journal of Ocular Oncology and Oculoplasty

Journal homepage: https://ijooo.org/

Editorial

Oxidative stress and antioxidants in ocular disorders

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ARTICLE INFO

Article history:
Received 10-04-2024
Accepted 27-04-2024
Available online 03-05-2024

Free radicals are generated during physiological oxidation-reduction reactions being carried out in the powerhouse of cell-mitochondria and endoplasmic reticulum. These free radicals contain unpaired electrons which together with electrophilic molecules are known as reactive oxygen species (ROS) and reactive nitrogen species (RNS).[1,2] Endogenous sources of ROS

are produced as byproducts of various metabolic processes and enzymes: Xanthine oxidase (XO) generates superoxide and hydrogen peroxide (H_2O_2) when oxidizing xanthine to uric acid.[3] Endothelial nitric oxide synthase (eNOS), when uncoupled during endothelial dysfunction, generates superoxide instead of nitric oxide.

Cyclooxygenases (COX), Phospholipase A2, Lipoxygenase, and Cytochrome P450 also contribute to ROS production. ROS are also closely linked to inflammation, where immune cells generate excessive ROS to combat pathogens, potentially exacerbating inflammation and tissue damage.[4–6] Exogenous Sources of ROS are air pollution, tobacco smoke and ultraviolet (UV) radiation etc.[7–10]

To counteract the harmful effects of ROS body has antioxidant defense system in place which consists of enzymes like superoxide dismutase (SOD), catalase (CAT), heme oxygenase (HO) and glutathione peroxidase (GPX). Some non-enzymatic scavengers are vitamin E, vitamin C, and glutathione (GSH).[11] Imbalance between generation of these free radicals and their neutralization by antioxidants leads to oxidative stress. Thus causing damage to various components of the cell by ROS. It causes modification of proteins, lipids and DNA. ROS react with DNA molecules causing oxidation of bases and deoxyribose which causes base modification, rearrangement of DNA sequences, miscoding of DNA, gene duplications or activation of oncogenes. These processes are responsible for carcinogenesis and various other pathologies.[12]

Ocular system with high metabolic activity and permanent exposure to light is extremely susceptible to oxidative stress. It is proposed to be involved in etiopathogenesis of various ocular pathologies like dry eye, pterygium, cataract, keratoconus, Fuchs endothelial corneal dystrophy, diabetic retinopathy, age related macular degeneration, retinal vein occlusion, retinopathy of prematurity and ocular malignancies etc.[13,14]

1. Dry Eye Diseases

It is a multifactorial disorder. Oxidative stress has a major contribution to its development and progression. A meta-analysis revealed that patients with Dry Eye Disease (DED) tend to have higher levels of oxidative stress markers in their tear fluid and conjunctival specimens, indicating a significant link between oxidative stress and DED. The oxidative stress markers that were found to be elevated include lipid peroxide, myeloperoxidase, nitric oxide (NO) synthase, xanthine oxidase/oxidoreductase, 4-HNE, and

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https://doi.org/10.18231/j.ijooo.2024.001

malondialdehyde (MDA). These markers suggest increased lipid oxidation, ROS production, and oxidative damage in DED.[15]

Furthermore, the study noted that patients with DED exhibit impaired antioxidant functions. In particular, the expression of key antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD) was reduced in conjunctival epithelial cells compared to healthy controls.[16] This reduced expression of antioxidant enzymes suggests that DED may involve not only an increase in oxidative stress but also a decreased capacity to neutralize ROS, potentially contributing to the disease's progression and severity. Aging is one of the risk factors for DEDs which causes an increase in oxidative stress due to declining antioxidant defense mechanism.

ROS induce inflammatory cytokines such as IL-1, IL-6 and TNF-alpha which are responsible for DED. These levels correlate with disease severity.[17–19]

Decreased levels of SOD expression with elevated oxidative stress markers were noted in mice with meibomian gland dysfunction which is major factor behind tear film instability.[20]

Oxidative damage to lacrimal gland has also been proposed for the etiopathogenesis of DED.

Therapeutic approach to manage oxidative stress in DED is by giving antioxidants like vitamin A and E, and coenzyme Q10 topically in the form of tear substitutes.[21] Lactoferrin was also found to have a beneficial role in treatment of DED.[22] Iodide iontophoresis uses electrical current to drive iodide ions into body tissues. This technique has been applied to the eye to increase the antioxidant capacity of tear fluid, potentially benefiting patients with DED. Studies suggest that it can improve symptoms, tear film stability, and reduce morphological changes in DED patients. However, its use is limited by the potential cytotoxic effects of iodide on corneal epithelial and endothelial cells.[23–25]

2. Pterygium

Oxidative stress due to phototoxic effects of UV radiation plays a crucial role in pathogenesis of pterygium. Significant higher levels of oxidative DNA damage marker 8-OHdG were found in pterygium specimens.[26]

Antioxidants have been identified as a potential therapeutic tool for treating pterygium. Phenolic compounds, such as flavonoids, carotenoids, curcumin, ellagic acid, and chalcones, are known for their anti-inflammatory and antioxidate properties.[27] Curcumin, in particular, has shown promising results in reducing the proliferation of pterygium fibroblasts.[28] Other therapeutic strategies focus on targeting ROS-related pathways and signaling molecules that contribute to pterygium. For instance, bevacizumab, a recombinant humanized anti-VEGF antibody, is used in perioperative subconjunctival injections to lower the recurrence rate of pterygium.[29–31] Additionally, cyclosporine A, an immunosuppressive agent, has demonstrated the ability to suppress cell migration and reduce the expression of MMP-3 and MMP-13, resulting in fewer recurrences when used as an adjuvant with pterygium excision.[32]

3. Keratoconus

In a meta-analysis by Navel et al, a marked decrease in antioxidant levels was noted in keratoconus patients. Increased levels of proinflammatory cytokines like IL-6, TNF-alpha and MMP were seen. This imbalance leads to keratocyte apoptosis and changes in the corneal extra cellular matrix leading to disease progression.[33] Flavonoids have shown to protect against UV rays induced stress. Lactoferrin loaded contact lenses are also one of the therapeutic options available. Vitamin D supplementation helps in reduction of inflammation and oxidative stress.[34,35]

4. Cataract

The ongoing metabolic processes in lens lead to formation of reactive oxygen species (ROS), which may harm lens cells and increase the risk of cataracts. Additionally, sunlight exposure can lead to ROS formation through photoexcitation, where absorbed light shifts from a photoexcited singlet state to an excited triplet state, causing ROS generation.[36]

To counteract these harmful effects, the lens employs several antioxidants and protective mechanisms. Glutathione peroxidase and catalase neutralize hydrogen peroxide and lipid peroxide, reducing oxidative stress. Superoxide dismutase (SOD) converts superoxide radicals into less harmful substances, and ascorbate (vitamin C) in the lens's outer layers neutralizes superoxide, peroxide, and hydroxyl ions while also scavenging singlet oxygen and thiol radicals.

Additionally, the lens has natural protection against ultraviolet (UV) radiation through aromatic amino acids like tryptophan, fluorophores, and 3-hydroxykynurenine, which absorb and filter UV rays, preventing UV-induced damage.[37] These antioxidants and protective mechanisms help maintain the clarity and health of the lens by reducing oxidative stress and minimizing the effects of ROS. Supplementation of vitamin E, lutein, zeaxanthin or carotenoids is related to reduced risk for age-related cataract.

5. Age Related Macular Degeneration

Excessive production of reactive oxygen species (ROS) can activate cellular signaling pathways that drive inflammation and other harmful effects. ROS can stimulate the mitogen-activated protein kinases (MAPKs) and nuclear factor

kappa B (NF-κB) pathways, leading to higher levels of inflammatory cytokines like interleukin-1 beta (IL-1β), interleukin-18 (IL-18), and tumor necrosis factor alpha (TNF-α). This is mediated through the NLRP3 inflammasome and caspase-1 [38]. ROS also influence angiogenesis by increasing vascular endothelial growth factor (VEGF) via hypoxia-inducible factor alpha (HIF-α). Higher VEGF levels can cause abnormal blood vessel growth and choroidal vascular dysfunction. Additionally, ROS can reduce nitric oxide (NO) levels, diminishing its vasoprotective role, which further contributes to vascular problems. [39]

Anti VEGF therapy has shown to have major role in its treatment. Lutein and zeaxanthin are well-known carotenoids that support eye health, particularly in reducing the risk of age-related macular degeneration (AMD). The Age-Related Eye Disease Study (AREDS) showed that daily supplementation could help slow AMD progression. The supplement regimen consisted of a combination of vitamin C, vitamin E, cupric oxide, zinc, and beta-carotene, which are antioxidants that protect against oxidative stress. This combination was found to be effective in reducing the risk of AMD progression in the study's participants. Novel treatment targeting P62 and Nrf2 have shown beneficial effects. [40,41]

6. Ocular Malignancies

Cancer is a complex process with three main stages: initiation, promotion, and progression. Oxidative stress, caused by an imbalance of reactive oxygen species (ROS) and antioxidants, plays a role in all three stages. In the initiation stage, ROS can damage DNA, leading to gene mutations and structural changes that initiate cancer development. During the promotion stage, ROS may disrupt gene expression, cell-to-cell communication, and second messenger systems, leading to increased cell proliferation and decreased apoptosis, encouraging the growth of initiated cells. In the progression stage, oxidative stress can cause further DNA alterations and genomic instability, promoting more aggressive tumor characteristics and the potential for metastasis.

This interaction with oxidative stress across all stages underscores its role in cancer development and progression, indicating the importance of maintaining a healthy balance between ROS and antioxidants to help mitigate cancer risk. [42,43]

Antioxidants have gained significant interest in cancer therapy due to their ability to neutralize oxidizing free radicals, which helps prevent cellular damage during chemotherapy. The use of antioxidants in chemotherapy aims to protect normal tissues from oxidative damage without negatively impacting the effectiveness of tumor-targeting treatments. Research on antioxidant supplementation during chemotherapy has shown that there are two approaches to using antioxidants in cancer therapy. (i) Preventive low doses protect both normal and tumor cells from oxidative damage, potentially reducing side effects without impacting chemotherapy outcomes. (ii) Therapeutic high doses of antioxidants can inhibit the growth of cancer cells while sparing normal cells, contributing to enhanced cancer treatment. Recent reviews have highlighted the following benefits of administering antioxidants alongside chemotherapy:

Antioxidants at specific doses do not disrupt the efficacy of chemotherapy in targeting cancer cells. Improved cytotoxic effects: Antioxidants can enhance the destructive effects of chemotherapy on cancer cells while providing a protective barrier for normal tissues. This can lead to increased patient survival and better therapeutic responses. [44]

Overall, the integration of antioxidants into cancer therapy shows promise for reducing chemotherapy-induced damage to normal tissues and potentially improving cancer treatment outcomes. However, further research is needed to understand the optimal types and doses of antioxidants for safe and effective use in cancer therapy.

Various studies have investigated potential therapeutic agents to combat oxidative stress in ocular diseases, with a focus on antioxidants and other related compounds. Antioxidant supplementation, such as with vitamins A and E, has been examined in numerous studies, but the results have been contradictory. This inconsistency suggests that while antioxidants can play a role in reducing oxidative stress, their effectiveness may depend on specific conditions or individual responses.

One promising agent in this field is idebenone, a synthetic analogue of Coenzyme Q_{10} (CoQ_{10}). Approved by the European Medicine Agency (EMA) in 2015, idebenone is the only disease-specific medication for Leber's Hereditary Optic Neuropathy (LHON), a genetic condition leading to vision loss. Its approval represents a significant advancement in targeted treatments for specific ocular diseases related to oxidative stress.

Another key area of interest involves the Nrf2 (Nuclear factor erythroid 2-related factor 2) pathway. Nrf2 is a crucial transcription factor that regulates antioxidant enzyme expression, playing an essential role in cellular defense against oxidative stress. Disturbances in Nrf2 function have been implicated in several ocular diseases, making the modulation of this pathway a promising therapeutic approach. By enhancing Nrf2 activity, it may be possible to increase the body's natural antioxidant defense mechanisms, thereby reducing oxidative stress-related damage in the eye. [45]

Despite these promising leads, it's important to note that while experimental studies have yielded encouraging results, comprehensive clinical trials are necessary to confirm the safety and effectiveness of these therapeutic

approaches. These studies are crucial to determining the appropriate dosages, long-term effects, and specific applications for different ocular diseases influenced by oxidative stress.

7. Conflict of Interest

None.

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Cite this article: Maurya RP, Tiwari K. Oxidative stress and antioxidants in ocular disorders. *IP Int J Ocul Oncol Oculoplasty* 2024;10(1):1-5.