Review Article

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Plant Derived Antioxidants and Their Protective Action on Ultraviolet-induced Corneal Injury: A Narrative Review

Biochemistry Section

K DEEKSHA[1], RAHIMA BANU[2]

ABSTRACT

Cornea acts as the first line of primary defense against various harmful effects of Ultraviolet (UV) radiation. Constant UV exposure leads to various ocular surface diseases such as pterygium, photokeratitis, and may also lead to ocular surface neoplasias. Available literature suggests association between UV induced oxidative damages and corneal diseases. Prolonged exposure to UV radiation leads to cellular modifications such as activation of NF-κB leading to pro-inflammatory cytokine release and apoptosis. Upregulation of Matrix Metalloproteinases (MMPs) particularly MMP-1, MMP-2, and MMP-9, involved in tissue remodelling and degradation of extracellular matrix. Changes in cytokine expression which includes IL-1, IL-6, IL-8, and TNF-α, which are involved in inflammation and cellular injury. Genetic changes include downregulation of PAX6, a critical gene for eye development and maintenance and UV-induced activation of Deoxyribonucleic Acid (DNA) damage pathways such as JNK and MAPK, leading to apoptosis. This review mainly focuses on the use of natural antioxidants derived from plants such as *Rosmarinus officinalis*, *Curcuma longa* (Curcumin), *Camellia sinensis* (Green tea polyphenols), *Centella asiatica, Ginkgo biloba, Allium cepa* (Quercetin), Glycyrrhiza glabra (Glycyrrhizin), *Zingiber officinale* (Ginger), *Nigella sativa,* Lycopene which can be used as therapeutic targets (NF-κB signaling pathway, MAPK and JNK pathways, P53 phosphorylation, MMPs (e.g., MMP-1, MMP-2, MMP-9), oxidative stress markers] in treating UV-induced inflammation and oxidative damages in cornea. PubMed literature search was performed using keywords antioxidants, ultraviolet radiation, oxidative stress, inflammation, cornea on July 3rd 2021, which resulted in 165 papers of which 81 were chosen after applying specific filters and relevant curation by the authors. This study reviews the various biochemical pathways involved in cell injury and cell death in response to UV exposure. The study also reviews the natural antioxidants and the various medicinal plants from where these are derived. The authors conclude that inflammatory mediators have a major role in stimulating oxidative stress leading to apoptosis and cell death and ocular surface diseases such as photokeratitis, pterygium, Climatic Droplet Keratopathy (CDK), Dry Eye Disease (DED), pinguecula, corneal ulceration. Targeting these inflammatory mediators by the use of natural antioxidants which are dietary-derived plant polyphenols with anti-inflammatory potential are reported to have beneficial effects.

Keywords: Corneal diseases, Oxidative stress, Ultraviolet radiation

INTRODUCTION

Cornea acts as a physicochemical barrier which protects the intra-ocular structures from the external ocular injury [1]. It comprises of five layers, mainly the outer epithelial layer, Bowman's membrane, stroma, Descemet's membrane, and inner endothelial layer [2]. The chief source of UV radiation is from the sun. Based on the wavelength, the UV radiation is divided into three types namely UVA (320-400 nm), UVB (290-320 nm) which reaches the earth, and UVC (100-290 nm) rays which is filtered by the ozone layer [3]. People are exposed to UV-A and UV-B radiation mainly during their outdoor activities such as construction work, agriculture, fishing, social science work, information and communication technology, industry, transport work, among others [4]. Most of the UV-C is absorbed by stratospheric ozone and hence its influx is only through occupational exposure [5]. Acute and chronic skin or eye disorders, or photosensitive diseases like photokerato-conjunctivitis (welder's flash) and skin erythema results from UV-C exposure (9795 mJ/cm^2) produced by the welding arc or exposure to germicidal lamps [6-8].

Constant UV exposure leads to various ocular surface diseases such as pterygium, photokeratitis, and may also lead to cancers of the ocular surface. Currently, there are various herbal eye drops used in the treatment of eye diseases. Ophthacare™ eye drops is a herbal preparation composed of extracts of *Carum copticum* seeds, *Terminalia belerica* fruits, *Emblica officinalis* fruits, *Curcuma longa, Ocimum sanctum* leaves, *Rosa damascena* petals, *Cinnamomum camphora* and honey. It is used in the treatment of clinical conditions associated with ocular surface diseases such as pterygium, dry eye and pinguecula [9]. Itone™ is a polyherbal formulation made of 19 herbal ingredients which includes *Azadirachta indica, Moringa pterygosperma, Eclipta alba, Boerhaavia diffusa, Carum copticum, Terminalia chebula, Terminalia belerica, Emblica officinalis, Santalum album*, mukta, *Ocimum sanctum, Vitex negundo, Curcuma longa, Mentha piperata, Cinnamomum camphora, Amomum subulatum, Rosa centifolia, Saindhavalaba,* and madhu. It is used in the treatment of several ocular diseases like corneal ulcers, keratitis, conjunctivitis, trachoma, blepharitis, etc., [10]. *Elaneer Kuzhambu* from the brand Sreedhareeyam is a Ayurvedic formulation composed of *Glycyrrhiza glabra, Emblica officinalis, Terminalia chebula, Terminalia bellerica, Berberis aristata,* Rock salt, *Picrorhiza kurroa, Cinnamomum camphora,* tender coconut water and honey. This formulation is used in the treatment of different eye ailments like corneal ulcer, pterygium, etc., [11].

The present review mainly focuses on the therapeutic potential of plant-derived antioxidants in targeting UV-induced inflammation and oxidative damages in cornea. The present review will focus on the inflammatory mediators or pathways involved during UV exposure in the cornea and how they respond when it is subjected to natural antioxidants.

MATERIALS AND METHODS

The PubMed literature search was performed using keywords antioxidants, ultraviolet radiation, oxidative stress, inflammation, cornea during the period, July 3rd 2021 to December 4th 2022, which resulted in 165 papers of which 81 were chosen after applying specific filters and relevant curation by the authors. Original research articles and systematic reviews were included; editorials,

commentaries, and non-peer-reviewed sources were excluded from the study. Articles specifically addressing the role of natural antioxidants in preventing or treating UV-induced inflammation or oxidative damage in the cornea were included in this review.

UV-induced Oxidative Stress and the Role of Inflammatory Mediators

The initiation of UV injury begins with biochemical and immunologic perturbations that cause inflammation [12,13]. During inflammation Reactive Oxygen Species (ROS) and Nitrogen Species (RNS) are produced, which in turn lead to oxidative stress followed by cell death [14-16]. UV radiation stimulates the ground state O_2 resulting in the production of variety of ROS, which leads to membrane lipid peroxidation and destruction [17-19]. Lipid peroxidation leads to the destruction of the antioxidant enzymes where in the imbalance between the antioxidant defense system takes place [20-22]. This will further lead to the activation pro-inflammatory cytokines which will lead to cell death or tumour initiation [23,24]. Nitric Oxide (NO) synthesis in inflammatory and epithelial cells is catalysed by Nitric Oxide Synthase (NOS), especially inducible NOS (iNOS). Inflammatory cytokines such as interferon-γ (IFNγ), interleukin 1β (IL1β) and Tumour Necrosis Factor-α (TNF-α) also induce iNOS [25].

The UV radiation causes various molecular changes in the cornea which include altered activity in the levels of Nuclear Factor-kB (NF-kB), cytokines, MMPs and PAX 6 expression. In the cornea, NF-kB is an initiator of cell death and a key initiator of production of a cytokine in response to injury. Similarly, cytokines up-regulate MMP production. Pro-inflammatory cytokines such as IL-1β and TNF-α upregulate MMP production by activating signaling pathways like NF-κB and MAPK. These pathways stimulate transcription factors that bind to MMP gene promoters, increasing their expression and leading to extracellular matrix degradation [26,27]. Cell death upon UV exposure due to the translocation of NF-kB is observed in corneal epithelial cell line. Upon UV exposure, ROS are generated, triggering intracellular signaling cascades such as the IκB Kinase (IKK) pathway. IKK phosphorylates the inhibitor protein IκBα, leading to its degradation. This allows NF-κB (typically a p65/p50 dimer) to translocate from the cytoplasm to the nucleus, where it activates genes involved in inflammation and apoptosis, contributing to cell death in corneal epithelial cells [28]. Treating the cells with NF-kB inhibitors such as sulfasalazine and SN-50 could protect the cells from UV induced cell death. Immunostaining shows the translocation of NF-kB in the nucleus prior to cell death, two hours post UV irradiation which suggests its role in cellular death cascades [29].

PAX6 is considered a key regulator of eye development in vertebrates, structural formation, differentiation, maintenance, and repair processes for which it is termed as master "oculogenic" control gene. The term "master control genes" was introduced by Lewis EB to describe homeotic genes, particularly in the *Bithorax Complex* of *Drosophila,* which control major developmental decisions. PAX6, often termed a "master oculogenic gene," contains both a paired box domain and a homeobox domain, and encodes a transcription factor critical for the morphogenesis of the eye, brain, and central nervous system. It governs the differentiation and maintenance of ocular tissues, and its expression is tightly regulated by factors like CCCTC-binding Factor (CTCF), which suppresses PAX6 expression upon overexpression, especially under UV-induced stress in corneal epithelial cells [30-32].

MMPs are proteolytic enzymes which are important in tissue remodeling and wound healing. They are found in inactive forms which get activated upon proteolytic cleavage. When active, they are capable of degrading and forming the extracellular matrix components and cytokines [33]. Gelatinases, such as MMP-2 and MMP-9, and collagenases, such as MMP-1 and MMP-8, are studied in-depth in the cornea [34-37]

UV-induced changes in the corneal epithelium are accredited to the upregulation of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α in the epithelium and stroma of the cornea [38-42]. IL-6 and IL-8 are found to be expressed in the superficial epithelium and IL-8 expression is seen in vascular endothelium exposed to low-dose, 40 mJ/cm^2 of UVB [43]. In UVB-irradiated Pterygium Epithelial Cells (PEC), dose-dependent increase in the expression of IL-6 and IL-8 was reported [44]. UVB-irradiation (20 mJ/cm^2) upregulated the pro-inflammatory cytokine (TNF-α) in corneal epithelial cells [45].

Natural Antioxidants and their Therapeutic Role in UV Induced Oxidative Stress

A number of natural antioxidants are available that can be used to suppress inflammatory mediators and resulting UV-induced oxidative stress [46]. Several naturally available antioxidants derived from plants such as curcumin (*Curcuma longa*), epigallocatechin gallate (*Camellia sinensis*), quercetin (*Allium cepa*), glycyrrhizin (*Glycyrrhiza glabra*), and thymoquinone (Nigella sativa) have been shown to inhibit UV-induced oxidative damage by suppressing inflammatory responses. Flavonoids, such as genistein, epigallocatechin-3-gallate, epicatechin, apigenin and silibinin; phenylpropanoids, such as caffeic acid phenylethylester, curcumin, thymol and zingerone; polyphenols such as, resveratrol, quercetin; gallic acid, etc., have been reported in literature, to alleviate cellular damage caused by UV radiation [47]. This review further focuses on natural antioxidants which are reported to reduce UV induced oxidative damage in the eye with special emphasis on cornea.

Epigallocatechin-3-gallate (EGCG): The EGCG are the functional actives present in green tea with high antioxidant activity. They are known to have protective activities in various eye diseases such as glaucoma, Age-related Macular Degeneration (AMD), diabetic retinopathy, cataract, and DED and they are proven by various in-vitro and in-vivo studies that they protect eye cells from oxidative stress [48,49]. UVB radiation induced damage in mice of the cornea was found to be reduced after treatment with EGCG eye drops which is mostly due to the increase in antioxidant enzyme activity and lipid peroxidation and protein oxidation inhibition [50].

EGCG was known to protect human corneal epithelial cells by inhibiting the phosphorylation of the Mitogen-activated Protein Kinases (MAPKs) and c-Jun N-Terminal Kinase (JNK), and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFκB). MAPKs are a family of serine/threonine kinases that play a crucial role in transducing extracellular stimuli into intracellular signals. Upon UV radiation, MAPKs such as p38 and JNK (c-Jun N-terminal kinase) are activated through phosphorylation by upstream kinases like MAPK Kinases (MKKs). This activation leads to the expression of pro-inflammatory genes, stress response genes, and apoptotic factors in corneal epithelial cells [51]. JNK, a member of the MAPK family, is specifically activated by environmental stressors like UVB. Upon activation, it phosphorylates c-Jun, a component of the transcription factor AP-1, leading to increased expression of pro-apoptotic and inflammatory genes. JNK activation results in cell death, DNA damage response, and inflammation in ocular surface cells [52]. NF-κB is activated by UV radiation through the generation of ROS, which stimulate the IKK (IκB kinase) complex. IKK phosphorylates the inhibitor IκBα, leading to its degradation and allowing NF-κB to translocate into the nucleus. Once in the nucleus, NF-κB upregulates genes responsible for inflammation, immune responses, and apoptosis. Thus, EGCG's inhibition of these pathways under UV stress helps prevent oxidative damage, inflammation, and cell death in human corneal epithelial cells [53].

Tannic Acids (TA): Tannic acids are the plant polyphenols which is known to possess antioxidant and anti-inflammatory properties. There are no studies on the effect of TA on UV radiation induced injury in corneal cells but other studies have been reported wherein the antioxidant and anti-photoaging properties are discussed.

TA prevented imbalance in the redox mechanism, cell damage and photoaging in L929 fibroblasts [54]. Tannin acid due to their antioxidant properties was used in in-vitro studies as antioxidant coated lenses which was proven reduce the ROS mediated oxidative stress induced cytotoxicity [55].

Glycyrrhizic Acid (GA): Glycyrrhizic acid (GA) is an active compound found in the roots of licorice plants (*Glycyrrhiza glabra* which is also known as Glycyrrhizin) [56]. GA treatment was known to attenuate the inflammation and oxidative stress in Mouse Corneal Epithelial Cells (MCEC) and the cornea of diabetic mice by reducing the inflammatory cytokine IL-1β levels and increasing the antioxidant enzyme levels such GPX-1 and 2, SOD-2, HO-1 [57]. GA was reported to reduce the inflammation mediated corneal neovascularisation in rabbit eyes [58].

Rosmarinic Acid (RA): Rosmarinic acid is a phenolic compound present in *Rosmarinus officinalis* which is reported for their antioxidant, anti-inflammatory, and anti-cancer properties [59]. Pterygium is the fibrotic disease where there is uncontrolled proliferation of conjunctival tissue to the cornea which is mainly caused by UV radiation. RA was found to decrease PEC viability and reduced the fibrosis by decreasing collagen type I production and down-regulating TGF-β1/Smad signaling thereby showing the antifibrotic effect [60]. RA was reported to reduce the production of intercellular ROS in PECs by inducing cell death [61].

Asiatic Acid (AA): Asiatic acid is a triterpenoid isolated from *Centella asiatica* extracts has been previously reported to reduce oxidative stress and inflammation due to their antioxidant functions [62,63]. Asiatic acid was found to decrease the generation of inflammatory factors such as IL-8, IL-6, IL-1β, TNF-α, and TGF-β in LPS-stimulated human corneal epithelial cells by inhibiting the intracellular ROS concentrations and improved GSH generation [64]. Asiatic acid suppressed the UVA irradiation induced ROS production, oxidative stress and increased the expression of MMP-2 in human keratinocytes [65].

Coumaric acids: It is a phenolic acid which is widely distributed in many plants and human diets such as cereals, fruits, and vegetables, possessing versatile medicinal activities including antioxidant, cardioprotective, antimelanogenic, antimutagenic, antiplatelet, anti-inflammatory, and immunomodulatory actions [66]. Coumaric acid (4-coumaric acid) by their free radical scavenging activity protects rabbit corneal-derived cells from the harmful effects of UV-B irradiation by enhancing the affected antioxidant defense systems and reduced the UV-induced oxidative damage [66,67]. A 4-coumaric acid (4-CA) protected the rabbit eye tissues, from UVB radiation by its free radical scavenging and antioxidant properties [68].

Caffeine: Caffeine is one of the natural components of coffee and tea known to play multiple roles in the regulation of cell cycle, signal transduction, DNA repair and apoptosis [69-72]. Caffeine blocks UV induced p53 phosphorylation leading to DNA damage in human corneal epithelial cells [73]. Caffeine was reported to suppress the UV radiation induced cellular response in corneal epithelial cells such as JNK signaling pathway activation and prevented apoptosis [74]. Caffeine was reported to protect UVB induced cataract in sprague-dawley rats and reduced the lens sensitivity [75].

Quercetin: Quercetin is a flavonoid and polyphenolic compound commonly present in fruits and vegetables such as apples, onions, and berries which is well known for its antioxidant, anti-inflammatory, neuroprotective and cardioprotective functions [76,77]. Quercetin has known to show anti-inflammatory and antioxidant effects on TNF-α or Ultraviolet (UV)-B radiation induced human conjunctival (IOBA-NHC) and corneal (HCE) epithelial cell lines [78]. Quercetin containing eye drops reduced the IL-1a production which is the inflammatory response of the ocular surface in a DED mouse model [79].

Resveratrol: Trans-resveratrol is a non-flavonoid polyphenolic compound found in several dietary sources, such as grapes, mulberries, peanuts, and red wine [80]. Resveratrol reduced the UVA-induced cell death; lowered H_2O_2 production, MAPK activation and the expression of COX-2 in retinal pigment epithelial cells [81].

DISCUSSION

The UV radiation is a major environmental factor that induces oxidative stress and inflammation in the cornea, leading to various ocular diseases like pterygium, photokeratitis, and cataracts [9]. UV exposure triggers the production of ROS, which activate inflammatory mediators like NF-κB, MAPKs, and pro-inflammatory cytokines, resulting in cell death and tissue damage [25-27].

Natural antioxidants derived from plants, such as EGCG, tannic acids, glycyrrhizic acid, rosmarinic acid, asiatic acid, coumaric acids, caffeine, quercetin, and resveratrol, have shown promising protective effects against UV-induced ocular damage. These antioxidants work by scavenging ROS, inhibiting inflammatory pathways, and enhancing antioxidant defense systems. For instance, EGCG and caffeine inhibit key inflammatory pathways like NF-κB and JNK [51,52], while glycyrrhizic acid and asiatic acid reduce inflammation and oxidative stress in corneal cells [57,58,62,63].

CONCLUSION(S)

Oxidative stress is known to play a major role in various ocular surface diseases. Hence, there is a growing interest in discovering alternative novel topical therapeutics for the treatment of radiation or inflammation induced ocular surface diseases. In the past five years, there has been emerging evidence of dietary-derived plant polyphenols with the potential health benefits such as flavonoids (*Camellia sinensis*), alkaloids (*Catharanthus roseus*), terpenoids (*Ginkgo biloba*), and stilbenes (*Vitis vinifera*), which possess antioxidant and anti-inflammatory properties and contribute to health benefits including reduced risk of cardiovascular diseases, neuroprotection, anti-cancer activity, and improved eye health. Exposure to UVB and UVA radiation leads to several deleterious health effects, particularly affecting the skin (e.g., skin cancer, photoageing) and the eye (e.g., pterygium, cataract, and photokeratitis), primarily due to inflammation and oxidative damage caused by DNA damage, protein denaturation, and ROS generation. UV induced Inflammation and oxidative damage are the major aspects discussed in this review. Both of them are interconnected to each other. Inflammatory mediators produced during UV exposure also aggravate the oxidative damage and in response to inflammation can also occur. In short, inflammatory mediators play a key role in mediating UV-induced oxidative damage. Targeting any of these inflammatory mediators such as TNF-α, IL-1β, IL-6, COX-2, and NF-κB by small molecules which are plant based possessing both antioxidant and anti-inflammatory potential not only eases the direct effect of UV radiation on cells, but also decrease the inflammation induced oxidative stress leading to apoptosis and necrosis. Plant derived natural molecules can be promising for therapeutic use in UV-induced corneal injury and solicits further clinical research.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Basic Sciences, Yenepoya School of Allied Health Sciences, Yenepoya Deemed to be University, Mangalore, Karnataka, India.
2. Tutor, Department of Biochemistry, Yenepoya Medical College, Yenepoya Deemed to be University, Mangalore, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
K Deeksha,
Assistant Professor, Department of Basic Sciences, Yenepoya School of Allied Health Sciences, Mangalore, Karnataka, India.
E-mail: deekshak@yenepoya.edu.in

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