Published in final edited form as:
Curr Med Chem. 2011 ; 18(6): 931–942.

Emerging Role of Antioxidants in the Protection of Uveitis Complications

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Abstract

Current understanding of the role of oxidative stress in ocular inflammatory diseases indicates that antioxidant therapy may be important to optimize the treatment. Recently investigated antioxidant therapies for ocular inflammatory diseases include various vitamins, plant products and reactive oxygen species scavengers. Oxidative stress plays a causative role in both non-infectious and infectious uveitis complications, and novel strategies to diminish tissue damage and dysfunction with antioxidant therapy may ameliorate visual complications. Preclinical studies with experimental animals and cell culture demonstrate significance of anti-inflammatory effects of a number of promising antioxidant agents. Many of these antioxidants are under clinical trial for various inflammatory diseases other than uveitis such as cardiovascular, rheumatoid arthritis and cancer. Well planned interventional clinical studies of the ocular inflammation will be necessary to sufficiently investigate the potential medical benefits of antioxidant therapies for uveitis. This review summarizes the recent investigation of novel antioxidant agents for ocular inflammation, with selected studies focused on uveitis.

Keywords

Antioxidants; eye; ocular inflammation; oxidative stress and uveitis

1. Introduction

For many years, uveitis has been considered to be a single disease entity. However, as knowledge of the disease process grew with increased sophistication of immunological, microbiological, biochemical and molecular techniques, it has become clear that uveitis entails a multitude of diseases [1, 2]. Uveitis is a common cause of vision loss, accounting for 5 – 15 % of all cases of blindness worldwide, affecting individuals of all ages, genders, and races [3 – 6]. In the United States, uveitis is reportedly responsible for an estimated 30,000 new cases of legal blindness annually and is also on the rise [3, 5]. In fact, in a largest population-based uveitis study in the United States so far, the incidence of uveitis has been found to be ~ 3 times more than that of previous estimates [7, 8]. Although prevalence studies have shown that anterior uveitis is by far the most common type, there are also posterior forms of intraocular inflammation [3]. The complications of autoimmune diseases,

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Conflict of Interest: NONE

bacterial infections, viral infections and chemical and metabolic injuries are associated with a variety of molecular and biochemical events that lead to ocular inflammation, particularly uveitis [3, 9]. Furthermore, many chronic inflammatory diseases are associated with an elevated risk of uveitis, e.g. rheumatoid arthritis [10, 11], juvenile idiopathic arthritis [12 – 15], systemic lupus erythematosus [16], polyarteritis nodosa, relapsing polychondritis, Wegener's granulomatosis, scleroderma, Behcet's disease [17], Reiter's disease, inflammatory bowel disease (ulcerative colitis and Crohn's disease) [18] and ankylosing spondylitis [19, 20]. While it is not clear how uveitis is initiated in the setting of chronic inflammation, accumulating evidence strongly supports the association between uveitis complications and inflammation. Furthermore, the breakdown of the blood-aqueous barrier in uveitis involves cellular infiltration, an increase in protein permeability, and upregulation of cytokines such as TNF-α, IL-6, chemokines such as MCP-1, and MIP-1 in the aqueous humor (AqH) and uveal regions [21]. Thus, exposure of cells near the blood-aqueous barrier to inflammatory cytokines and chemokines could trigger various autocrine/paracrine effects that could eventually cause cytotoxicity, leading to apoptosis or proliferation. Since redox-sensitive transcription factors such as NF-κB and AP1 are known to transcribe the genes for cytokines and chemokines, NF-κB and AP1 inhibitory agents such as steroids and antioxidants are being used against uveitis. However, steroids or other drugs that suppress the immune system to control the inflammation have many serious side effects, and severely diminish the patient's quality of life. Inflammation is invariably associated with increased oxidative stress by elevated reactive oxygen species (ROS), which could alter cellular and molecular targets and pathways crucial to normal tissue homeostasis [22 – 24]. Multiple studies have shown that ROS and oxidative stress are significant components of such pathological conditions. Further, a number of studies have indicated the potential use of antioxidants in experimental animals as well as in humans. In this review, we have described how oxidative stress is critical to the ocular inflammation of varied origin and possible therapeutic application of various antioxidants including flavonoids, vitamins, plant sterols, and ROS scavengers.

2. Uveitis

The immune system, which routinely helps to protect us from germs or infectious agents, can become deranged or dysregulated leading to an autoimmune attack on a part of our own body. Common autoimmune diseases include Behcet's disease [25 – 30], Reiter's disease [31 – 34], inflammatory bowel disease [35 – 37] and juvenile chronic arthritis (JCA) [38 – 44]. In these diseases, often the autoimmune disease is systemic, i.e., a variety of organs throughout the body system are attacked, including various parts of the eye. The eye may be affected as a target of immune inflammatory attack in any of the autoimmune diseases. However, in some cases the eye may be the specific and only target affected by certain autoimmune diseases. Such diseases include ocular cicatricial pemphigoid (45, 46), and Mooren's corneal ulcer [47 – 49]. Uveitis can also be caused by a viral infection (for example, cytomegalovirus, as seen in patients with AIDS) [50, 51] , a fungal infection (such as histoplasmosis) [52 – 55], an infection caused by a parasite (such as toxoplasmosis; a newborn may develop uveitis if the mother was exposed to toxoplasmosis during pregnancy) [56 – 58] and most common bacterial infections (such as caused by Helicobacter [59 – 61], Yersinia [62 – 66], Salmonella [67, 68], Shigella [69], and Chlamydia [70 – 75]. In addition numerous clinical cases have been described in which no cause could be determined (idiopathic uveitis). Recently, several novel infectious agents have been shown to be implicated in the development of uveitis, including Rickettsioses. West Nile virus infection, Rift valley fever, Dengue fever, and Chikungunya, which suggest increased threat to the vision [56].

Although the initial events leading to uveitis in humans are not always clear, the eventual loss of vision has always been ascribed to the ocular tissue damage caused by amplification of the inflammatory processes [3 – 5]. The uveal tract includes the iris, ciliary body, and choroids, which represents the vascular organ of the eye. Uvea provides most of the blood supply to the intraocular structures; it acts as a conduit for immune cells, particularly lymphocytes, to enter the eye. Consequently, the uveal tract is represented in many intraocular inflammatory processes, irrespective of which tissue or cell is the original target of the immune process. The figure-1 shows major forms of uveitis.

Various reports show that ROS are obligatory mediators of the cytokine and chemokine-induced inflammation [76, 77]. Cytokines and chemokines induce intracellular ROS generation by mitochondrial respiratory chain reaction, the arachidonic metabolic reactions of Cox-2, and the membrane-bound superoxide- generating enzyme NADPH oxidase. The generation of ROS in turn activates the redox-sensitive transcription factors such as NF-κB and AP-1 [78 – 80]. Activation of redox-sensitive transcription factors plays a central and crucial role in the inflammation. This mechanism is associated with the over-expression of inflammatory cytokines and iNOS and Cox-2 enzymes, increasing NO and PGE2 [81 – 83]. These local messenger molecules act further in autocrine and paracrine fashion and elevate ROS. The ROS in turn activate various genes that are involved in cytotoxicity. For example, the pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 play important roles at the initial stages of cell growth or apoptosis. Among the proinflammatory cytokines, TNF-α is known to be recognized as a central mediator in the pathophysiology of chronic inflammatory bowel diseases such as Crohn's and ulcerative colitis, which cause increased risk of uveitis; recent studies have shown the use of anti-TNF-α therapy to treat uveitis [84 – 88]. Since generation of cytokines such as TNF- α is mediated through NF-κB dependent transcriptional activation, some investigators have also examined the effect of NF-κB inhibitors as well as antioxidants those prevent activation of NF-κB in prevention of ocular inflammation leading to uveitis [81 – 83, 89]. The results demonstrating that antioxidants prevent uveitis complications suggest that the oxidative stress plays a critical role in the pathophysiology of uveitis.

3. Oxidative stress and uveitis

Inflammation during uveitis has a strong correlation with the oxidative stress. The presence of lipid peroxidation products in eye tissues, including the retina as well as aqueous humor during experimental uveitis has been demonstrated in many studies [90 – 96]. Many studies have also demonstrated the presence of ROS which caused protein and DNA modifications in the uveitis eye [93, 94, 97]. It has been suggested that increased ROS levels during inflammation could be due to increased oxygen consumption or decreased antioxidative defense in the concerned tissue. The increased levels of ROS in the ocular cells cause redox imbalance leading to activation of redox signaling intermediates, which activate transcription factors such as NF-κB and result in the transcription of inflammatory marker genes [98 – 104]. Once formed, the inflammatory markers, including cytokines, chemokines, growth factors, iNOS, and COX-2 further exacerbate the oxidative stress starting a vicious cycle of unregulated inflammation. The excessive ROS generation also weakens the tissue's own antioxidant defense system, which further aggravates the inflammation and ROS production and cause tissue damage in uveitis. This evidence led us to suggest that oxidative stress could be a key player in initiation and progression of uveitis, and therefore, the use of ROS quenchers, antioxidants and other similar agents could be beneficial in treating uvieitis (Figure-2).

In an animal model of uveitis where bacterial endotoxin is used as inducer of inflammation in the eye, infiltration of inflammatory cells into the ciliary body and choroid precedes

inflammation [21]. Among the infiltrating cells, polymorphonuclear leukocytes (PMNs) are one of the first to enter the ocular tissues. These cells are known to produce oxygen free radicals by the action of NADPH oxidase using NADPH as an electron donor in order to kill microbes. Subsequently, to initiate oxidative stress, other ROS species including H_2O_2, ·OH and HOCL are also produced. These oxidative molecules in turn exert their toxic effects on the adjacent tissues which comprise an important event for the perpetuation of intraocular inflammation. The affected cells secrete myriad of inflammatory markers, including chemokines, which attract more inflammatory cells in the affected tissue and further aggravate the inflammation. Increased ROS induces the expression adhesion molecules such as ICAM, which helps in the leukocyte adhesion and infiltration. Increase in oxidative stress also activates many proteases, including metalloproteases (MMP) which chew-up intra-cellular and extracellular proteins resulting in tissue injury. Since oxygen radicals are powerful initiators of peroxidation of various tissue constituents such as membrane lipids and extracellular matrix proteins, they could cause severe tissue damage associated with disease pathogenesis. Thus, oxidative stress is the main mechanism of an infection or bacterial toxins –induced uveitis and regulating or controlling the oxidative stress could be beneficial in amelioration of infection-induced uveitis.

In case of autoimmune uveitis, damage to the photoreceptor membrane lipids and other retinal cells constitute a major step in pathogenesis, which results in severe damage to the retinal wall [105 – 108]. Since photoreceptors are especially rich in polyunsaturated fatty acids, they are more susceptible to peroxidation by oxygen radicals. Further, because photoreceptors are rich in mitochondria and thus are in a constant flux of oxygen, they are more prone to oxidative damage and peroxidation. New evidence such as mitochondrial DNA damage, overexpression of iNOS in the photoreceptor mitochondria, and peroxynitrite-mediated nitration of the photoreceptor mitochondrial proteins during early uveitis suggest that mitochondrial oxidative stress could be one of the initial events for retinal damage and increased inflammation in EAU [109]. Further, infiltration of inflammatory cells and subsequent release of cytokines and chemokine also increase the ROS levels in the retina, including photoreceptor cells [110]. Studies in the experimental models of auto-immune uveitis have demonstrated the presence of fatty acid hydroperoxides from retina and choroids, which form mostly by the peroxidation of membrane lipids. Once formed, the hydroperoxides can augment the lipid peroxidation process resulting in altered membrane fluidity and loss of cellular function. The oxidized membrane lipid products, especially low molecular weight aldehydes such as 4-Hydroxynonenal (HNE), are known to be cytotoxic. Moreover, fatty acid hydroperoxides are also known to be chemotactic to PMNs and increase the inflammatory processes. However, irrespective of presence of inflammatory cells, oxidative stress-induced alterations in the photoreceptors cells could be early process in the development of auto-immune uveitis [111]. Thus, oxidative stress has a strong correlation with the disease pathogenesis during uveitis.

4. Oxidant sources in ocular tissues

In normal ocular physiology, the chromophore present in retina cells absorbs energy and goes to the higher excited state called singlet. It immediately releases energy, which dissipates without harming the cells, and returns to ground state. However, when chromophores absorb energy and go from a singlet to triplet state, which has a longer lifetime, can react with oxygen and form free radicals and reactive oxygen species, which can potentially damage the eye. The ROS can react with the cellular and extra cellular proteins and affect their normal function leading to tissue damage and inflammation. The chromophores in the eye keep changing throughout life and with aging their nature changes, which could be harmful to the eye. The ocular chromophores include proteins and nucleic acids in the cornea, kynurenins in the lens, rhodopsin, retinals, and melanins in the retina

and the age modified chromophores are xanthurenic acids, a modified form of kynurenins and are phototoxic [112 – 114]. Similarly, retina starts accumulating a mixture of photosensitive chromophores called lipofuscin, which absorbs light and cause damage to the retina [114]. Besides, there are many other sources of oxidative stress in the eye. The eye is an immune privileged organ and usually has no macrophages. However, due to oxidative damage to the ocular tissues and blood vessels integrity of blood-ocular barrier compromised and secretion of cytokines and chemokines attracts macrophages and other inflammatory cells to the eye and a cascade of inflammatory reaction starts. The inflammatory cells release ROS, including hydroxyl radicals and superoxides, which can aggravate the inflammation and damage the eye tissues [109, 115, 116]. Therefore, both photo-oxidation mechanism and inflammation have common component, ROS and other free radicals which react with cellular components and damage tissue. Since the eye has an excellent antioxidant system, which will be discussed in a short while, that destroys these ROS and free radicals and prevents that damage to the eye. However, with the age and in disease condition the antioxidant defense decreases and oxidants, which were kept in control otherwise, start harming the eye.

In an inflammatory condition such as uveitis, the sources of oxidants are mostly PMN and macrophages, independent of the etiology of the disease [93]. When activated, these cells release a variety of reactive molecules, including superoxide, hydrogen peroxide and hypoclorous acid, which in turn can form highly reactive species such as hydroxyl radicals. Superoxide is molecular oxygen with an unpaired electron released by neutrophils upon activation. Superoxide can react with a water molecule and form highly reactive products such as hydrogen peroxide and hydroxyl radical. Though most of the hydrogen peroxide is derived from dismutation of superoxide by neutrophils with the help of SOD, it is also formed by other enzymatic reactions catalyzed by catalase and GPx. Hypoclorous acid is mainly formed by myeloperoxidase, which catalyze the oxidation of halides in the presence of hydrogen peroxide. Phagocytes are the main source of hypoclorous acid. It can react rapidly with amines, amino acids, sulfhydryl compounds, thioethers, aromatics, and other unsaturated carbon groups. Most importantly, hypochlorous acids can react with other oxygen metabolites generated by the superoxide to form hydroxyl radical. The hydroxyl radicals (.OH) have shown to be extremely potent oxidants. They are formed primarily by the reaction of superoxide and hydrogen peroxide and presence of iron catalyzes the formation of hydroxyl radicals. The hydroxyl radicals can readily react with various organic and inorganic molecules and thus are very harmful to the cells. Hydroxyl radicals derived from superoxide can interact with lipid membranes and can form potentially damaging organic free radical such as lipid aldehydes. In addition, these free radicals can degrade DNA, alter vascular permeability, and potentiate inflammation by generation of chemotactic factors and augment an inflammatory response (Figure-2).

5. Antioxidant systems and uveitis

Ocular tissues are replete with an antioxidant system probably because the eye is the target of many potent oxidants. For example, exposure to a light and subsequent photosensitizing mechanism, which constitutes the ocular physiology, may lead to the formation of ROS. It is well established that ROS and antioxidant systems are involved in pathological processes in the eye, including uveitis. The human eye is endowed with an antioxidant system which deals with the daily onslaught of ROS, e.g. cornea has vitamin C, vitamin E, superoxide dismutase (SOD), catalase and glutathione (GSH), in addition the lens possesses lutein, and the retina contains melanin, lutein, zeaxanthin and a very high concentration of glutathione. The antioxidant system includes both enzymatic and non-enzymatic molecules. The enzymatic antioxidants comprise SOD, catalase and glutathione perxidase (GPx) [117] while the non-enzymatic antioxidant group includes GSH, vitamin A, vitamin C, and vitamin E.

Once oxygen free radical is formed, SOD catalyses its conversion to H_2O_2 and H_2O. Catalase then converts H_2O_2 into H_2O and O_2 and glutathione peroxidase reduces H_2O_2 to H_2O. GSH is an important reducing agent that is required by catalase for the conversion of H_2O_2 into H_2O. Similarly, vitamin A, vitamin C, and vitamin E are known to be potent antioxidants and ROS quenchers [118]. Vitamin E, being lipid soluble, is located within cell membranes where it can interrupt lipid peroxidation by quenching ROS and thus may modulate redox-sensitive intracellular signaling pathways. Vitamin A, formed from β-carotene, is one of the main constituents of the retinal wall and plays an important role in the visual cycle as well as in cellular defense. β-carotene is a potent antioxidant which can reduce free radicals and prevent tissue damage. Vitamin C, a strong antioxidant, protects proteins, lipids, and DNA from the oxidative damage. Ascorbic acid uptake by the retina is an energy dependent process and concentration of vitamin C in the retina is 20 times higher than in the plasma, suggesting that vitamin C plays an antioxidant role to protect the retina. Vitamin C has also been detected in human tears and aqueous humor in high concentration compared to plasma. Thus, these enzymatic and non-enzymatic antioxidants constitute an important defense system against oxidative stress–induced diseases (Figure-3). In uveitis, the antioxidant system of the eye becomes weak with severely reduced levels of GSH and vitamins, reduced activities of antioxidant enzymes, including SOD, GPx and catalase. With the reduced potency of the antioxidant system, the ROS mediated damage continues, which helps in the progression of the inflammation and disease.

6. Antioxidant treatments for uveitis

Uveitis is known to be caused due to increased oxidative stress, which results in an inflammatory process and enhanced pathogenic mechanism. Various oxidative markers have been shown to be elevated in the eye during experimental uveitis and antioxidants of varied origins and chemical natures have been shown to be very effective in reducing the oxidative stress and resolving inflammation in experimental animal models. Animal models of uveitis have been useful in testing new therapeutic approaches to treat intraocular inflammation. Similar to uveitis in humans, experimental uveitis in animals is genetically controlled. Therapies for experimental uveitis include treatment with antibodies (Abs) against cytokines, surface T-cell molecules, major histocompatibility complex (MHC) class II molecules, as well as anti-inflammatory steroids and antioxidants [119 – 142]. Understanding the immunopathogenic mechanisms of uveitis in rodent models that closely mimic human uveitis is of great importance to develop novel therapeutic approaches. EIU is an animal model of acute ocular inflammation induced by the administration of LPS [21]. In rats the inflammation peaks 24 h after the LPS injection. LPS enhances the expression of various inflammatory mediators, such as TNF-α, IL-6, Cox-2, IFN-γ, iNOS, MCP-1 as well as the production of PGE2 and nitric oxide, all of which contribute to the development of EIU, resulting in the breakdown of the blood–ocular barrier and in the infiltration of leukocytes into ocular tissues. Although EIU was originally used as a model of anterior uveitis, increasing evidence shows that it also involves inflammation in the posterior segment of the eye, with recruitment of leukocytes that adhere to the retinal vasculature and infiltrate the vitreous cavity. Experimental autoimmune uveitis (EAU) is an animal model for the inflammatory eye diseases such as endogenous posterior uveoretinitis (EPU), which is thought to have an autoimmune origin. EAU is a well-characterized, robust, and reproducible model that is easily monitored and quantitated [108]. Immunization of animals at distant sites with retinal antigens and appropriate adjuvants results in a disease with many of the clinical and histopathologic features similar to that of the human disease. The ability to induce EAU in various gene-manipulated, including transgenic mouse strains makes the EAU model suitable for the study of basic mechanisms, as well as in clinically relevant interventions. In both these rodent models inflammation due to cytokines and chemokines is the major cause of uveitis and NF-κB is the major transcription factor that transcribes these

genes. Here we have presented a summary of studies that showed or suggested the beneficial use of different types of antioxidants such as Flavonoids or alkaloids, carotenoids, vitamins, plant sterols and synthetic ROS scavengers in the experimental uveitis models (Table 1). Furthermore, various other molecules that do not possess anti-oxidant properties have been shown to prevent uveitis associated inflammation in experimental animals, a summary of these compounds has been shown in Table 2. In the following sub-sections, we will discuss these anti-oxidant and non-antioxidant molecules in detail.

6.1. Flavonoids

Flavonoids are polyphenolic in nature and comprise a complex group of compounds containing benzene ring(s). Flavonoids are ubiquitously found in plants, mostly in the vibrantly colored flowers and fruits, and are known for their antioxidant properties [143, 144]. They protect the plants from various insects and microbes. The presence of phenolic hydroxyl groups in flavonoids has been suggested to be responsible for their anti-oxidant properties. The human diet is replete with flavonoids as much as they have been linked with many health benefits as they activate the production of enzymes that potentiate the body defense system. Many flavonoids have been shown to be anti-tumorogenic, anti-angiogenic, vaso-protective, neuro-protective, and anti-oxidative [143 –147]. As summarized in Table 1, various flavonoids have been used in the experimental animals to prevent uveitis.

Many studies suggest that dark colored fruits such as berries; including blackberry, raspberry, and strawberry are rich in flavonoids and polyphenolic compounds and are endowed with beneficial properties in vision and eye health [147]. The fruit of Aronia (Aronia melanocarpa; Family: Rosaceae), a native to North America, contains high levels of polyphenol compounds and was shown recently that a crude extracted preparation contains a potent antioxidative effect *in vitro* and *in vivo*. Ohgami et al. [148] showed that Aronia fruit extracts decreased the number of inflammatory cells, the protein concentration, and the levels of NO, PGE2, and TNF-α in the aqueous humor in a dose-dependent manner and thus could prevent EIU in rats. Another study by Jin et al. [149] showed the beneficial effect of Blue honeysuckle (*Lonicera caerulea* L.) extracts on EIU in rats, probably by inhibiting the NF-κB dependent signaling pathway and the subsequent inhibition of proinflammatory mediators. Similarly, Gupta et al. [150] showed an anti-inflammatory effect of aqueous extract of Curcuma longa and Berberis aristata extract against EIU in rabbits. Rahimi et al. [151] have hypothesized the beneficial use of green tea in uveitis due to the presence of polyphenols such as catechins, including pigallocatechin gallate, which is the most active component of green tea and their specific effects on uveitis should be investigated in human trials. Kubota et al. [125] have shown that reservatrol prevented EIU-associated cellular and molecular inflammatory responses by inhibiting oxidative damage and redox-sensitive NF-κB activation. The Ginkgo biloba extract (GBE) has been used in Chinese traditional medicine for centuries for various disorders such as memory disorders, obstructive arteriosclerosis, Alzheimer's disease, ischaemic heart disease, cerebral infarction, aging, and age-related macular degeneration. A study by Ilieva et al. [152] indicated that GBE had a significant anti-ocular inflammatory effect on EIU in rats by affecting inflammatory factors such as NO, TNF-α, PGE2 and MCP-1 production. Shiratori et al. [153] showed that flavonoids from grapefruit (Citrus paradise) such as naringin and naringenin suppressed the development of EIU in a dose-dependent manner. Both treatments with naringin and naringenin produced reductions in PGE2 and NO concentrations in the aqueous humor. All these antioxidants described here are well known to control the production of reactive oxygen species as well as their dependent activation of redox-sensitive transcription factors such as NF-κB and AP1. Further, most of the flavinoids have shown to prevent the activation of several key enymes such as aldose reductase that controls the oxidative stress signals.

6.2. Vitamins

Vitamins have long been associated with the human health and diseases. The role of deficiency of vitamins in ocular inflammation and pathogenesis is not clearly understood. However, since vitamins, especially vitamin A, vitamin C, and vitamin E are considered non-enzymatic antioxidants; they could play an important role in the prevention and amelioration of ocular inflammation [118]. In the Behcet's disease which is one of the major causes of non-infectious uveitis, Kandi et al. [154] have shown that the levels of vitamins E, C, B1, B2 and flavin mononucleotide (FMN) were significantly lower in the patients compared to the control. There are numerous studies which suggest the use of vitamin E in uveitis. However, there have been conflicting reports regarding beneficial use of vitamin E in uveitis. For example, Cid et al. [155] revealed that in experimental lens-induced uveitis in Brown Norway rats, vitamin E-deficient animals had the most severe destruction of the retina, while those animals receiving the vitamin E-supplemented diet exhibited the best preservation of the retinal architecture. However, in the bovine-albumin-induced uveitis in New Zealand albino rabbits, Yucel et al. [156] showed that in all vitamin-E-treated animals, clinical and histopathological study of the retina and uvea revealed no significant changes in comparison with those in untreated rabbits. Pararajasegaram et al. [157] showed suppression of S antigen-induced uveitis in Lewis rats by vitamin E supplementation. Vitamin C is known for its anti-oxidant effect due to strong ROS scavenger properties. A study by Kukner et al. [158] demonstrated that i.p. administration of vitamin C reduced the oedematous effects of experimental uveitis on the retina in the guinea pigs. Recently, our laboratory has shown the beneficial effects of vitamin B1 analogue benfotiamine on experimental uveitis in rats [82]. Benfotiamine is shown to inhibit redox-sensitive transcription factor NF-κB during oxidative stress, which could be the probable route of its beneficial effect against inflammation in uveitis. All the vitamins investigated for preventing inflammatory complications work through their anti-oxidant potential.

6.3. Carotenoids

Carotenoids are natural lipid-soluble pigments that are found in phytoplankton, algae, plants, and a few fungi and bacteria. Carotenoids are known to scavenge free radicals and singlet oxygen reactive species thereby have the potent antioxidant mechanism [159]. It is therefore, postulated to be beneficial in the regulation of oxidative stress-induced inflammation, including uveitis. Several studies have demonstrated the use of carotenoids in the experimental models of uveitis. In a study by Ohgami et al. [160], Astaxanthin (AST), a carotenoid derived from marine animals and vegetables, could suppress the development of EIU in a dose-dependent manner in rats by the suppression of NO, PGE2, and TNF-α production, through directly blocking NOS enzyme activity. Another study by Suzuki et al. [134] has observed that AST reduced ocular inflammation in rat eyes with EIU by downregulating proinflammatory factors and by inhibiting the NF-κB-dependent signaling pathway. Fucoxanthin is yet another carotenoid that has been extensively studied in various disease conditions, including cancer-preventing, antimutagenic effects. Fucoxanthin is found in common edible seaweeds such as *Sargassum fulvellum*. In a recent study by Shiratori et al. [161] Fucoxanthin has been shown to suppress the development of EIU and resulted in the reduction of PGE2, NO and TNF-α concentration in the aqueous humour, indicating that fucoxanthin suppresses the inflammation of EIU by blocking the iNOS and COX-2 protein expression. The carotenoids such as lutein and zeaxanthin are found abundantly in the macular pigment. Several studies have reported that lutein consumption could lower the risk of age-related macular degeneration (AMD), cataracts, and other eye diseases. There are two proposed mechanism of protection offered by lutein against photooxidative damage in the ocular tissue, by filtering the damaging blue light and as an antioxidant that scavenges light-induced reactive oxygen species. Leutin has also been shown to suppress the EIU in experimental rats [162]. The anti-inflammatory role of leutin and other carotenoids could be

due to their ability to inhibit NF-κB -dependent signaling pathways and the subsequent production of proinflammatory mediators, which exacerbates the inflammatory pathologies.

6.4. ROS scavengers

Many synthetic antioxidants and ROS scavengers have been used in the experimental models to alleviate the inflammation caused by oxidative stress. The most widely used anti-oxidant of this category is N-acetylcysteine (NAC) which is an *N*-acetyl derivative of the amino acid L-cysteine, and acts as a precursor in the formation of glutathione, a natural antioxidant [163]. The thiol (sulfhydryl) groups in NAC confer antioxidant effect and reduce free radicals. NAC has been shown in many studies to protect against endotoxin-induced oxidative stress and inflammation. Numerous studies have shown that NAC prevents production of TNF-α in mouse, protects against endotoxin-induced oxidative stress, improves macrophage function in endotoxemic mice, protects against endotoxin-induced lung inflammation in mice, and improves function of immune cells, including lymphocytes and macrophages isolated from endotoxin-induced mice. More recently NAC has been shown to offer protection against EIU in Lewis rats by reducing the expression of proinflammatory cytokines such as TNF-α, IL-6, and adhesion molecules such as endothelial leukocyte adhesion molecule-1 (E-selectin) as well as intercellular adhesion molecule-1 (ICAM-1) [142]. Similarly, S-nitrosothiol S-nitrosoglutathione (GSNO), a physiologic metabolite of NO and GSH and a slow NO donor, has been shown to be several-fold more potent than GSH against oxidative stress caused by peroxynitrite ($ONOO^-$). The beneficial effects of GSNO have been demonstrated in inflammatory diseases such as ischemia-reperfusion injury and in the ocular inflammation caused by autoimmune response in interphotoreceptor retinoid-binding protein (IRBP)-induced EAU in mice [164]. The GSNO treatment is found to attenuate the levels of TNF-α, IL-1β, IFN-γ, and IL-10 in retinas, Further, splenocytes from GSNO treated mice is shown to lower antigen-specific T-cell proliferation in response to IRBP, and production of cytokine.

Recently, pyrrolidine dithiocarbamate (PDTC), an antioxidant, is shown to be effective in inhibiting NF-κB and thus could offer the therapeutic benefits in acute and chronic inflammatory conditions where NF-κB plays a major role, including uveitis [129]. Ohta et al. [129] has demonstrated in EIU rats that PDTC reduced ocular inflammation in EIU rat by down regulating the expression of pro-inflammatory cytokine by inhibiting the NF-κB-dependent signaling pathway. Another study by Fang et al. [120] has shown that in ocular inflammation in experimental autoimmune anterior uveitis, PDTC inhibited the expression of proinflammatory cytokines, TNF-α and IFN-γ and augmented the expression of anti-inflammatory cytokines, IL-10, and suggested that application of NF-κB inhibitors could be used therapeutically in acute anterior uveitis. Furhter, in an autoimmune-induced uveitis model, Kitamei et al. [89] has also shown that PDTC ameliorated the clinical symptoms of EAU mice and significantly reduced the histopathological score, expression of cytokines sucha as TNF-α and IL-1b, and abrogated T-cell proliferation and cytokine production. These effects of PDTC could be attributed to the suppression of effector-phase responses, including inflammation via regulation of NF-κB activity. Another NF-κB inhibitor, dehydroxy methyl epoxyquinomicin has also been known to ameliorate experimental autoimmune uveoretinitis in mice [165].

6.5. Plant Sterols

In the past over one decade, the role of plant sterols or phytosterols in human health has been investigated extensively [166]. Their role as cholesterol controlling agents in hypercholesterolimic patients has been attributed to steric hindrance by inhibiting the absorption of cholesterol from diets in the intestine [167]. Phytosterols have been shown to possess immunological activity as demonstrated in animal models of inflammation and *in*

vitro and *in vivo* models of colorectal and breast cancer. Further, epidemiological studies correlate the dietary intake of phytosterols and reduced risk of various diseases in humans. In the past one decade, the direct immune modulatory activity of phytosterols on human lymphocytes has been shown and the mechanism of action in cancer cells has been elucidated. Donald et al. [168] has demonstrated that in a randomized placebo-controlled trial in the treatment of pulmonary tuberculosis the phytosterol/glucoside mixture-treated group demonstrated a faster clinical recovery. In a recent study, we have demonstrated that guggulsterone, a plant derived steroid isolated from the gum resin of the *Commiphora mukul* tree, could ameliorate the inflammation in the EIU rat eye [83]. Although the exact mechanism of prevention remains to be determined, it is suggested that guggulsterone exerts its anti-inflammatory effects by suppressing the activation of the transcription factor NF-κB in response to different pro-inflammatory mediators.

6.6 Aldose reductase (AR) inhibitors

Recently, our laboratory and others have presented many evidences that AR inhibitors are potent anti-inflammatory agents and could prevent many oxidative stress–induced diseases, including an ocular inflammatory condition, uveitis [81]. The exact mechanism of beneficial effects of AR inhibitors are not yet known, but we have presented convincingly that during an oxidative insult AR get activated and cause increased activation of ROS and downstream signaling, eventually activating NF-κB, which in turn transcribes inflammatory genes and cause pathogenesis. Therefore, inhibition of AR could be anti-oxidant and anti-inflammatory as inhibition of AR has been shown to inhibit ROS formation and production of inflammatory cytokines and chemokines. Indeed, we have demonstrated that using structurally different pharmacological AR inhibitor or genetically silencing the mRNA by siRNA could effectively block the inflammation in varied disease models. A detailed role of AR inhibitors in prevention of uveitis has been reviewed separately [169]. Subsequent to our findings in the bacterial endotoxin-induced uveitis in rat, we have extended our study and investigated the efficacy of AR inhibitors in experimental autoimmune uveitis models in rats and mice.

6.7. Other non-antioxidant treatments for uveitis

Besides above mentioned anti-oxidant therapeutic strategies in the amelioration of both infectious and non-infectious uveitis, many other approaches have been tested in experimental models as well as in patients. The soluble antibodies against inflammatory cytokines such as TNF-α, IL-17, leukocyte function associated antigen-1α (LFA-1α) have been used extensively in the prevention and amelioration of uveitis of varied etiology. These studies are summarized in Table 2. Since TNF-α is well know mediator of inflammation during uveitis, targeting this cytokine with soluble antibodies appears to be an attractive therapeutic strategy and numerous clinical studies have reported the use of TNF-α antibodies, infliximab, in human patients with encouraging outcomes and very few side effects [121]. Similarly, LFA-1α Abs has been shown to be potent inhibitors of established autoimmune uveitis and could be applicable to the prevention as well as treatment of T-cell-mediated autoimmune diseases [170]. New evidence indicates the involvement of IL-17 in the pathogenesis of autoimmune-mediated diseases. A recent study by Amadi-Obi et al. [171] has demonstrated the role of IL-17 in the mediation of EAU, suggesting that Th1 cells may mitigate uveitis by antagonizing the Th17 phenotype through the IFN-g–mediated induction of IL-27 in target tissue. Furthermore, antagonism of Th17 by IFN-γ and/or IL-27 could be used for the treatment of chronic inflammation. Antibodies against IL-17 have been shown to attenuate EAU in rats [172].

Other approaches such as Amino acid copolymers [173], siRNA against inducible co-stimulator (ICOS) [174], IL-1 receptor agonist [175], Dexamethasone [176], angiotensin II

type 1 receptor blocker Telmisartan [177, 178], glucosamine [179], vaclosporin (LX211) [180], chitinase inhibitors [181], vascular adhesion protein-1 inhibitors [182], methylprednisolone acetate [183], cloricromene, a coumarin derivative [184], vasoactive intestinal peptide-loaded liposomes [185], oligodeoxynucleotide [186], DAF [187] and gene therapy [190] have been shown to contain inflammation in the experimental model of uveitis. Most of these experimental studies present an opportunity to explore novel therapeutic methods for uveitis, which includes sight-threatening diseases such as Behcet disease, birdshot retinochoroidopathy, Vogt- Koyanagi-Harada, sympathetic ophthalmia and ocular sarcoidosis.

7. Conclusions and future perspective

Uveitis is an intraocular inflammatory condition resulting from an infection or autoimmune response in the body and is characterized by the presence of severe oxidative stress and inflammation in the local tissue. We have discussed various options available to us today in the form of experimental and some clinical studies to treat or prevent this sight threatening disease. The potentiation of the body's anti-oxidant system by the administration of different therapeutic molecules could contain the inflammation and consequently, the disease. Various antioxidants are present naturally in our diet or available as synthetic supplements and have been shown to prevent infection-induced or auto-immune –induced ocular inflammation in experimental models. Similarly, inhibitors of important signaling molecules in the oxidative stress-induced signaling are also effective in ameliorating the inflammation in experimental models. Since antioxidants and vitamins are being generally taken as food supplements, their use in preventing uveitis needs regourous investigations. Further, the use of antioxidants in combination with conventional treatments could result in more potent therapeutic options for uveitis and may reduce the side effects associated with the use of steroid in uveitis therapy. Screening of new compounds and antioxidants for preventing uveitis will reduce the use of steroid, which generally reduce patient's quality of life. Further, studies are required to understand the pleiotropic effects of antioxidants, which can interfere with many biological and immunological pathways and precise molecular mechanisms by which these agents reduce inflammation. Taking advantage of potent anti-inflammatory property of antioxidants and vitamins, they could also be used to prevent inflammatory pathologies other than in an ocular system.

Acknowledgments

NIH grants GM71036 and EY018591 to KVR.

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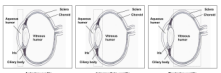

Figure-1.
Various forms of uveitis.

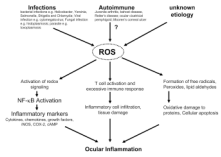

Figure-2.
Schematic represention of role of oxidative stress in uveitis complications.

Figure-3.
Effect of antioxidants in preventing events related to uveitis complications.

Table: 1

Prevention of Experimental Uveitis by Antioxidants

#	Antioxidants	Mechanism of Action	R & D Status	References
	Flavinoids/Alkaloids			
1	Aronia extract	Suppression of expression of iNOS & COX-2	In vitro & In vivo studies	[148]
2	Blue honeysuckle extract	Inhibition of NF-κB-dependent signaling	In vitro & In vivo studies	[149]
3	Curcumin	Possible COX-2 inhibition	In vivo & clinical studies	[150, 188]
4	Green tea	Minimize DNA damge, anti-inflammatory	In vitro & in vivo studies	[151]
5	Resveratrol	Suppression of oxidative damage, Inhibition of NF-κB activation	In vivo studies	[125]
6	Ginkgo biloba extract	Suppression of expression of iNOS	In vitro & In vivo studies	[152]
7	Berberis aristata extract	Possible COX-2 inhibition	In vivo studies	[150]
8	Naringin	Suppression of PGE2 & NO	In vivo studies	[153]
9	Naringenin	Suppression of PGE2 & NO	In vivo studies	[153]
	Vitamins			
10	Benfotiamine (Vitamin B1 analogue)	Inhibition of PKC & NF-κB	In vitro & In vivo studies	[82]
11	Vitamin C	Strengthen antioxidant system	In vivo & clinical studies	[158, 189]
12	Vitamin E	- NA -	In vivo & clinical studies	[155, 156, 157, 189]
	Carotenoids			
13	Astaxanthin	Inhibition of NF-κB-dependent signaling pathway; Suppression of NOS enzyme activity	In vitro & In vivo studies	[134, 159, 160]
14	Fucoxanthin	Suppression of expression of iNOS & COX-2	In vitro & In vivo studies	[161]
15	Lutein	Inhibition of NF-κB pathway	In vitro & In vivo studies	[123]
	ROS Scavengers			
16	N-acetylcysteine	Reduce ROS generation Reduce expression of pro-inflammatory cytokines	In vivo studies	[163]
17	S-nitrosoglutathione	Anti-inflammatory	In vivo studies	[164]
	Plant Sterol			
18	Guggulsterone	Inhibition of NF-kB	In vitro & In vivo studies	[83]

Table: 2

Prevention of Experimental Uveitis by Non-antioxidants

#	Non-antioxidants	Mechanism of Action	R & D Status	References
1	Anti-LFA-1-α antibody	Activation of T cells	In vivo studies	[170]
2	Anti-IL-17 antibody	Blockage of endogenous IL-17	In vivo studies	[171]
3	Amino acid copolymers	Competitive binding to antigen presenting cells & Induction of immunosuppressive cytokine secreting regulatory T cells.	In vitro & vivo studies	[173]
4	siRNA	Silencing targeted RNA	In vivo studies	[174]
5	Recombinanat adeno-virus	Gene therapy	Recombinanat adeno-virus	[190]
6	Polylactic-glycolic acid (PLGA)	Anti-inflammatory corticosteroids	In vivo studies	[176]
7	Telmisartan (Receptor Blocker)	Blockage of angiotensin II Type 1 receptor	In vivo studies	[177, 178]
8	Glucosamine (Sugar Monosachharide))	Inhibition of NF-κB-dependent signaling pathway	In vitro & vivo studies	[179]
9	LX211 (voclosporin)	Inhibition of lymphocytes and T-cells proliferation	In vitro & vivo studies	[180]
10	Chitinase inhibitors	Inhibition of acidic mammalian chitinase	In vivo studies	[181]
11	Vascular adhesion protein-1 inhibitor	Inhibition of recruitment of leucocytes	In vivo studies	[182]
12	Methylprednisolone acetate	-NA-	In vivo studies	[183]
13	Cloricromene	Inhibition of TNF-α	In vivo studies	[184]
14	Aprotinin	ROS scavenger	In vivo studies	[158]
15	Melatonin	ROS scavenger	In vivo studies	[158]
16	NF-κB inhibitor	Inhibition of NF-κB	In vitro & In vivo studies	[89, 165]
17	Infliximab	Anti-TNF-α antibody	In vivo studies	[121]
18	DAF	Modulation of T-cell response	In vivo studies	[187]
19	Oligodeoxynucleotide	Expression of suppressive oligonucleotide motif	In vivo studies	[186]
20	Peptide	Immunomodulation of intraocular macrophages and deviant stimulation of T-cells	In vivo studies	[185]
21	Zopolrestat, Fidarestat	Inhibition of aldose reductase	In vitro & In vivo studies	[81]
22	Anti- αβ TCR monoclonal antibody	Blockage of αβ T-ceel receptor	In vivo studies	[122]
23	T-cell receptor V beta 8.3 peptide vaccine	Vaccination	In vivo studies	[141]
24	Caffeic acid phenethyl ester	Inhibiting NF-κB Suppressing ROS production	In vivo studies	[138]
25	MAPK Inhibitor	Inhibition of MAPK pathway	In vitro & In vivo studies	Ramana et al. (Unpublished observation)