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Review

Neuroprotective Role of Cannabinoids in Retinal Disease

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Abstract

Cannabinoids, compounds that interact with the endocannabinoid system, have shown promising neuroprotective effects in various neurodegenerative diseases, including those affecting the retina. This review evaluates evidence for the presence and action of cannabinoids in the retina, their function in protecting against oxidative stress and modulating neuroinflammation, and the outcomes observed in animal models of retinal diseases such as glaucoma and age-related macular degeneration (AMD), the most common causes of vision loss. Cannabinoids have proven effective in reducing the neurodegeneration seen in these eye diseases, acting via the CB1 and CB2 cannabinoid receptors. The cannabinoid neuroprotective effect is often of a similar magnitude to the other proven therapy of medical dosage of vitamins, though it confers a greater risk due to neurotoxicity with high THC:CBD ratios, making the vitamin therapy of greater efficacy when time is available. Given the increased ratio of THC:CBD in commercial cannabis strains, rising from 10:1 at the beginning of this century to 100:1 now, the risk of neurotoxicity has increased, reducing the neuroprotective benefit. The proven safety and efficacy of vitamin therapy may be a more viable neuroprotective method than cannabinoid use for chronic conditions, with cannabinoids proving their utility in more acute conditions. This review evaluates both the method of action of cannabinoids and the receptor pathway utilized and compares the suggested therapeutic applicability of cannabinoids with proven vitamin therapy.

Keywords: cannabinoids; neuroprotection; glaucoma; AMD; oxidative stress

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1. Introduction

Retinal neurodegenerative diseases such as glaucoma and AMD are major causes of irreversible blindness worldwide. These conditions are characterized by progressive loss of retinal neurons due to mechanisms including oxidative stress, inflammation, and apoptosis [1–3]. Much recent evidence indicates that an important aspect of the retinal degenerative diseases is an impaired retinal vasculature, diminishing retinal perfusion. Restoration of the retinal vasculature can be achieved with nutrient supplementation, and the vasculature health ascertained by assessing decreases in retinal venous pressure and plasma homocysteine levels [4]. Such efforts have shown that both AMD [5] and glaucoma [6] can be successfully kept in check with appropriate vitamin and mineral supplementation, following the AREDS2+ formulation.

While a lifestyle medicine strategy of nutrient restoration is a viable chronic solution to these degenerative diseases, an acute solution appears to be available with cannabinoids. Cannabinoids, both natural and synthetic, have been explored as potential neuroprotective agents capable of targeting these pathological processes. Use of such compounds may provide a rapid, acute treatment when the slower chronic treatments are unavailable. While cannabinoids show neuroprotective and anti-inflammatory potential in preclinical models,

their clinical use for retinal diseases is limited by short-lived effects, visual side effects, lack of sustained IOP reduction, formulation challenges, and insufficient evidence for efficacy [7–9].

1.1. Cannabinoid Receptors in the Retina

Experimental studies using electroretinography, immunohistochemistry, and molecular biology techniques have confirmed the functional presence of cannabinoid receptors and their involvement in retinal signaling and visual function [10–13]. See Table 1 for a summary of findings.

Table 1. Cannabinoid receptors in the retina.

Aspect	Findings
Receptor Types	CB1 in neuronal layers, CB2-RPE, PR, RGC
Functions	Modulate adaptation, processing, neurotransmission
Experimental Evidence	Electrophysiology, molecular anatomy, behavioral assays
Clinical Relevance	Potential therapies for retinal disease

RPE = retinal pigmented epithelium, PR = photoreceptor, RGC = retinal ganglion cell.

The vertebrate retina expresses the two main types of cannabinoid receptors: CB1 and CB2. There has been a wide array of published work, especially in rodents and humans, on the presence, distribution, and function of cannabinoid receptors in the retina. CB1 receptors are found in both the inner and outer plexiform layers and are primarily located in retinal ganglion cells (RGCs), photoreceptors, bipolar and amacrine cells [10,13–15]. CB2 receptors are largely expressed in retinal pigmented epithelium, retinal ganglion cells, photoreceptors, and the inner plexiform layer [10,14–17]. This distribution suggests that cannabinoids could directly modulate both neural and immune responses within the retinal microenvironment.

Cannabinoid receptors regulate neurotransmitter release and modulate synaptic activity in the retina. Activation of CB2 receptors can inhibit voltage-gated calcium channels in bipolar cells to regulate glutamatergic synaptic transmission [13,15]. One study has shown that endocannabinoid signaling enhances visual responses in low-light conditions by increasing RGC excitability via AMPK-dependent inhibition of chloride channel activity [12].

Cannabinoids modulate the sensitivity and excitability of retinal synapses in a dynamic, activity-dependent manner in the mouse retina. Agonists of cannabinoid receptors can reduce spontaneous spiking and light-driven responses in ON-sustained RGCs, while antagonists have the opposite effect [18]. This mechanism counters dopamine signaling in the retina, which impacts the switch between rod- and cone-mediated vision as the retina modulates to differing lighting conditions.

Cannabinoid receptor activation is associated with neuroprotective effects in the retina, including protection against oxidative stress, excitotoxicity, and cell death in models of retinal degeneration, diabetic retinopathy, and glaucoma [18,19].

1.2. Glutamate and Neurotoxicity

Glutamate is the most common excitatory neurotransmitter in the eye, as it is present throughout the retinal layers and is actively used by photoreceptors, bipolar cells, and RGCs [20]. Glutamate is also toxic to neurons when it is present at elevated levels outside the cells [21]. Indeed, glutamate levels in the vitreous humor of glaucomatous patients are twice those of non-glaucoma patients, and this elevated glutamate is believed to be a means by which glaucomatous patients have a reduced visual field [22]. Experimentally exposing the retina to elevated exogenous glutamate triggers an excitotoxic cell loss via

NMDA receptors [23]. The excitotoxic RGC loss can be at least partially ameliorated with activation of CB1 and/or CB2 receptors, revealing a neuroprotective effect of cannabinoids in the retina [24,25].

1.3. Glaucoma and Macular Degeneration

The most common degenerative eye diseases are glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy. Most of the evaluation of cannabinoids as neuroprotectants has used a glaucoma model, with the expectation that similar results may hold true for diabetic retinopathy due to the similar progression of cell loss in the disease, and an expectation that any neuroprotective effect may provide a benefit for advanced AMD.

Glaucoma is a neurodegenerative disease that kills retinal ganglion cells starting from the periphery of the retina and developing toward the fovea at the center [26]. Since the optic nerve is comprised of retinal ganglion cell axons, glaucoma is clinically assessed as a cupping or excavation of the optic nerve and by progressive loss of visual field [27]. Glaucoma in a majority of cases is detected by an elevated intraocular pressure, though a significant fraction of individuals of Asian descent present with normal intraocular pressure [4]. This elevated pressure is believed to trigger the excitotoxic action on RGCs, resulting in degeneration of these RGCs. Glaucoma is treated principally by reducing intraocular pressure, meaning those with normal pressure have little effective means to prevent progressive vision loss.

Recent clinical studies have shown that progression of both glaucoma and AMD can be halted with a modified AREDS2 formulation [5,6]. This vitamin/mineral treatment uses medical levels of vitamins to rescue AMD-stressed photoreceptors and to restore sufficient vascular perfusion in glaucoma and AMD. This has been documented by measuring the retinal venous pressure in human patients and finding that while it is elevated in both diseases, this AREDS2-type formulation (Ocufolin forte) decreases this pressure, restoring normal perfusion and drainage from the eye [4,28]. Of note, this treatment is equally effective for normal tension (normal pressure) glaucoma [6].

2. Cannabinoids and Oxidative Stress

There are many reports in the scientific literature investigating the relationship between cannabinoids, in particular cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), and oxidative stress. The research spans in vitro studies, animal models, and some clinical observations. Table 2 summarizes the observed findings.

Oxidative stress contributes significantly to retinal damage in diseases like AMD, glaucoma, and diabetic retinopathy. Cannabinoids have demonstrated antioxidant properties that mitigate oxidative damage in a number of tests. They have been shown to upregulate endogenous antioxidant enzymes and downregulate oxidative stress in AMD via CB1 action on human retinal pigmented epithelial cells [29].

Table 2. Cannabinoids and oxidative stress.

Cannabinoid	THC	CBD
Antioxidant effect	Strong	Moderate to strong
Mechanism	ROS scavenging Enzyme modulation	ROS scavenging Mitochondrial protection
Potency vs. classical antioxidant	Same or more: BHT Same or more: vitamin E,C	Same or more: vitamin E,C
Source	[30,31]	[31,32]

2.1. Cannabinoids and Neuroprotection

Cannabinoids reduce oxidative stress and reactive oxygen species, as well as lower cytokine production, specifically tumor necrosis factor and interleukins IL-1β and IL-6, in a hypoxia-ischemic model [32]. In this case, cannabinoid action was stimulated by the agonist, WIN 55,212-2. And in an experiment using cannabinol, it was found to preserve mitochondrial function as a strong neuroprotective action [33].

Further, it has been shown that Δ9-THC protects retinal neurons from glutamate-induced oxidative stress. The same study also found that cannabidiol (CBD), a non-psychoactive cannabinoid, provided neuroprotection independent of CB1 receptors [25].

The cannabinoid THC has shown neuroprotective action in non-retinal neuronal systems. THC is protective for cerebral neurons against ouabain-induced excitotoxicity [34], it protects against glutamate-induced toxicity in cultured neurons [35], and it is neuroprotective of forebrain neurons in a Parkinson model [36].

In the retina, there have been a wealth of studies showing neuroprotection from cannabinoids. The endocannabinoid, anandamide, eases inflammation by action on the Müller glial cells [37]. Anandamide also protects retinal amacrine neurons from AMPA excitotoxicity via CB1 activation [38] and acts via CB1 and transient receptor potential vanilloid 1 (TRPV1) to modulate Ca^{2+} balance in retinal neurons, providing neuroprotection [39]. TRPV1 has been proposed to regulate retinal ganglion cell excitability and may provide neuroprotection of these cells with physiological anandamide levels [40].

Studies using synthetic cannabinoids HU210 and WIN 55,212-2 have also shown neuroprotective effects in the retina. HU210 protected photoreceptors in a model for retinitis pigmentosa [41]. WIN 55,212-2 was protective of retinal ganglion cells in rats subjected to elevated intraocular pressure [42], as well as in a glutamate-induced toxicity model in mice [24].

2.2. Modulation of Neuroinflammation by Cannabinoids

Chronic inflammation is another hallmark of retinal degeneration. Cannabinoids, particularly through CB2 receptor activation, have been shown to suppress microglial activation [43] and reduce pro-inflammatory cytokines such as TNF-α and IL-1β [32,44]. Similarly, cannabinoid action on the CB2 receptor provided neuroprotection in hippocampal neurons by inhibiting activation of interleukins IL-1β, IL-6, and TNF, and thus suppressing the microglial response [45]. Additionally, CBD has shown anti-inflammatory effects in models of diabetic retinopathy by reducing oxidative and nitrosative stress [46], and CBD acts on both a CBD-activated receptor termed G-protein coupled receptor-3 and another pathway to suppress inflammatory activation of astrocytes and microglia [47].

2.3. Antioxidant Activity of Cannabinoids

Both THC and CBD have demonstrated antioxidant properties in various models. For example, in differentiated human neuronal SH-SY5Y cells exposed to oxidative stress inducers such as hydrogen peroxide and amyloid-β (in the presence of Cu(II)), cannabis extracts and pure THC reduced reactive oxygen species formation. CBD also showed antioxidant effects, but they were less potent than THC under these conditions [30,31].

The action of cannabinoids in combating oxidative stress appears to be via several mechanisms. Inhibition of ROS formation induced by neurotoxic insults, as in the Alzheimer's model described above; modulation of antioxidant enzyme levels (superoxide dismutase); and direct scavenging of free radicals [30,48,49].

Both THC and CBD prevent oxidative damage as effectively as, or better than, established antioxidants like α-tocopherol (vitamin E) and ascorbate (vitamin C) [31].

2.4. Potential Mechanism of Action by Cannabinoids

Cannabinoids have shown neuroprotective effects in models of neurodegenerative diseases (e.g., Alzheimer's, Parkinson's, ALS), attributed in part to their ability to reduce oxidative stress and modulate neuroinflammation [30,48,49].

CBD can modulate redox balance by altering the levels and activity of antioxidant molecules, independently of cannabinoid receptor activation [50,51]. This includes effects on mitochondrial function and the attenuation of ROS generation [49].

The endocannabinoid system itself is implicated in the control of oxidative signaling, suggesting that both endogenous and plant-derived cannabinoids may influence oxidative stress in various pathological conditions [48].

2.5. Antioxidant Effect Differences Between THC and CBD

CBD and THC both provide significant antioxidant effects, but through somewhat different mechanisms. CBD acts through direct ROS neutralization, metal chelation, and upregulation of endogenous antioxidant defenses, while THC primarily scavenges free radicals and supports neuronal health by reducing oxidative stress. CBD may offer greater protection in certain neurotoxicity models, while both cannabinoids can act synergistically for enhanced antioxidant benefits [31,52–54].

Both CBD and THC display strong antioxidant properties, often comparable to or exceeding those of well-known antioxidants like vitamin C and vitamin E [31,54]. CBD may be more effective than THC in certain neurotoxicity models, particularly in protecting neurons from glutamate-induced damage [31]. Studies have observed synergistic and antagonistic interactions between CBD and THC regarding their antioxidant activities, suggesting that their combined effects can be greater or different than when used alone [54].

Table 3 is a summary of CBD and THC effects as antioxidants and their observed differences, as follows:

Table 3. Key differences between CBD and THC.

Aspect	CBD	THC
Psychoactivity	Non-psychoactive	Psychoactive
Direct ROS Scavenging	Yes	Yes
Enzyme Modulation	Upregulates SOD, GPx	Preserve DA, tyrosine hydroxylase
Metal Chelation	Yes	Not prominent
Neuroprotection	Strong (esp. w/glutamate)	Strong (esp. w/DA)
Comparative Potency	Stronger than vitamin C/E	Correlated w/extract content
Synergy	Enhanced when incl THC	Enhanced when incl CBD

DA = Dopamine, SOD = superoxide dismutase, GPx = glutathione peroxidase.

CBD acts as a direct antioxidant by neutralizing reactive oxygen species (ROS) due to its molecular structure [52,53]. CBD chelates transition metal ions, reducing the Fenton reaction and subsequent free radical production, and it upregulates endogenous antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) [52]. CBD prevents depletion of essential trace elements (Zn, Se) needed for antioxidant enzyme activity and demonstrates neuroprotective effects by reducing lipid peroxidation, ROS accumulation, and protein degradation in neuronal models [52,53]. Importantly, CBD is more protective against glutamate-induced neurotoxicity than ascorbate (vitamin C) or α-tocopherol (vitamin E) [31].

THC scavenges free radicals and reduces oxidative stress, thereby protecting neurons [53]. THC reduces dopamine depletion and preserves tyrosine hydroxylase activity by inhibiting oxidative stress in neuronal models, and its antioxidant activity is closely

correlated with its concentration in cannabis extracts. THC exhibits anti-inflammatory properties, which indirectly support antioxidant defenses [53].

2.6. Impact of THC:CBD Ratios on Neuroprotection

The neuroprotective effects of cannabis extracts are strongly influenced by the ratio of THC to CBD. Studies reveal that the balance between these two cannabinoids can determine whether an extract is neuroprotective, neutral, or possibly neurotoxic under certain conditions. There has been a litany of arguments in natural healing circles that the THC:CBD ratio of about 10:1 seen in earlier versions (1990s) of the marijuana available was more appropriate for protecting nervous system function. But in recent decades, the plants have been bred for increasing levels of THC to the detriment of CBD, with ratios approaching 100:1, and with four times the THC in the plant now as compared to 30 years ago [55]. The rationale has apparently been to maximize the psychotropic effect by increasing THC levels, but this may have reduced the medical effect of newer strains, as a decrease in CBD and concomitant increase in THC is considered to reduce the medicinal utility. A summary of these observations is in Table 4 and is detailed below.

Table 4. THC:CBD ratio and neuroprotective effect.

THC:CBD Ratio	Observed Effect on Neurons
High THC, Low CBD	Neurotoxic, worsened injury
Balanced/High CBD	Neuroprotective, reduced damage
CBD Alone	Strong, consistent neuroprotection
THC Alone	Less consistent, sometimes neurotoxic

Extracts or combinations with high THC and low CBD concentrations have been shown to exacerbate neuronal injury and tissue disorganization in models of oxygen-glucose deprivation, a common experimental proxy for ischemic brain injury. Specifically, 1 μM THC combined with only 0.05 μM CBD produced significant neurotoxic effects [56]. As the relative concentration of CBD increases in the presence of THC, the neurotoxic effect is diminished and eventually disappears. This suggests that CBD may buffer some of the adverse effects of THC on neurons [56]. Extracts with higher CBD relative to THC (such as an extract with 10 μM CBD and 5 μM THC) demonstrated significant neuroprotective effects, reducing neuronal damage and restoring tissue organization after injury. Lowering the THC content in these higher-CBD mixtures reduced the neuroprotective effect, indicating a synergistic interaction at certain ratios [56].

In direct comparisons, CBD alone provided significant protection against neuronal damage and tissue disorganization, while THC alone was less consistent and, in some cases, increased markers of neuronal injury. The protective effect of THC is mediated primarily through CB1 receptors, while CBD's neuroprotection involves TRPV2, 5-HT1A, and PPARγ pathways, which may explain their different roles and interactions in neuroprotection [56].

Additional research confirms that both THC and CBD can exert antioxidant and neuroprotective effects, but the presence of CBD may reduce some of THC's side effects and enhance the therapeutic profile of cannabis extracts [57].

The neuroprotective properties of cannabis extracts are optimized when the ratio of CBD to THC is balanced or weighted toward CBD. High-THC, low-CBD formulations may be neurotoxic, while higher CBD content can buffer THC's adverse effects and enhance neuroprotection. These findings underscore the importance of cannabinoid ratios in designing therapeutic cannabis products for neurological health [56,57].

2.7. THC vs. CBD in Neuroprotection

There is some conflict as to whether THC or CBD is the more important neuroprotective agent. The data reviewed above affirm that each has shown neuroprotective properties, with the THC neuroprotection mediated via the cannabinoid receptors, while CBD is not mediated via cannabinoid receptors and may function by reducing reactive oxygen species (ROS). Another difference has been the experimental model used, with THC more effective in dopamine models and CBD more effective in glutamate-induced toxicity.

The recently observed cautions of high THC:CDB ratios losing neuroprotection and showing neurotoxicity may indicate that the more powerful neuroprotective function is from an appropriate ratio of THC:CBD. If this is the case, it presents a powerful caution to the use of the commercial strains of cannabis now available as compared to those tested in previous decades.

3. Cannabinoids in Models of Retinal Disease

Multiple reports indicate cannabinoids modulate neurotransmitter release, oxidative stress, and inflammatory responses in the retina, supporting their potential as therapeutic agents for retinal diseases [17,58]. The endocannabinoid system is increasingly recognized as a target for developing new therapies for retinal pathologies, including glaucoma and AMD, though most evidence is from preclinical studies [19,58]. The various mechanisms of action of cannabinoids are described below and summarized in Table 5.

Table 5. Mechanisms of cannabinoid neuroprotection against oxidative damage.

Mechanism	Description/Effect	Source
Free radical scavenging	Neutralizes ROS directly	[30,31,50]
Inhibition of ROS formation	Reduce mitochondrial ROS production	[30,50]
Modulation of signaling paths	Activates ECS, modulates Ca/excitotoxicity	[31,59]
Enhance antioxidant enzymes	Upregulates endogenous antioxidants	[50,59]
Neuroinflammation reduction	Suppresses cytokines, microglial activation	[59]
Receptor-independent effects	Antioxidant action w/o CB1/CB2 activation	[31]
Support BBB and neurogenesis	Maintains BBB, promotes neurogenesis	[59]

BBB = Blood Brain Barrier, ECS = Endocannabinoid System.

3.1. Cannabinoids and Prevention of Oxidative Damage

Cannabinoids combat oxidative neuronal damage through a combination of direct antioxidant effects, modulation of cellular signaling, enhancement of endogenous defenses, and reduction of neuroinflammation, making them promising agents for neuroprotection in oxidative stress-related conditions [31,50,51,59]. Cannabinoids, including THC and CBD, protect neurons from oxidative damage through multiple interrelated mechanisms.

3.1.1. Free Radical Scavenging

Both THC and CBD possess intrinsic antioxidant properties, allowing them to directly neutralize reactive oxygen species (ROS) and other free radicals. This direct scavenging has been demonstrated in various models, where cannabinoids reduced ROS formation induced by hydrogen peroxide, β-amyloid, and other oxidative insults [31,50,51].

3.1.2. Inhibition of ROS Formation

Cannabinoids can inhibit the production of ROS within neurons. For example, CBD has been shown to reduce mitochondrial superoxide generation and decrease ROS production following oxidative challenges in neuronal and non-neuronal cells [50]. THC-rich cannabis extracts also significantly reduce ROS formation in neuronal cultures exposed to oxidative stressors [30].

3.1.3. Modulation of Cellular Signaling Pathways

Cannabinoids influence several signaling pathways involved in oxidative stress. Activation of the endocannabinoid system, particularly CB1 and CB2 receptors, leads to reduced oxidative stress and neuroinflammation, contributing to neuronal survival [59]. Cannabinoids also modulate calcium-dependent excitotoxicity by protecting against glutamate-induced toxicity, which is partly mediated by overactivation of NMDA and other glutamate receptors [31].

3.1.4. Enhancement of Endogenous Antioxidant Defenses

Cannabinoids may upregulate the expression and activity of endogenous antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, further strengthening the cell's ability to counteract oxidative damage [50,59].

3.1.5. Neuroinflammation Reduction

By reducing the release of pro-inflammatory cytokines and inhibiting the overactivation of microglia and astrocytes, cannabinoids decrease secondary oxidative damage associated with neuroinflammation [59].

3.1.6. Receptor-Independent Antioxidant Effects

Some antioxidant and neuroprotective actions of cannabinoids, especially CBD, occur independently of classical cannabinoid receptors, as demonstrated by their ability to protect neurons even in the presence of cannabinoid receptor antagonists [31].

3.1.7. Additional Protective Actions

Cannabinoids also help maintain blood–brain barrier integrity, reduce neuronal excitotoxicity, and may promote neurogenesis, all of which indirectly support neuronal resistance to oxidative stress [59].

3.2. Suppression of Neuroinflammation

Cannabinoids have consistently reduced neuroinflammation by modulating immune cell activity, decreasing pro-inflammatory cytokines, and protecting neurons. These findings support the therapeutic potential of cannabinoids in neuroinflammatory and neurodegenerative diseases [60–62].

A substantial body of research demonstrates that cannabinoids, both plant-derived (such as THC, CBD, and cannabigerol) and synthetic, can reduce neuroinflammation through several mechanisms.

3.2.1. Cannabinoid Receptors and Neuroinflammation

Cells involved in neuroinflammation express functional cannabinoid receptors and produce endocannabinoids. During neuroinflammatory conditions, components of the cannabinoid signaling system are upregulated, and activation of these receptors generally elicits anti-inflammatory effects. Studies in rodent models of multiple sclerosis show that cannabinoid agonists can ameliorate both the progression and symptoms of neuroinflammation [63].

3.2.2. Mechanism of Action

Cannabinoids reduce neuroinflammation by inhibiting afferent neuronal firing and the release of inflammatory neuropeptides [61]; modulating immune cell function, leading to decreased production of pro-inflammatory cytokines (such as IL-1β, TNF-α, and IFN-γ) [62]; directly affecting vascular smooth muscle and inflammatory cells; and silencing small-diameter neurons to reduce inflammation [61].

3.2.3. Cannabinoids Evaluated

Cannabidiol (CBD): Demonstrated anti-inflammatory effects in various in vitro, ex vivo, and in vivo models, including reducing inflammation in the gastrointestinal tract and CNS [60,64].

Cannabigerol (CBG): Shown to reduce pro-inflammatory cytokine levels and neuronal death in models of neuroinflammation and neurodegeneration [62].

Tetrahydrocannabinol (THC): Exhibited anti-inflammatory effects in animal models, such as reducing immune cell infiltration and cytokine production in allergic contact dermatitis, with some actions independent of CB1/CB2 receptors [62].

3.2.4. Therapeutic Implications

Reviews highlight that the endocannabinoid system is a promising target for developing treatments for neuroinflammatory diseases, including multiple sclerosis and neurodegenerative disorders, due to its regulatory role in immune responses and neuroprotection [60].

3.3. Glaucoma

Glaucoma involves progressive degeneration of RGCs, often associated with elevated intraocular pressure (IOP). Cannabinoids have shown promise in protecting retinal ganglion cells against excitotoxicity, as well as transiently lowering intraocular pressure. Multiple reports have indicated that Δ9-THC and endocannabinoids have a neuroprotective effect, in addition to their role in lowering IOP [25,65–68]. The synthetic cannabinoid WIN55,212-2 offers neuroprotection against excitotoxicity and oxidative damage [24].

Specifically, in an NMDA-induced excitotoxic model, the co-application of NMDA with WIN55-212.2, or with an extract prepared from marijuana, the cannabinoids were effective in protecting up to 50% of the RGCs in this acute excitotoxic model [24]. Intriguingly, the extract proved more consistent in neuroprotection and was more effective than in other published reports with THC. This may indicate that activation of both the CB1 and CB2 receptors is necessary for a maximal effect, or that other components present in the extract act in a different fashion to potentiate or otherwise enhance the neuroprotection. This interpretation is supported by evidence finding cannabidiol, a non-psychoactive component of marijuana, to confer neuroprotection in ischemic or excitotoxic conditions [69,70].

Cannabinoids, including THC and CBD, have demonstrated neuroprotective effects in glaucoma models. In NMDA excitotoxic rat models, both THC and CBD protected retinal cells by reducing peroxynitrite levels, and these effects appeared to be independent of CB1 and CB2 receptor activation [65]. Endocannabinoids such as anandamide have shown neuroprotection against retinal cell death induced by high intraocular pressure (IOP), one hallmark of glaucoma, through CB1 receptor engagement. While animal studies and early human trials have shown that THC can transiently lower IOP, there are side effects and tolerance issues. CBD, in contrast, may transiently increase IOP [65]. CB1 and CB2 receptor agonists have been shown to protect against retinal ischemia and excitotoxicity in animal models, further supporting their neuroprotective potential in glaucoma [19].

Additionally, it has been reported that delivery of either synthetic or endocannabinoids has equivalent effectiveness. In their report, an intravitreal injection of the cannabinoid showed the same level of neuroprotection of retinal ganglion cells as a topical application of the cannabinoid on the sclera [24]. Such a finding is promising if any cannabinoids were to be developed for treatment.

3.4. Age-Related Macular Degeneration (AMD)

In AMD, particularly the dry form, photoreceptor and RPE degeneration are central features. Cannabinoids have been shown to protect RPE cells from oxidative damage [29] and to mitigate light-induced retinal degeneration [19,71,72].

In models of light-induced retinal degeneration, which share features with human AMD, stimulation of CB1 receptors improved photoreceptor survival and reduced glial reactivity. Cannabidiol (CBD) significantly reduced oxidative stress and neurotoxicity, preventing retinal cell death in a rat model of diabetic retinopathy, which shares degenerative features with AMD [19].

Mixed CB1/CB2 agonists and CB2-selective agonists have shown neuroprotection in models of NMDA-induced excitotoxicity and other retinal degeneration paradigms. Some studies have found that CB1 antagonists (such as rimonabant) or genetic deletion of CB1 can also be protective in certain models, suggesting complex roles for cannabinoid signaling depending on disease context and receptor subtype [19].

Overall, studies have demonstrated that cannabinoids, both plant-derived and endogenous, exert neuroprotective effects in animal models of glaucoma, AMD, and related retinal diseases, mainly by reducing oxidative stress, modulating neurotransmission, and protecting against cell death. The findings to date support further investigation into cannabinoid-based therapies for retinal neurodegeneration [19,65,73].

3.5. Counter-Effects and Concerns of Cannabinoids

While cannabinoids show neuroprotective and anti-inflammatory potential in preclinical models, their clinical use for retinal diseases may be limited by short-lived effects, visual side effects, lack of sustained IOP reduction, formulation challenges, and insufficient evidence for efficacy in conditions like AMD. Caution is advised due to these limitations and potential adverse effects [7–9,74]. These concerns are summarized in Table 6.

Table 6. Key cautions in the use of cannabinoids.

Caution	Details
Transient IOP reduction	Short-term impact
Visual function impairment	Affects contrast and night vision
Limited AMD efficacy	Little effect for AMD
Safety and abuse potential	Impractical for long-term use in glaucoma
Formulation and dosing challenges	No standardization for ocular preps
Possible IOP increase with CBD	Some evidence for elevated IOP

IOP = Intraocular Pressure.

3.5.1. CBD Importance

There are several caveats to the use of cannabinoids in the treatment of eye disease. In addition to the previously described differentiation of CB1 and CB2 effects, in which neuroprotection may be activated via both receptor types, or may involve cannabinoid activation in combination with other effects, such as a suppression of inflammation and oxidative stress. This raises the concern as to whether the psychoactive component of cannabis is necessary for neuroprotection, or whether CBD may be sufficient in some cases.

3.5.2. IOP Reduction Is Not Relevant

There are other reasons for caution, such as the transient impact, potential adverse ocular effects, and safety issues. Cannabinoids, including THC and CBD, can lower intraocular pressure (IOP), but the effect is short-lived and not sustained enough for practical glaucoma management. There is a lack of well-formulated and standardized ocular cannabinoid preparations, making consistent dosing and delivery a challenge [8].

3.5.3. Cannabinoid Negative Side Effects

Major ophthalmology organizations caution that marijuana (in any form) is not a safe or practical medication for reducing eye pressure in glaucoma due to its short duration of action, side effects, and potential for abuse. Both topical and systemic cannabinoid analgesics can relieve acute ocular pain but have marked limitations in their safety profile, including the risk of systemic side effects and potential for abuse or dependency [74].

3.5.4. Cannabinoid Deleterious Impact

Cannabinoids may transiently impair several aspects of vision, including night vision, depth perception, contrast sensitivity (both binocular and monocular), and dynamic visual acuity [9]. Some studies indicate that cannabinoids can cause transient increases in IOP, particularly with CBD, which could be counterproductive in glaucoma management [7]. There is very little clinical evidence supporting the use of cannabis or CBD for treating macular degeneration (AMD), either wet or dry forms.

Perhaps most concerning are some effects of chronic cannabinoid use. Whether endogenous or synthetic cannabinoids are used, there is a measurable down-regulation of the CB1 receptor with chronic use. This down-regulation impacts the protective utility of cannabinoids, as there is a loss of the neuroprotective effect in some studies [75,76]. In addition, chronic cannabinoid use creates retinal dysfunctions with adverse effects on photoreceptors, bipolar cells, and RGCs [76,77].

There is now strong evidence that cannabinoid use doubles the risk of cardiovascular mortality. In a recent meta-analysis, it was found that cannabis use was associated with a doubling of major adverse cardiovascular events, including a doubling of the likelihood of death from these adverse events [78]. Additionally, a recent meta-analysis of reports shows that cannabis with the high THC levels seen currently increased negative mental health outcomes, in particular psychosis, schizophrenia, depression, and anxiety [79]. It would seem, then, that the enhanced risk from cannabis in causing retinal dysfunctions and raising the risk of cardiac mortality would argue for a cautious approach to its use as a therapeutic.

4. Conclusions

Cannabinoids offer multifaceted neuroprotection in retinal diseases by reducing oxidative stress, suppressing inflammation, and directly protecting neuronal cells. Preclinical models support their therapeutic potential in glaucoma, diabetic retinopathy, and AMD. The growing evidence that cannabinoid neuroprotection is mediated by both CB1 and CB2 receptors, with CB2 having a greater role, provides caution for the use of medical marijuana. In recent years, the marijuana strains commercially available have had an increasing THC component (which principally activates CB1 receptors and produces the psychotropic effect) and a decreasing CBD component (which activates CB2 receptors that reduce inflammation and oxidative stress). It may be that these newer strains, which continue to focus on enhancing the psychedelic experience, are reducing the medicinal value of marijuana in treating nervous system dysfunction. It may be that the role of CBD, or the THC:CBD ratio, or other compounds in the marijuana plant are more pertinent for restoring neural function, and that the progressive decrease in CBD in commercially available strains is decreasing their medical value to the detriment of patients. This is particularly essential because multiple studies have shown down-regulation of the CB1 receptor in response to chronic cannabinoid application. If the commercially available strains have an increasing THC component, it may be that medicinal utility is being sacrificed to maintain a psychoactive effect in the face of developing tolerance.

Additionally, the evidence showing neuroprotection via presumed activation of the CB2 receptor using a spice (saffron) [80] lends credence to lifestyle medical treatments that seek to modify diet and activity to reduce agents of oxidative stress. Coupled with the mounting clinical evidence that nutritive solutions are effective in treating conditions such as glaucoma and AMD [5], these findings may show that restored vascular retinal health may couple with such endogenous CB2 activation as an effective chronic therapy for reducing the risk of retinal disease. Focusing on CB2 activation and using the less toxic cannabis component of CBD in place of THC (or using other spice or herbal compounds to activate CB2) appears to be the viable route forward in exploring cannabis components in neuroprotection. And with the documented cardiac risks from THC [78], there is further reason to shun use of the newer commercial strains that have higher THC:CBD ratios than previous ones when seeking a neuroprotective effect. Based on the current data of the effect of the different compounds and the counter effects, these newer strains seem to be designed for neurotoxicity rather than neuroprotection.

Figure 1 summarizes the current state of understanding of the neuroprotective effects of the proven AREDS2+ vitamin therapy (the slow neuroprotection route in the left column of the figure) and the CBD-dominant cannabis therapy (the fast neuroprotection route, adjacent to the AREDS2+ column). It contrasts the THC-dominant effects of neurotoxicity and cardiotoxicity (in the right half of the figure).

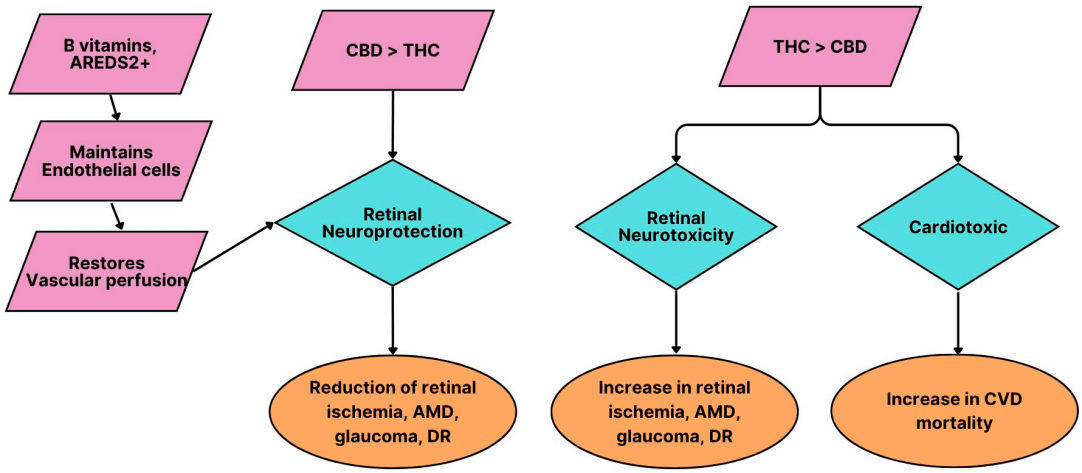


Figure 1. Summary schematic of neuroprotection (left side of figure) by AREDS2+ vascular support or CBD, and THC effects of neurotoxicity and cardiotoxicity (right side of figure).

We suggest experiments that evaluate the relative impact of nutritional remedies be compared with CBD as well as with THC to further delineate the mechanism of action and the most effective path forward to protecting vision from degenerative diseases. Given the importance of the CB2 receptor and of the relative CBD levels, as well as the utility of using less psychoactive products in treating eye disease, crafting studies that use the knowledge discussed in this review to evaluate therapies with CBD and vitamins, such as the AREDS2+ proven therapies, may provide a productive avenue for the development of useful treatments in degenerative retinal diseases.

Reflections on a Quarter Century of Cannabinoid Research

The promise of cannabinoid neuroprotection in the retina has long been just that, a promise. Twenty-five years ago was the first work showing a retinal neuroprotective effect for cannabinoids under glaucomatous conditions in a murine model [81], along with a THC protective effect in the cerebrum [82], followed by evidence in diabetic retinopathy conditions [25]. The ensuing two decades witnessed an increase in data regarding the

cannabinoid protective role, but less clarity as to the mechanism or specific receptors involved. Earlier studies point to an important role for THC and the CB1 receptor. As time progressed, the importance of CBD in the neuroprotective function became more evident, though via a different receptor or by modulating the cannabinoid receptor activity. What has been increasingly clear is that both components in an effective ratio are more effective than either singly.

While extracts from cannabis tested 25 years ago showed great promise for neuroprotection, this has become less clear in recent years as the THC:CDB ratio has climbed. Additionally, recent evidence has shown that with higher THC and lower CBD levels, a neurotoxic effect is seen. This has also been the case for THC, which has a potent cardiotoxic effect. Thus, the neuroprotective efficacy of cannabinoids may rely on the presence of CBD with THC. CBD alone is less protective. THC alone or with low CBD concentrations may become toxic.

Over this same time period, commercial strains of cannabis have had a dramatically increasing level of THC coupled with a decreasing level of CBD [83]. Given that neuroprotection for retinal neurons is observed when CBD is present along with smaller levels of THC, and that neurotoxicity is observed when THC levels are much higher than CBD, one conclusion is that THC, coupled with CBD (the 10:1 ratio seen in previous decades), is the more effective neuroprotectant. Having THC levels well in excess of CBD (the 100:1 ratio often seen in contemporary strains) is less effective as a neuroprotectant. This latter point may simply be because the elevated THC levels seen in contemporary strains are having a counter effect of neurotoxicity.

Over this same time period, the THC to CBD ratio has increased tenfold [83]. We speculate that this may explain the changing published evidence over the past two decades for neural protection by cannabis. The increased THC levels in products available in recent years may be creating a tolerance that drives the need for ever-increasing THC concentrations to produce similar psychotropic effects. But this same increased THC, coupled with a decreased CBD, is less effective at neuroprotection and indeed may be counterproductive due to the reported neurotoxicity and cardiotoxicity of THC with little CBD present.

Thus, the promise of cannabinoid neuroprotection remains a promise, rather than a certainty. We suggest that studies focus more on preparations with 10:1 ratios of THC:CBD to avoid the toxic effect and find an effective solution for retinal neuroprotection. Either the modulating effect of CBD or its neuroprotective effect via a non-cannabinoid system may be valuable in finding optimal neuroprotection with THC and CBD.

Meanwhile, first the AREDS regimen and then AREDS2 have proven efficacy as neuroprotectants in AMD, slowing the progression of this debilitating disease. And now with the treatment of AREDS2-like plus B vitamins, which support endothelial cells, improvement in vascular perfusion in the retina is gained. Improving vascular perfusion is proving to be a more effective therapy against AMD and has been effective with diabetic retinopathy and glaucoma, including low-tension glaucoma. Thus, there is an effective slow neural protectant available. Using THC/CBD as a fast neuroprotectant, it will provide a very useful tool in the treatment of retinal disease.

Having such a solution may provide a beneficial therapy in cases of acute trauma or toxic events in the retina. The proven efficacy of an AREDS2-type treatment as a neuroprotectant in AMD, glaucoma, and diabetic retinopathy provides us with a slow neuroprotectant [4–6]. Availability of AREDS2-like products, such as Ocufolin, makes such treatment convenient for daily use. This appears to currently be the most effective long-term neuroprotection for retinal diseases such as AMD, glaucoma, and diabetic retinopathy.

Having a cannabinoid available for fast neuroprotection would provide a quicker-acting therapy upon detection of one of these diseases.

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Abbreviations

The following abbreviations are used in this manuscript:

AMD	Age-related Macular Degeneration
RGC	Retinal Ganglion Cells
RPE	Retinal Pigmented Epithelium
CBD	Cannabidiol
THC	Δ9-Tetra-Hydro Cannabinol
NMDA	N-Methyl-D-Aspartate
IOP	Intraocular Pressure

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