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# Therapeutic Potential of Cannabinoids in Glaucoma – Hit or Myth? - A Review

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**Abstract**

**Introduction:** Glaucoma is a leading cause of irreversible blindness, characterized by elevated intraocular pressure (IOP) that damages the optic nerve. Current treatments mainly focus on reducing IOP, but some patients do not respond adequately to conventional therapies. Cannabinoids, particularly Δ9-tetrahydrocannabinol (Δ9-THC), have been investigated as potential adjunctive treatments for glaucoma. Studies have shown varying effects of cannabinoids on IOP regulation, though their precise mechanisms remain unclear.

**Aim of Study:** This study aims to evaluate the therapeutic potential of cannabinoids in the treatment of glaucoma by examining their effects on IOP, their mechanisms of action, and the risks and benefits associated with their use.
**Material and methods**: A comprehensive literature review of studies on the therapeutic potential of cannabinoids in glaucoma was conducted using the PubMed database.
**Results and Conclusions:** Cannabinoids, especially Δ9-THC, have demonstrated the ability to reduce IOP in both healthy individuals and glaucoma patients. However, the effect is typically short-lived, lasting only 3-4 hours. The efficacy of cannabinoids in reducing IOP is influenced by the method of administration (oral, intravenous, inhalation) and the delivery system used for topical application. Despite some promising results, the use of cannabinoids as a mainstream glaucoma treatment is limited by factors such as the short duration of action, the potential for addiction, and the occurrence of adverse effects like tachycardia, hypotension, and cognitive impairment. Although cannabinoids offer a unique approach to glaucoma management, further research is necessary to address these limitations and determine their long-term therapeutic viability.

**Keywords:** glaucoma, cannabinoids, cannabinoid receptors, intraocular pressure

## 1. Introduction

Glaucoma is a chronic neurological condition affecting the visual system, characterized by increased intraocular pressure (IOP), which can lead to irreversible vision loss. The World Health Organization ranks glaucoma as the third leading cause of permanent blindness (8.5%), following cataracts and uncorrected refractive errors (1). Currently, the only available treatments for this condition are reducing the production or improving the outflow of aqueous humor (2). Cannabinoids have been studied as potential anti-glaucoma drugs since the early 1970's (3). Marijuana is one of the most widely used psychoactive substances worldwide. Although it remains illegal in many countries, in some, its use for medical or recreational purposes is permitted, and the process of its legalization is gaining momentum (4). The Cannabis sativa plant has been used both as a medicine and a psychoactive substance for centuries. Its cultivation dates back approximately 12,000 years, originally in Central or Southeast Asia (5). In ancient civilizations such as China, Egypt, Greece, India, and the Roman Empire, hemp was used to make fibers for ropes and nets, food, and seeds for oil production. Medical marijuana, including Cannabis sativa or its derivatives such as Δ9-tetrahydrocannabinol (Δ9-THC), is used in the treatment of various conditions, including chronic pain, spastic disorders associated with multiple sclerosis, weight loss, and nausea and vomiting related to chemotherapy. It is also recommended for the treatment of cancer pain, acquired immunodeficiency syndrome (AIDS), Parkinson's disease, Crohn's disease, post-traumatic stress disorder (PTSD), and glaucoma (6). The potential use of cannabinoids in glaucoma treatment stems from their hypotensive properties that affect IOP. Many studies focus on the effects of cannabinoids in lowering IOP and their potential neuroprotective properties (7, 8).
The growing interest in cannabinoids among the public and the scientific community requires a deeper understanding of their mechanisms of action in the eye. Therefore, this review

describes the mechanisms of cannabinoid action in glaucoma therapy, presents available evidence regarding their role in treatment, efficacy, and side effects, as well as discusses their addictive potential and long-term health consequences.

## 2. Glaucoma

Glaucoma is a multifactorial, progressive neurodegenerative disease and the leading cause of irreversible blindness (9). It is estimated that more than 70 million people worldwide suffer from glaucoma, and this number is projected to reach 111.8 million by 2040, mainly due to the aging population (10, 11). Glaucoma is characterized by the loss of retinal ganglion cells and thinning of the retinal nerve fiber layer (12). Changes in the tissue of the neuroretinal rim of the optic nerve head lead to the cupping of the optic disc and gradual narrowing of the visual field. Patients experience a gradual, concentric loss of the visual field, which is associated with the deepening of the optic disc cupping. The disease often progresses asymptomatically for a long time, which means that the number of people with glaucoma is much higher than those who are aware of their condition. The most common type of glaucoma is primary open-angle glaucoma, but other types also exist, such as primary angle-closure glaucoma and secondary glaucomas, which arise due to other diseases (13).

The etiology of primary open-angle glaucoma is often referred to as mechanical or vascular. The mechanical process involves the compression of axons due to elevated intraocular pressure, while the vascular mechanism includes disturbances in blood flow and perfusion pressure at the back of the eye, leading to damage to the eye's structure (14). The main risk factors for glaucoma include myopia, advanced age, female gender, and genetic predisposition, with only chronic elevation of intraocular pressure being modifiable. IOP results from a delicate balance between the production of aqueous humor inside the eye and its outflow. The most common cause of elevated IOP is impaired outflow of aqueous humor through the trabecular meshwork, located in the iridocorneal angle. High IOP disrupts the homeostasis of the retina and optic nerve, leading to mechanical damage and hypoperfusion. Consequently, current glaucoma treatments focus on lowering IOP through pharmacological and surgical methods (12).

According to the current guidelines of the American Academy of Ophthalmology, the goal is to lower intraocular pressure to a level where the disease progression is sufficiently slowed to prevent impairment of the patient's function. Typically, the initial goal is a 20-50% reduction in pressure, which requires constant monitoring of the patient's health (15). Various classes of IOP-lowering drugs are available for this purpose. Prostaglandin analogs are the first-line drugs, which reduce the outflow resistance of aqueous humor, resulting in increased flow (16). Other drug groups, such as carbonic anhydrase inhibitors and β-blockers, are less effective and usually used as second-line treatments. Recently, Rho-kinase inhibitors have also been approved as IOP-lowering drugs, which work by modulating the cytoskeleton, primarily increasing the outflow of aqueous humor through the trabecular meshwork and adjacent tissues (17). When pharmacotherapy does not lead to sufficient reduction in intraocular

pressure, surgical procedures may be necessary. Laser trabeculectomy is the most commonly performed incisional surgery to lower intraocular pressure. It lowers pressure by inducing biological changes in the trabecular meshwork, resulting in the removal of a fragment of the meshwork or adjacent tissues, which increases the outflow of aqueous humor (18).
Although there are many anti-glaucoma medications and surgical procedures available to lower IOP, a significant number of patients still experience disease progression despite appropriate treatment (19).

## 3. Cannabinoids

### 3.1. Cannabinoid Receptors

The receptors with which all types of cannabinoids bind are cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) (20). CB1 receptors are present in many structures of the eye, such as the cornea, iris, ciliary body (including its epithelium, ciliary muscle, and blood vessels), trabecular meshwork, Schlemm's canal, and retina. In the retina, CB1 receptors are localized in the ganglion cell layer, inner and outer plexiform layers, inner nuclear layer, and also in the outer segments of photoreceptors (21). CB2 receptors, on the other hand, are primarily found in the cornea, trabecular meshwork, and retina. Their presence in the retina has been described in various cell types, such as amacrine, bipolar, Müller, and microglial cells, as well as in retinal ganglion cells (RGC) and the retinal pigment epithelium (22). In addition to CB1 and CB2 receptors, cannabinoids also bind to non-cannabinoid G-protein-coupled receptors (GPR). These include GPR18, GPR55, and GPR119. The GPR18 receptor is present in the ciliary and corneal epithelium, trabecular meshwork, and retina (23). The GPR55 receptor, also referred to as the cannabinoid receptor type 3, interacts with endocannabinoids, phytocannabinoids, and synthetic cannabinoids (24). It is found in the trabecular meshwork and rods of the retina (25). Additionally, GPR55 is widely distributed in various tissues of the body, including the central nervous system and immune system (24).

### 3.2. Phytocannabinoids, Synthetic Cannabinoids, and Endocannabinoids

Cannabinoids are classified into three main groups: phytocannabinoids, synthetic cannabinoids, and endocannabinoids. This term includes all chemical compounds that bind to cannabinoid receptors, producing effects similar to those obtained from cannabis (26). Phytocannabinoids are natural chemical compounds found in the flowers and leaves of cannabis plants—*Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Of the approximately 113 isolated cannabinoids, the most important are tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN) (27). Tetrahydrocannabinol is the main psychoactive component of cannabis, acting through the activation of CB1 and CB2 receptors. THC primarily affects the central nervous system and peripheral tissues, causing psychoactive effects as well as analgesic, antispasmodic, and neuroprotective actions. THC is characterized by its partial agonism at cannabinoid receptors, meaning its effect can act both as an agonist and an antagonist, depending on the ratio of receptors in the tissues and the presence of other cannabinoids (28, 29). The neuroprotective effects of THC are associated with its activity at CB1 receptors, and the so-called "tetrad" of psychoactive effects includes hypolocomotion, hypothermia, catalepsy, and analgesia. Due to these properties, THC may be used in the

treatment of conditions such as glaucoma, particularly for reducing intraocular pressure (IOP) and pain (29, 30).

Cannabidiol is one of the main phytocannabinoids in cannabis, known for its broad therapeutic range, including anti-inflammatory, analgesic, antioxidant, and neuroprotective properties. Unlike THC, CBD does not cause psychoactive effects and primarily acts as a modulator of cannabinoid receptors rather than a direct activator (30). CBD interacts with the CB1 receptor as an antagonistic allosteric modulator, which reduces THC's strength and mitigates its psychoactive effects. It also binds to the CB2 receptors, supporting its anti-inflammatory and neuroprotective actions (29). Cannabinol is a byproduct of THC oxidation and has low psychoactive activity.

Although CBN does not directly affect CB1 receptors in the same way as THC, it exhibits anti-inflammatory, analgesic, sedative, and neuroprotective effects (8). Synthetic cannabinoids are a group of psychoactive substances that are chemically manufactured and include a variety of chemical structures. They can be divided into several main groups, such as classical, non-classical, aminoalkylindoles, eicosanoids, and hybrids. These substances are capable of binding not only to cannabinoid receptors but also to non-cannabinoid receptors. Since synthetic cannabinoids are typically full agonists of cannabinoid receptors, they exhibit a higher affinity for these receptors than natural Δ9-THC, leading to stronger psychoactive effects (31). Synthetic cannabinoids are laboratory-produced, and their composition may include both naturally occurring compounds, such as dronabinol, and completely synthetic substances like nabilone. Many of these synthetic cannabinoids have been studied for their potential therapeutic applications, but due to their potentially potent psychoactive effects, clinical use requires careful dosing control.

Endocannabinoids are eicosanoid neurotransmitters. The best-studied endocannabinoids are anandamide (AEA), palmitoylethanolamide (PEA), and 2-arachidonoylglycerol (2-AG) (32). Endocannabinoids play an important role in ocular physiology- 2-AG and PEA are present in large amounts in the retina, where they help maintain balance in neurotransmission processes and regulate intraocular pressure (33). Endocannabinoids, such as 2-AG and AEA, interact with cannabinoid receptors in different ways: 2-AG is a full agonist, while AEA is a partial agonist of CB1 and CB2 receptors, and PEA binds to them weakly (34). The balance of endocannabinoids is maintained by synthesizing and degrading enzymes. Major synthesizing enzymes include diacylglycerol lipase α/β and N-arachidonoyl phosphatidylethanolamine phospholipase D, while degradation mainly occurs through fatty acid amide hydrolase and monoacylglycerol lipase (30). Studies suggest that low levels of 2-AG and PEA are associated with elevated intraocular pressure in glaucoma patients, indicating the important role of the endocannabinoid system in regulating IOP (35).

### 3.3. Mechanisms Affecting Intraocular Pressure Reduction

The location and key distribution of cannabinoid receptors suggest that cannabinoids may influence intraocular pressure by both increasing the outflow of aqueous humor and reducing its production (36). Cannabinoids can significantly affect the regulation of intraocular pressure by acting on the ciliary muscle and Schlemm's canal, as well as modifying cyclooxygenase-2 activity (37). These mechanisms rely on interaction with the CB1 receptor

and modulation of the cyclooxygenase pathway and prostanoid synthesis (38). Unlike the CB1 receptor, the CB2 receptor does not appear to be involved in lowering intraocular pressure (39).

### 3.4. Neuroprotective Effects of Cannabinoids

Cannabinoids exhibit neuroprotective effects in glaucoma through several mechanisms. Primarily, they inhibit the toxic effects of glutamate, nitric oxide, and endothelin-1, which are associated with the degeneration of retinal ganglion cells. Glutamate, which is neurotoxic, may accelerate optic nerve damage in glaucoma (40). Activation of CB1 and CB2 receptors reduces its release, protecting RGCs from degradation caused by this neurotransmitter (41).
Cannabinoids also inhibit the production of nitric oxide and inflammatory cytokines, reducing oxidative stress and protecting RGCs from damage (42).
The vasodilatory properties, induced by activation of CB1 and CB2 receptors, counteract the vasoconstrictive effects of endothelin 1. As a result, blood flow to the optic nerve head is increased, further supporting neuroprotective protection in glaucoma (43). Additionally, the anti-inflammatory properties of cannabinoids contribute to the protection of retinal nerve cells (44).

## 4. The Effect of Cannabinoids on Intraocular Pressure

Studies conducted on healthy individuals and patients with ocular hypertension and glaucoma have shown the impact of cannabinoids, especially Δ9-THC, on intraocular pressure. They have demonstrated that different cannabinoids may affect IOP differently. This variability in effects could be due to the complex interaction between cannabinoid receptors and mechanisms regulating IOP, although the exact causes have not yet been fully elucidated.
Research has shown that marijuana and Δ9-THC can lower IOP when administered orally, intravenously, or through smoking. In studies with 60-65% of patients, both with and without glaucoma, a reduction in IOP of around 25% was observed. Furthermore, increasing the dose was associated with a greater reduction from the baseline IOP, although this effect only lasted for 3-4 hours, with no clear relationship between dose and duration of action (45).
In many studies, Δ9-THC, when used topically as eye drops, was less effective in reducing IOP compared to oral, intravenous, or inhaled forms. Natural cannabinoids are highly lipophilic, meaning they do not dissolve in aqueous carriers, which are typically better tolerated by the eye. Consequently, most studies on the topical use of cannabinoids employed a light mineral oil as a carrier. However, as a substance that is insoluble in water, mineral oil has limited permeability through the cornea. After application, less than 5% of the administered dose reaches the intraocular tissues, which is why many studies did not find significant effects from topical cannabinoid administration (38). In recent years, new substances like cyclodextrins have emerged as potentially more effective carriers for cannabinoids, improving their permeability through the cornea and increasing ocular tolerance.
The topical administration of WIN55212-2, a synthetic and selective CB1 receptor agonist, combined with 2-hydroxypropyl-β-cyclodextrin, demonstrated effectiveness in lowering IOP. The authors of this study did not report significant side effects, and their solution showed good stability and tolerance. IOP decreased significantly by 15% and 23% (in the groups

receiving 25 μg and 50 μg, respectively) 30 minutes after administration, reaching maximum reduction 60 minutes post-administration, with a tendency to return to baseline two hours later (46).

## 5. Addictive Effects of Cannabinoids

Typically, individuals who use marijuana occasionally do not develop dependence. However, some studies suggest that occasional users may gradually develop dependency traits over time, experiencing changes in brain structures such as the nucleus accumbens (9). Chronic, long-term use of marijuana is associated with a high risk of addiction, including for patients using it medicinally. Research shows that individuals who begin using marijuana in their teenage years are more prone to developing dependence, with a risk of up to 17% (47).

To achieve a sustained reduction in IOP in glaucoma patients, it would be necessary to use marijuana at least six to eight times a day, which would simultaneously increase the risk of addiction.

Evidence also suggests that tolerance to marijuana can develop, reducing its therapeutic effectiveness at a constant dose. Abrupt cessation of marijuana uses in glaucoma patients who are dependent on it can result in Cannabis Withdrawal Syndrome. This syndrome is classified by the presence of at least three of the following symptoms within a week after stopping use: irritability, sleep disturbances, decreased appetite, weight loss, anxiety, nervousness, low mood, and somatic symptoms. These symptoms typically peak on the third or fourth day after cessation and resolve after about two weeks (48).

Δ9-THC, as the primary psychoactive compound in cannabis, increases dopamine levels in brain structures such as the striatum and prefrontal cortex (49). This leads to changes in sensory perception, hallucinations, paranoid thoughts, mood swings, and impaired cognitive functions such as memory and learning ability (50). Individuals with Cannabis Use Disorder often experience co-occurring mental health disorders, including psychosis, especially at high doses (51).

## 6. Adverse Effects of Cannabinoids

Cannabis use is associated with toxic behavioral and organ effects and is contraindicated in individuals with severe cardiovascular, liver, kidney, or psychiatric conditions (52). Acute effects include euphoria, relaxation, altered sense of time, perceptual changes, and intensification of sensory experiences. Active intoxication can impair short-term memory, attention, reaction time, and motor skills. Additionally, cannabinoids can lead to tachycardia and hypotension. Chronic use of cannabis is linked to reduced cell-mediated and humoral immunity, chronic bronchitis, lung changes resembling emphysema, increased risk of lung cancer, as well as teratogenic effects during pregnancy and fertility disturbances in both sexes (53).

Heavy marijuana users have been found to report lower life satisfaction, poorer health, and more problems in interpersonal relationships compared to non-users (54). Studies on IOP reduction through cannabinoids have reported adverse effects on the nervous, cardiovascular, ophthalmic, pulmonary, gastrointestinal, hepatic, renal, dermatological, and muscular systems (55). Neurological effects include dizziness, drowsiness, anxiety, euphoria, or hallucinations.

There are also reactions from the gastrointestinal and cardiovascular systems, such as abdominal pain, nausea, vomiting, tachycardia, hyper- or hypotension, and fainting. Ocular effects include conjunctival congestion, light sensitivity, and blurred vision, which limit their long-term use in therapy (31).

## 7. Conclusion

Cannabinoids, particularly Δ9-THC, show potential in lowering intraocular pressure (IOP) in glaucoma patients, but the effects are temporary, usually lasting a few hours. While oral, intravenous, and inhalation methods seem more effective than topical applications, their use in glaucoma treatment faces challenges such as poor bioavailability and the need for frequent dosing. Cannabinoid use also carries risks, including addiction, cognitive impairments, and potential cardiovascular issues. Tolerance and withdrawal symptoms may complicate long-term use for glaucoma management. Although cannabinoids may be considered as adjuncts in glaucoma therapy, their current role is limited, and further research is needed to improve delivery methods and assess long-term safety and effectiveness.

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### Author's contribution

Conceptualization: [AK], [RK], [MJ], [AP]
Methodology: [AK], [MJ], [MK]
Software: [AK], [JG], [RK]
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Writing - rough preparation: [AK], [JG], [RK], [MK]
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