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Phytocannabinoids and the eye – a systematic review

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ABSTRACT

Recently, the use of marihuana for medical purposes has become more common. It can lead to many desired effects within the eye, as well as several adverse ones (i.a.: decrease in intraocular pressure, reduction of corneal pain and suppression of inflammation after chemical injury of cornea, treatment of blepharospasm, reduction of nystagmus, decrease in corneal endothelial cell density, eye irritation). There have not been enough studies with human subjects done on the safety and effectiveness of cannabis use in ophthalmology. Although synthetic cannabinoids combined with modulation of the endocannabinoid system might become the future of ophthalmology, more studies on this topic should be conducted.

KEY WORDS: marijuana (marihuana), medical marijuana (marihuana), phytocannabinoids, Δ-9-tetrahydrocannabinol.

INTRODUCTION

Despite certain controversies, **marijuana** – or the dried leaves and flowers of the hemp plant (*Cannabis sativa* L.) – is increasingly used in medicine for therapeutic purposes.

Cannabinoids are neurotransmitters of the endocannabinoid system. Based on their origin, they can be classified into three groups: plant cannabinoids (**phytocannabinoids**, e.g. tetrahydrocannabinol, cannabidiol), animal cannabinoids (endocannabinoids: anandamide (AEA), 2-arachidonoylglycerol (2-AG)), and synthetic cannabinoids (e.g. synthetic tetrahydrocannabinol – dronabinol, synthetic analogue of tetrahydrocannabinol – nabilone).

The **endocannabinoid system** plays a role in the body's homeostatic processes. For example, it is involved in the regulation of appetite, sleep, and rest. Dysfunctions of the endocannabinoid system are observed in a range of conditions including schizophrenia, multiple sclerosis, Huntington's disease, and Parkinson's disease [1].

The wide spectrum of **marijuana** activity prompted research aimed at isolating its biologically active substances. In the 1960s, researchers discovered tetrahydrocannabinol (THC) – the most potent hallucinogen present in marijuana and also the main compound responsible for the therapeutic effect of cannabis [2]. Aside from **delta-9-tetrahydrocannabinol** (Δ9-THC), other important phytocannabinoids found in marijuana include: **cannabidiol** (**CBD** – recognized as beneficial for the adjunctive treatment of epilepsy, neurodegenerative diseases, mental disorders; devoid of hallucinogenic activity), cannabichromene (CBC), cannabinol (CBN), Δ8-THC (more stable Δ9-THC isomer). THC and CBD are formed from their precursors, i.e. tetrahydrocannabinolic acid (THC-A) and cannabidiol acid, respectively, as a result of their decarboxylation after exposure of hemp to light [3]. Interestingly, the precise composition of hemp depends on the growing conditions. In the human body, Δ9-THC acts mainly via widely distributed cannabinoid receptors, the most important of which are CB1R and CB2R, only discovered in the 1990s [4]. In physiological terms, the two receptors belong to the endocannabinoid system. CB1 receptors are found in the nervous system on axons and nerve endings (primarily in the brain), and also in the heart, adipocytes, liver, endothelial cells (e.g. in the coronary artery), and the smooth muscle of blood vessels. They have also been identified in the cornea (epithelium, endothelium), trabecular meshwork, Schlemm's canal, ciliary body (epithelium, blood vessels), ciliary muscle, endothelium in the anterior segment of the eye, pupillary sphincter, retina (outer photoreceptor segments, inner and outer plexiform layer, inner nuclear layer, ganglionic layer). In contrast, CB2 receptors are present on the cells of the immune system and blood cells (CB2R activation produces an antiinflammatory effect), as well as in the brain, heart, liver, pancreas, bone tissue, endothelium (including cerebral vessels and coronary artery), smooth muscle and trabecular meshwork [4-8]. Some authors rule out the presence of CB2 re-

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ceptors in the eye, which may be due to the fact that in healthy individuals CB2R expression in the cornea and structures in the anterior eye segment is low. Experimental models of uveitis indicate that the development of inflammation in the tissues of the anterior segment of the eye may be accompanied by an increased CB2R expression to attenuate the inflammation. CB2Rs have been identified in the rat retina, hence it has been hypothesized that they are also present in the human retina [9]. CBD and CBN do not bind to CB1 receptors [10]. Cannabinoids can also act via non-endocannabinoid transmission elements and pathways such as TRP family receptors, and GABAergic, serotonergic, cholinergic and dopaminergic systems [11]. The presence of numerous targets for phytocannabinoids in the eye suggests that marijuana should play a role in a range of ocular processes. The so-called "medical marijuana", which is available in Polish pharmacies authorized to fill prescriptions for narcotic drugs, comes in two forms: as a compounded drug and a finished drug product. The compounded drug is available primarily in dried (herb) form. The legislator has also permitted the use of pharmaceutical cannabis tinctures and resins as pharmacological raw materials (Act of 7 July 2017 amending the Act on Counteracting Drug Addiction and the Act on the Reimbursement of Medicines, Foodstuffs Intended for Particular Nutritional Uses, and Medical Devices, which entered into force in November 2017). As the finished drug product, medical marijuana is available in the form of oral spray. The compounded drug, based on dried cannabis flowers, contains approximately 19% THC (+/-10%) and 1% or less CBD. Pharmacies source the herb from companies that grow "medical cannabis" (outside Poland) in strict compliance with Good Manufacturing Practice requirements. This form of medical marijuana is not regulated by any specific prescription requirements, and physicians prescribing marijuana treatment must be guided by the current state of medical knowledge. Dried herb should be inhaled using a vaporizer. The device does not burn the herb. Instead, it "vaporizes" it, which involves heating and evaporating the active ingredients. The process prevents the release of substances producing toxic effects on the respiratory tract (as is the case when smoking a marijuana "joint" or "blunt"). However, it has been argued that the safety of the marijuana vaporization process should be assessed more rigorously [12]. Other problems include poor availability of dried cannabis in Polish pharmacies and its high price (approx. PLN 60 per 1 g of herb). The other type of medical marijuana is a finished drug product formulated as oral spray. A single dose (puff of spray) contains almost the same amounts of THC and CBD (2.7 mg THC and 2.5 mg CBD). The drug is approved for the treatment of spasticity in multiple sclerosis. In other countries, e.g. in the USA, oral dosage forms of synthetic cannabinoids (dronabinol and nabilone capsules) have also been approved for therapeutic use. The pharmacokinetics of THC depends on the route of administration. Interestingly, the biochemical activity of THC in plasma (maximum concentration, changes in concentration over time) after inhalation and intravenous administration is strikingly similar [13]. THC-containing drops exhibit low bioavailability as a result of poor absorption caused by high lipophilicity of THC. Inhaled THC is very rapidly absorbed into the blood, with no observed individual variation in absorption rates. Because of its equally rapid distribution to the body's tissues the clinical effects of marijuana are observed even before smoking is stopped, i.e. within a few minutes [13, 14]. The dose and hence the potency of phytocannabinoids depend on the dynamics with which the patient vapes marijuana and the depth of inhalation. Compared to the inhaled route, the onset of activity after an oral dose of THC occurs later (within 30-90 minutes, with maximum effects achieved within 2-3 hours) and at a lower plasma concentration, but also persists longer (4 to 12 hours depending on the dose) [15]. Orally administered THC is characterized by low systemic bioavailability (equal to approximately one-third of the inhaled THC dose), not only because of the first-pass effect, but also chemical degradation in the body. The absorption of orally administered THC is slow and irregular [13], and exhibits individual variation. The systemic bioavailability of CBD after inhalation is approximately 31% (11-45%), and its plasma effects and metabolism are similar to THC [15]. There have been reports highlighting the possibility of developing tolerance to phytocannabinoids. This applies mainly to the effects achieved through the activation of CB1 receptors. Tolerance develops in a characteristic manner for each activity, i.e. to a varying degree and at different time points. The tendency might be beneficial if tolerance concerned the undesirable effects of marijuana. A study conducted with 12 healthy volunteers demonstrated the development of cardiovascular tolerance after 18-20 days of THC use by the oral route or by inhalation (heart rate, orthostatic drops in blood pressure) [16]. There are no reports on the development of tolerance to the effects induced by the stimulation of CB2 receptors [17]. Furthermore, the discontinuation of longer treatment with marijuana or Δ9-THC can trigger withdrawal symptoms which, as research shows, are most severe 3-4 days after treatment termination. The withdrawal symptoms should resolve within approximately two weeks [18]. The controversy over medical marijuana treatment is related to its numerous adverse effects that seem to outweigh the potential benefits. The adverse reactions associated with medical marijuana are mainly due to its addictive potential and psychotropic effects. Possible manifestations include panic attacks, anxiety, restlessness or sedation, euphoria or dysphoria, dizziness, short-term memory impairment, productive symptoms, perceptual disturbances, drowsiness, a decline in concentration, and an associated elevated risk of traffic accidents. Among other body reactions, an increase in heart rate, reduced tear production, and eye redness (interestingly, also after oral administration) have been reported. Chronic use of medical marijuana may lead to cognitive impairment. Moreover, it is possible that some of the adverse effects turn out to be permanent. As mentioned above, patients using marijuana on a long-term basis may also develop withdrawal effects when they stop using it. Smoking marijuana may cause changes in

the oral cavity and respiratory mucosa [19], but medical marijuana is not expected to contain toxic ingredients that are found in the herb obtained illegally from unverified sources. Nevertheless, the safety of the marijuana vaporization process should be rigorously assessed in order to rule out the risk of oncogenic effects in the respiratory tract.

AIM

The aim of this paper is to review the literature found in the NCBI database with a view to determining the effects of phytocannabinoids – active substances present in marijuana – on the organ of sight and their potential applications in ophthalmology. In addition, the literature reports on synthetic cannabinoids and modulation of the endocannabinoid system as future therapeutic options for various ophthalmic conditions are briefly presented. The scope of the paper excludes a discussion of publications addressing the effects of marijuana used concurrently with other psychoactive substances, alcohol and drugs.

DISCUSSION

Phytocannabinoids and the protective apparatus of the eye

Phytocannabinoids (THC and CBD in the form of tincture or capsules) and a synthetic analogue of THC (dronabinol) can affect the **eyelids**. However, the study findings concerning this aspect are somewhat contradictory. For example, a reduction of blepharospasm has been reported during phytocannabinoid therapy (as adjunctive treatment to botulinum toxin injections in patients with persistent residual symptoms). The spasmolytic effects were attributed to CBD (either through the activation of GABA or inhibition of serotonin reuptake) or THC (through the modulation of dopaminergic neuronal activity) [20, 21]. Other reported effects involving the eyelids include ptosis and eyelid tremor, which are probably secondary to reduced tear secretion and ocular surface irritation (and associated photophobia) as well as eyelid swelling (here, the mechanism possibly involves the TRPA1 receptor responsible for cannabinoid sensory transmission through which phytocannabinoids may cause dry eyes and ocular irritation) [11, 22].

The findings of studies conducted on various animals (mice, rats, monkeys) suggest that cannabinoids (CBD, THC, anandamide) used at high doses can induce ptosis. According to one hypothesis, this may be a manifestation of the withdrawal syndrome, as the CB1R antagonist induces ptosis [11].

Individuals who smoke marijuana or take it orally have been found to develop **conjunctival** congestion due to vasodilation. In addition to biochemical activity, ocular irritation observed in marijuana smokers may also be attributed to the effect of smoke itself on the ocular surface. A reduction in tear production is also observed, which may lead to contact lens intolerance [23]. Phytocannabinoids are known to cause dry eyes and ocular irritation, probably through the activation of the TRPA1 receptor [11]. Ocular irritation after the administration of phytocannabinoid drops may be due to the presence of carrier substances in the formulation.

Phytocannabinoids and the anterior eye segment

The application of phytocannabinoids in ophthalmology is mainly related to their lowering **effect on the intraocular pressure** (IOP). This property can be potentially useful in the treatment of glaucoma, as IOP elevation is one of the main risk factors for damage to the optic nerve in patients with glaucomatous neuropathy. In 1971, American scientists Robert Hepler and Ira Frank found that an hour after smoking marijuana, the intraocular pressure in 11 healthy individuals decreased by approximately 25% [23, 24]. Further analyses showed that glaucoma patients also experienced an IOP drop. Research on animals (rabbits, dogs, monkeys) as well as human studies conducted in subsequent years attributed this effect mainly to Δ9-THC (and its metabolites), and to a lesser extent also to Δ8-THC (and its metabolites) and CBN. Nabilone has also been found to reduce the IOP. In contrast, CBD has been shown to have a widely divergent impact on the IOP (decrease in IOP vs. no effect on IOP vs. increase in IOP) [25-29]. The hypotensive potential of phytocannabinoids on the IOP depends on their route of administration. Δ9-THC administered intravenously, orally or sublingually, or via inhalation, shows an ability to lower the IOP. However, in view of its high lipophilicity and hence low water solubility, the most desirable ophthalmic dosage form – eye drops with phytocannabinoids – currently fails to bring satisfactory results in reducing the IOP. For example, in rabbit studies, Δ9-THC and Δ8-THC administered intravenously were found to have a significantly greater effect on lowering the IOP than in the form of drops [27]. In a 1982 study, 1% Δ9-THC drops administered four times a day for one week did not affect the IOP in humans in any way [30]. In another volunteer study conducted one year earlier, there was likewise no IOP decrease after the administration of drops with Δ9-THC [31]. Research is currently underway to achieve better absorption rates of drops with phytocannabinoids (microemulsions, use of cyclodextrins as carriers) [32]. Possible future treatments of glaucoma may include drops containing synthetic cannabinoids such as WIN 55212-2 (a cannabimimetic agent), which demonstrated an IOP lowering effect in a study with eight glaucoma patients [33]. In another study, conducted by Flach *et al.*, nine patients with end-stage refractory open-angle glaucoma received marijuana administered via the oral route as an adjunctive therapy to the standard antiglaucoma treatment. IOP reduction was observed in all patients, and the therapeutic goal was achieved in four subjects, but the IOP decrease was not sustained on a long-term basis. In addition to developing tolerance to the effects of marijuana, the patients also reported a number of adverse reactions, which prompted them to drop out of marijuana treatment over a period of 1-9 months [34].

In their 2006 paper, Tomida *et al.* evaluated the effect of sublingually administered phytocannabinoids on the IOP in six patients with ocular hypertension or early stage open-an-

gle glaucoma. The IOP measured two hours after taking a 5 mg dose of Δ9-THC was significantly lower than after taking placebo, but after four hours it returned to the baseline. A 20 mg dose of CBD failed to reduce the IOP at all, while 40 mg of CBD caused a transient IOP increase four hours after the application [29]. Although multiple studies have been conducted to evaluate the IOP-reducing effect induced by phytocannabinoids, the exact mechanism underlying this action has not yet been elucidated. One of the first studies in glaucoma patients showed that an IOP drop after marijuana inhalation was preceded by an increase in heart rate along with a decrease in blood pressure, and might be secondary to a drop in perfusion pressure in the capillary network of the ciliary body via marijuana-induced peripheral vasodilation (35). However, the IOP reduction as a result of a slight decrease in blood pressure seems to be marginal. Furthermore, even a small drop in arterial blood pressure is potentially harmful to the optic nerve, as it may lead to impaired perfusion and, consequently, induce the progression of glaucomatous neuropathy. In an experiment on rabbits, with various marijuana phytocannabinoids administered intravenously and injected directly into the ventricles of the brain, it was shown that a decrease in the IOP and blood pressure occurred exclusively after intravenous administration of Δ9-THC. Thus, the role of the central nervous system in the mechanism of phytocannabinoid-induced IOP reduction was excluded [36]. It has been hypothesized that the local IOP-lowering activity is due to increased outflow of the aqueous humor or an increase in its drainage through the choroid and sclera. A decrease in the production of aqueous humor is another possible explanation. These effects may occur either directly via the activation of CB1 receptors in the eye or indirectly through the induction of endogenous prostaglandin synthesis by THC [37, 38]. In vivo studies on rabbits have potentially ruled out the role of CB2R in lowering the IOP. Rabbits with normal IOP were administered eye drops containing a CB2R agonist (JWH-133), which failed to produce a decrease in the IOP. However, it is conceivable that the outcome was due to the poor absorption of JWH-133 (low solubility in water) [39]. The level of IOP decrease depends on the dose of phytocannabinoids, but at the same time the dose has no correlation with the duration of the effect. A completely different impact of marijuana was reported in a 2014 study conducted in Tel Aviv. The paper describes the case of a 35-year-old man abusing marijuana who developed an episode of acute angle closure (AAC) in one eye. The cause of AAC was ciliochoroidal effusion, which caused a change in the anatomy of the eye, leading to the detachment and anterior rotation of the ciliary body. The authors claimed that supraciliary effusion was an idiosyncratic reaction to marijuana, which – in the reported case – acted via the serotonergic pathway (serotonin and serotonergic receptors were detected in the ciliary body and aqueous humor). In the opinion of the authors, the patient did not develop AAC in the other eye (where the angle was wide and open) because of prompt prophylactic administration of appropriate medications into the asymptomatic eye [40].

Based on the evaluation of corneas in 56 eyes of people using marijuana at least three times a week during the last year prior to the study, Polat *et al.* showed that phytocannabinoids reduced corneal endothelial cell density (i.e. caused a decrease in the number of cells per mm^3). The effect was similar to that observed in the aging process, after intraocular procedures or an injury, or as a result of smoking and alcohol abuse. However, unlike in the circumstances listed above, no changes in cell morphology were noted as a result of marijuana use. According to the author, the reduction in the number of endothelial cells is most likely due to the toxicity resulting from prolonged marijuana use, which kills endothelial cells and inhibits the influx of new cells. The exact mechanism underlying the toxic effect of marijuana on the endothelium has not been discovered. Interestingly, a decrease in endothelial cell density was not accompanied by a reduction in central corneal thickness, which turned out to be comparable between the study and control groups [41].

In animal studies, the topical application of phytocannabinoids has led to the development of corneal opacities. Long-term (9 days) administration of a marijuana extract or Δ9-THC alone into feline eyes using osmotic mini pumps caused corneal opacities of major severity, along with conjunctival congestion and chemosis (observation made during the study of the effect of marijuana on the IOP). The corneal changes were more severe after using Δ9-THC alone than the marijuana extract. Following the topical application of CBD and short-term administration of Δ9-THC, no adverse effects in the anterior segment of feline eyes were noted. The underlying cause of corneal opacification may have been reduced tear production and dehydration of the cornea in a mechanism involving the inhibition of corneal endothelial pumps through the activation of CB1 receptors, leading to the leakage of aqueous humor from the cornea. Corneal opacities have also been reported in dogs after oral administration of synthetic cannabinoids. However, the effect was considered to be a response to synthetic cannabinoids specific to this subspecies, as no similar corneal damage was seen in other animals (rats and rhesus macaques) [25, 28, 42].

Promising results have been obtained in studies evaluating eye drops with cannabinoids in the treatment of chemical corneal burns. Studies on mice have shown that the phytocannabinoids Δ8-THC and CBD, and the synthetic cannabinoid HU-308 (a CBD derivative), can reduce corneal pain and decrease the inflammatory response after chemical burns. These effects are caused by the activation of 5-HT1A and CB2 receptors by CBD and HU-308, and the activation of CB1R and TRPV1 by Δ8-THC. The latter receptor is present in the cells together with CB1R, and in the endings of the optic nerve, i.e. a branch of the trigeminal nerve [43].

Studies on animals conducted by Murataeva *et al.* indicate that CB2R receptor activation plays a beneficial role in corneal healing (mainly by regulating chemotaxis) [44]. In another study, Yang *et al.* demonstrated that the mutual interaction between CB1R and TRPV1 (CB1R activation suppresses the proinflammatory response stimulated by TRPV1

injury) improved the healing of wounds in the animal cornea and reduced scarring [45].

The observation that the process of angiogenesis induces the expression of CB1 receptors was a starting point for an experiment on mice which found that inactivation of the CB1 receptor may be therapeutically relevant in the treatment of corneal neovascularization [46].

The literature reports are not unanimous on the pattern of effects produced by marijuana on the pupil. Divergent study findings (no effect, mydriasis, miosis) may be due to the different conditions under which the pupil diameter was measured [22, 23, 47]. One of the more interesting studies (conducted in 21 healthy subjects), showed that smoking marijuana was followed by a slight constriction of the pupil (within five minutes) with sustained response to light [23].

Phytocannabinoids and the posterior eye segment

Phytocannabinoids exert their effects on vascular bed function and affect the cardiovascular system largely through vascular endothelial cannabinoid receptors. The consumption of marijuana is followed by various hemodynamic changes, mainly an increase in heart rate (by up to 50-60%, depending on the dose), but also a decrease in vascular resistance and the associated orthostatic drops in blood pressure [16]. *In vitro* studies suggest that THC has a prothrombotic effect by activating thrombocytes (via the cannabinoid receptors located on their surface) [48]. There is a case report of an 18-year-old patient developing central retinal vein occlusion (CRVO) – only in one eye – approximately 15 minutes after smoking marijuana. After ruling out internal causes (abnormalities in the blood coagulation system, heart, kidney, liver, and thyroid), based on the temporal correlation between the onset of CRVO and marijuana smoking, and the reported hemodynamic and rheological impact of marijuana, it was concluded that THC was the causative factor behind retinal venous occlusion reported in the patient [49].

Based on PERG findings, Schwitzer *et al*. argued that in regular phytocannabinoid users the functions of the retinal ganglion cells became disrupted, leading to a delay in transmission between the retina and the visual cortex [50]. However, objections were raised with regard to the study's conclusions, including both the methodology and procedures for conducting analyses (e.g. the researchers' failure to consider potential contamination of the marijuana used by the subjects with other substances and its possible impact on the results, and lack of analysis of other electrophysiological assessments in the study patients) [51].

The suspicion that THC might induce toxic retinal effects in chronic marijuana users has also been raised by Chinese researchers. After two months of daily intraperitoneal administration of THC to mice, ERG abnormalities were noted, suggesting damage to the photoreceptor layer as well as thinning and increased apoptotic activity within the outer nuclear layer. The cause was determined as an elevated inflammatory response and an increase in oxidative stress induced by THC [52]. A nosological entity referred to as hallucinogen persisting perception disorder (HPPD) was described. The criteria for the diagnosis of HPPD include permanent or recurrent disturbances in color vision, afterimages, perceptions of objects and textures moving in front of the eyes, halos around objects, macropsia, and micropsia [53]. Zobor *et al*. conducted a number of ophthalmic examinations (visual acuity, color vision, dark adaptation, field of view, ERG, mERG, EOG, EPT – electrically evoked phosphene thresholds) in one patient diagnosed with HPPD and in four patients abusing cannabis (in the form of leaf smoking), who did not report any visual disturbances (control group). In the patient with HPPD, mild deviations in EOG as well as EPT abnormalities were observed. In the control group, all test results were within the limits of normal [54]. However, an important limitation of the study was the small size of the study group.

Reversing the situation, it can be hypothesized that blocking the cannabinoid receptors may potentially inhibit retinal degeneration. In a study on mice, intraperitoneal administration of a CB1 receptor antagonist not only halted the degenerative process in the retina (similar to human retinitis pigmentosa), but also helped achieve full healing [55].

However, there are also studies with the opposite findings, reporting antioxidant properties and the resulting potential cytoneuroprotective activity of phytocannabinoids containing a phenolic group (Δ9-THC, CBD, CBN). This action is claimed to be independent of CB1 receptors [10]. In some of the available studies it was found that Δ9-THC and CBD had the ability to prevent glutamate-induced retinal ganglion cell death (a model of apoptosis occurring in glaucoma) by antagonizing the effect of NMDA. Part of neuroprotection was claimed to occur through the stimulation of the CB1R [56, 57].

There are also reports of the neuroprotective effect of endocannabinoids (AEA and 2-AG) and synthetic cannabinoids, primarily in the prevention of retinal ischemia (vasodilatory role). Based on these findings, cannabinoids could provide a novel therapeutic option for retinal degenerative diseases or glaucomatous neuropathy [57, 58].

The immunomodulatory effect induced by the activation of CB2 receptors was investigated in an experimental mouse model of autoimmune retinochoroiditis. A highly selective CB2 receptor agonist was shown to significantly reduce inflammation [59].

In an **experimental model of endotoxin-induced uveitis** (corresponding to bacterial uveitis), 1.5% drops with the synthetic cannabinoid HU-308 (a CBD derivative) displayed antiinflammatory activity [60].

In an experiment on mice, CB2R activation with a synthetic agonist was found to reduce the inflammation and vitreoretinal proliferations intended to correspond to human **proliferative vitreoretinopathy** which is observed after trauma, in inflammation, or as a complication of retinal detachment surgery [61].

Phytocannabinoids and the locomotor apparatus of the eye

Smoking marijuana has been reported to reduce **nystagmus**. The literature includes a case report of a 52-year-old patient with multiple sclerosis in whom acquired pendular nystagmus (and oscillopsia previously not responding to pharmacological treatment) were successfully inhibited approximately 30 minutes after smoking cannabis leaves. The effect was sustained for four to five hours after smoking two cannabis "joints". Interestingly, no such effects were noted after oral administration of nabilone tablets or hemp oil capsules [62].

Another case report found in the literature concerns a 19-year-old man with congenital nystagmus who, as he explained, smoked marijuana six to seven times a day from the age of 14 in order to improve visual acuity. It was established that marijuana smoking indeed caused a reduction in the amplitude, frequency and intensity of nystagmus (especially when one eye was covered), contributing to improved visual acuity [63].

CONCLUSIONS

There have been numerous publications highlighting the potential applications of phytocannabinoids in ophthalmology, for example to lower intraocular pressure, treat corneal burns, reduce corneal pain, and alleviate nystagmus and blepharospasm. On the other hand, marijuana has also been reported to produce a range of adverse effects on the organ of sight, such as a decrease in endothelial cell density or irritation of the ocular surface. Of note is the ambivalence of some findings of the effects of phytocannabinoids on the retina: toxicity to photoreceptors and ganglion cells vs. retinal neuroprotection.

The main therapeutic application of marijuana in ophthalmology is in the treatment of glaucoma. However, on account of the short duration of action (3-5 hours), poor absorption rate of the most desirable ophthalmic dosage form, i.e. drops (high lipophilicity of THC) and a number of potential systemic adverse effects associated with each form of marijuana, it does not seem to be superior to the standard antiglaucoma treatment (eye drops, laser therapy, glaucoma surgery). There is also not enough research on the effects of marijuana on the preservation of the visual field. Medical marijuana therapy can be considered in patients with absolute glaucoma and painful eye, when pain is not effectively controlled with conventional analgesic treatment.

The vast majority of studies investigating the effects of phytocannabinoids on the eye are animal research. Most human studies are reports on one or a small number of cases, which precludes any general conclusions as to the specific effects of phytocannabinoids, their therapeutic efficacy, safety or adverse effects (also in a long-term perspective). Establishing statistically significant study groups with humans is difficult in view of the potential harmfulness of cannabis.

The future of ophthalmology may belong to synthetic cannabinoids, potentially free from the adverse effects of natural phytocannabinoids, as well as modulation of the endocannabinoid system by regulating the production of endocannabinoid compounds, as well as selective inhibition and selective activation of cannabinoid receptors. This could provide a new therapeutic modality for a range of conditions including corneal neovascularization, retinal degenerative diseases or uveitis and retinitis.

DISCLOSURE

The authors declare no conflict of interest.

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