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MEDICAL CANNABIS: MECHANISMS OF ACTION AND THERAPEUTIC TARGETS

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Abstract

Introduction: In recent years, multiple publications underscored many beneficial properties associated with medical marihuana. Its current applications encompass pain relief, multiple sclerosis, the treatment of anxiety disorders, Dravet syndrome and other. It can potentially extent to the treatment of patients with fibromyalgia or in people with diabetic complications. The expansive potential of medical cannabis in the prevention and treatment of many diseases is seen in its complex and multidirectional mechanisms of action. Medical marihuana has impact on cannabinoid receptors, and it exerts effects through many other molecular targets.

Aim of the study: This review seeks present mechanisms of action of medical marihuana and explore its potential therapeutic targets.

Materials and methods: A comprehensive review of literature available in the PubMed and Google Scholar databases was performed, using the following keywords: "medical marihuana", "medical cannabis", "medical marihuana mechanism of action", "therapeutic targets of medical marihuana", "endocannabinoid system", “medical marihuana in pain treatment”, “medical marihuana amygdala body”, “medical marihuana serotonin receptors”.

Conclusions: Medical marihuana emerges as a promising candidate in the treatment of many diseases and common condition. However, further research is imperative to ascertain the effects of the drug and transform it into an effective medication which maximizes benefits and minimalizes side effects.

Keywords: medical marihuana, medical cannabis, medical marihuana mechanism of action, therapeutic targets of medical marihuana, endocannabinoid system, medical marihuana in pain treatment, medical marihuana amygdala body, medical marihuana serotonin receptors.

Introduction

Medical marihuana harbors significant potential therapeutic and medicinal properties related to various compounds, particularly Δ-9- tetrahydrocannabinol (THC) and cannabidiol (CBD). Historically, marihuana was taken as a drug without medical usage because of the widely recreational use especially among younger population. (1-3)

Nevertheless, cotemporary understanding shows that Cannabis has plenty of therapeutic benefits ranging from pain relief to treatment of the conditions like multiple sclerosis. The purpose of that article is to present the mechanism of THC and CBD action. Furthermore, we would explore the diverse uses of medical marijuana. (4)

History of medical marijuana

The first historical record about the medical properties of marijuana come from China in 2737 BC. Shen Nung considered the father of Chinese medicine, documented cannabis in the treatment of malaria, rheumatism, and gout. Around 1550 BC, The Ebers Papyrus described the use of hemp seeds as suppositories for hemorrhoids. In 300 AD marijuana was administered during labor to alleviate pain. In the 13th century, doctors prescribed hemp oil to treat uterine diseases. The first mention of hemp in Polish literature appeared in the 16th and 17th centuries thanks to the botanist and doctor Szymon Syreński. In his document, he emphasized the psychoactive properties of the plant. In the 18th century, botanist Krzysztof Kluk characterized hemp in his textbook as a plant possessing medicinal, sleep-inducing, and pain-relieving properties. In 1785, the French naturalist Jean-Baptiste Lamarck isolated a new species - Cannabis indica, until then no species were distinguished. The plants were considered one species, Cannabis sativa L. - hemp. In 1850, hemp was added to the United States Pharmacopoeia. Soon after, marijuana was widely used throughout the United States for medicinal purposes and could be easily purchased in pharmacies and convenience stores. Unfortunately, the lack of control over its availability led to the misuse of marijuana, and there were reports of its addictive effects. Consequently, in 1941, hemp was removed from the United States Pharmacopoeia and its medicinal use was no longer recognized in America. In 1985, medical marijuana returned to medicine in the form of dronabinol, a synthetic form of THC. The FDA has approved dronabinol for patients who suffer from nausea and vomiting caused by chemotherapy. In 1992, in response to a surge in requests from patients with AIDS

for medical marijuana, the pharmaceutical drug dronabinol gained approval for the treatment of AIDS wasting syndrome. In 2003, Canada became the first country in the world which approved the use of medical marijuana. In Poland, medical marijuana was legalized in January 2017. Since then, the interest in the herb of cannabis among doctors and patients has increased significantly. It has contributed to further research on the effects of its active ingredients and the search for further therapeutic targets for medical marijuana. (1,5-7)

Chemical composition

THC - tetrahydrocannabinol and CBD – cannabidiol are isomers of each other. They are the principle chemical substances contained in hemp. (8,9)

While, they are not the only cannabinoids found in marijuana, even if they are responsible for its most crucial therapeutic effect. Over 600 cannabinoid compounds have been identified in cannabis herbs. In addition to THC and CBD we discovered CBG – cannabigerol which in marijuana occurs in the form of cannabigerolic acid – CBGA. When the plant grows at high temperature, CBGA convert to THC and CBD. (10)

We observe synergistic and antagonistic effects between individual cannabinoids which is used in the production of medical marijuana. The most favorable ratio of THC to CBD is 20:1. (8)

Another group of chemicals found in marijuana are terpenes. They are mainly responsible for the organoleptic properties of individual marijuana varieties. In addition, terpenes themselves may have certain effects, e.g., myrcene has a soothing and relaxing effect, which will help fall asleep with no effort. (8)

The endocannabinoid system

Cannabinoids, chemical compounds with their own system in the body called the endocannabinoid system. It was discovered in 1988, and its action in the human body was confirmed in 1992.

The system has two main types of receptors, CB1 located mainly in the CNS (central nervous system), primarily in the brain and amygdala and CB2 receptors occurring peripherally, on the surface of immune system cells, and to a lesser extent in the CNS. (11)

Characteristic neurotransmitters found in this system include endocannabinoids, among which are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), exhibiting structural similarities to phytocannabinoids present in hemp. (12)

Lytic enzymes, such as FAAH (fatty acid amide hydrolase), are part of this system as well. It oversees the breakdown of endocannabinoids post-receptor utilization. (13,14)

THC's structure resembles anandamide, one of the endocannabinoids produced by the endocannabinoid system. Anandamide binds to CB1 and CB2 receptors. By supplying THC from cannabis to the body, the brain is informed that the ECS (endocannabinoid system) begins to produce large amounts of anandamide. This causes relaxation, improvement of appetite, and reduction of pain. (15)

CBD, conversely, plays a pivotal role in activating the endocannabinoid system, fostering increased production of cannabinoids, and stimulating CB2 receptors located within the immune system.

Cannabidiol additionally inhibits the metabolic enzyme FAAH, accountable for the degradation of anandamide. This mechanism leads to an elevation in the endocannabinoid levels within the body. Furthermore, CBD mitigates the psychoactive effects of THC. (12)

THC – pharmacology and pharmacokinetics

Tetrahydrocannabinol acts as an agonist of CB1 receptors and, to a lesser extent, stimulates CB2 receptors. Being highly lipophilic, THC readily traverses the blood-brain barrier, binding subsequently to CB1 receptors, inducing psychoactive effects. (9)

When smoked, some THC undergoes decomposition, with only 20-70% of the substance reaching the lungs. The bioavailability of THC stands at 18%. (16)

The peak concentration in cerebral circulation is achieved approximately 30 minutes after consumption, with a biological half-life of 20 hours.

Furthermore, owing to its pronounced lipophilicity, THC accumulates in fat tissue. Consequently, THC elimination, primarily through urine, occurs at a slow pace and is constrained by its storage. Hence, determining the time of substance ingestion based on urine tests is not feasible. (17)

THC undergoes first-pass metabolism in the liver, which is why oral intake of cannabis is uncommon. (18)

THC modulates pain processing at the spinal cord level by activating CB1 receptors. It also enhances the activity of opioid receptors, allowing its use as an analgesic in combination with opioids to reduce their dosage. (9)

CBD – pharmacology

In contradistinction to THC, CBD has no psychoactive effect. Cannabidiol affects many receptors in the body and the exact mechanisms of action are not fully understood. CBD is an allosteric modulator of cannabinoid receptors. It reduces addition to medical marijuana because CBD changes the shape of the conformational sites of some cannabinoid receptors which results in a weaker psychoactive effect of THC. (9,19,20)

Cannabidiol, an allosteric modulator of cannabinoid receptors, alters the conformational sites of select cannabinoid receptors, leading to a diminished psychoactive effect of THC. This alteration contributes to a reduced inclination towards dependence on medical marijuana.

In addition to its effect on GABA-A receptors, CBD affects the GPR-55 receptor, TRPV1 vanilloid receptors and inhibits adenosine reuptake. The cumulative result of these actions manifests as the anticonvulsant effect. CBD functions as a GPR-55 receptor antagonist, This receptor stimulates the intracellular release of calcium, which ultimately resulting in diminished hyperexcitability of neurons in epileptic tissue. It also influences anti-cancer and anti-osteoporotic effects. CBD inhibits vanilloid receptors by desensitizing them which also leads to analgesia. (21-23)

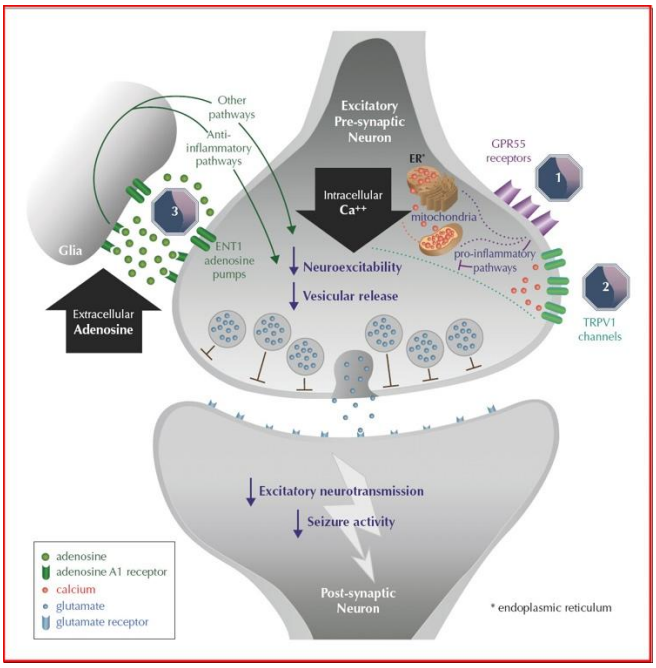
Adenosine is conveyed to the nerve cell through the ENT1 nucleoside transporter; elevation in its extracellular concentration diminishes the excitability of the neuron. (21)

CBD exerts an anti-anxiety effect through modulation of the GABA-A receptor and antagonistic action against the serotonin 5-HT3 receptor in the amygdala. The involvement of the medical marijuana on the 5-HT3 receptors in amygdala has impact on pain feeling. Furthermore, CBD is presumed to exhibit an anxiolytic effect through its agonistic interaction with the 5-HT1A receptor. (24)

The antagonistic effect of cannabidiol on the 5-HT3 receptor leads to an antiemetic effect, where medical marijuana is currently irreplaceable. The 5-HT3 receptor resides at the terminals of the vagus nerve and in the remote region at the base of the fourth ventricle, housing a chemoreceptor trigger zone. release and triggers the vomiting reflex. (25,26)

Cannabidiol inhibits the reuptake of anandamide, influencing various physiological functions, including learning, memory, food intake, and sleep. Moreover, anandamide inhibits the proliferation of cancer cells. Augmenting its concentration yields advantages in daily functioning and exerts a preventive effect in cancer development. (5)

CBD exhibits robust anti-inflammatory effects through modulation of peroxisome proliferator-activated receptors (PPARs), specifically targeting the gamma subunit. Three subtypes of PPARγ are known: PPARγ1, widely distributed; PPARγ2 selectively found in adipose tissue; and PPARγ3, present in macrophages. Stimulation of these receptors induces an anti-inflammatory effect by suppressing the expression of pro-inflammatory genes. The production of cytokines, acute-phase proteins and metalloproteases is reduced. Additionally, PPAR also stimulates the catabolism of pro-inflammatory eicosanoids. (5)
Through the inhibition of the pro-inflammatory response, we concurrently mitigate damage to the body. This mechanism further enhances anti-cancer and anti-diabetic effects. (5)



Proposed multimodal mechanism of action of CBD in epilepsy. (27)

Potential uses of medical marijuana

Medical marijuana finds use in palliative medicine and oncology therapy. Taking medical marijuana relieves severe pain in these patients, alleviates nausea and has anti-cancer attribute. Activating CB1 receptors affects the action of neurotrophic growth factors such as BDNF or

GDNF, which are responsible for activating the expression of tumor necrosis factor TNF-alpha. This factor triggers apoptosis. Medical marijuana also suppresses the cell cycle of neoplastic tissue and inhibits angiogenesis in the vicinity of the tumor. (28)
The antiemetic effect is also used in the treatment during chemotherapy and stimulates the appetite in patients who suffer from anorexia. Furthermore, it is utilizable in individuals diagnosed with HIV, who also struggle with the lack of appetite and whose body is cachectic. (29)

The most well-doceumented usage of medical marihuana is her analgesic properties. Medical marijuana can be used for several types of pain. It inhibits nociceptive (post-traumatic) pain, neuropathic pain and chronic pain could be attributed to deficiencies of endogenous cannabinoids.
Post-traumatic pain might result from a pro-inflammatory response that is inhibited by the action of CBD and THC. CBD blocks macrophages and pro-inflammatory mediators. THC constrains the production of pro-inflammatory cytokines. Additionally, THC stimulates CB1 receptors at the level of the spinal cord, and CBD works by affecting the GABA neurotransmitter. It diminishes the transmission of pain signals to the brain. (30)
Neuropathic pain e.g. during Parkinson disease, diabetes, shingles, multiple sclerosis, derives from breakdown in the protective layer of nerve cells. We have only hypothesis that medical marihuana could relieve neuropathic pain. CBD produces the peripheral antinociception during the acute treatment of the neuropathic pain and it partially involved the participation of the 5-HT1A and TRPV1 receptors. (25,29,30)
The current evidence for the use of cannabis and its derivatives in chronic pain conditions and fibromyalgia are promising and present a new approach to treatment. It is anticipated that fibromyalgia is presumably associated with the deficiency of endocannabinoids. THC is an agonist of endocannabinoids and it stimulate the endocannabinoid system to produce more its own neurotransmitters. Moreover, CBD increases the amount of endogenous anandamide. In consequence, medical marihuana could be useful in fibromyalgia treatment. (32)

When it comes to the dose of the drug, the quantitative evidence establishes that while the higher dose of cannabis extracts did result in reduced pain intensity in spinal cord trauma or disease, there was no significant difference in neuropathic pain relief between higher and lower THC doses. (2)

Cannabis relieves joint stiffness, therefore it has been undergoing testing for use in rheumatology and in the treatment of multiple sclerosis. (28)

The anti-anxiety effect of marijuana on the amygdala and the reward system opens the way to further research in the treatment of depression or addiction e.g. to tobacco or opioids. The research showed that we could decrease the opioid dose by adding medical marihuana in treatment. (28)

Medical marijuana lowers intraocular pressure, so it could be used in ophthalmology. Moreover, it probably works by influencing the endothelial receptor of blood vessels for anandamide, which would be effective in the treatment of hypertension. (33)

Cannabis is also used in epilepsy, e.g. drug-resistant epilepsy in Dravet syndrome, early childhood epileptic encephalopathy and drug-resistant epilepsy with focal seizures after the ineffectiveness of the third or subsequent line of treatment due to its anticonvulsant effect. (33,35)

Medicines which contain medical marijuana or her compounds:

1. **Sativex** - a spray for use in the oral cavity, containing 27 mg THC and 29 mg CBD/ml, registered for the treatment of spasticity in patients over 18 years of age with multiple sclerosis. (29)
2. **Epidiolex** (CBD) - oral solution containing 100 mg/ml of cannabidiol, registered for the treatment of Lennox-Gastaud syndrome (LGS) and Dravet syndrome in patients over 2 years of age. (35)
3. **Marinol** (dronabinol at a dose of 2.5 mg, 5 mg, 10 mg in the form of capsules with sesame oil) - indicated in anorexia, AIDS with weight loss and in nausea and vomiting caused by chemotherapy when standard antiemetics have failed. (3)
4. **Acomplia** (rimonabant, 20 mg) (2016-2018) - CB1 receptor agonist in the brain, adipose tissue, muscle tissue and liver. Registered for the treatment of obesity. Withdrawn from the market due to frequent side effects, including increased levels of liver transaminases. (36)

Conclusions

Provided data evidence comprehensive profile of use for marijuana. It has great potential in palliative care and pain relief. Mechanisms guiding the action of the marijuana are insufficiently elucidated and this subject necessitates meticulous consideration, since the final observed effect is invariably the aggregate of the multidirectional response of the drug. THC and CBD impact on the receptors of the cannabinoid system, but also on serotonin receptors, GABA-A receptors, vanilloid receptors, GPR-55, PPAR and others. Despite the amount of research, currently on the market there are willingly used preparations with marijuana for multiple sclerosis and Dravet syndrome.

Medical marijuana has a diverse array of applications, and more research is required to determine the effects of the pharmaceutical agent.

Disclosure

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As a review, our work does not contain new data or analyses. Therefore, there are no specific data sets or data availability for reporting. The information and findings presented in this review are based on previously published research, which can be accessed through the appropriate sources cited in the reference section.

Declaration of conflict of interest

The authors declare that there are no significant conflicts of interest related to this research work.

Bibliography

1. Lal S, Shekher A, Puneet, Narula AS, Abrahamse H, Gupta SC. Cannabis and its constituents for cancer: History, biogenesis, chemistry and pharmacological activities. Pharmacol Res. 2021;163:105302. doi:10.1016/j.phrs.2020.105302

2. Ebbert JO, Scharf EL, Hurt RT. Medical Cannabis. Mayo Clin Proc. 2018;93(12):1842-1847. doi:10.1016/j.mayocp.2018.09.005

3. Tagen M, Klumpers LE. Review of delta-8-tetrahydrocannabinol (Δ^8 -THC): Comparative pharmacology with Δ^9 -THC [published correction appears in Br J Pharmacol. 2023 Jan;180(1):130]. Br J Pharmacol. 2022;179(15):3915-3933. doi:10.1111/bph.15865

4. Dharmapuri S, Miller K, Klein JD. Marijuana and the Pediatric Population. Pediatrics. 2020;146(2):e20192629. doi:10.1542/peds.2019-2629

5. Gupta K, Walton R, Kataria SP. Chemotherapy-Induced Nausea and Vomiting: Pathogenesis, Recommendations, and New Trends. Cancer Treat Res Commun. 2021;26:100278. doi:10.1016/j.ctarc.2020.100278

6. Crocq MA. History of cannabis and the endocannabinoid system. Dialogues Clin Neurosci. 2020;22(3):223-228. doi:10.31887/DCNS.2020.22.3/mcrocq

7. Charitos IA, Gagliano-Candela R, Santacroce L, Bottalico L. The Cannabis Spread throughout the Continents and its Therapeutic Use in History. Endocr Metab Immune Disord Drug Targets. 2021;21(3):407-417. doi:10.2174/1871530320666200520095900

8. Amin MR, Ali DW. Pharmacology of Medical Cannabis. Adv Exp Med Biol. 2019;1162:151-165. doi:10.1007/978-3-030-21737-2_8

9. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol. 2008;153(2):199-215. doi:10.1038/sj.bjp.0707442

10. Nachnani R, Raup-Konsavage WM, Vrana KE. The Pharmacological Case for Cannabigerol. J Pharmacol Exp Ther. 2021;376(2):204-212. doi:10.1124/jpet.120.000340

11. Di Marzo V, Piscitelli F. The Endocannabinoid System and its Modulation by Phytocannabinoids. Neurotherapeutics. 2015;12(4):692-698. doi:10.1007/s13311-015-0374-6

12. Lu HC, Mackie K. Review of the Endocannabinoid System. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021;6(6):607-615. doi:10.1016/j.bpsc.2020.07.016

13. Biernacki M, Skrzydlewska E. Metabolism of endocannabinoids. Postepy Hig Med Dosw (Online). 2016;70(0):830-843. Published 2016 Aug 11. doi:10.5604/17322693.1213898

14. De Petrocellis L, Ligresti A, Moriello AS, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol. 2011;163(7):1479-1494. doi:10.1111/j.1476-5381.2010.01166.x

15. Mock ED, Gagestein B, van der Stelt M. Anandamide and other N-acylethanolamines: A class of signaling lipids with therapeutic opportunities. Prog Lipid Res. 2023;89:101194. doi:10.1016/j.plipres.2022.101194

16. Singh D, Lippmann S. Vaping medical marijuana. Postgrad Med. 2018;130(2):183-185. doi:10.1080/00325481.2018.1413281

17. Wennberg E, Windle SB, Filion KB, et al. Roadside screening tests for cannabis use: A systematic review. Heliyon. 2023;9(4):e14630. Published 2023 Mar 22. doi:10.1016/j.heliyon.2023.e14630

18. Potschka H, Bhatti SFM, Tipold A, McGrath S. Cannabidiol in canine epilepsy. Vet J. 2022;290:105913. doi:10.1016/j.tvjl.2022.105913

19. Potschka H, Bhatti SFM, Tipold A, McGrath S. Cannabidiol in canine epilepsy. Vet J. 2022;290:105913. doi:10.1016/j.tvjl.2022.105913

20. Xiong W, Koo BN, Morton R, Zhang L. Psychotropic and nonpsychotropic cannabis derivatives inhibit human 5-HT(3A) receptors through a receptor desensitization-dependent mechanism. Neuroscience. 2011;184:28-37. doi:10.1016/j.neuroscience.2011.03.066

21. Gray RA, Whalley BJ. The proposed mechanisms of action of CBD in epilepsy. Epileptic Disord. 2020;22(S1):10-15. doi:10.1684/epd.2020.1135

22. Alexander C, Vasefi M. Cannabidiol and the corticoraphe circuit in post-traumatic stress disorder. IBRO Neurosci Rep. 2021;11:88-102. Published 2021 Aug 21. doi:10.1016/j.ibneur.2021.08.001

23. Rosenberg EC, Chamberland S, Bazelot M, et al. Cannabidiol modulates excitatory-inhibitory ratio to counter hippocampal hyperactivity. Neuron. 2023;111(8):1282-1300.e8. doi:10.1016/j.neuron.2023.01.018

24. Rodrigues Tavares, L. R., Baptista-de-Souza, D., Canto-de-Souza, L., Planeta, C. D. S., Guimarães, F. S., Nunes-de-Souza, R. L., & Canto-de-Souza, A. (2023). The Reversal of Empathy-Induced Hypernociception in Male Mice by Intra-Amygdala Administration of Midazolam and Cannabidiol Depends on 5-HT3 Receptors. Cannabis and cannabinoid research, 8(2), 335–347. https://doi.org/10.1089/can.2022.0132 - 5ht3

25. Kowalski CW, Ragozzino FJ, Lindberg JEM, et al. Cannabidiol activation of vagal afferent neurons requires TRPA1. J Neurophysiol. 2020;124(5):1388-1398. doi:10.1152/jn.00128.2020

26. Louis-Gray K, Tupal S, Premkumar LS. TRPV1: A Common Denominator Mediating Antinociceptive and Antiemetic Effects of Cannabinoids. Int J Mol Sci. 2022;23(17):10016. Published 2022 Sep 2. doi:10.3390/ijms231710016

27. Gray RA, Whalley BJ. The proposed mechanisms of action of CBD in epilepsy. Epileptic Disord. 2020;22(S1):10-15. doi:10.1684/epd.2020.1135

28. Mottarlini F, Fumagalli M, Castillo-Díaz F, et al. Single and Repeated Exposure to Cannabidiol Differently Modulate BDNF Expression and Signaling in the Cortico-Striatal Brain Network. Biomedicines. 2022;10(8):1853. Published 2022 Aug 1. doi:10.3390/biomedicines10081853

29. Pagano C, Navarra G, Coppola L, Avilia G, Bifulco M, Laezza C. Cannabinoids: Therapeutic Use in Clinical Practice. Int J Mol Sci. 2022;23(6):3344. Published 2022 Mar 19. doi:10.3390/ijms23063344

30. Lee G, Grovey B, Furnish T, Wallace M. Medical Cannabis for Neuropathic Pain. Curr Pain Headache Rep. 2018;22(1):8. Published 2018 Feb 1. doi:10.1007/s11916-018-0658-8

31. Patricio F, Morales-Andrade AA, Patricio-Martínez A, Limón ID. Cannabidiol as a Therapeutic Target: Evidence of its Neuroprotective and Neuromodulatory Function in Parkinson's Disease. Front Pharmacol. 2020;11:595635. Published 2020 Dec 15. doi:10.3389/fphar.2020.595635

32. Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis and Pain: A Clinical Review. Cannabis Cannabinoid Res. 2017;2(1):96-104. Published 2017 May 1. doi:10.1089/can.2017.001733.

33. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology. 1980;87(3):222-228. doi:10.1016/s0161-6420(80)35258-5

34. Potschka H, Bhatti SFM, Tipold A, McGrath S. Cannabidiol in canine epilepsy. Vet J. 2022;290:105913. doi:10.1016/j.tvjl.2022.105913

35. Georgieva D, Langley J, Hartkopf K, et al. Real-world, long-term evaluation of the tolerability and therapy retention of Epidiolex® (cannabidiol) in patients with refractory epilepsy. Epilepsy Behav. 2023;141:109159. doi:10.1016/j.yebeh.2023.109159

36. Ducobu J, Sternon J. Le rimonabant (Acomplia), inhibiteur spécifique du système endocannabinoïde [Rimonabant (Acomplia), specific inhibitor of the endocannabinoid system]. J Pharm Belg. 2005;60(3):89-91.