THE EFFECT OF DELTA-9-TETRAHYDROCANNABINOL ON DELAYED-ONSET MUSCLE SORENESS

By

HANNAH MICHELLE ROSEN

_____

A Thesis Submitted to The W.A. Franke Honors College

In Partial Fulfillment of the bachelor's degree
With Honors in

Physiology

THE UNIVERSITY OF ARIZONA

M A Y 2 0 2 3

Approved by:

Dr. Douglas Keen
Department of Physiology

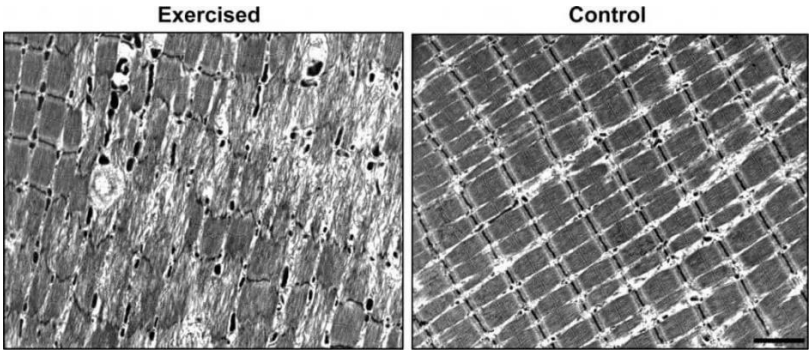
Abstract:

Many individuals have experienced “muscle fever” or delayed-onset muscle soreness (DOMS) after an intense workout. Microtrauma occurs in myofibers commonly involved with intensive eccentric exercises. Due to inflammation from the microinjury, DOMS can occur. As the steady inclination of states across America are legalizing the use of recreational marijuana, companies are beginning to sell delta-9-tetrahydrocannabinol (Δ9-THC) containing products that claim to reduce somatic pain and speed up recovery time to allow gym goers and athletes to return to their workouts at a faster rate. The overall purpose of this paper is to take an objective view of whether the literature supports Δ9-THC as a remedy for DOMS. The major results found were that Δ9-THC can be a potential candidate to reduce DOMS after an intense workout through the reduction of pain and anti-inflammatory properties. There are high expression levels of cannabinoid receptor 1(CB1R) in the hippocampus which are involved in regulating nociceptive perception. Upon Δ9-THC interacting with the CB1R, this inhibits neurotransmitter release reducing the signal of pain to the pre-frontal cortex. Since Δ9-THC can bind to the body’s cannabinoid receptor 2 (CB2R) found in the endocannabinoid system, this activates immunosuppression through the induction of apoptosis, inhibition of cell proliferation, and the suppression of cytokine production. Thus, cannabis may represent a promising therapeutic agent to reduce DOMS and allow quicker recovery time from the associated mechanisms of pain and inflammation reduction.

Introduction:

Many people experience soreness and aching pain throughout the body about 48-72 hours post-workout. This condition is known as delayed-onset muscle soreness (DOMS). After strenuous exercise, muscular pain, most prominently in skeletal muscle and myo-tendonous

junctions, occurs from a combination of micro tears, also known as z-line streaming, to the muscle tissue, increased inflammation, and muscle remodeling of which cause DOMS (Lieber).



Citation: http://www.machtmedicalgroup.com/2020/09/why-so-sore-the-curious-case-of-doms/

Figure 1. *On the right image, one can see an organized pattern of sarcomeres from the control group before strenuous exercise. The image on the left displays microtears to the tissue, loss of z-discs, and disorganized patterns to the sarcomere post exercise.*

Most prominently, DOMS is displayed within individuals that perform exercises that are new to them. This means that not only individuals new to the gym experience DOMS, even athletes in exquisite condition that undergo training requiring exercises they have not yet become accustomed to, can experience the delayed pain (Lieber).

A potential remedy to this discomfort is an oral consumption of delta-9-tetrahydrocannabinol (Δ9-THC). The proposed mechanism displays how Δ9-THC interacts with the body's endocannabinoid system which regulates the physiological processes of pain, mood, hunger, and many other important functions (Capodice). Within the endocannabinoid system, there are two main types of receptors, cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R). CB1R resides predominantly in the central nervous system (CNS) and is the most abundant GCPR in the brain. CB2R exists primarily outside the CNS and is associated with the immune system (Alger). Both receptors are 7-transmembrane receptors or G protein-coupled receptors (GPCRs). To activate either receptor, CB1R or CB2R has to bind an endogenous ligand, a natural agent the body produces. Although the body's endocannabinoid system did not

evolve to react with cannabis, the plant has similar features to the naturally produced ligands (Alger).

CB1R has two major endogenous ligands, N-arachidonoylethanolamide (anandamide) and two-arachidonolyl glycerol (2-AG) (Alger). There has been no identified cannabinoid ligands that only binds to CB2R (Malfitano). When orally ingested, THC is denatured though stomach acid found in the gut and about 95% of total radioactivity labeled THC was found to be absorbed in the gastrointestinal tract in an oil type of ingestant but it's unclear the difference between oils and syrups due to the natural breakdown of products and lack of further studies (Grotenhermen). The maximal plasma concentration of Δ9-THC occurs around 60-120 minutes after ingestion but, in some cases, maximal plasma concentrations can be seen as late as 4-6 hours (Grotenhermen). Since cannabis has been utilized to reduce pain and inflammation, a major cause of DOMS, researchers have noted Δ9-THC as a possible candidate to decrease nociceptive perception of soreness and lessen inflammation after the gym to heal the z-line streaming at a faster rate (Bridgeman). The purpose of this paper is to take an objective view of whether the literature supports delta-9-tetrahydrocannabinol as a remedy for DOMS.

Review of Literature:

The endocannabinoid system (ECS) is composed of a densely packed network of chemical signals and cellular receptors throughout the brain and body which modulates neutral activity and function. In the brain, the ECS mainly influences the neuronal synaptic connections that include appetite, memory, immune functions, neuroprotection, and pain modulation (Battista). Within the ECS, there are endogenous cannabinoids, also known as endocannabinoids (eCBs), the cannabinoid receptors, CBR1 and CBR2, and the proteins that synthesize, transport and degrade the eCBs. Endogenous cannabinoids are lipid mediators that include esters, amides,

and ethers of long chain polyunsaturated fatty acids that are isolated from the brain and peripheral tissue. Since Δ9-THC can mimic the actions of eCBs, Δ9-THC can interact with the various biological processes associated with the ECS (Battista).

The most bioactive eCBs are N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonoylglycerol (2-AG). Although there are five other eCBs found, there is very limited research and has not been widely studied therefore, the main eCBs that will be focused on are AEA and 2-AG (Battista). Similarly, to other eicosanoids, AEA and 2-AG are synthesized on demand by Ca2+ influx (cell depolarization), or through the movement of intracellular Ca2+ stores after activating Gq/11 protein-coupled receptors (Marzo). The Gq/11 receptor is a G protein alpha subunit that couples to GCPR to activate beta-type phospholipase C (PLC-β) enzymes (Marzo). Phosphatidylinositol 4,5-bisphosphate (PIP2) is then hydrolyzed to diacyl glycerol (DAG) and inositol trisphosphate (IP3) by PLC-β. Acting as a second messenger, IP3 signals to release stored calcium in the cytoplasm. The idea of the on-demand synthesis of the eCBs is that there are precursor membrane lipids that can be released, usually by lipases, and are activated by GCPRs or increased intracellular Ca2+ levels (Lu). Unlike neurotransmitters which are synthesized then stored in vesicles, the on-demand characteristic of eCBs allows a very precise temporal and spatial release (Lu). The administration of eCBs by the body allows seconds or less to interact with cannabinoid receptors, however, when consuming exogenous cannabis such as Δ9-THC, the receptor engagement sustains for minutes and longer depending on quantity consumption (Lu). As a result of longer receptor activation, the effects of exogenous administration of Δ9-THC can differ from the effects of eCBs that are physiologically released.

The eCBs are produced in the postsynaptic cell of a neuron and due to their polar nature, they cannot pass across the cell membrane by simple diffusion. Since there is little evidence of

use for ATP or sodium, carrier-mediated facilitated diffusion is suggested as the mechanism for eCB transport (Lu). There is significant evidence that suggests AEA and 2-AG are transported by the same eCB membrane transporter (EMT). Once connected to the transporter, the eCBs travel in the reverse direction across the cleft to interact with the CB1Rs on the pre-synaptic terminal (Alger). Since Δ9-THC is a lipophilic molecule, there is no required carrier for transport across to the pre-synaptic cleft. As a result of transport in the opposite direction of a normal synaptic transmission, eCBs are generally considered to use retrograde signaling. By reducing Ca2+ influx into presynaptic terminals through retrograde action, eCBs can inhibit neurotransmitter release at the pre-synaptic terminals (Alger). This mechanism is specifically important when considering eCBs inducing antinociceptive effects which will be discussed further on in this paper.

To terminate eCB signaling, hydrolysis of the arachidonic group from the ethanol amine in AEA or the hydrolysis of the arachidonic group from the glycerol in 2-AG, can lead to the endocannabinoid's degradation (Lu). AEA hydrolysis is primarily carried out by fatty acid amino hydrolase (FAAH) while 2-AG hydrolysis occurs from monoacylglycerol lipase (MAGL) or alpha/beta-hydrolase domain containing 6 (ABDH6) (Lu). Once the arachidonic acid is hydrolyzed from either AEA or 2-AG, the remaining structures can be utilized as a substrate for cyclooxygenases to produce prostaglandins or for direct metabolism by cyclooxygenase-2 (COX-2) to produce prostamides from AEA or prostaglandin glycerol esters from 2-AG (Lu). Therefore, once the degradation of eCBs occurs, this does not simply indicate the termination of signaling, but rather a transformation to a different type of signaling.

Of the cannabinoids known, only Δ9-THC binds to cannabinoid receptors with high affinity (Marzo). CB1Rs are mainly found in the CNS and some in the peripheral nervous system

as well as in the heart, testis, vascular tissues, and on cells of the immune system (Begg). An estimated 30% of CB1R were seen in the activated state from endogenous endocannabinoids while 70% are inactive (Kearn). This indicates that most CB1R are in the inactive state allowing Δ9-THC to bind to 70% of receptors which can produce significant effects. The expression of CB2Rs are limited to primarily immune cells which upon activation, displays anti-inflammatory properties (Begg). In the CB2R, there is a 68% amino acid homology with the CB1R in the transmembrane domains and overall, a 44% homology which, despite the low homology, the pharmacological components are remarkably similar and have somewhat similar affinities to both the receptors (Begg). However, 2-AG and AEA have a slightly higher binding affinity to CB1Rs (Howlett). CB1R and CBR2 are coupled to the inhibitory Gi/o family of proteins which inhibits adenylyl cyclase and regulates Ca2+ and K+ channels (CB1R only) and activates mitogen-activated protein kinase (Howlett). CB2Rs can modulate the chemical messengers (i.e., cytokines and immune cell migration) primarily involved with the immune system (Jensen).

As mentioned before, the ECS can inhibit neurotransmitter release in the pre-synaptic terminals of neurons. When examining antinociception, Δ9-THC inhibits the release of the neurotransmitter glutamate which is an excitatory neurotransmitter that transmits synaptic sensations such as pain (Russo). Specifically, the inhibition occurs in the hippocampus on CB1Rs and reduces NMDA responses to glutamate by 30-40% (Russo). An experimental study was conducted on 15 healthy volunteers to examine the effects of Δ9-THC (low (2%), medium (4%), and high doses (8%)) on human pain response. This study utilized intradermal capsaicin pain response using a randomized, double-blind crossover trial. The results indicated a significant decrease in pain with a medium and high dose of cannabis and there was no observed effect with the low cannabis dose (Hill). With the significant decrease in pain, researchers began

to conduct studies on the effectiveness of medical marijuana in pain management with chronic pain patients. Medical cannabis was found to effectively treat chronic pain and produced a significant improvement in the management of chronic pain (MacCallum). There have been reports that marijuana has replaced opioid analgesics due to its clinical significance (Wiese B, Lucas P, Reiman, Vigil J). Randomized studies suggested that up to 25 milligrams daily of Δ9-THC can significantly reduce pain compared to the placebo (Zajicek, Svendsen). Another study conducted among cannabis users found that efficacy of cannabis for pain management is higher than prescription pain medication (Perron). With the inhibition of the release of glutamate, the significant improvement of chronic pain management, and the efficacy of cannabis compared to prescription pain medication, Δ9-THC may pose a promising therapeutic agent for anti-nociception related to DOMS.

When considering the inflammation associated with the micro-tears of the sarcomeres in DOMS, this inflammation can slow down recovery time in skeletal muscle. While inflammation is a natural process in the body, it can also hinder healing (Peake). The inflammatory process begins immediately after an acute injury to the sarcomeres by increasing blood flow surrounding the injured area. The arterioles will dilate, and the capillary beds become more permeable to allow proteins, macrophages, neutrophils, eosinophils, cytotoxic T-cells (CD8+), T regulatory cells, and mast cells into the interstitial space (Peake). CB2Rs are found primarily on the cells of the immune system and play a role in immunosuppression through the induction of apoptosis, inhibition of cell proliferation, and the suppression of cytokine production (Nagarkatti). Under normal conditions, apoptosis is required to maintain homeostasis. The extrinsic pathway of apoptosis is activated by the ligation of the death receptor, CD95, on the surface of the cell

which activates caspases 3,8, and 10 (Nagarkatti). The intrinsic pathway of apoptosis is activated via the mitochondria and caspase 9 (Nagarkatti).

When considering cannabis, Δ9-THC has demonstrated the activation of apoptosis in macrophages, dendritic cells, T cells, and B cells (McKallip). This process was mediated via the activation of Bcl-2, a protein family involved in the regulation of apoptotic cell death, and caspase-1 (Zhu). Δ9-THC has demonstrated higher levels of apoptosis in naïve lymphocytes when compared to mitogen-activated lymphocytes due to the downregulation of CB2R after lymphocyte activation from a mitogen (McKallip). Therefore, data suggests that naïve lymphocytes may be more susceptible to induce apoptosis by Δ9-THC rather than mitogen-activated lymphocytes. Several studies have also reported that Δ9-THC induces apoptosis in antigen presenting cells (Nagarkatti). Via the ligation of CB2R and activation of caspase 2, 8, and 9, Δ9-THC activated apoptosis in bone marrow-derived dendritic cells (Do).

Another mechanism of reduced inflammation mediated by Δ9-THC, is the deregulation of cytokine production by T cells. Δ9-THC has been found to suppress type 1 helper T cell (Th1) proliferation which inhibits the production of interferon-gamma (IFN-γ), IL-2, and IL-12 (Yuan). IFN-γ can potentiate pro-inflammatory signaling by activating nitric oxide production and inhibits NLRP3 inflammasome activation (Kopitar-Jerala). IL-2 promotes inflammation by generating Th1 and Th2 effector cells. IL-12 is a key cytokine that drives inflammatory responses and aids in the activation of several cytotoxic immune cells. Since Δ9-THC suppresses Th1 and the pro-inflammatory cytokines the cell produces, reduction of inflammation can occur.

Results

Δ9-THC may pose a promising remedy to speed up recovery time associated with DOMS. Since the cannabinoid can interact with the body's natural ECS, Δ9-THC can activate

the system at significant levels. Δ9-THC can bind to CB1Rs in the pre-synaptic terminal to reduce the influx of Ca2+ causing inhibition of the neurotransmitter glutamate to be released. The disruption of the release inhibits communication of neurons to send signals of pain to the prefrontal cortex. With delayed onset-muscle soreness, the symptoms of pain can range from soreness to the touch to severe debilitating pain. The severity of the symptoms directly correlates to the intensity and duration of the exercise. The soreness increases to a peak between 24-72 hours then subsides by 7 days after the activity (Lee). This discomfort can reduce athletic performance and limit joint range of motion (Cheung). For many athletes, the recovery time damages their ability to train properly since they cannot display their peak performance during the healing process. Some studies found that cannabis may be more effective in pain management than prescription pain medication. By inhibiting the communication of pain to the pre-frontal cortex, Δ9-THC may aid in anti-nociception to enhance athletic performance and reduce the recovery time needed to heal in DOMS.

When undergoing unaccustomed eccentric exercise, inflammation occurs as a result of muscle damage which can slow down recovery time. Δ9-THC has demonstrated its ability to reduce inflammation at sites of skeletal muscle damage through the activation of apoptosis of specific immune cells and decreasing pro-inflammatory cytokine productions. Unlike necrosis, apoptosis is not harmful to the body and does not induce any inflammatory reactions. Δ9-THC interacts with CB2Rs on dendritic cells to activate apoptosis. Δ9-THC also inhibits the production of pro-inflammatory cytokines such as IFN- γ, IL-2, and IL-12 by suppressing the production of Th1 cells. The reduction of inflammation is important in muscle recovery because with prolonged inflammation from z-line streaming, this induces persistent swelling and can cause the tissue to become stiffer and less flexible which significantly increases the susceptibility

of further injury (Nielsen). Equivalent to muscle soreness, inflammation can also reduce athletic performance. Through the activation of apoptosis on immune cells and the reduction of cytokine release, Δ9-THC may reduce inflammation associated with DOMS.

Conclusion

Δ9-THC does not enhance performance, but rather quickens recovery time post-workout. Cannabis is a newly studied substance as laws have begun to change and many mechanisms in the way Δ9-THC impacts the body are still not well understood. Currently, researchers are examining different conditions with potential treatments of marijuana. There are studies looking at patients who are diagnosed with epilepsy, Alzheimer's disease, Crohn's disease, multiple sclerosis, and many other conditions, and examining if cannabis can be a viable treatment option to aid their associated symptoms. Δ9-THC may be used to control abdominal pain in patients with inflammatory bowel disease and possibly aid in the reduction of inflammation in the gastrointestinal tract. There is still further research to be conducted to determine the exact mechanisms of aid. In cancer patients, marijuana is often used to help manage the side effects of chemotherapy. Although more research needs to be conducted, cannabis may be utilized as a tool to reduce inflammation and pain, whether from an intense workout or from a disease.

To further this research, I would want to examine the combination of whey protein powder and cannabis as a supplement post-workout to see if the amino acids from the protein powder and the reduction of inflammation and pain from the Δ9-THC would speed up recovery time at an even faster rate. Cannabis does not impact the muscle tissue directly, but rather only interacts with CB1Rs in the CNS and CB2Rs on immune cells. Δ9-THC reduces the inflammation surrounding the damage and hinders the pain signals to the brain. Therefore, by combining whey protein which has all the essential amino acids that the body can use for repair,

there may be a direct healing to the muscle along with anti-inflammatory and anti-nociception properties from the cannabis.

References:

Alger, Bradley. Getting high on the endocannabinoid system. Cerebrum. 2013 Nov 1;2013:14. PMID: 24765232; PMCID: PMC3997295.

Alger B, Kim J, Supply and demand for endocannabinoids, Trends in Neurosciences, Volume 34, Issue 6, 2011, Pages 304-315, ISSN 0166-2236, https://doi.org/10.1016/j.tins.2011.03.003.

Battista N, Di Tommaso M, Bari M and Maccarrone M. The endocannabinoid system: an overview. 2012. Front. Behav. Neurosci. 6:9. doi: 10.3389/fnbeh.2012.00009

Begg M, Pacher P, Bátkai S, Osei-Hyiaman D, Offertáler L, Mo F, Liu J, Kunos G. Evidence for novel cannabinoid receptors, Pharmacology & Therapeutics, Volume 106, Issue 2, 2005, Pages 133-145, ISSN 0163-7258, https://doi.org/10.1016/j.pharmthera.2004.11.005.

Bie B, Wu J, Foss JF, Naguib M. An overview of the cannabinoid type 2 receptor system and its therapeutic potential. Curr Opin Anaesthesiol. 2018 Aug;31(4):407-414. doi: 10.1097/ACO.0000000000000616. PMID: 29794855; PMCID: PMC6035094.

Bridgeman MB, Abazia DT. Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. P T. 2017 Mar;42(3):180-188. PMID: 28250701; PMCID: PMC5312634.

Capodice JL, Kaplan SA. The endocannabinoid system, cannabis, and cannabidiol: Implications in urology and men's health. Curr Urol. 2021 Jun;15(2):95-100. doi: 10.1097/CU9.0000000000000023. Epub 2021 May 28. PMID: 34168527; PMCID: PMC8221009.

Cheung K, Hume P, Maxwell L. Delayed onset muscle soreness: treatment strategies and performance factors. Sports Med. 2003;33(2):145-64. doi: 10.2165/00007256-200333020-00005. PMID: 12617692.

Do Y, McKallip R, Nagarkatti M, Nagarkatti P. Activation through cannabinoid receptors 1 and 2 on dendritic cells triggers NF-kappaB-dependent apoptosis: novel role for endogenous and exogenous cannabinoids in immunoregulation. J Immunol. 2004 Aug 15;173(4):2373-82. doi: 10.4049/jimmunol.173.4.2373. PMID: 15294950.

Grinspoon, Peter. The endocannabinoid system: Essential and mysterious. Harvard Health. August 11 2021. Retrieved from https://www.health.harvard.edu/blog/the-endocannabinoid-system-essential-and-mysterious-202108112569

Grotenhermen, Franjo. Pharmacokinetics and Pharmacodynamics of Cannabinoids. Clin Pharmacokinet 42, 327–360 (2003). https://doi.org/10.2165/00003088-200342040-00003

Hill K, Palastro M, Johnson B, and Ditre J.Cannabis and Pain: A Clinical Review. Cannabis and Cannabinoid Research. Dec 2017.96-104.http://doi.org/10.1089/can.2017.0017

Howlett, Allyn. The cannabinoid receptors, Prostaglandins & Other Lipid Mediators, Volumes 68–69, 2002, Pages 619-631, ISSN 1098-8823, https://doi.org/10.1016/S0090-6980(02)00060-6.

Kearn, C.S., Greenberg, M.J., DiCamelli, R., Kurzawa, K. and Hillard, C.J. (1999), Relationships Between Ligand Affinities for the Cerebellar Cannabinoid Receptor CB1 and the Induction of GDP/GTP Exchange. Journal of Neurochemistry, 72: 2379-2387. https://doi.org/10.1046/j.1471-4159.1999.0722379.x

Kopitar-Jerala, Nataša. The Role of Interferons in Inflammation and Inflammasome Activation. Front Immunol. 2017 Jul 25;8:873. doi: 10.3389/fimmu.2017.00873. PMID: 28791024; PMCID: PMC5525294.

Lee J, Healy J. Delayed onset muscle soreness. Delayed Onset Muscle Soreness - an overview | ScienceDirect Topics. 2011. Retrieved from https://www.sciencedirect.com/topics/neuroscience/delayed-onset-muscle-soreness

Lieber, Richard L. PhD; Fridén, Jan MD, PhD. Morphologic and Mechanical Basis of Delayed-Onset Muscle Soreness. Journal of the American Academy of Orthopaedic Surgeons 10(1):p 67-73, January 2002.

Lu H, Mackie K. Review of the Endocannabinoid System, Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, Volume 6, Issue 6, 2021, Pages 607-615, ISSN 2451-9022, https://doi.org/10.1016/j.bpsc.2020.07.016.

Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients, International Journal of Drug Policy, Volume 42, 2017, Pages 30-35, ISSN 0955-3959, https://doi.org/10.1016/j.drugpo.2017.01.011.

MacCallum C, Russo E. Practical considerations in medical cannabis administration and dosing, European Journal of Internal Medicine, Volume 49, 2018, Pages 12-19, ISSN 0953-6205, https://doi.org/10.1016/j.ejim.2018.01.004.

Malfitano A, Sreemanti B, Maresz K, Bifulco M, Dittel M. What we know and do not know about the cannabinoid receptor 2 (CB2), Seminars in Immunology, Volume 26, Issue 5, 2014, Pages 369-379, ISSN 1044-5323, https://doi.org/10.1016/j.smim.2014.04.002

Marzo, Di. Endocannabinoids: synthesis and degradation. In: et al. Reviews of Physiology Biochemistry and Pharmacology. Reviews of Physiology, Biochemistry and Pharmacology, vol 160. Springer, Berlin, Heidelberg. https://doi.org/10.1007/112_0505

McKallip R, Lombard C, Martin B, Nagarkatti M, Nagarkatti P. Delta(9)-tetrahydrocannabinol-induced apoptosis in the thymus and spleen as a mechanism of immunosuppression in vitro and

in vivo. J Pharmacol Exp Ther. 2002 Aug;302(2):451-65. doi: 10.1124/jpet.102.033506. PMID: 12130702.

Nagarkatti P, Pandey R, Rieder S, Hegde V, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. Future Med Chem. 2009 Oct;1(7):1333-49. doi: 10.4155/fmc.09.93. PMID: 20191092; PMCID: PMC2828614.

Nielsen, D. The truth about inflammation and injury recovery. July 2021. Recoup Fitness. Retrieved from https://recoupfitness.com/blogs/news/the-truth-about-inflammation-and-injury-recovery

Peake J, Neubauer O, Della Gatta P, Nosaka K. Muscle damage and inflammation during recovery from exercise. J Appl Physiol (1985). 2017 Mar 1;122(3):559-570. doi: 10.1152/japplphysiol.00971.2016. Epub 2016 Dec 29. PMID: 28035017.

Perron B, Bohnert K, Perone A, Bonn-Miller M, Ilgen M. Use of Prescription Pain Medications Among Medical Cannabis Patients: Comparisons of Pain Levels, Functioning, and Patterns of Alcohol and Other Drug Use. Journal of Studies on Alcohol and Drugs 2015 76:3, 406-413

Reiman A, Welty M, Solomon P. Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report.Cannabis and Cannabinoid Research. Dec 2017.160-166. http://doi.org/10.1089/can.2017.0012

Russo E, Hohmann A. Role of Cannabinoids in Pain Management. In:, et al. Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches. 2013. Springer, New York, NY. https://doi.org/10.1007/978-1-4614-1560-2_18

Svendsen K, Jensen T, Bach F. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial BMJ 2004; 329 :253 doi:10.1136/bmj.38149.566979.AE

Vigil J, Stith S, Adams I, Reeve A. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS ONE 12(11): e0187795. https://doi.org/10.1371/journal.pone.0187795

Wiese B, Wilson-Poe A. Emerging Evidence for Cannabis' Role in Opioid Use Disorder. Cannabis and Cannabinoid Research. Dec 2018.179-189.http://doi.org/10.1089/can.2018.0022

Yuan M, Kiertscher S, Cheng Q, Zoumalan R, Tashkin D, Roth M, Δ9-Tetrahydrocannabinol regulates Th1/Th2 cytokine balance in activated human T cells, Journal of Neuroimmunology, Volume 133, Issues 1–2, 2002, Pages 124-131, ISSN 0165-5728, https://doi.org/10.1016/S0165-5728(02)00370-3.

Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study):

Multicentre randomised placebo-controlled trial. 2003. The Lancet, 362(9395), 1517–1526. https://doi.org/10.1016/s0140-6736(03)14738-1

Zhu W, Friedman H, Klein T. Delta9-tetrahydrocannabinol induces apoptosis in macrophages and lymphocytes: involvement of Bcl-2 and caspase-1. J Pharmacol Exp Ther. 1998 Aug;286(2):1103-9. PMID: 9694974.

Zou S, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. Int J Mol Sci. 2018 Mar 13;19(3):833. doi: 10.3390/ijms19030833. PMID: 29533978; PMCID: PMC5877694.