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Review Article

Cannabinoid as Pain Modulation: The Review

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Abstract

Cannabinoids are the most commonly recognized herbal plant, having much medicinal importance from ancient times and plays an important role in Indian culture. Now a day's cannabinoids are used for many therapeutic purposes, and under clinical trial by various institutions. In the latest discovery within humans, it was found that we also have cannabinoids, receptors, and enzymes in our body, so it is termed as endocannabinoids, it consists of receptors CB1 and CB-2, endocannabinoids and their enzyme. Most of the phyto-cannabinoids work in these receptors, which result in Ant inflammatory, analgesic, antioxidant, antiemetic, antifungal, antibiotic, AChE inhibitor. The most common effect shown is pain modulation, in this article we are getting into various methods by which phyto-cannabinoids modulate pain signals in our body and all the clinical trial which is ongoing or complicated the trial on cannabis.

Keywords: Tetrahydrocannabinol (THC), CANNABINOIDS, Endocannabinoid system (ECS), Excitatory postsynaptic potential (EPSP).

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INTRODUCTION

The most common name of cannabis is ganja, "charas" and in India most commonly found in Hilly area mountain of Uttrakhand[6] and most of the places, cannabis plant have a big history of mythological and spiritual use, it also makes a place in the Ayurveda treatment from ancient time[1], recently been cannabis is removed from heard drugs, in India government is seeking to give its as legal to use in medicinal purpose. This might be a big step if it is legal in India. It is surprising to know that cannabis is legal in India but after 1985 it comes under the Narcotic and psychoactive drug act 1985.

According to this act, the products of cannabis and its derivatives have become illegal in India. But exploitation of this plant and its use in the treatment remains in the user for many years after putting these drugs in an illegal category, all India institutes of medical science 2019 did a survey and found that 2.3 million Indians consumed it. These all might be the main reasons in India for the ban in open use of cannabis for medical and research purposes is not been established and developed.

But the question arises that why cannabis is used in the ancient treatment of pain and other diseases, what chemical it has that show the big relief of pain and feel high, increase hunger, make your eyes red, brain function becomes slow. These all questions are been answered in this article according to chemical composition and their mode of action.

The components of cannabis is been studied more closely in institutional labs in 1980 by Turner and found above 420 compounds in cannabis active chemical compounds and 1990 Sparacino scheduled 200 other compounds which are activated within different temperature.

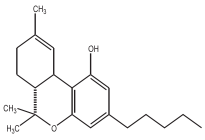
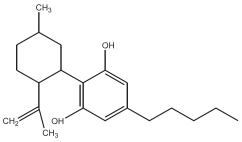
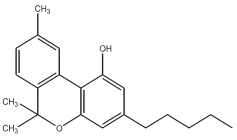
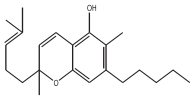
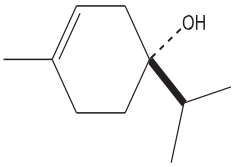
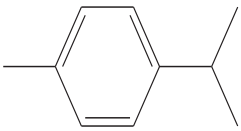
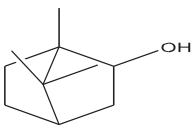
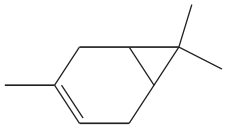
This review article is an aggregation of many research articles and clinical trials, a database such as Google Scholar, PubMed, and clinicalTrials.gov are used. Inclusion criteria include research articles and clinical trials completed and exclusion criteria include review articles, news articles, and systemic reviews. All the research papers are examined and understood for the extraction of important data. A total of 31 articles are used, this article are having more than 40 citations.

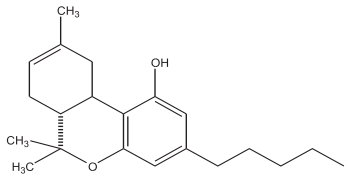
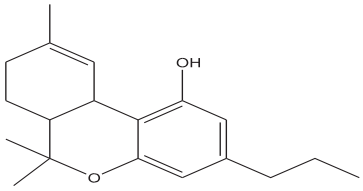
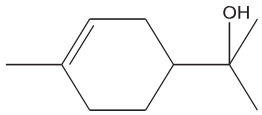
CANNABINOIDS

This compound is defined by Mechoulam and Gaoni (1967) as the composition of C12 terpene phenolic compounds produced by cannabis, in 1999 Pate proposed the word "phyto-cannabinoids" [4] to name the C_{21} compounds synthesize by cannabis plant. In 1964 it's been found that Tetrahydrocannabinol (THC), shows major pharmacological effects in cannabis plant [1], this compound is been identified and synthesized.

Endogenous receptor ligands and a wide number of synthetic cannabinoid analogues are found in Cannabis sativa L, monoterpenoid systems have been used as a numbering system for phyto-cannabinoids, this system listed total of 66 phyto-cannabinoids which is classified into different identification, most belonging to several sub classification [5].

Table 1

Structure	Properties
"Δ-9-tetrahydrocannabinol" (THC) 	Con 0.1-25% BP 157 Medical use: Anti-analgesic Anti-inflammatory Anti-Oxidant Anti-emetic Euphoria
"Cannabidiol" (CBD) 	Con 0.1-2.89% BP 160-180 Medical use: Anti-inflammatory Anti-spasmodic Anti-oxidant Anti-psychotic Analgesic
"Cannabinol" (CBN) 	Con 0.0-1.6% BP 185 Medical use: Anti-biotic Sedative
"Cannabichromene" (CBC) 	Con 0.0-0.65% BP 220 Medical use: Anti-inflammatory Anti-biotic Anti-fungal
"terpineol-4-ol" 	Con 0.0004% BP 209 Medical use: Acetylcholinesterase inhibitors, Anti-biotic Anti-oxidant Anti- malarial
"p-cymene" 	Con 0.0004% BP 177 Medical use: Anti-biotic Anti-candida Acetylcholinesterase Inhibitor
"Borneol" 	Con 0.008% BP 210 Medical use: Anti-biotic
"Δ-3-carene" 	Con 0.004% BP 177 Medical use: Anti-biotic Anti-candida Acetylcholinesterase inhibitor

"Δ-8-tetrahydrocannabinol" (Δ-8-THC) 	Con 0.0-0.1% BP 175-178 Medical use: It is less psychoactive and more stable than 9-THC, Antiemetic
"Tetrahydrocannabivarin" (THCV) 	Con 0.0-1.36% BP grater then 220 Medical use: Analgesic and euphoria
"α-terpineol" 	Con 0.02% BP 217-218 Medical use: Acetylcholinesterase inhibitor, Anti-malarial, Anti-oxidant

Structure of constituents obtained from [26, 27] Concentration of constituents [28, 29] Boiling/melting point [30, 31]

PHARMACOKINETICS OF CANNABINOIDS

Absorption:

Cannabis is been done moistly through inhalation, oral administration, and less commonly through Ophthalmic administration, rectal administration.

Mostly the inhalation of cannabis is done through burning the compound and inhaling the smoke, as we know by table1 the compound is activated at different temperatures. TCH is ben detected after one puff of cannabis cigarette, and blood peak plasma concentration is reached within 3-4 min after the sequence of round [15, 14]. The systemic bioavailability range between (10-35%) but it also depends on the pattern of smoking, holding of breath, inhalation amount, frequency of intake, and dose of puff [16]. During the nineties, an experiment is done by using a machine that simulate the pattern of cannabis smoking. There are many types of the pattern of smoking is tested, the most common way smoking shows that 16%-19% of THC in mainstream smoke if whole cannabis cigarette was smoked in one puff then mainstream concentration will be 69%[17]. When it was compared with another root of administration it was found the site of action is high in inhaling[23], and then oral, In an experiment, it was found that oral absorption is slow and show its peak plasma concentration after 60-120 minutes[3,5] shown in fig, Bioavailability is reduced due to 1st past liver metabolism, however, it depends on the vehicle used, it was found the oil vehicle with radioactive THC showed 95% absorption from gastro intestinal track[2], 6-4% absorption is shown when administer through ophthalmic, and shown peak plasma concentration in 1 hour[18].

Distribution

TCH distribution uses the physicochemical property, this TCH formed a bond with 95% to plasma protein, highly to lipoproteins, and less to albumin [19]. So it is known to speedily distribute into well-vascularized organs like the liver, heart, brain, but distribution may be affected by body size and composition, and any disease state which will influence the permeability of blood-brain barriers. Chronic use of cannabis may accumulate in adipose tissue with subsequent release may cause the increase t1/2 life.

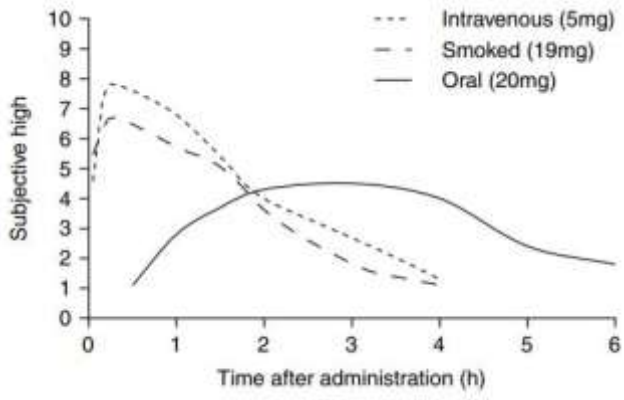


Figure 1: Systemic bioavailability of Δ9-tetrahydrocannabinol (THC)

Metabolism

TCH is metabolized mainly in the liver by an enzyme of Cytochrome P450 (CYP450) complex [21, 22] and isozymes [22] CYP2C9, CYP2C12 and CYP3A4 and excreted by breast milk [20], urine and feces, due to having the property of lipophilic THC can cross the placenta [20]. CBD is also metabolized in the liver by CYP2C19 and CYP3A4. Accept the liver it was found that many other tissues can metabolize the cannabinoids but in a lesser amount compared to the liver. Plasma clearance is reported to be 197 ± 50 ml/min for women and for men 248 ± 62 ml/min.

Table 2:

Subjects	Systemic bioavailability (%)		Formulation	Reference
	average	range		
Oral				
11 frequent6 or infrequent users	6±3	4-12	THC in chocolate cookie	39
6 men, 6 women	10-20		THC in Sesame oil	31
7 men, 10 women	7±3	2-14	THC in sesame oil	41
Inhalational				
9 heavy users	23±6	6-56	Marijuana cigarette	38
9 light users	10±7	2-22	Marijuana cigarette	38
5 heavy users	27±10	16-39	Marijuana cigarette	42
4 light users	14±1	13-14	Marijuana cigarette	42
11 frequent or infrequent users	18±6	8-24	THC in cigarette	39
Rectal				
2 Patients with spasticity	190-220% of oral bioavailability		Suppository with THC-hemi succinate	25

Elimination

Estimation of the elimination half-life of THC varies a fast initial half-life approx. 6 min and long terminal half-life 22hours [14], relatively long elimination half-life is observed in heavy uses. CBD has also been reported to have along with terminal half-life, average half-life following intravenous dosing observed to be 24 ± 6 hours and post inhalation to be 31 ± 4 hours. The cause for the reduced elimination of THC from plasma is due to the re-diffusion of THC from body fat and other tissue into the blood [22].

ENDOCANNABINOID SYSTEM

The Endocannabinoid system (ECS) is the biological system produced by our body composed of endocannabinoids, enzymes, and receptors all over the body. Human ECS helps to regulate all the physiological system, insuring every system working regulation. Endocannabinoids are produced by the body itself, there are two main types 1st ANDAMIDE[9], which is responsible for running high, and the blissful state that comes from exercise and meditation, and 2nd is 2-AG is the most dominant endocannabinoid responsible for managing appetite, pain response, and immune function. An enzyme of ECS work as the recycle of Endocannabinoid for other use these are present within the ECS. Receptors are present all over the body, there are two categories of receptors present Cannabinoid Receptor1 (CB_1), Cannabinoid Receptor 2 (CB_2). ECS works on the lock and key method.

RECEPTORS OF ECS

CB1 and **CB2**

These receptors are mostly found in the brain, it may be considered as brain cannabinoid receptors, these receptors are present in the form of G-protein coupled receptors, and this GPCR CB1 is densely present in the hippocampus, cerebellum, Globus pallidum, substantia nigar. CB1 with GABA (Gama aminobutyric acid) is highly present in sensory and motor regions and primarily on peripheral and central neurons in presynapse.

The distribution of these receptors in the brain will be different in adults and neonates, (Romero et al. 1997) found that it is highly danced in white matter areas at an early age of life. The activation of these receptors may result in a decrease in cyclic adenosine monophosphate, stimulation of mitogen-activated protein kinase activity.

These receptors are present all over the body and are assumed to mostly link with the immune system, lungs, kidney, respiratory system, eyes, bones, skin, etc.

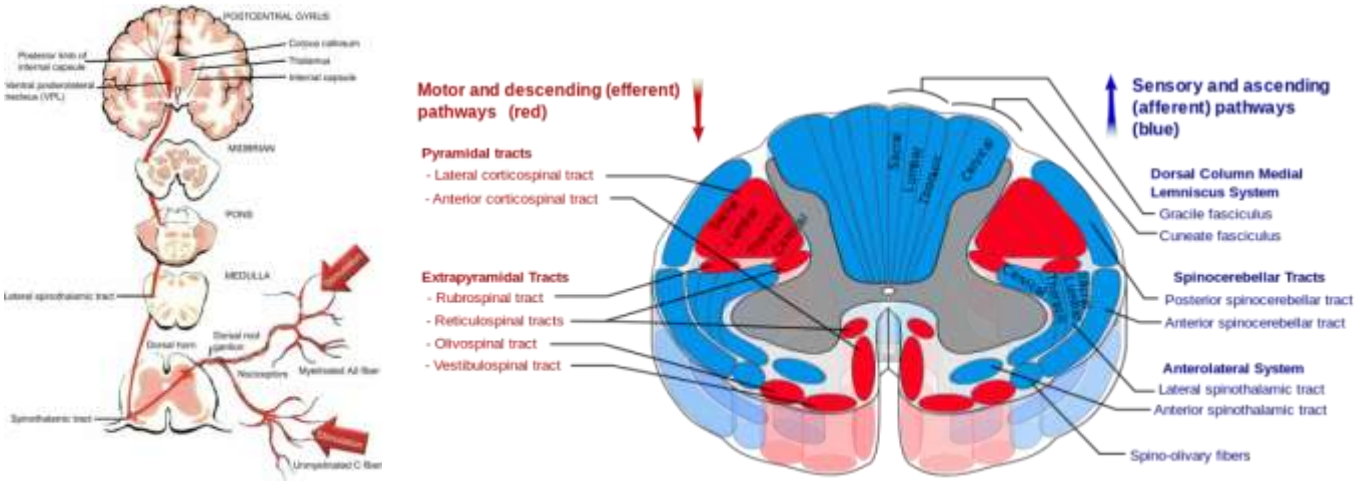


Figure 2: pain pathway Copyright Scientific American Medicine[32]

CANNABINOID IN PAIN RELIVE

Spinal code and its general anatomy

The spinal cord works as a relay station, it transmits impulse about pain, pressure, temperature from the periphery. The spinal cord is a cylindrical, elongated important part of the central nervous system, except for the central nervous system it works as the nerve tissue linking and helps to channelize the impulse all over the body. The spinal cord is lined by a membrane commonly known as meninges, which consist of three membranes most outer layer Dura mater, in middle

arachnoid mater, and most inner membrane in the Pia mater. The inner side of the spinal cord contains Grey matter and white matter in the surrounding grey matter, it consists of two posteriors, (which are composed of the cell body that is linked with nerve fibers that carry stimulation from the periphery of the body) and two anterior columns. The nerve fibers coming out from the posterior (dorsal) side of the spinal cord from the posterior root of the ganglion are connected to the posterior nerve root, which brings the signal.

Whenever our cells undergo damage due to burning, trauma, infection, autoimmune, allergic reaction results in initiating a cascade of reactions which result in the production of inflammatory mediators (cytokines, histamine, prostanoids, and neuropeptides) (Richardson and Vasko, 2002), these inflammatory mediators cause the vasoconstriction followed by vasodilation and increase vascular permeability that results in swelling. These mediators also activate the nociceptor sensory ending which works as a receptor of pain (Costigan and Woolf, 2000).

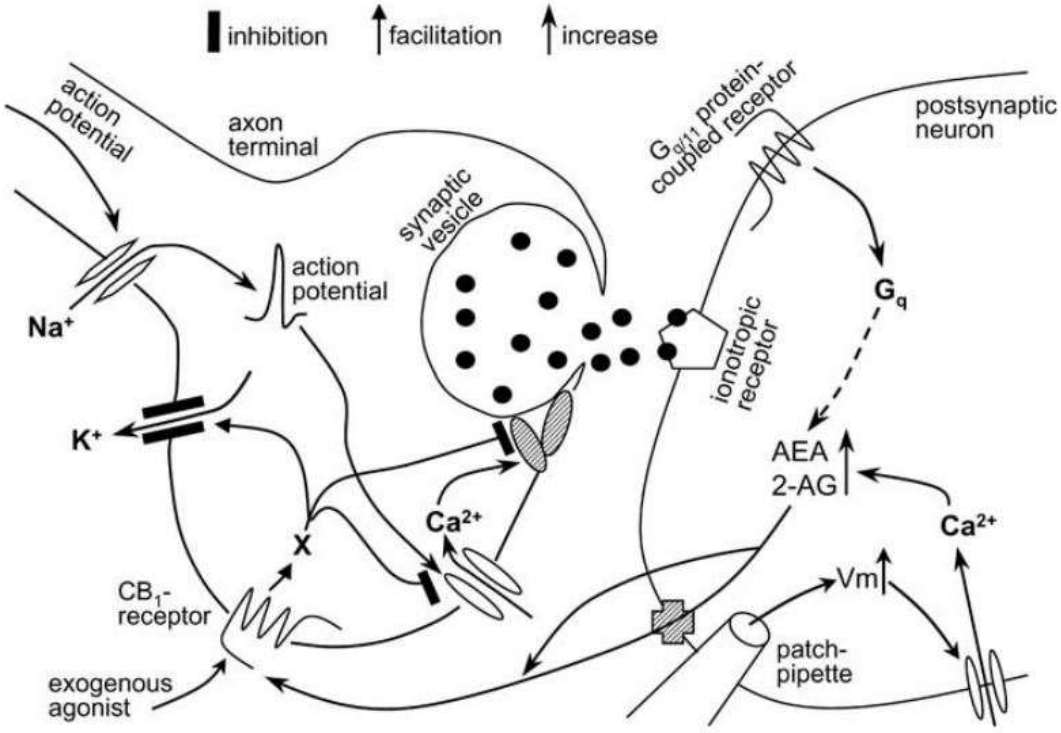


Figure 3: effect of Cannabinoid on Synaptic Transmission [25]

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage" the system of pain is also named as "nociceptive system", in the peripheral nerve nociceptors Aδ (this are small myelinated nerve cell that produces fast localized sharp pain), and C fibers (these fibers are non-myelinated, slow localized pain)activated by noxious stimulation lead to increase the sensor potential in the sensory end or free nerve ending, the action potential is trigger when there is sufficiently high sensory potential.

This potential is conducted to the posterior root of the ganglion (dorsal horn), the nociceptors release the pain neurotransmitters such as substance P which coexists with excitatory neurotransmitter glutamate, which causes EPSP (excitatory postsynaptic potential) in the membrane of the second-order neuron will receive this impulse, and this impulse is transmitted directly to the brain, the impulse will travel through spinothalamic pathway directly into the thalamus, the thalamus is known as the relay station as well.

The somatosensory cortex presents in the postcentral gyrus of the brain which correlates with a different part of the body, whenever the second order neuron has the impulse, it passes to the third order neuron and then to the somatosensory pathway which helps in the discrimination of pain area and intensity. This whole pathway is called ascending pathway. There is also a descending pathway, which regulates the ascending pathway functioning, whenever the DCML (dorsal column media lemniscus pathway which is the sensory pathway of the central nervous system which convert fine touch, vibration) whenever it activated by deep touch, etc. it activates the inhibitory neuron in substantia gelitanosa, this neuron release the inhibitory neurotransmitters Enkephalin which binds to nociceptors, which cause close of calcium channel leading to less excitatory neurotransmitter (substance p, glutamate), it led to less excitatory postsynaptic potential, hyperpolarization and decrease action potential frequency.

Pain modulation by Cannabinoids

Normally in human body contain feedback mechanism which modulate the intensity of pain produced by ascending pathway, this system as we know descending pathway, these pathway are endogenous ant nociceptive pathway, in 1969 (by Reynolds) in an rate experiment is observe that, by electrical stimulation of PAG (dorsolateral periaqueductal grey) result in big relief of pain, dorsolateral periaqueductal grey (PAG) and rostral ventromedial medulla (RVM) are the most important site for analgesia producing site by opioid, apart from this it is also the site for cannabinoid CB1 receptors[28,30]. It is been seen that cannabinoid produce more satisfactory effect then opioid, its due to opioid have less receptor then cannabinoid in spinal cord, the effectiveness is associated with an up regulation of CB11 receptor.

Cannabinoids work to modulate pain in substantia gelatinosa by reducing the neurotransmission molecule (substance-p and glutamate) by blocking calcium channel of nociceptor [20].2nd the activation of the CB1 receptor at presynaptic neuron

inhibits the transmitter from neurotransmitter [12] vesicles, it involves three mechanism inhibition of voltage-dependent calcium channels, at soma dendritic regions of neuron which lead to the presynaptic inhibition. Activation of potassium channel, in soma dendritic region of neurons lead to the open of potassium channels for longer time which lead to hyperpolarization and shorten the action potentials.

Clinical trials

Mark A. Ware MBBS, Tongtong Wang Ph.D. et.al [10] "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial"

This study is approved by the McGill University Health Centre Research Ethics Committee. The study was designed under a randomized, double-blind, placebo-controlled, four-period crossover design. Total twenty-three participants in this study, among them cannabis doses of (0%, 2.5%, 6%, 94%, and placebo tetrahydrocannabinol) were delivered as single three times a day inhalation. The participants are directed to inhale for 5 seconds and hold it for 10 seconds and then exhale. [10]

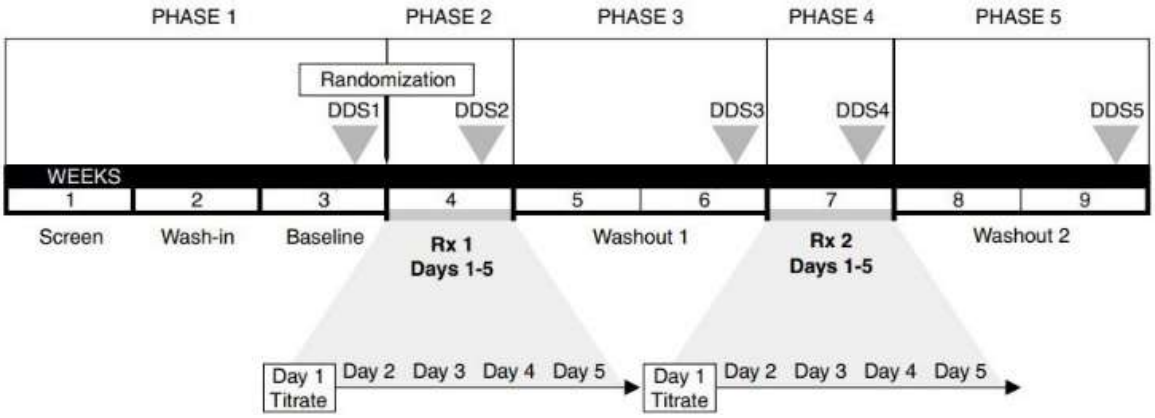
The outcome is measured, assessed of sleep using Leeds Sleep Evaluation Questionnaire [7], mood effects is examine by short-form Profile of Mood States was used [14], and health related quality of life is measured through EQ-5 D.

This research has found primary outcome higher dose (9.4%) THC shows the low intensity of pain occurrence and also found that 904% of TCH participants show more drowsiness and reported a higher number of sleeping hours.

Ronald J Ellis*, 1, Will Toperoff1 et.al

"Smoked Medicinal Cannabis for Neuropathic Pain in HIV [12]: A Randomized, Crossover Clinical Trial" Cannabis shows medicinal use in various illnesses, including neuropathic pain due to HIV distal sensory polyneuropathy [12], 33 participants are selected suffering from this disease. This research is single group, double-blind, placebo-controlled, and crossover trial, Phase-II and phase is divided into 5 study phase, 1st one-week wash-in phase, 2nd five days of smoked active or placebo and 3rd 2 weeks wash-out phase,4th five days smoked active or placebo cannabis and 5th two weeks final wash-out. The participants are HIV positive, adults, and have a DSPN pain intensity scale of 5.

The outcome is measured by 'Descriptor Differential scale' pain intensity scale, the participants are given THC concentration of 2%, 4%, 1%, 6%, 8%. Primary analysis shows that pain significantly reduce in patient takin 8% cannabis comparison with placebo, the increase in heart rate of 30 points after smoking, blood pressure alter and change in viral load and Cluster of differentiation 4 count have no change in cannabis and placebo.



CONCLUSION

Cannabinoids show a major potential in the treatment of pain, two types of cannabinoids are present, endocannabinoid and extrapyramidal cannabinoids, normally humans have an endocannabinoid system that has receptors, enzymes, endocannabinoids which are known to maintain the normal functioning of all mechanisms. Majorly CB1 is present in CNS and CB2 is the most abundantly present in lungs, liver, kidney, etc. in immune cells. The analgesic effects are achieved by various mechanisms, such as inhibition neurotransmitters and neuropeptides from the presynaptic nerve ending, activation of descending pathway. Many of the clinical trials are done on Cannabis for the treatment of chronic pain it is been found that at a higher dose it shows higher effectiveness as compared to other analgesic drugs[10,12], but with that, it also produces adverse drug reactions of sedation, improper motor movement. In the clinical trial, it is also found that administration and bioavailability of cannabis are higher if we take it through inhalation [14, 15], most of the research suggests the effective practice of cannabis as a drug for the management of pain is using a dermal patch having TCH.

Conflicts of interest

I declared that there is no conflict of interest

REFERENCES:

1. Turner CE, Elsohly MA, Boeren EG. Constituents of Cannabis sativa L. XVII. A review of the natural constituents. J Nat Prod [Internet]. 1980; 43(2):169–234. Available from: http://dx.doi.org/10.1021/np50008a001
2. Wall ME, Sadler BM, Brine D. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol, in men and women. Clin Pharmacol Ther. 1983; 34(3):p.352–63.
3. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther [Internet]. 1980; 28(3):409–16. Available from: http://dx.doi.org/10.1038/clpt.1980.181
4. Watson SJ, Benson JA Jr, Joy JE. Marijuana and medicine: assessing the science base: a summary of the 1999 Institute of Medicine report. Arch Gen Psychiatry [Internet]. 2000; 57(6):547–52. Available from: http://dx.doi.org/10.1001/archpsyc.57.6.54
5. W. Slikker, M. G. Paule, S. F. Ali, A. C. Scallet, J. R. Bailey. Behavioral, Neurochemical, and Neurohistological Effects of Chronic

Marijuana Smoke Exposure in the Nonhuman Primate. CRC Press; 1992. P.56

6. India cannabis industry 2019 [Internet]. Apsaseed.org. [cited 2022 Apr 9]. Available from: https://web.apsaseed.org/news/cannabis-industry-asia-apsa-2019-country-highlights/india
7. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations - a review. Psychopharmacology (Berl) [Internet]. 1980; 71(2):173–9. Available from: http://dx.doi.org/10.1007/bf00434408
8. Shacham S. A shortened version of the Profile of Mood States. J Pers Assess [Internet]. 1983; 47(3):305–6. Available from: http://dx.doi.org/10.1207/s15327752jpa4703_14
9. Maccarrone M, Finazzi-Agró A. The endocannabinoid system, anandamide and the regulation of mammalian cell apoptosis. Cell Death Differ [Internet]. 2003; 10(9):946–55. Available from: http://dx.doi.org/10.1038/sj.cdd.4401284
10. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ [Internet]. 2010; 182(14):E694-701. Available from: http://dx.doi.org/10.1503/cmaj.091414
11. Hohmann, A. G., Martin, W. J., Tsou, K., & Walker, J. M. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. Life Sciences, 1995; 56(23–24):2111–2118. https://doi.org/10.1016/0024-3205(95)00196
12. Ellis, R. J., Toperoff, W., Vaida, F., van den Brande, G., Gonzales, J., Gouaux, B., Bentley, H., & Atkinson, J. H. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 2009; 34(3):672–680. https://doi.org/10.1038/npp.2008.120
13. Martin WJ, Lai NK, Patrick SL, Tsou K, Walker JM. Ant nociceptive actions of cannabinoids following intraventricular administration in rats. Brain Res [Internet]. 1993;629(2):300–4. Available from: http://dx.doi.org/10.1016/0006-8993(93)91334-o
14. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids: I.absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Anal Toxicol. 1992;16(5):276–82.DOI: https://doi.org/10.1093/jat/16.5.276
15. Perez-Reyes M, Guiseppi SD, Davis KH, Schindler VH, Edgar Cook C. Comparison of effects of marihuana cigarettes of three different potencies. Clin Pharmacol Ther [Internet]. 1982; 31(5):617–24. Available from: http://dx.doi.org/10.1038/clpt.1982.86
16. Davis KH Jr, McDaniel IA Jr, Cadwell LW, Moody PL. Some smoking characteristics of marijuana cigarettes. In: The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects. Elsevier; 1984. p. 97–109.
17. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Anal Toxicol. 1992 Sep-Oct; 16(5):276-82. doi: 10.1093/jat/16.5.276. PMID: 1338215.
18. Chiang CW, Barnett G, Brine D. Systemic absorption of delta 9-tetrahydrocannabinol after ophthalmic administration to the rabbit. J Pharm Sci [Internet]. 1983; 72(2):136–8. Available from: http://dx.doi.org/10.1002/jps.2600720210
19. Leuschner JT, Harvey DJ, Bullingham RE, Paton WD. Pharmacokinetics of delta 9-tetrahydrocannabinol in rabbits following single or multiple intravenous doses. Drug Metab Dispos. 1986 Mar-Apr; 14(2):230-8. PMID: 2870899.
20. Blackard C, Tennes K. Human placental transfer of cannabinoids. N Engl J Med [Internet]. 1984; 311(12):797. Available from: http://dx.doi.org/10.1056/NEJM198409203111213
21. Matsunaga T, Iwawaki Y, Watanabe K, Yamamoto I, Kageyama T, Yoshimura H. Metabolism of delta 9-tetrahydrocannabinol by cytochrome P450 isozymes purified from hepatic microsomes of monkeys. Life Sci [Internet]. 1995; 56(23–24):2089–95. Available from: http://dx.doi.org/10.1016/0024-3205(95)00193-a
22. Chiang CN, Rapaka RS. Pharmacokinetics and disposition of cannabinoids. NIDA Res Monogr. 1987; 79:173–88. PMID: 2830536
23. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet [Internet]. 2003; 42(4):327–60. Available from: http://dx.doi.org/10.2165/00003088-200342040-00003
24. Timpone JG, Wright DJ, Li N. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIVwasting syndrome. AIDS Res Hum Retroviruses. 1997; 13(4):p.305–15.
25. Engler B, Freiman I, Urbanski M, Szabo B. Effects of exogenous and endogenous cannabinoids on GABAergic neurotransmission between the caudate-putamen and the globus pallidus in the mouse. J Pharmacol Exp Ther [Internet]. 2006; 316(2):608–17. Available from: http://dx.doi.org/10.1124/jpet.105.092718
26. Bisset NG, Wichtl M. Herbal drugs and phytopharmaceuticals: A handbook for practice on a scientific basis. Stuttgart, Boca Raton: CRC Press; 1994.p.337-339
27. Leonard BE. Therapeutic uses of cannabis. British medical association (BMA). Harwood academic publishers, UK. 1997. £11.99. ISBN 90-5702-318-0. Hum Psychopharmacol [Internet]. 1998; 13(8):592–592. Available from: http://dx.doi.org/10.1002/(sici)1099-1077(1998120)13:8<592::aid-hup58>3.3.co;2-n
28. Veszki P, Verzár-Petri G, Mészáros S. Comparative phytochemical study on the cannabinoid composition of the geographical varieties of cannabis Sativa l. Under the same conditions. Acta Hortic [Internet]. 1980; 96:95–104. Available from: http://dx.doi.org/10.17660/actahortic.1980.96.49
29. Fournier G, Richez-Dumanois C, Duvezin J, Mathieu JP, Paris M. Identification of a new chemotype in Cannabis sativa: cannabigerol-dominant plants, biogenetic and agronomic prospects. Planta Med [Internet]. 1987; 53(3):277–80. Available from: http://dx.doi.org/10.1055/s-2006-962705
30. Buckingham J. Dictionary of natural products. London: Chapman & Hall; 1992.p.142
31. The essential oils. Volume III. (the individual essential oils of the plant families Rutaceae and labiatae.) by ERNEST GUENTHER. D. van Nostrand company, inc., New York, 1949. Xvi+777 pp. Illustrated. 15×23.5cm. Price $10. J Am Pharm Assoc (Sci) [Internet]. 1950; 39(4):243. Available from: http://dx.doi.org/10.1002/jps.3030390420
32. Basbaum AI, Julius D. Toward better pain control. Sci Am [Internet]. 2006; 294(6):60–7. Available from: https://www.scientificamerican.com/article/toward-better-pain-contro/